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Original Article

Comparative effects of SGLT2 inhibitors, pioglitazone, DPP-4 inhibitors, and sulfonylureas on dementia risk in type 2 diabetes

Yu-Hsin Yen [a,1], James Cheng-Chung Wei [b,c,d], Yao-Min Hung [r,s,t,u], Shih-Yi Lin [e], Fu-Shun Yen [f,1], Heng-Jun Lin [g,h], Yu-Han Huang [g,h], Der-Yang Cho [i,j,k], Chii-Min Hwu [l,m,**], Chih-Cheng Hsu [n,o,p,q,*]

[a] Duke-NUS Medical School, 8 College Rd, Singapore, 169857, Singapore
[b] Department of Allergy, Immunology & Rheumatology, Chung Shan Medical University Hospital, No. 110, Sec. 1, Jianguo N. Rd., South District, Taichung City, 40201, Taiwan
[c] Institute of Medicine, Chung Shan Medical University, Taichung City, 40201, Taiwan
[d] Graduate Institute of Integrated Medicine, China Medical University, Taichung, 40402, Taiwan
[e] Division of Endocrinology and Metabolism, Taichung Veterans General Hospital, 160, Sec. 3, Taichung-Kang Road, Taichung, 407, Taiwan
[f] Dr. Yen's Clinic, No. 15, Shanying Road, Gueishan District, Taoyuan, 33354, Taiwan
[g] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[h] College of Medicine, China Medical University, Taichung, Taiwan
[i] Translational Cell Therapy Center, Department of Medical Research, China Medical University Hospital, Taichung, 404327, Taiwan
[j] Department of Neurosurgery, China Medical University Hospital, Taichung, 404327, Taiwan
[k] Graduate Institute of Biomedical Sciences, China Medical University, Taichung, 404327, Taiwan
[l] Faculty of Medicine, National Yang Ming Chiao Tung University School of Medicine, No.155, Sec.2, Linong Street, Taipei, 11221, Taiwan
[m] Section of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, No.201, Sec. 2, Shipai Road, Beitou District, Taipei, 11217, Taiwan
[n] Institute of Population Health Sciences, National Health Research Institutes, 35 Keyan Road, Zhunan, Miaoli County, 35053, Taiwan
[o] Department of Health Services Administration, China Medical University, Taichung, 40402, Taiwan
[p] Department of Family Medicine, Min-Sheng General Hospital, 168 ChingKuo Road, Taoyuan, 33044, Taiwan
[q] National Center for Geriatrics and Welfare Research, National Health Research Institutes, No. 95-1, Xuefu Rd., Huwei Township, Yunlin County, 632007, Taiwan
[r] Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
[s] College of Health and Nursing, Meiho University, Pingtung, Taiwan
[t] Master Program in Biomedicine, College of Science and Engineering, National Taitung University, Taitung, Taiwan
[u] Fooyin University College of Nursing, Kaohsiung, Taiwan

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ABSTRACT

Introduction: Dementia risk is significantly amplified by type 2 diabetes (T2D). This study compares the impact of sodium-glucose cotransporter 2 inhibitors (SGLT2is) against pioglitazone, dipeptidyl peptidase-4 inhibitors (DPP-4is), and sulfonylureas on dementia risk.

Methods: Using Taiwan's National Health Insurance Research Database (2000–2021), researchers emulated target trials with propensity-score matching. Cox proportional-hazards and Kaplan-Meier analyses estimated adjusted hazard ratios (aHRs) for dementia subtypes.

Results: Over a mean follow-up of 2.9 years, SGLT2i users had significantly lower cumulative incidences of all-cause and vascular dementia (all log-rank $p < 0.05$). Compared to pioglitazone, SGLT2i use was associated with lower risks of all-cause dementia (aHR 0.78, 95% CI 0.73–0.83) and vascular dementia (aHR 0.83, 95% CI 0.69–0.99). Alzheimer's risk reductions were not statistically significant.

Abbreviations: T2D, type 2 diabetes; SGLT2is, sodium-glucose cotransporter 2 inhibitors; DPP-4is, dipeptidyl peptidase-4 inhibitors; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker.

* Corresponding author at: Institute of Population Health Sciences, National Health Research Institutes.
** Corresponding author at: Section of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital.
E-mail addresses: yvonneyen26@gmail.com (Y.-H. Yen), jccwei@gmail.com (J.C.-C. Wei), ymhung1@gmail.com (Y.-M. Hung), sylin@vghtc.gov.tw (S.-Y. Lin), yenfushun@gmail.com (F.-S. Yen), hengjun.cmuh@gmail.com (H.-J. Lin), yuhan6527@gmail.com, viyi98.cmuh@gmail.com (Y.-H. Huang), dycho@tool.caaumed.org.tw (D.-Y. Cho), chhwu@vghtpe.gov.tw (C.-M. Hwu), cch@nhri.edu.tw (C.-C. Hsu).
[1] Yu-Hsin Yen and Fu-Shun Yen contributed equally in this work.

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Discussion: In these nationwide emulated trials, SGLT2is were associated with lower risks of all-cause and vascular dementia compared with pioglitazone, DPP-4is, and sulfonylureas.

1. Background

Dementia remains a progressive and ultimately fatal disorder of irreversible brain injury, defined by decline in cognition, mood, and behavior, with no curative therapy currently available [1]. Alzheimer's disease accounts for 60% to 70% of dementia cases, followed by vascular dementia (15%–20%) [2]. The societal burden is substantial, reducing quality of life while placing heavy strain on caregivers and healthcare systems [1]. In the United States, more than 7 million individuals aged ≥65 years are living with dementia, supported by nearly 12 million family caregivers [1]. Globally, 57.4 million people were affected in 2019, and the number is projected to rise to 152.8 million by 2050 [3]. In Taiwan, older adults surpassed 14% of the population in 2018, with dementia prevalence approaching 8% (≈350,000 individuals), a figure expected to exceed 600,000 by 2060 [4,5]. Although novel disease-modifying therapies for Alzheimer's disease have recently been introduced, their benefits remain modest, highlighting the importance of preventive strategies [6].

Diabetes mellitus increases the risk of dementia by 1.5- to 2.5-fold [4]. Proposed mechanisms include chronic hyperglycemia, recurrent hypoglycemia, insulin resistance, oxidative stress, vascular dysfunction, inflammation, and advanced glycation end products [7]. These mechanistic overlaps raise the possibility that antidiabetic therapies can be repurposed as preventive strategies against dementia [6,7]. Among oral antidiabetic drugs, metformin has been associated with lower dementia risk, often in comparisons against sulfonylureas [8,9]. Notably, Zheng et al. demonstrated that, compared with no pharmacological treatment, metformin may exert neuroprotective effects beyond glycemic control and lower dementia risk [10]. Dipeptidyl peptidase-4 inhibitors (DPP-4is) may also provide cognitive benefits in Alzheimer's disease and reduce dementia risk in diabetes [8,11]. Thiazolidinediones (TZDs), which can cross the blood–brain barrier, have been linked to reduced dementia incidence [4,12,13]. By contrast, sulfonylureas appear to confer little or no protection [8,14].

Sodium–glucose cotransporters are widely expressed in brain tissue [9], and sodium–glucose cotransporter-2 inhibitors (SGLT2is) have shown potential to attenuate cognitive decline and reduce dementia risk compared with placebo or other oral agents [6,15,16]. However, the comparative effectiveness of different antidiabetic classes remains poorly defined, and direct head-to-head evidence against pioglitazone—a drug with established neuroprotective properties—remains lacking. In Taiwan, where metformin is the universal first-line therapy [4], discerning the dementia-related outcomes of second-line agents is particularly relevant for clinical decision-making. To address this gap, we conducted nationwide emulated target trials[17] to compare the effects of SGLT2is, pioglitazone, DPP-4is, and sulfonylureas on dementia risk in patients with type 2 diabetes.

2. Methods

2.1. Study population and data sources

This study was conducted using data from Taiwan's National Health Insurance Research Database (NHIRD), which is derived from the nationwide National Health Insurance (NHI) program. Established in 1995, the NHI is a single-payer system that provides universal healthcare coverage to approximately 23.86 million residents of Taiwan. The NHIRD contains comprehensive healthcare information, including patient demographics, diagnostic codes, medical procedures, and prescription records, all coded according to the International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) [18]. Ethical approval for the study was obtained from the Research Ethics Committee of China Medical University Hospital [CMUH112-REC1-117(CR-2)]. To ensure patient confidentiality, all records were anonymized and linked through encrypted identifiers. Because the NHIRD consists exclusively of de-identified data, informed consent was not required. China Medical University Hospital IRB e-mail: cmuh.irb@tool.caaumed.org.tw.

2.2. Target trial emulation

We adhered to the Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) guidelines to construct an observational framework that closely mirrored randomized clinical trials [17]. This approach enabled us to compare the effects of SGLT2is with those of pioglitazone, DPP-4is, and sulfonylureas in patients with T2D, employing an open-label (unblinded) trial emulation design. To align with the conceptual design of a randomized trial, we defined key components, including eligibility criteria, treatment allocation, intervention strategies, follow-up procedures, primary outcomes, causal contrasts, and analytic plans. We then mapped these trial elements to the available observational data to reproduce the protocol and conduct analyses (Supplementary Table 1). This approach allowed us to approximate the design and inferential rigor of randomized controlled trials while leveraging real-world data.

2.3. Study eligibility criteria

Data from January 1, 2000, through December 31, 2021, were analyzed. We identified patients with newly diagnosed T2D who initiated antidiabetic treatment during this period. To enhance diagnostic accuracy, T2D was defined as at least two outpatient claims or one hospitalization with a T2D diagnosis code (Supplementary Table 2). This algorithm has been validated in Taiwan, demonstrating a sensitivity of 90.9% and a positive predictive value of 92.0% [19].

Patients were excluded if they were younger than 40 years or older than 100 years at the time of diagnosis, had missing demographic information (sex or age), had an index year outside 2016–2020, were undergoing dialysis, had a prior diagnosis of type 1 diabetes or dementia, or died or were lost to follow-up within six months of the index date.

2.4. Assigned treatment strategies and groups

In the emulated trial, patients who initiated SGLT2is after a diagnosis of T2D were assigned to the SGLT2i group. Those who initiated pioglitazone, DPP-4is, or sulfonylureas served as comparator groups. The index date was defined as the date of the first prescription for the assigned medication. Because SGLT2is became available in Taiwan only after May 1, 2016, all index dates were restricted to May 1, 2016, or later.

2.5. Study outcomes and follow-up

The primary outcome was all-cause dementia, defined as a composite of Alzheimer's disease, vascular dementia, and unspecified dementia. The unspecified dementia category included cases with Alzheimer's disease ICD codes without prescriptions for dementia-related drugs, as well as diagnoses of Pick's disease, senile brain degeneration, and

dementia with Lewy bodies. Secondary outcomes included: (1) Alzheimer's disease, identified using specific ICD codes, requiring at least two outpatient visits or one hospitalization, along with prescriptions for dementia-related medications. (2) Vascular dementia identified using validated ICD codes (Supplementary Table S2). Previous studies have validated the use of ICD coding in administrative datasets, demonstrating acceptable accuracy for identifying dementia diagnoses [20, 21].

For each patient, follow-up began on the index date and continued until the first occurrence of an outcome, death, or the end of the observation period (December 31, 2021), whichever came first.

2.6. Emulation of a target trial

To mitigate confounding and approximate randomization, SGLT2i users were matched 1:1 with contemporaneous comparators using propensity score matching via the nearest neighbor method. Matching initially required an exact match on the eighth digit of the propensity score; if no suitable match was found, the criterion was progressively relaxed to the first digit. The matching process began with a caliper width of 0.0000001 and was gradually expanded up to 0.1 for unmatched cases. To further optimize the matching quality, we reassessed the criteria and performed an additional matching step using a greedy algorithm, ensuring that each SGLT2i user was paired with the comparator having the closest propensity score. Balance between groups was assessed using standardized mean differences (SMDs), with an SMD <0.1 indicating adequate covariate balance. Covariates included demographic variables, comorbidities, and the Charlson Comorbidity Index (CCI) [22], as well as the number and classes of oral antidiabetic drugs and the use of insulin, antihypertensive drugs, aspirin, and statins. Diabetes duration was defined as the interval between the first diagnosis and the index date.

2.7. Analysis plan and statistical analysis

The primary causal estimand was the intention-to-treat (ITT) effect of the assigned treatment strategy. Time-to-event analyses were performed using Kaplan–Meier methods to estimate cumulative incidence, and group differences were evaluated with the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using multivariable Cox proportional hazards models, with robust sandwich estimators applied to account for variability in standard errors.

To address the impact of competing events, Fine and Gray's subdistribution hazard model was applied, with death considered a competing risk. Sensitivity analyses were conducted by excluding individuals who developed dementia within one year after the index date, and the associations were reassessed using multivariable Cox proportional hazards models. Subgroup analyses evaluated the risk of all-cause dementia across categories of sex, age, overweight status, smoking history, CCI score, and diabetes duration. To examine whether the associations differed according to cumulative treatment duration, participants were classified into <200, 200–399, and >399 days of treatment. These cut-off points were selected to provide clinically interpretable duration categories while maintaining adequate sample sizes and numbers of outcome events within each stratum. Corresponding exposure-duration categories were applied to pioglitazone, DPP-4is, and sulfonylureas for comparison of all-cause dementia risk. Finally, E-values were computed to assess the potential influence of unmeasured confounding on the observed associations.

All statistical tests were two-sided, with $p < 0.05$ considered significant. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics of participants

From June 1, 2000, to December 31, 2021, patients with newly diagnosed type 2 diabetes were identified from the NHIRD. Following the application of exclusion criteria, the emulated target trials included 90,953, 70,819, and 50,189 propensity score–matched pairs for comparisons of SGLT2is versus pioglitazone, DPP-4is, and sulfonylureas, respectively (Supplementary Figures S1, S2 and S3). Baseline characteristics were well balanced between treatment groups, with SMDs <0.1 across most variables (Supplementary Tables S3-S5). The study population had a mean (SD) age of 61.78 (10.70) years, 55.0% were men, 2.33% had mild cognitive impairment as defined by ICD codes, and the mean (SD) diabetes duration was 8.46 (5.75) years in the emulated trial comparing SGLT2is with pioglitazone (Supplementary Table S3), and the mean (SD) follow-up duration for the outcome of all-cause dementia was 2.90 (1.30) years.

3.2. Main outcomes of SGLT2is versus pioglitazone

In this emulated target trial, treatment with SGLT2is was associated with a significantly lower risk of all-cause dementia (adjusted hazard ratio [aHR] 0.78, 95% confidence interval [CI] 0.73–0.83) and vascular dementia (aHR 0.83, 95% CI 0.69–0.99), whereas no significant difference was observed in the risk of Alzheimer's disease (aHR 0.90, 95% CI 0.79–1.02) compared with pioglitazone (Table 1).

In analyses accounting for death as a competing event, the association between SGLT2i use and a lower risk of all-cause dementia remained robust (aHR 0.80, 95% CI 0.75–0.86), whereas reductions in the risks of Alzheimer's disease and vascular dementia were not statistically significant (Table 1). Similarly, when dementia cases diagnosed within one year after the index date were excluded, SGLT2i use continued to be associated with a significantly lower risk of all-cause dementia (aHR 0.77, 95% CI 0.71–0.83), while the associations with Alzheimer's disease and vascular dementia remained nonsignificant (Table 1).

Kaplan–Meier analyses further demonstrated that SGLT2i users had significantly lower cumulative incidences of all-cause dementia (log-rank $p < 0.001$) and vascular dementia (log-rank $p = 0.028$) than pioglitazone users, whereas the difference in Alzheimer's disease was not statistically significant (log-rank $p = 0.061$) (Fig. 1).

3.3. Main outcomes of SGLT2is versus DPP-4is

In this emulated target trial, the use of SGLT2is was associated with significantly lower risks of all-cause dementia (aHR 0.64, 95% CI 0.58–0.72), and vascular dementia (aHR 0.68, 95% CI 0.51–0.91), whereas no significant difference was observed in the risk of Alzheimer's disease (aHR 0.87, 95% CI 0.71–1.08) compared with DPP-4is (Table 2).

When death was considered as a competing event, the associations remained robust for all-cause dementia (aHR 0.66, 95% CI 0.59–0.74) and vascular dementia (aHR 0.69, 95% CI 0.52–0.93). However, the reduction in Alzheimer's disease risk did not achieve statistical significance (Table 2). Similarly, after excluding dementia cases diagnosed within the first year after the index date, SGLT2i use continued to be associated with a significantly reduced risk of all-cause dementia (aHR 0.69, 95% CI 0.61–0.78) and vascular dementia (aHR 0.67, 95% CI 0.48–0.92), whereas the association with Alzheimer's disease remained non-significant (Table 2).

Kaplan–Meier analyses further showed that SGLT2i users had significantly lower cumulative incidences of all-cause dementia (log-rank $p < 0.001$) and vascular dementia (log-rank $p = 0.006$) than DPP-4i users, whereas the difference in Alzheimer's disease was not statistically significant (log-rank $p = 0.081$) (Fig. 2).

Table 1
Outcome risks in the emulated trial of SGLT2is versus pioglitazone.

	Pioglitazone users			SGLT2i users			SGLT2i vs. pioglitazone users				
	n	PY	IR	n	PY	IR	cHR	(95% CI)	aHR†	(95% CI)	E-value
All-cause dementia	1841	266,653	6.90	1438	268,705	5.35	0.77	(0.72, 0.83)***	0.78	(0.73, 0.83)***	1.89
All-cause dementia[a]	1841	266,653	6.90	1438	268,705	5.35	0.79	(0.73, 0.84)***	0.80	(0.75, 0.86)***	
All-cause dementia[b]	1472	265,367	5.55	1126	267,799	4.20	0.76	(0.7, 0.82)***	0.77	(0.71, 0.83)***	
Alzheimer's disease	494	268,714	1.84	441	270,246	1.63	0.88	(0.78, 1.01)	0.90	(0.79, 1.02)	1.46
Alzheimer's disease[a]	494	268,714	1.84	441	270,246	1.63	0.90	(0.79, 1.03)	0.93	(0.82, 1.06)	
Alzheimer's disease[b]	391	266,887	1.47	351	268,900	1.31	0.89	(0.77, 1.03)	0.91	(0.79, 1.05)	
Vascular dementia	260	268,962	0.97	214	270,552	0.79	0.82	(0.68, 0.98)*	0.83	(0.69, 0.99)*	1.72
Vascular dementia[a]	260	268,962	0.97	214	270,552	0.79	0.83	(0.69, 1.00)*	0.85	(0.71, 1.02)	
Vascular dementia[b]	206	267,066	0.77	173	269,139	0.64	0.83	(0.68, 1.02)	0.85	(0.69, 1.04)	

SGLT2i, sodium-glucose cotransporter 2 inhibitor; PY, person-years; IR, Incidence rate per 1000 person-years; cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.
aHR†: Model adjusted for age groups, sex, comorbidities, medications, and duration of type 2 diabetes as listed in Supplementary Table S3.
[a] : estimated using the Fine and Gray sub-distribution hazard model with death considered as a competing risk.
[b] : excluded patients diagnosed with dementia within one year after the index date, followed by multivariate analyses adjusting for the variables listed in Supplementary Table S3.
* $p < 0.05$, ** $p < 0.01$,.
*** $p < 0.0001$.

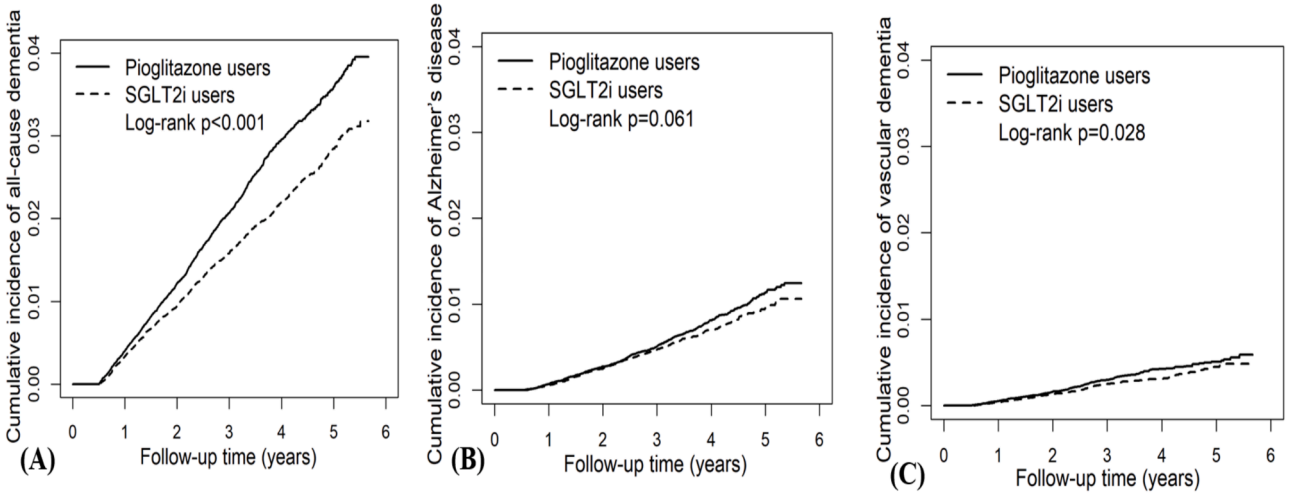

Fig. 1. Cumulative incidence of (A) all-cause dementia, (B) Alzheimer's disease, and (C) vascular dementia among SGLT2i and pioglitazone users.
Abbreviation: SGLT2is, sodium-glucose cotransporter 2 inhibitors.

Table 2
Outcome risks in the emulated trial of SGLT2is versus DPP-4is.

	DPP-4i users			SGLT2i users			SGLT2i vs. DPP-4i users				
	n	PY	IR	n	PY	IR	cHR	(95% CI)	aHR†	(95% CI)	E-value
All-cause dementia	782	184,125	4.25	501	186,260	2.69	0.63	(0.56, 0.71)***	0.64	(0.58, 0.72)***	2.48
All-cause dementia[a]	782	184,125	4.25	501	186,260	2.69	0.64	(0.57, 0.72)***	0.66	(0.59, 0.74)***	
All-cause dementia[b]	580	183,265	3.16	391	185,792	2.10	0.66	(0.58, 0.75)***	0.69	(0.61, 0.78)***	
Alzheimer's disease	188	184,989	1.02	158	186,727	0.85	0.83	(0.67, 1.02)	0.87	(0.71, 1.08)	1.55
Alzheimer's disease[a]	188	184,989	1.02	158	186,727	0.85	0.84	(0.68, 1.04)	0.89	(0.72, 1.11)	
Alzheimer's disease[b]	132	183,855	0.72	120	186,133	0.64	0.89	(0.7, 1.14)	0.96	(0.75, 1.23)	
Vascular dementia	115	185,067	0.62	78	186,824	0.42	0.67	(0.5, 0.89)**	0.68	(0.51, 0.91)**	2.3
Vascular dementia[a]	115	185,067	0.62	78	186,824	0.42	0.68	(0.51, 0.91)**	0.69	(0.52, 0.93)*	
Vascular dementia[b]	92	183,888	0.50	60	186,199	0.32	0.64	(0.46, 0.89)**	0.67	(0.48, 0.92)*	

SGLT2i, sodium-glucose cotransporter 2 inhibitor; DPP-4is, dipeptidyl peptidase-4 inhibitors; PY, person-years; IR, Incidence rate per 1000 person-years; cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.
aHR†: Model adjusted for age groups, sex, comorbidities, medications, and duration of type 2 diabetes as listed in Supplementary Table S4.
[a] : estimated using the Fine and Gray sub-distribution hazard model with death considered as a competing risk.
[b] : excluded patients diagnosed with dementia within one year after the index date, followed by multivariate analyses adjusting for the variables listed in Supplementary Table S4.
* $p < 0.05$,.
** $p < 0.01$,.
*** $p < 0.0001$.

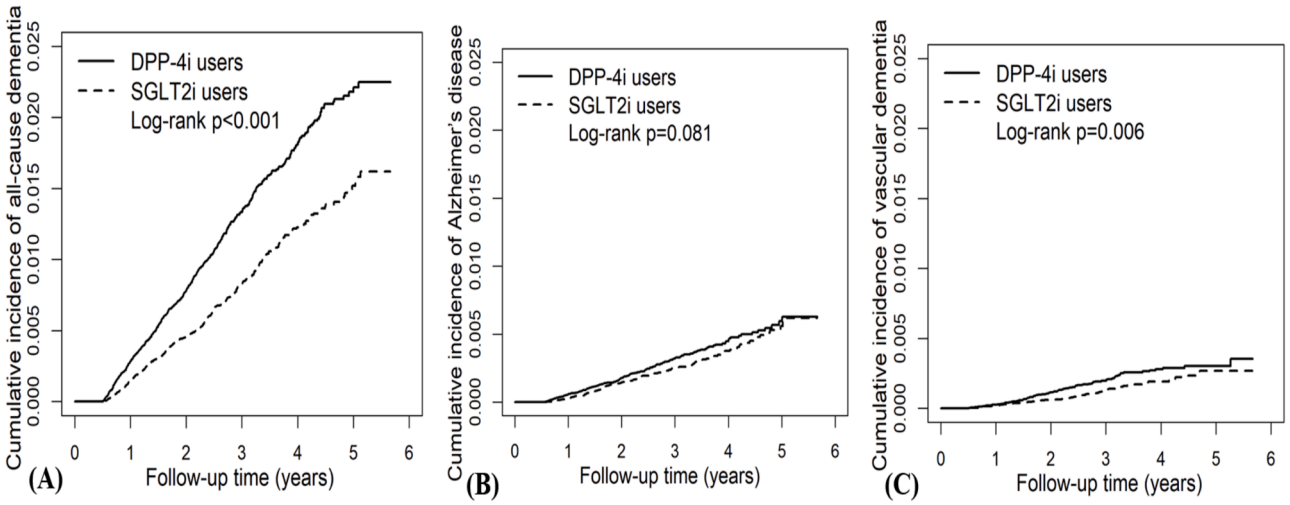

Fig. 2. Cumulative incidence of (A) all-cause dementia, (B) Alzheimer's disease, and (C) vascular dementia among SGLT2i and DPP-4i users.
Abbreviation: SGLT2is, sodium-glucose cotransporter 2 inhibitors; DPP-4is, dipeptidyl peptidase-4 inhibitors.

3.4. Main outcomes of SGLT2is versus sulfonylureas

In this emulated target trial, SGLT2i therapy was associated with significantly reduced risks of all-cause dementia (aHR 0.65, 95% CI 0.57–0.75) and vascular dementia (aHR 0.62, 95% CI 0.44–0.88), while the reduction in Alzheimer's disease risk did not reach statistical significance (aHR 0.97, 95% CI 0.75–1.26) compared with sulfonylureas (Table 3).

When accounting for death as a competing risk, the associations remained significant for all-cause dementia (aHR 0.67, 95% CI 0.59–0.78) and vascular dementia (aHR 0.65, 95% CI 0.46–0.91), whereas the association with Alzheimer's disease remained non-significant (Table 3). Similarly, after excluding dementia cases diagnosed within the first year of follow-up, SGLT2i use continued to be associated with a significantly lower risk of all-cause dementia (aHR 0.67, 95% CI 0.57–0.79) and vascular dementia (aHR 0.57, 95% CI 0.38–0.86), while the association with Alzheimer's disease remained not statistically significant (Table 3).

Kaplan–Meier analyses further demonstrated that SGLT2i users had a significantly lower cumulative incidence of all-cause dementia (log-rank $p < 0.001$) and vascular dementia (log-rank $p = 0.003$) than sulfonylurea users, whereas the difference in Alzheimer's disease was not statistically significant (log-rank $p = 0.31$) (Fig. 3).

3.5. Subgroup analyses, duration-stratified analyses, and E-value assessment

Subgroup analyses revealed that SGLT2i use was associated with a reduced risk of all-cause dementia compared with pioglitazone, DPP-4is, and sulfonylureas in most subgroups. However, exceptions were found in specific age groups (40–59 years) when compared with pioglitazone, and in the age groups 40–59 years and 80–100 years when compared with DPP-4is. Additionally, no significant differences were observed among smokers (compared to pioglitazone, DPP-4is, and sulfonylureas), patients with a CCI score of 0 (compared with pioglitazone), individuals with overweight (compared with pioglitazone, DPP-4is, and sulfonylureas), and patients with a shorter duration of diabetes (compared with DPP-4is) (Supplementary Tables S6–8).

In duration-stratified analyses, SGLT2i use was associated with lower risks of all-cause dementia across increasing cumulative treatment-duration categories compared with pioglitazone (aHRs: 0.95, 0.80, and 0.73 for <200, 200–399, and >399 days, respectively). Compared with DPP-4is (aHRs: 0.67, 0.59, and 0.65) and sulfonylureas (aHRs: 0.79, 0.54, and 0.59), the risk reduction was more pronounced after

Table 3
Outcome risks in the emulated trial of SGLT2is versus sulfonylureas.

	Sulfonylurea users			SGLT2i users			SGLT2i vs. sulfonylurea users				
	n	PY	IR	n	PY	IR	cHR	(95% CI)	aHR†	(95% CI)	E-value
All-cause dementia	530	125,298	4.23	327	126,326	2.59	0.61	(0.53, 0.7)***	0.65	(0.57, 0.75)***	2.43
All-cause dementia[a]	530	125,298	4.23	327	126,326	2.59	0.62	(0.54, 0.71)***	0.67	(0.59, 0.78)***	
All-cause dementia[b]	381	124,705	3.06	238	125,995	1.89	0.62	(0.52, 0.73)***	0.67	(0.57, 0.79)***	
Alzheimer's disease	124	125,815	0.99	110	126,596	0.87	0.88	(0.68, 1.13)	0.97	(0.75, 1.26)	1.21
Alzheimer's disease[a]	124	125,815	0.99	110	126,596	0.87	0.89	(0.69, 1.15)	1.00	(0.77, 1.30)	
Alzheimer's disease[b]	90	125,031	0.72	84	126,166	0.67	0.92	(0.68, 1.23)	1.03	(0.76, 1.39)	
Vascular dementia	85	125,829	0.68	51	126,667	0.40	0.59	(0.42, 0.84)**	0.62	(0.44, 0.88)**	2.6
Vascular dementia[a]	85	125,829	0.68	51	126,667	0.40	0.60	(0.43, 0.85)**	0.65	(0.46, 0.91)*	
Vascular dementia[b]	64	125,032	0.51	36	126,228	0.29	0.55	(0.37, 0.83)**	0.57	(0.38, 0.86)**	

SGLT2i, sodium-glucose cotransporter 2 inhibitor; PY, person-years; IR, Incidence rate per 1000 person-years; cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.
aHR†: Model adjusted for age groups, sex, comorbidities, medications, and duration of type 2 diabetes as listed in Supplementary Table S5.
[a] : estimated using the Fine and Gray sub-distribution hazard model with death considered as a competing risk.
[b] : excluded patients diagnosed with dementia within one year after the index date, followed by multivariate analyses adjusting for the variables listed in Supplementary Table S5.
* $p < 0.05$,.
** $p < 0.01$,.
*** $p < 0.0001$.

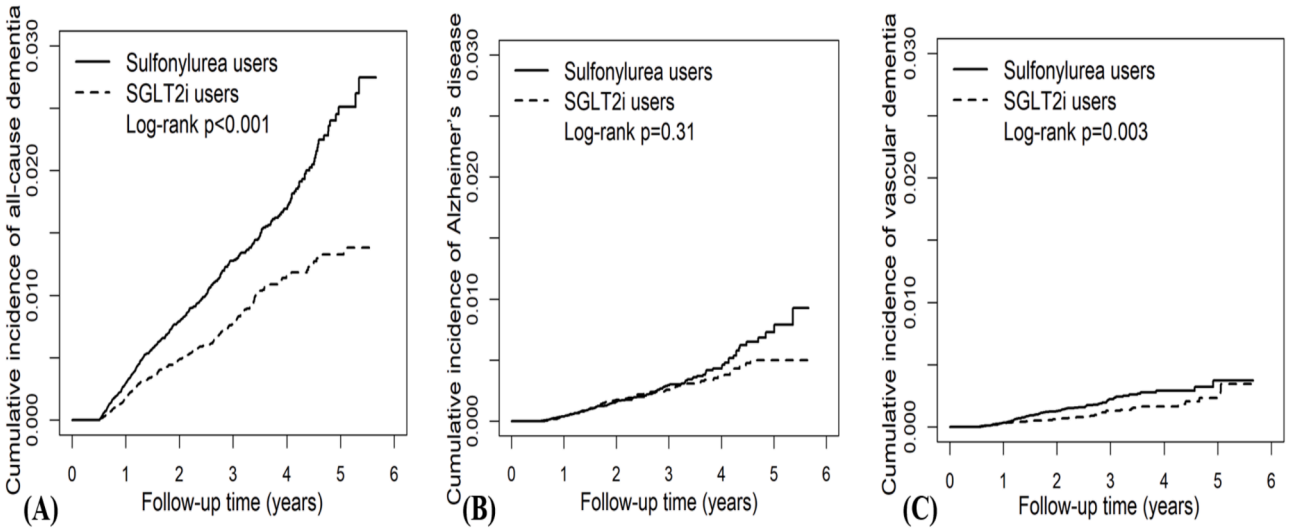

Fig. 3. Cumulative incidence of (A) all-cause dementia, (B) Alzheimer's disease, and (C) vascular dementia among SGLT2i and sulfonylurea users. Abbreviation: SGLT2is, sodium-glucose cotransporter 2 inhibitors.

≥200 days of treatment but appeared to plateau thereafter (Supplementary Table 9).

The calculated E-values for the associations between SGLT2i use and the risks of all-cause dementia and vascular dementia indicated moderate to strong robustness against unmeasured confounding. Specifically, the E-values were 1.89 and 1.72 for comparisons with pioglitazone (Table 1); 2.48 and 2.30 for comparisons with DPP-4is (Table 2); and 2.43 and 2.60 for comparisons with sulfonylureas (Table 3).

4. Discussion

Unlike prior studies that primarily compared SGLT2is with placebo or single agents, our nationwide emulated target trials provide head-to-head evidence across multiple second-line therapies, showing that SGLT2is consistently conferred lower risks of all-cause and vascular dementia compared with pioglitazone DPP-4is, and sulfonylureas. The reduction in all-cause dementia remained robust after accounting for death as a competing event and after excluding dementia diagnoses occurring within one year of the index date.

The consistency of our results with prior cohort studies[4,6,8,11–13,15,16] together with supporting meta-analyses, strengthens the validity of our findings. For instance, several analyses reported that TZDs, especially pioglitazone, were linked to a significantly reduced risk of all-cause dementia relative to non-TZD or DPP-4i users [23–25]. Similarly, two meta-analyses indicated that DPP-4i use was linked to a reduced risk of all-cause dementia relative to non-users or patients treated with sulfonylureas [2,26]. Multiple studies have also reported that SGLT2i use was associated with lower dementia risk compared with non-SGLT2i therapy [2,24,25,27]. In contrast, a meta-analysis of randomized controlled trials (RCTs) found no significant difference in dementia risk between SGLT2i users and controls [28]. Taken together, the available evidence suggests that pioglitazone, DPP-4is, and SGLT2is may offer some degree of protection against dementia in patients with T2D. Our study extends earlier observational findings by showing that SGLT2i use was linked to significantly reduced risks of all-cause dementia compared with pioglitazone, DPP-4is, and sulfonylureas, with consistent associations across subgroups stratified by age, sex, comorbidities, CCI, and diabetes duration. Furthermore, duration-stratified analyses showed lower risks of all-cause dementia with longer cumulative SGLT2i use compared with pioglitazone, whereas the associations appeared to plateau beyond 200 days in comparisons with DPP-4is and sulfonylureas.

Data on the impact of oral antidiabetic therapies on Alzheimer's disease and vascular dementia outcomes remain limited. Two cohort studies reported that SGLT2i use was associated with a significantly lower risk of Alzheimer's disease compared with DPP-4i and sulfonylurea use, respectively [29,30]. A systematic review and meta-analysis further suggested that both SGLT2is and TZDs reduced Alzheimer's disease risk compared with DPP-4is [24]. In contrast, a Bayesian network meta-analysis found that DPP-4is were associated with a lower Alzheimer's risk compared with sulfonylureas [26]. Other studies have reported null findings; a nationwide cohort showed no significant difference in Alzheimer's disease risk between DPP-4i users and non-users [11], and a meta-analysis of observational studies similarly found no significant association between DPP-4i use and Alzheimer's disease risk [2]. A meta-analysis of RCTs also reported that neither SGLT2is nor pioglitazone reduced Alzheimer's disease risk compared with non-users [28]. These results suggest uncertainty regarding the impact of oral antidiabetic therapies on Alzheimer's disease. In our study, SGLT2i therapy was not associated with a significant difference in the risk of Alzheimer's disease compared with pioglitazone, DPP-4is, or sulfonylureas. Consistent with the adjusted Cox analyses, the Kaplan–Meier analyses showed no statistically significant differences in the cumulative incidence of Alzheimer's disease between SGLT2i users and any of the three comparator groups. Thus, our findings do not support a significant association between SGLT2i use and Alzheimer's disease risk.

Vascular dementia is thought to result from insulin resistance and chronic hyperglycemia, which promote vascular injury and impaired cerebral blood flow [25]. Glucose-lowering agents may reduce risk through vascular benefits such as improved endothelial function and reduced arterial stiffness [8]. Prior evidence has been mixed: a nationwide Taiwanese cohort reported that DPP-4i use was associated with a significantly lower risk of vascular dementia compared with non-use [11], and a US-based cohort found SGLT2i use was associated with reduced risk compared with sulfonylureas [30]. Meta-analyses of observational studies also suggested lower vascular dementia risk with DPP-4is [2], while systematic reviews indicated potential benefit with DPP-4is and pioglitazone [24]. By contrast, a meta-analysis of RCTs found no significant association between SGLT2i use and vascular dementia [28]. In this context, our study provides the first nationwide head-to-head comparative evidence showing that SGLT2is were consistently associated with lower risks of vascular dementia compared with pioglitazone, DPP-4is, and sulfonylureas. These associations remained robust across sensitivity analyses and in competing risk models, thereby strengthening the case for SGLT2is as a potentially

associated with more favorable dementia-related outcomes in patients with T2D.

Several mechanisms may contribute to the observed associations between SGLT2i use and lower risks of all-cause and vascular dementia. SGLT2is favorably affect vascular and metabolic risk factors implicated in dementia, including hyperglycemia, insulin resistance, obesity, hypertension, and cardiovascular disease [2,8]. These effects may improve endothelial function, cerebral perfusion, and overall vascular health, potentially contributing to the lower risk of vascular dementia observed in our study [9,31,32]. However, these mechanisms remain hypothetical given the observational nature of our findings. Importantly, SGLT2i use was not associated with a significantly lower risk of Alzheimer's disease in any of the comparisons; therefore, our findings do not provide clinical evidence supporting a direct effect of SGLT2is on Alzheimer-specific neurodegenerative pathways. Longer-term studies are needed to determine whether SGLT2is have differential effects across dementia subtypes. The pharmacological characteristics of the active comparators may also partly account for the observed differences. Sulfonylureas are associated with a relatively high risk of hypoglycemia, particularly in older adults, and recurrent or severe hypoglycemic episodes may contribute to neuronal injury and cognitive decline [8,14]. In contrast, pioglitazone activates peroxisome proliferator-activated receptor-γ (PPAR-γ), improving insulin sensitivity and potentially exerting anti-inflammatory and neuroprotective effects [12,13]. These properties may partly explain why the association between SGLT2i use and lower dementia risk was less pronounced when pioglitazone, rather than sulfonylureas, served as the comparator. Nevertheless, these mechanistic explanations remain speculative and cannot be established from the present observational study.

Nevertheless, our study has several limitations. First, the NHIRD does not capture several potentially important clinical and lifestyle factors, including HbA1c levels, eGFR, and detailed information on smoking exposure, diet, alcohol use, physical activity, apolipoprotein E ε4 genotype, and family history. The absence of these variables limited our ability to directly account for glycemic control, renal function, smoking intensity, and genetic predisposition, all of which may influence dementia risk and could contribute to residual confounding [24,28]. We attempted to mitigate this limitation by incorporating available proxies, including comorbidities, insulin use, the type and number of oral antidiabetic agents, and diabetes duration, into the propensity score models. Nevertheless, residual confounding due to these unmeasured factors cannot be excluded. However, our use of a new-user, active--comparator design may reduce confounding by indication and immortal time bias, and the emulated target trial framework with extensive covariate adjustment may strengthen internal validity. The calculated E-values (1.72–2.60) may further suggest moderate to strong robustness against unmeasured confounding. Second, dementia diagnoses were based on ICD codes and prescription claims, without confirmation by gold-standard diagnostic tools such as neuroimaging, neuropsychological testing, or neuropathology. This may have led to underreporting or misclassification, particularly for Alzheimer's disease and vascular dementia [29]. However, prior validation studies indicate that administrative claims coding provides acceptable accuracy [19,20], and the inclusion of dementia-specific medications likely improved diagnostic reliability. To further minimize bias, we introduced a time lag between treatment initiation and outcome assessment to reduce reverse causation, and performed competing risk analyses, both of which yielded consistent findings. Third, the relatively short follow-up period for SGLT2i users (mean, 2.90 years) limits our ability to determine whether SGLT2i therapy is associated with long-term prevention of dementia, a disorder that typically develops over many years. Although we performed a sensitivity analysis excluding dementia diagnosed within the first year after treatment initiation, this 1-year lag period may not fully exclude patients with pre-existing subclinical cognitive decline or eliminate reverse causation. Therefore, the observed associations may reflect delayed clinical progression of subclinical cognitive impairment or short-term modification of vascular and metabolic risk factors rather than prevention of dementia [6,16]. Longer-term studies with extended lag periods are warranted to clarify whether these associations persist over the prolonged preclinical course of dementia. Fourth, because the study population was derived primarily from Taiwan, generalizability to other ethnic groups may be limited. Nonetheless, the results provide valuable insights for Asian populations, which remain underrepresented in dementia research. Finally, despite rigorous design features—including propensity score matching, active-comparator new-user design, and target trial emulation—residual confounding cannot be excluded. Ultimately, RCTs will be needed to confirm these findings.

5. Conclusion

In this nationwide series of emulated target trials, SGLT2i therapy was associated with lower risks of clinically diagnosed all-cause and vascular dementia compared with pioglitazone, DPP-4is, and sulfonylureas, whereas no significant differences were observed for Alzheimer's disease. Given the relatively short follow-up period and the observational nature of the study, these findings should not be interpreted as evidence that SGLT2is prevent dementia. Longer-term studies are warranted to determine whether these associations persist and to clarify their potential effects on specific dementia subtypes.

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Consent statement

Because the NHIRD consists exclusively of de-identified data, informed consent was not required.

Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

During the preparation of this manuscript, the authors used ChatGPT Plus to support language editing, enhance clarity and readability, and refine the overall tone of the text. All AI-assisted content was subsequently reviewed and revised by the authors, who assume full responsibility for the final manuscript and the accuracy and integrity of the cited references.

CRediT authorship contribution statement

Yu-Hsin Yen: Writing – original draft, Conceptualization. **James Cheng-Chung Wei:** Conceptualization. **Yao-Min Hung:** Formal analysis, Conceptualization. **Shih-Yi Lin:** Conceptualization. **Fu-Shun Yen:** Conceptualization. **Heng-Jun Lin:** Conceptualization. **Yu-Han Huang:** Data curation. **Der-Yang Cho:** Conceptualization. **Chii-Min Hwu:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Chih-Cheng Hsu:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Chih-Cheng Hsu reports financial support was provided by Taiwan Ministry of Health and Welfare Clinical Trial. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100691.

Data availability

Data of this study are available from the National Health Insurance Research Database (NHIRD) published by Taiwan National Health Insurance (NHI) Administration. The data utilized in this study cannot be made available in the paper, the supplemental files, or in a public repository due to the "Personal Information Protection Act'' executed by Taiwan government starting from 2012. Requests for data can be sent as a formal proposal to the NHIRD Office (https://dep.mohw.gov.tw/DOS/cp-2516-3591-113.html) or by email to stsung@mohw.gov.tw.

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