

Sodium–Glucose Cotransporter 2 Inhibitors and Lower Risk of Depression in Population with Type 2 Diabetes Mellitus: A Population-Based Active Comparator, New-User Design

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Purpose: This study aimed to investigate the association between the use of sodium–glucose cotransporter 2 inhibitors (SGLT2i) and the risk of developing depression in patients with type 2 diabetes mellitus.

Patients and Methods: This study used Taiwan's National Health Insurance Database and an active comparator new-user design to evaluate depression risk among 551,917 patients initiating SGLT2i or DPP4i between 2016 and 2018. The primary outcome was depression incidence, assessed over a three-year follow-up. Stratified Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) between groups.

Results: Among new SGLT2i users, 3255 cases of depression occurred (7.18 per 1000 person-years) versus 7190 cases among DPP4i users (10.12 per 1000 person-years). After adjustment for demographic and clinical covariates, SGLT2i use was consistently associated with a lower risk of depression in both the full cohort (adjusted HR = 0.77; 95% CI: 0.73–0.80) and the propensity score–matched cohort (adjusted HR = 0.77; 95% CI: 0.74–0.81). The association remained robust in multiple sensitivity analyses and across clinical subgroups.

Conclusion: SGLT2i use was associated with a reduced risk of depression among individuals with type 2 diabetes mellitus. These findings suggest potential neuropsychiatric benefits of SGLT2i and support further investigation into their broader therapeutic implications.

Keywords: sodium–glucose cotransporter 2 inhibitor, type 2 diabetes mellitus, depression

Introduction

Type 2 diabetes mellitus (T2DM) is a complex chronic disease that requires continuous medical care and comprehensive risk-reduction strategies extending beyond glycemic management.¹ T2DM is characterized by pancreatic β -cell dysfunction and insulin resistance, resulting in relative insulin deficiency.² According to the World Health Organization (WHO), approximately 14% of adults globally had T2DM in 2022.³ The prevalence of T2DM has been increasing recently,^{4–6} leading to substantial socioeconomic burdens associated with both direct healthcare costs and indirect consequences, such as loss of productivity.^{7–9} Consequently, effective T2DM management strategies that not only reduce hyperglycemia

but also address its systemic complications are of principal importance. The pathophysiology of T2DM is highly influenced by numerous factors, including chronic low-grade inflammation, which has been implicated in its progression.^{10,11} Among its various comorbidities, depression has been increasingly recognized as a significant concern.

Depression is a prevalent psychiatric disorder characterized by persistent sadness, anhedonia, and recurrent feelings of guilt.^{12–14} Its prevalence has exhibited a steady upward trajectory, and according to WHO projections, it is expected to become one of the leading causes of mortality by 2030.^{15,16} Depression is frequently comorbid with chronic diseases, such as T2DM, leading to a substantial decline in quality of life, increased disability, and elevated healthcare expenditures.^{17–19} The pathogenesis of depression is multifactorial and involves dysregulation of the hypothalamic–pituitary–adrenal axis, elevated circulating cortisol levels, chronic inflammation, and altered immune responses.^{18,20,21} This research has demonstrated that individuals with depression exhibit increased levels of proinflammatory cytokines in both the central nervous system and peripheral circulation, coupled with dysregulated immune cell activation. Furthermore, neurotransmitter imbalances have been implicated as a contributing factor to depressive disorders.²²

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) represent a novel class of antidiabetic agents that have gained importance recently as an essential component of T2DM management. In addition to their primary glucose-lowering effects, extensive evidence supports their multiple benefits, including significant cardiovascular protection and weight reduction.^{23,24} Furthermore, SGLT2i have been suggested to have antioxidant, anti-inflammatory, and antiapoptotic properties, which may confer neuroprotective effects in patients with T2DM-associated neurodegenerative complications and other neurological disorders.^{25,26} Considering these mechanisms, SGLT2i may contribute to modulating the risk of depression. Some pieces of evidence support the potential antidepressant effect of SGLT2i. For instance, previous animal studies have shown that dapagliflozin administration exerts antidepressant-like properties, potentially mediated by its influence on oxidative stress and neuroinflammatory pathways.^{27,28} However, considering that SGLT2i are a relatively novel therapeutic class, human studies investigating their potential effects on depression are scarce. Moreover, previous investigations have been limited by small sample sizes, inadequate adjustment for T2DM severity, or methodological limitations that limit causal inference.^{29,30}

Therefore, to address these gaps, this study employed population-based real-world data and used an active comparator new-user strategy to evaluate the association between SGLT2i use and the risk of depression in individuals with T2DM. This study aimed to confirm the potential neuropsychiatric benefits of SGLT2i for T2DM management.

Materials and Methods

Data Source

This study used data from the Taiwan National Health Insurance Database (NHID), which is maintained by the Ministry of Health and Welfare.³¹ The National Health Insurance (NHI) program has been implemented in Taiwan since 1995, and it allows data to be used for research purposes while ensuring the protection of personal privacy through anonymization and de-identification. The NHID, which has an enrollment rate exceeding 99%, is highly representative of the national population. As a valuable resource for healthcare and public health research, it provides essential evidence for healthcare policy development and clinical decision-making.

Study Design and Participants

We employed a cohort design with an active comparator new-user strategy, focusing on 551,917 patients who initiated treatment with SGLT2i or dipeptidyl peptidase 4 inhibitors (DPP4i) between January 1, 2016, and December 31, 2018. To ensure a new-user design, patients with any prior exposure to SGLT2i or DPP4i before the index date were excluded. This study then excluded patients concurrently using both SGLT2i and DPP4i; those diagnosed with depression, bipolar disorder, dementia, or anxiety disorder; those aged <20 years; and those with unspecified sex, to reduce confounding factors that may affect the study's outcomes. DPP4i were selected as the active comparator group because they share both therapeutic indication and reimbursement criteria with SGLT2i as second-line treatments for type 2 diabetes in Taiwan. Under the National Health Insurance program, both classes are typically prescribed after metformin failure, ensuring that patients initiating either therapy are drawn from comparable clinical settings. However, glucagon-like peptide-1 (GLP-1)

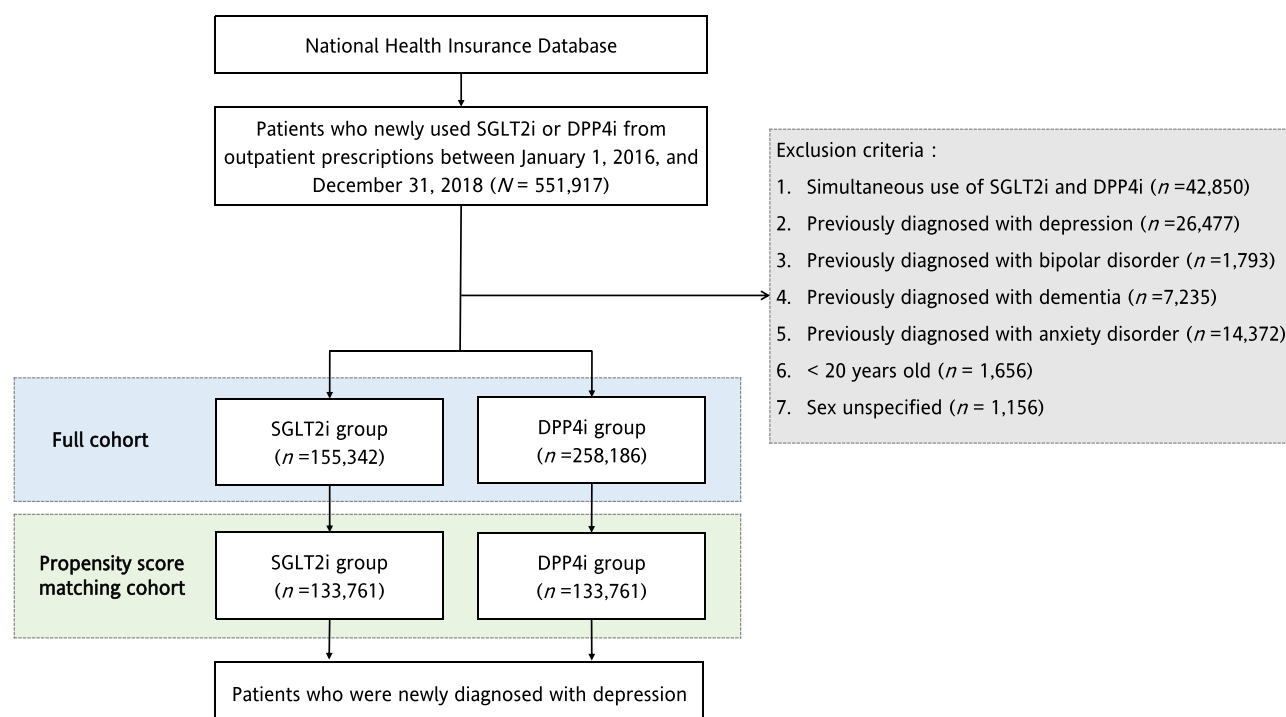


Figure 1 Flowchart of Patient Selection.

receptor agonists are reimbursed only for patients with advanced disease or established cardiovascular events, which restrict their applicability as a comparator group in this study. SGLT2i and DPP4i were classified based on the Anatomical Therapeutic Chemical (ATC) classification system: SGLT2i (ATC code A10BK) and DPP4i (ATC code A10BH). This selection ensured comparability between the groups, minimizing potential biases arising from differing treatment indications.³² Consequently, 155,342 patients were included in the SGLT2i group and 258,186 were included in the DPP4i group in the full cohort (Figure 1). The date of the first prescription of either SGLT2i or DPP4i was defined as the index date.

Furthermore, to minimize the potential effects of confounding factors, a propensity score matching (PSM) strategy was applied to obtain the balance characteristic between the two groups.³³ The PSM cohort was matched in a 1:1 ratio based on their propensity scores, which considered demographic data and comorbidities such as sex, age, index year, hypertension, stroke, hyperlipidemia, obesity, ischemic heart disease, heart failure, arrhythmia, chronic kidney disease, liver disease, diabetic retinopathy, diabetic neuropathy, rheumatoid arthritis, chronic obstructive pulmonary disease, insomnia, thyroid disease, smoking addiction, alcohol addiction, and the use of GLP-1 receptor agonists, metformin, sulfonylureas, insulin, α -glucosidase inhibitors, thiazolidinediones, combination antidiabetic drugs, and other antidiabetic medications. Baseline comorbidities and concomitant medications were defined based on the medical records within one year prior to the index date. These variables were assessed at baseline and treated as fixed covariates throughout the follow-up period. [Supplementary Table 1](#) presents the relevant International Classification of Diseases (ICD) and ATC codes. Finally, the PSM cohort comprised 431,916 patients (133,761 SGLT2i users and 133,761 matched DPP4i users).

Outcome Measurement and Sensitivity Analysis

The primary outcome of this study was the incidence of depression. Each study participant was individually tracked for 3 years from their index date to confirm whether they had been diagnosed with depression, defined by the following ICD codes: ICD-9-CM codes 296.2, 296.3, 300.4, 301.12, 309.0, 309.1, and 311 and ICD-10-CM codes F32, F33, F34.1, and F43.21. Moreover, sensitivity analyses were performed to assess the robustness of the results. In the first sensitivity analysis, depression cases were defined as patients with at least two or three diagnoses of depression. The second

sensitivity analysis included only patients with a principal diagnosis of depression. The third sensitivity analysis focused on identifying patients with major depressive disorder as depression cases. Furthermore, this study examined the dose–response relationship between the cumulative dose of SGLT2i and depression using the defined daily dose (DDD) as a standardized measure for dosage classification, categorizing patients into quartiles.

Statistical Analysis

All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA). The standardized difference (SDiff) was used to assess the demographic differences between the study and comparator groups. A SDiff value <0.1 indicates minimal imbalance in baseline covariates. Depression-free survival rates were calculated using Kaplan–Meier survival analysis. Stratified Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for comparing the risk of depression between SGLT2i and DPP4i users. To account for the competing risk of death, Fine–Gray subdistribution hazard models were additionally applied. Subgroup analyses were performed based on sex, hypertension, hyperlipidemia, chronic kidney disease, heart failure, ischemic heart disease, diabetic retinopathy, diabetic neuropathy, thyroid disease, insomnia, and the use of prior antidiabetic medications. In addition, we calculated E-values to evaluate the potential impact of unmeasured confounding.³⁴

Results

Table 1 presents the demographic and comorbidity distribution between the SGLT2i and DPP4i users. In the entire cohort, SGLT2i users had a higher proportion of males (57.77%) than females (42.23%), similar to DPP4i users (55.28% vs 44.72%). SGLT2i users were younger (58.15 ± 11.94 years) than DPP4i users (64.28 ± 13.25 years). When comparing comorbidities, hyperlipidemia and obesity were more prevalent among SGLT2i users, whereas stroke, chronic kidney disease, and COPD were more common among DPP4i users. Differences were also observed in the distribution of prior antidiabetic medication use. After PSM, baseline characteristics, comorbidities, and prior medication use were all well-balanced, minimizing bias.

Table 1 Baseline Characteristics and Comorbidities of Study Patients: Full Cohort and Propensity Score-Matched Cohort

Variables	Full Cohort (N = 413,528)			Propensity Score-Matched Cohort (N = 267,522)		
	SGLT2i Group n = 155,342	DPP4i Group n = 258,186	SDiff	SGLT2i Group n = 133,761	DPP4i Group n = 133,761	SDiff
Age (Mean ± SD)	58.15±11.94	64.28±13.25	−0.49	59.54±12.40	59.44±11.52	−0.01
Sex			−0.04			−0.03
Men	89,741 (57.77%)	142,726 (55.28%)		76,403 (57.12%)	76,531 (57.21%)	
Women	65,601 (42.23%)	115,460 (44.72%)		57,358 (42.88%)	57,230 (42.79%)	
Comorbidities						
Hypertension	95,190 (61.28%)	162,112 (62.79%)	−0.03	83,407 (62.36%)	82,280 (61.51%)	−0.02
Hyperlipidemia	101,388 (65.27%)	139,748 (54.13%)	0.23	85,885 (64.21%)	85,255 (63.74%)	−0.01
Stroke	3361 (2.16%)	12,168 (4.71%)	−0.14	3020 (2.26%)	3265 (2.44%)	0.01
Obesity	3552 (2.29%)	1907 (0.74%)	0.13	1694 (1.27%)	1917 (1.43%)	0.01
Chronic kidney disease	8517 (5.48%)	33,513 (12.98%)	−0.26	7640 (5.71%)	8,127 (6.08%)	0.02
Heart failure	5574(3.59%)	13,268 (5.14%)	−0.08	4688 (3.50%)	4886 (3.65%)	0.01
Arrhythmia	7339 (4.72%)	15,732 (6.09%)	−0.06	6393 (4.78%)	6525 (4.88%)	0.01
Ischemic heart disease	28,931 (18.62%)	41,865 (16.22%)	0.06	23,505 (17.57%)	23,575 (17.62%)	<0.01
Liver disease	14,122 (9.09%)	23,554 (9.12%)	−0.01	12,446(9.30%)	12,242 (9.15%)	−0.01
Diabetic retinopathy	6910 (4.45%)	12,628 (4.89%)	−0.02	5816 (4.35%)	5979 (4.47%)	0.01
Diabetic neuropathy	9745 (6.27%)	14,535 (5.63%)	0.03	8001 (5.98%)	8001 (5.98%)	<0.01
Rheumatoid arthritis	540 (0.35%)	1393 (0.54%)	−0.03	469 (0.35%)	509 (0.38%)	0.01
COPD	10,331 (6.65%)	24,393 (9.45%)	−0.10	9081 (6.79%)	9308 (6.96%)	0.01
Insomnia	6065 (5.43%)	38,399 (6.38%)	−0.05	7688 (5.75%)	7795 (5.83%)	<0.01
Thyroid disease	6176 (3.98%)	9286 (3.75%)	0.01	5251 (3.93%)	5210 (3.90%)	−0.01
Smoking addiction	2744 (1.77%)	4340 (1.68%)	0.01	2324 (1.74%)	2319 (1.73%)	−0.01

(Continued)

Table 1 (Continued).

Variables	Full Cohort (N = 413,528)			Propensity Score-Matched Cohort (N = 267,522)		
	SGLT2i Group n = 155,342	DPP4i Group n = 258,186	SDiff	SGLT2i Group n = 133,761	DPP4i Group n = 133,761	SDiff
Alcohol addiction	228 (0.15%)	678 (0.26%)	−0.03	211 (0.16%)	217 (0.16%)	<0.01
Antidiabetic medications						
GLP1-RAs	3003 (1.93%)	641 (0.25%)	0.16	627 (0.47%)	830 (0.62%)	0.02
Metformin	140,741 (90.60%)	190,743 (73.88%)	0.45	120,585 (90.15%)	119,333 (89.21%)	−0.03
Sulfonylureas	63,888 (41.13%)	98,514 (38.16%)	0.06	56,561 (42.29%)	56,561 (42.29%)	−0.02
Insulin	33,131 (21.33%)	39,387 (15.26%)	0.16	23,398 (17.49%)	24,246 (18.13%)	0.02
α -glucosidase inhibitors	30,006 (19.32%)	32,136 (12.45%)	0.19	22,022 (16.46%)	22,604 (16.90%)	0.01
Thiazolidinediones	27,556 (17.74%)	27,063 (10.48%)	0.21	20,538 (15.35%)	20,804 (15.55%)	0.01
Combination antidiabetic medications	44,149 (38.42%)	40,197 (15.57%)	0.31	31,606 (23.63%)	32,384 (24.21%)	0.01
Other antidiabetic medications	8266 (5.32%)	19,827 (7.68%)	−0.10	6989 (5.22%)	7248 (5.42%)	0.01

Notes: SDiff of 0.1 denotes meaningful imbalance in the baseline covariate.

Abbreviations: SGLT2i, sodium-glucose cotransporter-2 inhibitors; GLP1-RA, glucagon-like peptide-1 receptor agonists; DPP4i, dipeptidyl peptidase-4 inhibitors; SDiff, standardized difference.

Table 2 presents the incidence and risk of depression. Among new SGLT2i users, 3255 cases of depression were identified, with an incidence rate of 7.18 per 1000 person-years. In contrast, DPP4i users had 7190 cases, with an incidence rate of 10.12 per 1000 person-years. Kaplan–Meier survival analyses demonstrated higher depression-free survival in SGLT2i users compared with DPP4i users in both the full cohort (Figure 2A) and the PSM cohort (Figure 2B). The Cox proportional hazards regression model for the entire cohort showed that SGLT2i users had a 0.71-fold lower risk of depression (HR = 0.71, 95% CI: 0.68–0.74) than DPP4i users, with an adjusted HR of 0.77 (95% CI: 0.73–0.80). In the PSM cohort, SGLT2i users had a lower depression risk (HR = 0.78, 95% CI: 0.74–0.82) than DPP4i users, with an adjusted HR of 0.77 (95% CI: 0.74–0.81), consistent with a protective effect and corresponding to an E-value of 1.91. In competing risk analyses using Fine–Gray subdistribution hazard models, the results were consistent with the primary analysis (adjusted subdistribution HR = 0.80, 95% CI: 0.76–0.84; [Supplementary Table 2](#)).

Table 2 Incidence and Risk of Depression Among SGLT2i and DPP4i Users: Main Analysis, Dose-Response Assessment, and Sensitivity Analysis in Full and Propensity Score-Matched Cohorts

Exposure	Full cohort (N = 413,528)				Propensity Score-Matched Cohort (N = 267,522)	
	Events n (%)	Incidence Rate Per 1000 Person-year (95% CI)	Crude HR (95% CI)	Adjusted HR ^a (95% CI)	Crude HR (95% CI)	Adjusted HR ^a (95% CI)
SGLT2i user	3255 (2.10)	7.18(6.93–7.43)	0.71*** (0.68–0.74)	0.77*** (0.73–0.80)	0.78*** (0.74–0.82)	0.77*** (0.74–0.81)
DPP4i user	7190 (2.78)	10.12(9.89–10.36)	Ref.	Ref.	Ref.	Ref.
Cumulative doses of SGLT2i						
Dose level 1 (lowest)	904 (2.58)	8.98(8.41–9.59)	0.89** (0.83–0.95)	0.93 (0.84–1.03)	0.98** (0.97–0.99)	0.97*** (0.96–0.99)
Dose level 2	816 (2.09)	7.17(6.68–7.67)	0.71*** (0.66–0.77)	0.78*** (0.70–0.87)	0.96*** (0.95–0.97)	0.96*** (0.94–0.97)
Dose level 3	757 (1.97)	6.72(6.52–7.22)	0.67*** (0.62–0.72)	0.71*** (0.64–0.79)	0.95*** (0.93–0.96)	0.94*** (0.93–0.95)
Dose level 4 (highest)	778 (1.82)	6.15(5.73–6.60)	0.61*** (0.57–0.66)	0.61*** (0.54–0.68)	0.94*** (0.92–0.95)	0.93*** (0.92–0.94)
Sensitivity analysis						
Two diagnoses	2363 (1.52)	5.18(4.97–5.39)	0.70*** (0.67–0.74)	0.77*** (0.73–0.81)	0.80*** (0.75–0.85)	0.79*** (0.74–0.84)
Three diagnoses	1897 (1.22)	4.15(3.96–4.34)	0.70*** (0.66–0.74)	0.76*** (0.72–0.81)	0.79*** (0.74–0.85)	0.78*** (0.73–0.84)
Primary diagnosis	2103 (1.35)	4.62(4.42–4.82)	0.76*** (0.72–0.80)	0.78*** (0.74–0.83)	0.80*** (0.75–0.85)	0.80*** (0.75–0.85)
Major depressive disorder	1603 (1.03)	3.51(3.34–3.69)	0.67*** (0.64–0.72)	0.74*** (0.69–0.78)	0.76*** (0.71–0.82)	0.76*** (0.70–0.81)

Notes: ^aAdjusted for sex, age, hypertension, hyperlipidemia, stroke, obesity, chronic kidney disease, ischemic heart disease, heart failure, arrhythmia, liver disease, diabetic retinopathy, diabetic neuropathy, rheumatoid arthritis, chronic obstructive pulmonary disease, insomnia, thyroid disease, smoking addiction, alcohol addiction, GLP-1 RAs, metformin, sulfonylureas, insulin, α -glucosidase inhibitors, thiazolidinediones, combination antidiabetic medications, other antidiabetic medications. ** $p < 0.01$, *** $p < 0.001$.

Abbreviations: SGLT2i, sodium-glucose cotransporter-2 inhibitors; GLP1-RA, glucagon-like peptide-1 receptor agonists; DPP4i, dipeptidyl peptidase-4 inhibitors; HR, hazard ratio; CI, confidence intervals.

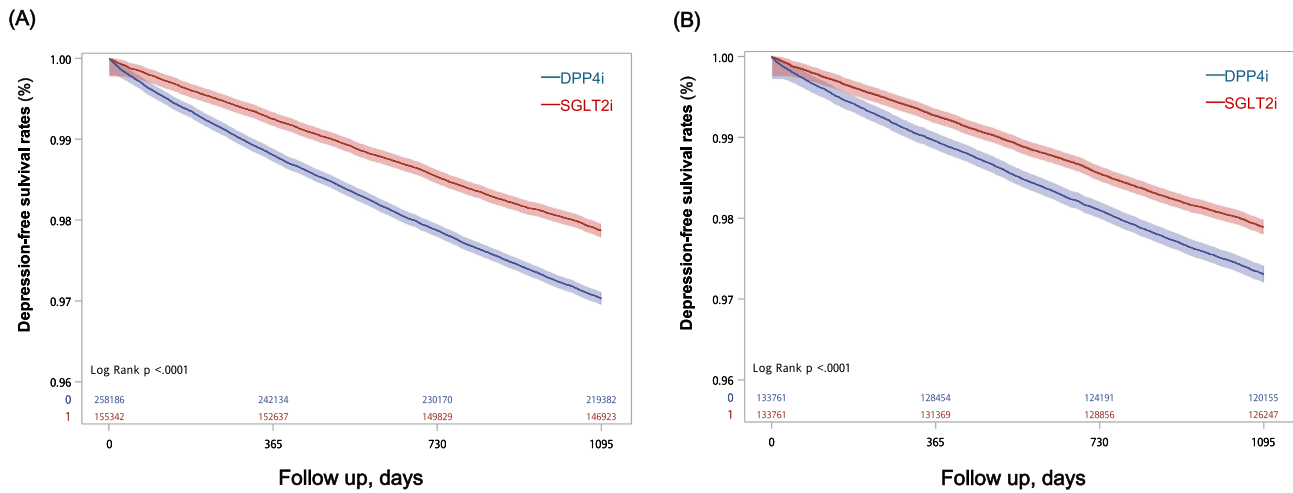


Figure 2 Kaplan–Meier Survival Curve Analysis: (A) Full Cohort (B) Propensity Score-matched Cohort.

Table 2 presents the dose–response analysis. The incidence of depression decreased with increasing cumulative SGLT2i dose: 8.98 per 1000 person-years in dose level 1 (<64.29 DDD), 7.17 in dose level 2 (64.29–168 DDD), 6.72 in dose level 3 (168–340 DDD), and 6.15 in dose level 4 (>340 DDD). In the PSM cohort, after adjusting for confounders, the HR of depression in the lowest dose group was 0.97 (95% CI: 0.96–0.99), whereas, in the highest dose group, the HR was 0.93 (95% CI: 0.92–0.94), suggesting a dose-dependent protective effect. Sensitivity analyses (**Table 2**) confirmed the protective effect of SGLT2i across different depression definitions, including requiring ≥ 2 or ≥ 3 depression diagnoses, primary diagnosis-only cases, and major depressive disorder diagnosis. In the PSM cohort, the adjusted HRs for these alternative definitions were 0.79, 0.78, 0.80, and 0.76, respectively.

Table 3 presents the results of the subgroup analyses, demonstrating that SGLT2i users had a lower risk of depression across most subgroups in both the entire and PSM cohorts. The protective effects were observed in both sexes; in patients with or without hypertension, hyperlipidemia, chronic kidney disease, ischemic heart disease, diabetic retinopathy, thyroid disease, or insomnia; and in those without heart failure. The association also persisted in patients without prior GLP1-RA use and in those with or without prior use of metformin, sulfonylureas, insulin, α -glucosidase inhibitors, or thiazolidinediones.

Discussion

This study, employing an active comparator new-user design, demonstrated a lower risk of depression among SGLT2i users than among DPP4i users, even after PSM and adjustments. These methodological approaches effectively minimized

Table 3 Subgroup Analyses in the Full Cohort and Propensity Score-Matched Cohort

Variables	Full Cohort (N =413,528)		Propensity Score-Matched Cohort (N =267,522)	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Sex				
Male	0.70*** (0.66–0.75)	0.76*** (0.71–0.82)	0.77*** (0.71–0.83)	0.76*** (0.71–0.82)
Female	0.74*** (0.70–0.77)	0.77*** (0.73–0.82)	0.79*** (0.74–0.85)	0.79*** (0.74–0.84)
Hypertension				
Yes	0.69*** (0.66–0.73)	0.77*** (0.73–0.81)	0.76*** (0.71–0.81)	0.77*** (0.72–0.82)
No	0.75*** (0.70–0.80)	0.77*** (0.71–0.83)	0.82*** (0.75–0.89)	0.80*** (0.73–0.87)
Hyperlipidemia				
Yes	0.72*** (0.68–0.76)	0.78*** (0.73–0.82)	0.78*** (0.74–0.83)	0.78*** (0.74–0.83)
No	0.71*** (0.67–0.76)	0.75*** (0.70–0.81)	0.77*** (0.71–0.84)	0.76*** (0.70–0.82)

(Continued)

Table 3 (Continued).

Variables	Full Cohort (N =413,528)		Propensity Score-Matched Cohort (N =267,522)	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Chronic kidney disease				
Yes	0.63*** (0.54–0.73)	0.74*** (0.63–0.87)	0.71*** (0.58–0.86)	0.77** (0.63–0.93)
No	0.74*** (0.71–0.77)	0.77*** (0.74–0.81)	0.78*** (0.75–0.83)	0.78*** (0.74–0.82)
Heart failure				
Yes	0.60*** (0.50–0.73)	0.77* (0.62–0.95)	0.77* (0.60–0.97)	0.88 (0.69–1.12)
No	0.72*** (0.69–0.75)	0.77*** (0.73–0.80)	0.78*** (0.74–0.82)	0.77*** (0.73–0.81)
Ischemic heart disease				
Yes	0.62*** (0.56–0.67)	0.73*** (0.66–0.80)	0.70*** (0.63–0.78)	0.75*** (0.67–0.84)
No	0.73*** (0.70–0.77)	0.78*** (0.74–0.82)	0.80*** (0.76–0.85)	0.78*** (0.74–0.83)
Diabetic retinopathy				
Yes	0.63*** (0.53–0.76)	0.67*** (0.56–0.81)	0.70** (0.56–0.88)	0.70** (0.56–0.88)
No	0.72*** (0.69–0.75)	0.77*** (0.74–0.81)	0.78*** (0.75–0.83)	0.78*** (0.74–0.82)
Diabetic neuropathy				
Yes	0.76*** (0.66–0.87)	0.80** (0.69–0.92)	0.79** (0.67–0.93)	0.81* (0.69–0.96)
No	0.70*** (0.67–0.74)	0.76*** (0.73–0.80)	0.78*** (0.74–0.82)	0.77*** (0.73–0.81)
Thyroid disease				
Yes	0.72*** (0.60–0.86)	0.75** (0.61–0.91)	0.74** (0.59–0.92)	0.73** (0.59–0.91)
No	0.71*** (0.68–0.74)	0.77*** (0.73–0.80)	0.78*** (0.74–0.82)	0.78*** (0.74–0.82)
Insomnia				
Yes	0.81** (0.73–0.91)	0.83** (0.74–0.93)	0.83** (0.73–0.95)	0.83** (0.73–0.95)
No	0.71*** (0.68–0.74)	0.75*** (0.72–0.79)	0.77*** (0.73–0.81)	0.76*** (0.72–0.81)
Prior GLP1-RAs use				
Yes	0.74 (0.47–1.16)	0.79 (0.49–1.27)	0.69 (0.39–1.23)	0.75 (0.41–1.36)
No	0.71*** (0.68–0.74)	0.77*** (0.73–0.80)	0.78*** (0.74–0.82)	0.77*** (0.74–0.81)
Prior metformin use				
Yes	0.73*** (0.70–0.76)	0.76*** (0.72–0.80)	0.76*** (0.72–0.81)	0.76*** (0.72–0.80)
No	0.75*** (0.67–0.84)	0.80*** (0.71–0.91)	0.91 (0.79–1.06)	0.89 (0.77–1.04)
Prior sulfonylureas use				
Yes	0.71*** (0.67–0.76)	0.77*** (0.72–0.83)	0.78*** (0.72–0.84)	0.77*** (0.71–0.83)
No	0.71*** (0.67–0.75)	0.76*** (0.71–0.80)	0.78*** (0.73–0.83)	0.77*** (0.72–0.82)
Prior insulin use				
Yes	0.66*** (0.61–0.72)	0.73*** (0.67–0.80)	0.73*** (0.66–0.81)	0.75*** (0.67–0.83)
No	0.70*** (0.67–0.74)	0.77*** (0.73–0.81)	0.79*** (0.75–0.84)	0.78*** (0.74–0.83)
Prior α -glucosidase inhibitors use				
Yes	0.66*** (0.60–0.73)	0.69*** (0.62–0.77)	0.70*** (0.63–0.79)	0.70*** (0.62–0.79)
No	0.72*** (0.69–0.75)	0.78*** (0.74–0.82)	0.80*** (0.76–0.84)	0.79*** (0.75–0.83)
Prior thiazolidinediones use				
Yes	0.73*** (0.65–0.81)	0.80*** (0.72–0.90)	0.80*** (0.70–0.90)	0.82** (0.72–0.94)
No	0.71*** (0.68–0.74)	0.76*** (0.72–0.80)	0.78*** (0.74–0.82)	0.76*** (0.72–0.81)

Note: Adjusted for gender, age, hypertension, hyperlipidemia, stroke, obesity, chronic kidney disease, ischemic heart disease, heart failure, arrhythmia, liver disease, diabetic retinopathy, diabetic neuropathy, rheumatoid arthritis, chronic obstructive pulmonary disease, insomnia, thyroid disease, smoking addiction, alcohol addiction, GLP-1 RAs, metformin, sulfonylureas, insulin, α -glucosidase inhibitors, thiazolidinediones, combination antidiabetic medications, other antidiabetic medications. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

bias and strengthened the validity of the observed association between SGLT2i use and depression risk. This protective trend remained robust across all sensitivity and subgroup analyses.

To date, limited research has explored this association. A Japanese cohort study examined the relationship between oral hypoglycemic agents and depression risk in patients with T2DM using clinical data from 2004 to 2018.³⁰ After adjustment, SGLT2i use was associated with a reduced risk of depression (adjusted OR = 0.09, 95% CI: 0.01–0.63). However, the small sample size (only one case of depression) limited the statistical power to detect definitive associations. Similarly, a nested case-control study from Denmark found that low doses of metformin, DPP4i, GLP1-RA, and SGLT2i were associated with a reduced risk of depression compared with nonusers, with SGLT2i demonstrating the strongest protective effect (OR = 0.55, 95% CI: 0.44–0.70).²⁹ However, because this study defined untreated patients with T2DM as the control group, potential selection bias may have influenced the strength of these associations.

The potential neuroprotective effects of SGLT2i against depression can be explained by several mechanisms. An experimental study investigating the effects of SGLT2i on neuroplasticity and blood–brain barrier (BBB) integrity in an animal model of depression demonstrated that dapagliflozin, when co-administered with an ethidium bromide (ETBR) blocker, enhanced BBB integrity and promoted neuroplasticity in rats exposed to chronic and unpredictable stress.²⁷ These effects were attributed to the modulation of the NLRP3 inflammasome and ETBR signaling pathways, contributing to antidepressant-like effects. Another study reported that dapagliflozin directly targeted the lateral habenula (LHb) in rats, activating the AMP-activated protein kinase (AMPK) signaling pathway, thereby inhibiting LHb neuronal activity, increasing the 5-HIAA/5-HT ratio in the dorsal raphe nucleus, and reducing diabetes-induced depressive behaviors.²⁸ These findings support the potential role of SGLT2i in neuropsychiatric regulation and are consistent with the results of this study. Importantly, emerging clinical evidence also points to a link between the anti-inflammatory and metabolic effects of SGLT2i and improved mental health outcomes. A recent investigation comparing patients with T2DM treated with SGLT2i versus sulfonylureas reported more favorable metabolic and neuroinflammatory biomarker profiles.³⁵ These changes were accompanied by fewer depressive symptoms, better cognitive performance, and improved quality of life. As T2DM is frequently associated with inflammation and oxidative stress linked to depression, these findings provide biological plausibility to our results.³⁶

In the subgroup analyses, SGLT2i use was associated with a reduction in depression risk across most subgroups. However, in patients with heart failure or prior GLP1-RA use, the association did not reach statistical significance, likely due to the limited sample size and insufficient statistical power. However, a protective trend was still observed, suggesting that further research with larger sample sizes is warranted to validate these findings. In contrast, in the subgroups of patients with hypertension, arrhythmia, ischemic heart disease, and chronic kidney disease, a protective effect against depression was observed following SGLT2i use. This may be due to the well-documented cardiovascular and renal benefits of SGLT2i, which have led to their preferential use in T2DM management.³⁷ The broader clinical adoption of SGLT2i in these populations may have increased the statistical power, contributing to more robust findings.

This study has some remarkable strengths. First, this study used the Taiwan NHID, which provides a large population-based dataset, thereby reducing selection bias, enabling long-term follow-up, and minimizing case attrition. Second, this study employed a new-user design to eliminate biases associated with time-related changes and ensure complete diagnosis of depression. Third, the active comparator design improved comparability between the SGLT2i and DPP4i groups, with further refinement achieved through PSM, thereby minimizing residual confounding. However, several limitations should be considered. First, because the NHID records medication dispensing dates rather than actual administration, patient adherence to the prescribed therapy could not be directly assessed. Second, the NHID lacks information on lifestyle behaviors, psychiatric symptoms, over-the-counter medication use, detailed psychological therapy records, and clinical assessments of T2DM and depression severity. Third, socioeconomic status and antidepressant prescriptions were not incorporated into the present analysis. To mitigate these issues, we implemented an active comparator new-user design, which enhances internal validity by improving comparability between treatment groups and reducing confounding by indication.^{38,39} To further quantify the potential impact of residual confounding, we calculated an E-value for the primary estimate, which reflects the strength of unmeasured confounding required to explain away the observed association. Finally, the observation period was relatively short because of the recent introduction of SGLT2i. Considering that T2DM is a chronic condition requiring long-term pharmacological management, future studies should extend follow-up durations to further elucidate the long-term effects and safety of SGLT2i in the modulation of depression risk.

Conclusion

In conclusion, this study provides robust evidence that SGLT2i use is associated with a lower risk of depression than DPP4i use in individuals with T2DM, suggesting a potential protective effect. This association remained consistent across the sensitivity and subgroup analyses. These findings highlight the potential neuropsychiatric benefits of SGLT2i for T2DM management. Clinicians should consider this potential advantage when developing individualized treatment strategies. Furthermore, additional research and clinical exploration into novel indications for SGLT2i can expand their therapeutic applications.

Ethics Statements

Ethics approval: This study was approved by the Institutional Review Board of Tri-Service General Hospital, Taiwan (B202205035).

Author Contributions

Ming-Jyun Kao, Ying-Chih Huang, Yu-Chieh Huang, Hui-Wen Yang and Li-Ting Kao conceived this study, participated in study design, and helped draft the manuscript. Ming-Jyun Kao, Hui-Wen Yang, Sheng-Yin To, and Yuan-Liang Wen conducted the statistical analysis. Ming-Jyun Kao, Ying-Chih Huang, Yu-Chieh Huang, Chun-Cheng Liao and Li-Ting Kao verified the analytical methods and helped draft the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Taipei Medical University-Shuang Ho Hospital, Taiwan (109HCP-07), Tri-Service General Hospital, Taiwan (TSGH-E-114285), and Medical Affairs Bureau, Taiwan (MNE-MAB-E-113194). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosure

Li-Ting Kao reports receiving research funding from IQVIA outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. ElSayed NA, McCoy RG, Aleppo G, American Diabetes Association Professional Practice C. Introduction and methodology: standards of care in diabetes-2025. *Diabetes Care*. 2025;48(1 Suppl 1):S1–S5. doi:10.2337/dc25-SINT
2. Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. Type 2 diabetes. *Lancet*. 2022;400(10365):1803–1820. doi:10.1016/S0140-6736(22)01655-5
3. Collaboration NCDRF. Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. *Lancet*. 2024;404(10467):2077–2093. doi:10.1016/S0140-6736(24)02317-1
4. Ong KL, Stafford LK, McLaughlin SA, et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the global burden of disease study 2021. *Lancet*. 2023;402(10397):203–234.
5. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. 2018;14(2):88–98. doi:10.1038/nrendo.2017.151
6. Musselman DL, Betan E, Larsen H, Phillips LS. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. *Biol Psychiatry*. 2003;54(3):317–329. doi:10.1016/S0006-3223(03)00569-9
7. Sheen YJ, Hsu CC, Jiang YD, Huang CN, Liu JS, Sheu WH. Trends in prevalence and incidence of diabetes mellitus from 2005 to 2014 in Taiwan. *J Formos Med Assoc*. 2019;118(Suppl 2):S66–s73. doi:10.1016/j.jfma.2019.06.016
8. Jaacks LM, Siegel KR, Gujral UP, Narayan KV. Type 2 diabetes: a 21st century epidemic. *Best Pract Res Clin Endocrinol Metab*. 2016;30(3):331–343. doi:10.1016/j.beem.2016.05.003
9. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes - global burden of disease and forecasted trends. *J Epidemiol Glob Health*. 2020;10(1):107–111. doi:10.2991/jegh.k.191028.001
10. Halim M, Halim A. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). *Diabetes Metab Syndr*. 2019;13(2):1165–1172. doi:10.1016/j.dsx.2019.01.040
11. Duncan BB, Schmidt MI, Pankow JS, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes*. 2003;52(7):1799–1805. doi:10.2337/diabetes.52.7.1799
12. Goldman LS, Nielsen NH, Champion HC. Awareness, diagnosis, and treatment of depression. *J Gen Intern Med*. 1999;14(9):569–580. doi:10.1046/j.1525-1497.1999.03478.x
13. Lu Y, Tang C, Liow CS, Ng WNW, Ho CSH, Ho RCM. A regression analysis of maladaptive rumination, illness perception and negative emotional outcomes in Asian patients suffering from depressive disorder. *Asian J Psychiatry*. 2014;12:69–76. doi:10.1016/j.ajp.2014.06.014
14. Rosenström T, Jokela M. Reconsidering the definition of major depression based on collaborative psychiatric epidemiology surveys. *J Affect Disord*. 2017;207:38–46. doi:10.1016/j.jad.2016.09.014
15. Mathers CD, Loncar D. Updated projections of global mortality and burden of disease, 2002–2030: data sources, methods and results. *Geneva: World Health Organization*; 2005;10.
16. Friedrich MJ. Depression is the leading cause of disability around the world. *JAMA*. 2017;317(15):1517.

17. Hay SI, Abajobir AA, Abate KH, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet*. 2017;390(10100):1260–1344.
18. Ruiz NAL, Del Ángel DS, Olguin HJ, Silva ML. Neuroprogression: the hidden mechanism of depression. *Neuropsychiatr Dis Treat*. 2018; Volume 14:2837–2845. doi:10.2147/NDT.S177973
19. Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? *J Clin Psychiatry*. 2003;64(12):1465–1475. doi:10.4088/JCP.v64n1211
20. Goodyer IM, Herbert J, Tamplin A, Altham P. Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *Br J Psychiatry*. 2000;177(6):499–504. doi:10.1192/bjp.177.6.499
21. Kohler O, Krogh J, Mors O, Eriksen Benros M. Inflammation in depression and the potential for anti-inflammatory treatment. *Curr Neuropsychopharmacol*. 2016;14(7):732–742. doi:10.2174/1570159X14666151208113700
22. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016;16(1):22–34. doi:10.1038/nri.2015.5
23. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol*. 2020;17(12):761–772. doi:10.1038/s41569-020-0406-8
24. Cai X, Yang W, Gao X, et al. The association between the dosage of SGLT2 Inhibitor and weight reduction in type 2 diabetes patients: a meta-analysis. *Obesity*. 2018;26(1):70–80. doi:10.1002/oby.22066
25. Bonnet F, Scheen A. Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: the potential contribution to diabetes complications and cardiovascular disease. *Diabetes Metab*. 2018;44(6):457–464. doi:10.1016/j.diabet.2018.09.005
26. Yariyebi H, Ashrafizadeh M, Henney NC, Sathyapalan T, Jamialahmadi T, Sahebkar A. Neuromodulatory effects of anti-diabetes medications: a mechanistic review. *Pharmacol Res*. 2020;152:104611. doi:10.1016/j.phrs.2019.104611
27. Muhammad RN, Ahmed LA, Salam RMA, Ahmed KA, Attia AS. Crosstalk among NLRP3 inflammasome, ETBR signaling, and miRNAs in stress-induced depression-like behavior: a modulatory role for SGLT2 inhibitors. *Neurotherapeutics*. 2021;18(4):2664–2681. doi:10.1007/s13311-021-01140-4
28. Dong D, Liu X, Ma L, et al. Dapagliflozin inhibits the activity of lateral habenula to alleviate diabetes mellitus-induced depressive-like behavior. *Exp Neurol*. 2023;366:114448. doi:10.1016/j.expneurol.2023.114448
29. Wium-Andersen IK, Osler M, Jørgensen MB, Rungby J, Wium-Andersen MK. Diabetes, antidiabetic medications and risk of depression—a population-based cohort and nested case-control study. *Psychoneuroendocrinology*. 2022;140:105715. doi:10.1016/j.psyneuen.2022.105715
30. Akimoto H, Tezuka K, Nishida Y, Nakayama T, Takahashi Y, Asai S. Association between use of oral hypoglycemic agents in Japanese patients with type 2 diabetes mellitus and risk of depression: a retrospective cohort study. *Pharmacol Res Perspect*. 2019;7(6):e00536. doi:10.1002/prp2.536
31. Hsieh CY, Su CC, Shao SC, et al. Taiwan's national health insurance research database: past and future. *Clin Epidemiol*. 2019;Volume 11:349–358. doi:10.2147/CLEP.S196293
32. Sendor R, Stürmer T. Core concepts in pharmacoepidemiology: confounding by indication and the role of active comparators. *Pharmacoepidemiol Drug Saf*. 2022;31(3):261–269. doi:10.1002/pds.5407
33. Kane LT, Fang T, Galetta MS, et al. Propensity Score Matching: a Statistical Method. *Clin Spine Surg*. 2020;33(3):120–122. doi:10.1097/bsd.0000000000000932
34. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167(4):268–274. doi:10.7326/m16-2607
35. Majid H, Islam SU, Kohli S. Neuroinflammation and metabolic dysregulation as predictors of cognitive impairment, depression, and quality of life in type 2 diabetes mellitus patients on SGLT2 inhibitors and sulfonylureas. *Inflammopharmacology*. 2025;33(8):4749–4758. doi:10.1007/s10787-025-01824-9
36. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. *Int J Physiol Pathophysiol Pharmacol*. 2019;11(3):45–63.
37. Tsai W-C, Hsu S-P, Chiu Y-L, et al. Cardiovascular and renal efficacy and safety of sodium-glucose cotransporter-2 inhibitors in patients without diabetes: a systematic review and meta-analysis of randomised placebo-controlled trials. *BMJ open*. 2022;12(10):e060655. doi:10.1136/bmjopen-2021-060655
38. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep*. 2015;2(4):221–228. doi:10.1007/s40471-015-0053-5
39. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*. 2015;11(7):437–441. doi:10.1038/nrrheum.2015.30

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