Frontiers in Neuroendocrinology 73 (2024) 101131

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review article

Sodium-glucose cotransporter-2 inhibitors and their potential role in dementia onset and cognitive function in patients with diabetes mellitus: a systematic review and meta-analysis

Yea Jin Youn [a,1], Seungyeon Kim [b,1], Hyun-Jeong Jeong [c], Young-Mi Ah [c,*], Yun Mi Yu [d,e,*]

[a] Graduate Program of Industrial Pharmaceutical Science, Yonsei University, Incheon, Republic of Korea
[b] College of Pharmacy, Dankook University, Cheonan, Republic of Korea
[c] College of Pharmacy, Yeungnam University, Gyeongsan, Republic of Korea
[d] Department of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, College of Pharmacy, Yonsei University, Incheon, Republic of Korea
[e] Department of Pharmaceutical Medicine and Regulatory Sciences, Colleges of Medicine and Pharmacy, Yonsei University, Incheon, Republic of Korea

ARTICLE INFO

Keywords:
Sodium-glucose cotransporter 2
Diabetes mellitus
Dementia
Incidence risk
Cognitive function
Systematic review
Meta-analysis

ABSTRACT

This systematic review and meta-analysis aimed to determine the association between the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors and dementia onset as well as cognitive function in patients with diabetes mellitus. We comprehensively searched the MEDLINE, Embase, and CENTRAL databases to select relevant studies published up to August 2023. The use of SGLT-2 inhibitors significantly lowers dementia risk compared to SGLT-2i non-users (Hazard ratio: 0.68, 95 % CI: 0.50–0.92). Furthermore, our findings indicated a positive effect of SGLT-2 inhibitor use on cognitive function score improvement, as demonstrated by the standardized mean difference of 0.88 (95 % CI: 0.32–1.44), particularly among populations with mild cognitive impairment or dementia. This systematic review and meta-analysis indicate a potential role of SGLT-2 inhibitors in reducing the risk of dementia in patients with diabetes mellitus. These findings underscore the need for well-controlled large clinical trials and future research in this field.

1. Introduction

Diabetes mellitus (DM) is a chronic disease associated with a range of complications, and its prevalence has increased globally. According to the International Diabetes Federation (2021), 10.5 % of the adult population (aged 20–79) was affected by DM. This number is projected to increase to 12.2 % by 2045. The prevalence of individuals with impaired glucose tolerance or impaired fasting glucose, who are at high risk for DM, has also been steadily increased (Cho et al., 2022). The number of older adults with DM was approximately 136 million (19.3 %) in 2019, and this figure is projected to rise to 276 million by 2045 (Sinclair et al., 2020).

The complications arising from DM, such as coronary heart disease, stroke, retinopathy, and nephropathy, impose a significant burden on both the quality of life of patients and the healthcare system. Therefore, clinical guidelines advocate considering the positive impact of pharmacological treatment on cardiorenal complications, alongside glycemic control (ElSayed et al., 2022b; Scheen and Bonnet, 2023). Moreover, apart from the well-documented vascular complications associated with DM, the likelihood of developing dementia is higher in individuals with DM than in the general population. Studies have reported that the relative risk of all-cause dementia in patients with DM ranges from 1.43 to 1.69. Furthermore, compared to the population without DM, the risk of vascular dementia is higher in this group, with a reported risk factor of 2.38 (Tomic et al., 2022). While the exact mechanism underlying the onset of dementia in patients with DM remains unclear, potential causes include disruption of the blood–brain barrier due to hyperglycemia and impaired insulin signaling (Steen et al., 2005; Rom et al., 2020). Given the significant disease burden posed by dementia and the lack of effective treatments Guideline Adaptation Committee (2016), the prevention of dementia in patients becomes a crucial concern. However, current clinical guidelines do not

* Corresponding authors at: College of Pharmacy, Yonsei University, 85 Songdogwahak-ro, Yeonsu-gu, Incheon 21983, Republic of Korea. College of Pharmacy, Yeungnam University, 280 Daehak-Ro, Gyeongsan, Gyeongsangbuk-do 38541, Republic of Korea.
E-mail addresses: ymah@ynu.ac.kr (Y.-M. Ah), yunmiyu@yonsei.ac.kr (Y.M. Yu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.yfrne.2024.101131
Received 18 November 2023; Received in revised form 3 February 2024; Accepted 10 February 2024
Available online 16 February 2024

offer strategies for selecting antidiabetic agents aimed at preventing cognitive dysfunction. Instead, they primarily recommend routine screening for the early detection of cognitive impairment (ElSayed et al., 2022a).

Recently, substantial research has been directed towards understanding the off-target effects of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, which extend to various body systems beyond their effects on kidney glycosuria (Dyck et al., 2022; Chen et al., 2023; Jenkins et al., 2023). SGLT-2 inhibitors, as pleiotropic drugs, have shown potential to impair T cell function in autoimmune diseases (Jenkins et al., 2023), and to mitigate heart failure and myocardial infarction by ameliorating oxidative stress and mitochondrial dysfunction (Dyck et al., 2022; Chen et al., 2023). Recent In addition to their diverse clinical and functional importance, some research has revealed the potential of SGLT-2 inhibitors to reduce the risk of dementia compared with that of a placebo or other antidiabetic agents (Tang et al., 2022; Tang et al., 2023; Tian et al., 2023). A meta-analysis, based on randomized controlled trials, highlighted a reduced risk of vascular dementia onset among participants using SGLT-2 inhibitors compared to that in those using a placebo, with an odds ratio (OR) of 0.11 and a 95 % confidence interval (CI) of 0.02–0.66. However, the primary outcome of the studies included in this meta-analysis was not dementia onset but rather cardiovascular outcomes, and the number of studies included was limited (Tang et al., 2022). Another meta-analysis of observational studies reported a reduced risk of all-cause dementia onset, with a relative risk of 0.62 and a 95 % CI of 0.39–0.97. However, this analysis included limited studies, and the hazard ratio (HR) and OR were treated as analogous (Tang et al., 2023). Recently, other studies reporting an association between SGLT-2 inhibitor use and dementia onset have been published (Siao et al., 2022; Proietti et al., 2023; Wu et al., 2023a), but no meta-analysis has specifically addressed the changes in cognitive function following the administration of SGLT-2 inhibitors.

Building on previous studies regarding the use of SGLT-2 inhibitors and cognitive dysfunction, our objective was to assess the impact of SGLT-2 inhibitor use on both the onset of dementia and changes in cognitive function. This evaluation encompasses the latest research findings and was conducted through a comprehensive systematic review and meta-analysis.

2. Material and methods

This study adhered to the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines, as detailed in Supplementary Table 1 (Page et al., 2021). The study protocol is available through the PROSPERO database (CRD42023461758). The literature search, study selection, data extraction, and bias assessment were performed independently by two authors (YJY and SYK). In cases of disagreement between the authors, a third investigator (YMY or YMA) resolved any discrepancies.

2.1. Search strategy and study selection

A systematic search of electronic databases, including MEDLINE, Embase, and CENTRAL, was conducted. All databases were screened from their inception to August 22, 2023, using a combination of keywords and Medical Subject Headings terms. “SGLT-2 inhibitor,” “dementia,” “cognitive function,” and related terms were used in the search. Supplementary Table 2 shows the complete search strategy.

Eligible studies satisfied the following inclusion criteria: (1) population: adults aged ≥18 years at the time of enrollment; (2) intervention: administration of SGLT-2 inhibitors; (3) comparison: no use of SGLT-2 inhibitors and/or use of other antidiabetic drugs; (4) outcomes: incidence of dementia as adjusted HRs or ORs and/or cognitive function score changes; and (5) study design: longitudinal comparative studies. The following studies were excluded: (1) nonhuman studies, including animal and *in vitro* studies; (2) reviews, meta-analyses, and ongoing studies; (3) case reports, case series, and single-arm studies; and (4) studies whose data were available only in the form of abstracts or posters. All records and additional full texts were reviewed according to the specified inclusion and exclusion criteria.

2.2. Data extraction

The selected studies were reviewed, and data were extracted using a standardized form that included the following elements: first author, publication year, study design, database utilized for the study, sample size, inclusion criteria, duration of follow-up, number of patients, sex, age, cognitive function assessment scale and baseline score, body mass index, comorbidities (such as hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, stroke, and depression), concomitant medications, types of SGLT-2 inhibitor (such as dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin), dosing regimen, controlled covariates, method of statistical analysis, and study outcomes.

2.3. Study outcomes

The primary outcome was to evaluate the incidence of all-cause dementia, including Alzheimer’s disease, vascular dementia, and dementia with Lewy bodies. The secondary outcome was to assess the change in cognitive function scores in the SGLT-2 inhibitor user group compared to that in the non-user group.

Cognitive function was assessed using the following scales: the Mini-Mental State Examination (MMSE), where a score of <24 indicates cognitive impairment (Pezzotti et al., 2008); the Montreal Cognitive Assessment (MoCA), where a score of <26 indicates increased severity of cognitive impairment (Mone et al., 2022a); and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), where a score of ≤70 indicates cognitive impairment (Dunham et al., 2014). Although not considered equivalent to the aforementioned scales, tests of verbal fluency, Babcock story recall, and attentive matrices were included, as they evaluate cognitive function.

2.4. Quality assessment

The quality assessment of the included randomized controlled trials (RCTs) was conducted using the ROB 2 (Risk of Bias 2) tool (Sterne et al., 2019). In contrast, the quality of the included non-RCTs was evaluated using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (Sterne et al., 2016). The ROB 2 tool assesses bias across five domains and assigns one of the following three levels of risk of bias judgment to each domain: low risk, high risk, or certain concern. Contrastingly, the ROBINS-I tool evaluates seven domains and assigns one of the following five levels of risk of bias judgment to each domain: low, moderate, serious, critical, or no information.

2.5. Data synthesis and analysis

The statistical computing software package R (version 4.3.1) was used for all meta-analyses. Pooled HRs and ORs, along with 95 % CI, were calculated using the generic inverse-variance method to assess the risk of dementia associated with SGLT-2 inhibitor use (Hahn et al., 2022).

We computed standardized mean differences (SMD) to pool the mean score changes from diverse cognitive function scales. The SMD equation divides the mean difference between the intervention and control groups using the standard deviation (SD). The following formula was used to obtain the SD of the pre-post mean changes (Higgins et al., 2019):

$$\mathrm{SD}change = \sqrt{SD^2baseline + SD^2final - (2 \times r \times SDbaseline \times SDfinal)}$$

where SD*baseline* corresponds to the SD value before treatment, SD*final*

represents the SD value after treatment, and the symbol "r" denotes the correlation between the baseline and final measurements (Yagiz et al., 2022). None of the studies provided an *r*-value or SD*change* value. Thus, the SD*change* value was determined by substituting a value of 0.7 for "r" in the equation to provide a conservative estimate (Park et al., 2023).

Interstudy heterogeneity was assessed using the chi-square test ($p < 0.1$) and inconsistency statistics (I^2) with a threshold of $I^2 > 50$ % (Deeks and Altman, 2011). In the presence of significant heterogeneity, we used a random effects model with inverse variance weighting; otherwise, we used a fixed-effects model. Subgroup analyses were conducted to assess the risk of dementia in the following categories: 1) age ≥60 years at enrollment; 2) study locations; 3) temporal dynamics; and 4) comparison groups. Sensitivity analysis involved leave-one-out cross-validation, sample size analysis, and the exclusion of studies rated as low quality in bias assessment.

3. Results

3.1. Study selection

Fig. 1 illustrates the process of selecting eligible studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). After manually adding one study and removing duplicates, we assessed the relevance of 189 articles based on their titles and abstracts and exclude 132 articles. We conducted full-text evaluations of the remaining 57 studies. Finally, we selected 12 studies, including three RCTs (Perna et al., 2018; Cheng et al., 2022; Zhao and Wang, 2022), three prospective cohort studies (Low et al., 2022; Mone et al., 2022a; Mone et al., 2022b), and six retrospective studies (Jens Bohlken and Kostev, 2018; Wium-Andersen et al., 2019; Mui et al., 2021; Siao et al., 2022; Proietti et al., 2023; Wu et al., 2023a), of which 11 were included in the quantitative synthesis.

3.2. Study characteristics

Table 1 describes the characteristics of the study protocols of the 12 included studies published between 2018 and 2023. All studies included patients with type 2 DM, and the number of participants per study ranged from 36 to 206,494, totaling 405,089. The mean age at baseline in the 12 studies varied from 55.1 to 80.7 years. The proportion of female participants ranged from 28.3 % to 58.0 % and was generally lower than that of male participants in most studies, except in a study conducted by Mone *et al.*, where female participants constituted 52.2–58.0 %. The number of studies that included SGLT-2 inhibitors was as follows: dapagliflozin (10 studies) (Jens Bohlken and Kostev, 2018; Perna et al., 2018; Wium-Andersen et al., 2019; Mui et al., 2021; Cheng et al., 2022; Low et al., 2022; Siao et al., 2022; Zhao and Wang, 2022; Proietti et al., 2023; Wu et al., 2023a), empagliflozin (10 studies) (Jens Bohlken and Kostev, 2018; Perna et al., 2018; Wium-Andersen et al., 2019; Mui et al., 2021; Low et al., 2022; Mone et al., 2022a; Mone et al., 2022b; Siao et al., 2022; Proietti et al., 2023; Wu et al., 2023a), and canagliflozin (8 studies) (Jens Bohlken and Kostev, 2018; Perna et al., 2018; Wium-Andersen et al., 2019; Mui et al., 2021; Low et al., 2022; Siao et al., 2022; Proietti et al., 2023; Wu et al., 2023a). Other SGLT-2 inhibitors, such as ertugliflozin, may have been included in the study; however, due to the lack of information confirmation was not possible. The follow-up duration ranged from 1 month to 7.2 years.

Among the included studies, four cohort and two case-control studies reported the risk of dementia, and three RCTs and three prospective cohort studies showed changes in cognitive function scores associated with SGLT-2 inhibitors. Among the studies evaluating changes in cognitive function scores, three studies enrolled participants with dementia or mild cognitive impairment (MCI) (Mone et al., 2022a; Mone et al., 2022b; Zhao and Wang, 2022). In contrast, the remaining three studies exclusively recruited participants with normal cognitive function and similar assessment scores (Perna et al., 2018; Cheng et al., 2022; Low et al., 2022). The baseline cognitive function scores were not significantly different among the three studies (Perna et al., 2018; Cheng et al., 2022; Low et al., 2022). Detailed characteristics of the study protocols and baseline population characteristics of the included studies are provided in Supplementary Table 3.

3.3. Dementia incidence

The pooled meta-analysis of HRs, comprising four retrospective studies, indicated a significantly lower risk of dementia incidence in the SGLT-2 inhibitor user group compared to that in the non-user group (HR

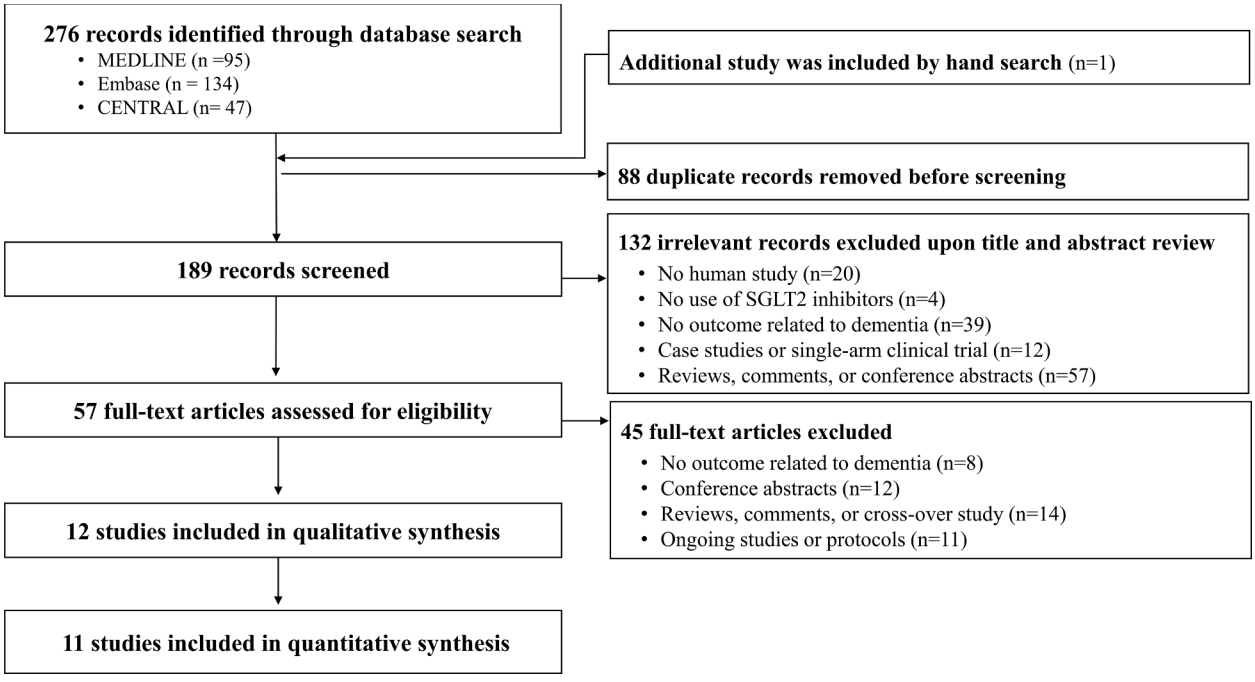

Fig. 1. Flow chart of the study selection process.

Table 1
Study protocol characteristics of the included studies.

First author (year), country	Data resources	Follow-up/ look-back period	Lag time, years	Drugs and sample size, n		Age, mean ± SD, years		Women, n (%)		Outcomes	Inclusion criteria
				SGLT-2i users	SGLT-2i non-users	SGLT-2i users	SGLT-2i non-users	SGLT-2i users	SGLT-2i non-users		
Randomized controlled trials											
Cheng (2022), China	NA	16 weeks	NA	D: 12	Liraglutide: 12 Acarbose: 12	57.0 ± 9.5	Liraglutide: 51.9 ± 10.2 Acarbose: 56.4 ± 8.9	5 (41.7 %)	Liraglutide: 6 (50 %) Acarbose: 7 (58.3 %)	MMSE	- Age: 40–75 years - MMSE > 24 points
Zhao (2021), China	NA	6 months	NA	D: 48	NL: 48	61.05 ± 8.43	59.41 ± 7.96	20 (41.7 %)	22 (45.8 %)	MMSE	- Older - MCI
Perna (2018), Italy	NA	12 months	NA	E, D, C:21	NL: 23	77.36 ± 7.98	77.00 ± 8.73	8 (38.1 %)	8 (44.4 %)	Verbal fluency, Babcock story recall test, and attentive matrices test	- Age > 65 years - MMSE ≥27 points
Prospective cohort studies											
Mone (HF) (2022), Italy	Sant'Angelo dei Lombardi Hospital, Azienda Sanitaria Locale Avellino	1 month	NA	E: 52	Metformin: 56 Insulin: 54	80.6 ± 6.6	Metformin: 80.0 ± 6.3 Insulin: 81.4 ± 5.5	29 (55.7 %)	Metformin: 33 (58.9 %) Insulin: 32 (59.2 %)	MoCA	- Age > 65 years - MoCA score ≤ 26 points
Mone (HBP) (2022), Italy	ASL (local health unit of the Italian Ministry of Health)	3 months	NA	E: 75	NL: 75	78.05 ± 7.5	78.62 ± 6.2	39 (52 %)	40 (53.3 %)	MoCA	- Age > 65 years, - MoCA score < 26 points
Low (2022), Singapore	Diabetes Centre in a public hospital and two primary care polyclinics in the Northern Region of Singapore	4.6 years (4.1–5.0)[a]	NA	E, D, C: 138	NL: 338	58.6 ± 6.8	61.5 ± 7.5	55 (39.9 %)	153 (45.3 %)	RBANS	- Age ≥45 years - No history of dementia in case notes
Retrospective cohort studies											
Proietti (2023), UK	TriNetX	3 years	NA	E, D, C: 5,049	NL: 5,049	66.7 ± 9.91	66.7 ± 11.3	1,413 (28.0 %)	1,445 (28.6 %)	Dementia incidence	- Age ≥18 years
Wu (2023), Canada	Ontario Diabetes Database, ODB, OHIP	2.8 years[b]	1	E, D, C: 36,513	DPP4i: 36,545	72.4 ± 5.38	72.41 ± 3.89	14,164 (38.8 %)	14,237 (39.0 %)	Dementia incidence	- Age > 66 years - No prior history of dementia
Siao (2022), Taiwan	Taiwan's National Health Insurance Research Database	2.7 years	NA	E, D, C: 103,247	NL: 103,247	<40:6176 40–49: 16,491 50–59: 32,130 60–69: 34,039 70–70: 11,881 ≥80:2,530	<40:6210 40–49: 16,535 50–59: 32,089 60–69: 34,094 70–70: 11,876 ≥80:2,446	45,417 (44.0 %)	45,578 (44.1 %)	Dementia incidence	- Age ≥20 years - No prior history of dementia
Mui (2021), Hong Kong	Clinical Data Analysis and Reporting System	472 days[b]	1	NL: 13,283	DPP4i: 26,545	61.18 (53.9–68.22)[a]	62.08 (54.14–69.68)[a]	5,089 (38.31 %)	10,831 (40.80 %)	Dementia incidence	- No prior diagnosis of all-cause dementia, AD with Lewy bodies/ parkinsonism, vascular/ frontotemporal dementia

(*continued on next page*)

Table 1 (*continued*)

First author (year), country	Data resources	Follow-up/ look-back period	Lag time, years	Drugs and sample size, n		Age, mean ± SD, years		Women, n (%)		Outcomes	Inclusion criteria
				SGLT-2i users	SGLT-2i non-users	SGLT-2i users	SGLT-2i non-users	SGLT-2i users	SGLT-2i non-users		
Case-control studies											
Wium (2019), Denmark	National Diabetes Register	7.2 years (3.5–11.5)[a]	NA	NL: 912	NL: 57,183	51.5	61.4	359 (39.0 %)	26,270 (46.0 %)	Dementia incidence	- Age ≥35 years - No prior history of dementia before registration in DNDR
Bohlken (2018), Germany	Nationwide Disease Analyzer database (IQVIA)	1 year[c]	NA	NL: 315	NL: 16,237	79.7 ± 6.9[b]		9,302 (56.2 %)[d]		Dementia incidence	- Age ≥60 years - Dementia diagnosis between 2013.01 and 2017.12

Abbreviations: AD, Alzheimer's disease; C: canagliflozin; D: dapagliflozin; DBP, diastolic blood pressure; DNDR, Danish National Diabetes Register; DPP4i, dipeptidyl peptidase IV inhibitors; E: empagliflozin; eGFR, estimated glomerular filtration rate; GDS, Geriatric Depression Scale; HbA1c, hemoglobin A1c; HF, heart failure; HBP, high blood pressure; ICD, International Classification of Diseases; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NA, not available; NL, not limited; ODB: Ontario Drug Benefit database, OHIP: Ontario Health Insurance Plan; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SBP, systolic blood pressure; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus; TriNetX: a global federated health research network with real-time updates of anonymized electronic medical records (EMRs); uACR, log-transformed urinary albumin-to-creatinine ratio; VaD, vascular dementia.

[a] Median (interquartile range).

[b] Mean follow-up period.

[c] Bohlken 2018: The follow-up period ranges from a minimum of one year to a maximum of five years.

[d] Bohlken 2018: The mean age and percentage of women were calculated based on the total population.

= 0.68, 95 % CI: 0.50–0.92) (Mui et al., 2021; Siao et al., 2022; Proietti et al., 2023; Wu et al., 2023a). The follow-up period (472 days–3 years), use of lag time (none or 1 year), study population (prevalent DM, new DM, or DM with atrial fibrillation), and consideration of blood glucose levels varied among the four studies. Despite these differences, all studies consistently reported a reduced risk of dementia onset in SGLT-2 inhibitor users. These disparities in study methodologies could contribute to the substantial heterogeneity observed in the meta-analysis (I^2 = 87 %). In addition, the relatively low HR reported by Siao *et al.* study (0.89, 95 % CI: 0.82–0.96) might be attributed to the specific study population, which included newly diagnosed patients with DM. Consequently, the average age of participants in the Siao *et al.* might be lower than that in the other studies, potentially influencing the study outcomes (Siao et al., 2022).

However, the pooled OR, comprising two retrospective studies, did not reach statistical significance (OR = 0.74, 95 % CI: 0.47–1.15) (Jens Bohlken and Kostev, 2018; Wium-Andersen et al., 2019). Substantial heterogeneity was observed among the studies (Fig. 2). The look-back period in the study by Bohlken *et al.*, which reported an insignificant OR for dementia onset (OR = 0.91, 95 % CI 0.72–1.16), was at least one year prior to the index date. This duration may be shorter than the look-back period in the study by Wium-Andersen *et al.* (interquartile range of follow-up 3.5–11.5 years), potentially contributing to differences in the reported outcomes (Jens Bohlken and Kostev, 2018; Wium-Andersen et al., 2019).

The subgroup analysis based on an age of ≥60 years at enrollment revealed that SGLT-2 inhibitor users had a lower risk of dementia than those who did not use SGLT-2 inhibitors (HR = 0.84, 95 % CI: 0.75–0.95) (Siao et al., 2022; Wu et al., 2023a). However, subgroup analyses based on other categories, including continent, use of lag time, and consideration of antidiabetic drugs used in the comparison groups, showed no significant differences in dementia risk between SGLT-2 inhibitor users and non-users (Table 2). Furthermore, the meta-analysis of subgroups revealed a high level of heterogeneity among studies (continents I^2 93,77 %; lag time I^2 90,89 %; and comparison I^2 90,89 %).

3.4. Change in cognitive function scores

Fig. 3 compares the changes in cognitive function scores between the users and non-users of SGLT-2 inhibitors, incorporating data from three RCTs and two prospective studies (Cheng et al., 2022; Low et al., 2022; Mone et al., 2022a; Mone et al., 2022b; Zhao and Wang, 2022). The SMD of the score changes did not differ significantly between the two groups. The study conducted by Perna *et al.*, included in the quality synthesis, demonstrated no significant difference in score changes in tests of verbal fluency, Babcock story recall, or attentive matrices (Perna et al., 2018).

However, in the subgroup analysis, which included participants with dementia or MCI, the changes in cognitive function score significantly favored SGLT-2 inhibitor users over non-users (SMD = 0.88, 95 % CI: 0.32–1.44) (Mone et al., 2022a; Mone et al., 2022b; Zhao and Wang, 2022). In studies targeting dementia or MCI, the patient cohort predominantly comprised older individuals. Conversely, in studies focusing on participants with normal cognition, the age ranges were generally younger (mean age in SGLT-2 inhibitor users: 61.05–80.6 vs. 57.0–58.6) Moreover, SMD tended to be larger in the study by Zhao and Wang. (6 months vs. 1–3 months) and Low *et al.* (4.6 years vs. 16 weeks) compared to other studies within the same subgroup, likely due to their extended follow-up durations (Cheng et al., 2022; Low et al., 2022; Mone et al., 2022a; Mone et al., 2022b; Zhao and Wang, 2022). In contrast to other studies, Cheng *et al.* used liraglutide as a control and reported a non-significant effect of SGLT-2 inhibitors on cognitive function (Cheng et al., 2022). Moreover, Mone *et al.* used a multivariable logistic regression analysis and demonstrated that the use of empagliflozin had a significant positive impact on ameliorating cognitive impairment (OR = 3.61, 95 % CI: 1.57–8.32) (Mone et al., 2022a). The study conducted by Low *et al.*, which used a linear regression analysis,

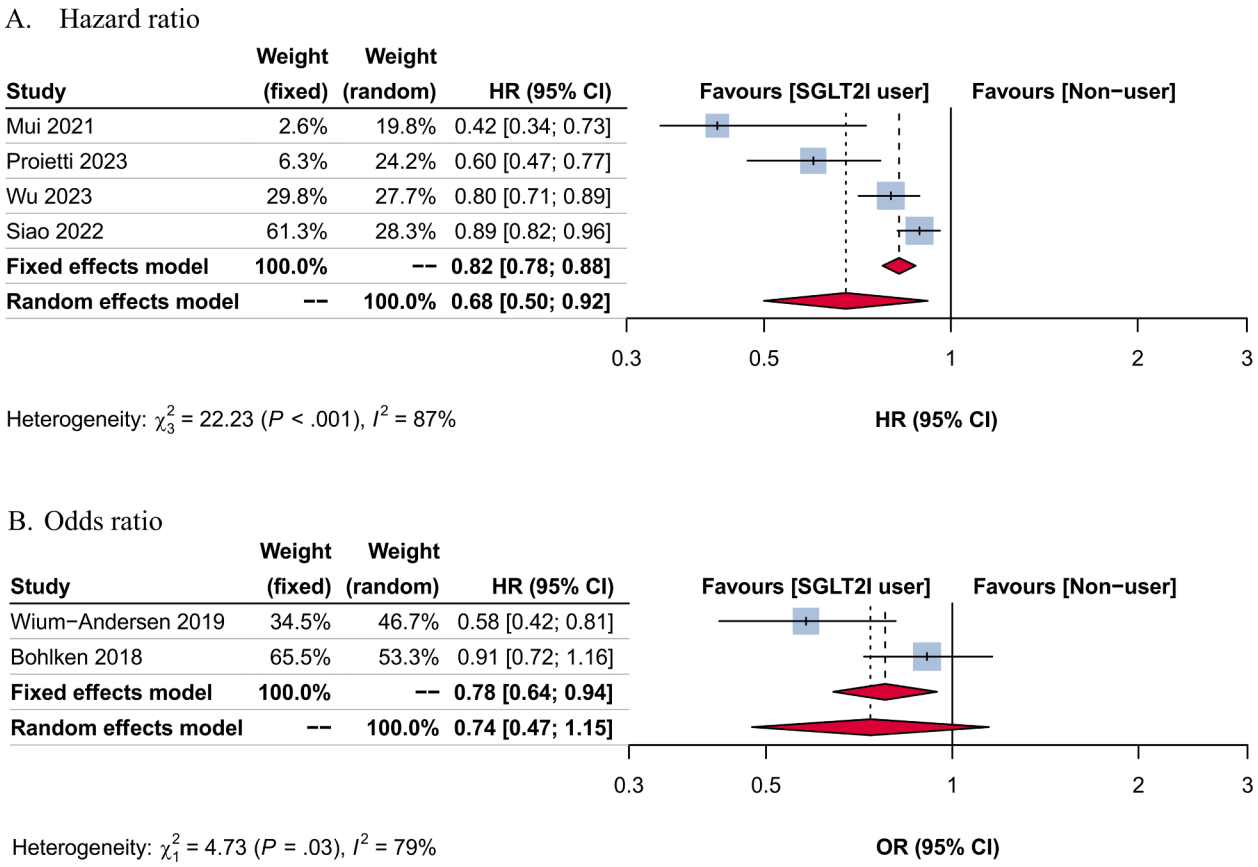

Fig. 2. Forest plot of dementia incidence risk with sodium-glucose cotransporter 2 inhibitors. (A) Hazard ratio and (B) Odds ratio.

revealed a positive association between SGLT-2 inhibitor use and the increase in RBANS total score when individuals took SGLT-2 inhibitors for 3 years (correlation coefficient = 0.54, 95 % CI: 0.13–0.95) (Low et al., 2022).

3.5. Quality assessment

The risk of bias assessment using ROB 2 revealed that two of the three RCTs had a low risk of bias. In contrast, the third RCT, conducted by Zhao and Wang, raised concerns about bias (Supplementary Fig. 1 and Supplementary Table 4). In the ROBINS-I assessment of non-RCTs, seven of the nine studies included in our analysis received a "moderate" rating for the risk of bias, with only two studies by Mone *et al.* demonstrating a low risk of bias. The primary reasons for this were a lack of clarity regarding deviations from the intended intervention and the presence of missing data (Supplementary Fig. 2 and Supplementary Table 5).

3.6. Sensitivity analysis

Sensitivity analysis was performed on four studies related to dementia incidence and three studies exploring the changes in cognitive function scores. The results indicated that excluding individual studies (leave-one-out) or considering variations in the sample size (the effects of a small sample size) had no significant impact on the findings (Supplementary Figs. 3 and 4).

4. Discussion

DM and its complications have come under increasing global scrutiny; therefore numerous studies have addressed the ancillary effects of glucose-lowering drugs beyond primary glycemic control (ElSayed et al.,

Table 2
Subgroup analysis of the risk of dementia incidence based on baseline population characteristics.

Variables	Number of studies (sample size)	Pooled HR (95 % CI)	I^2 (%)	*P-value*
Age ≥60 years at enrollment[a]	2 (169,924)	0.84 (0.75–0.95)	43	
Continents				
Asia	2 (246,322)	0.63 (0.30–1.31)	93	0.76
Europe or North America	2 (83,156)	0.71 (0.54–0.94)	77	
Exploring temporal dynamic				
1-year lag time	2 (122,886)	0.60 (0.32–1.12)	90	0.55
No lag time	2 (216,592)	0.74 (0.51–1.09)	89	
Comparison				
SGLT-2i users vs. DPP-4i users	2 (122,886)	0.60 (0.32–1.12)	90	0.55
SGLT-2i users vs. SGLT-2i non-users	2 (216,592)	0.74 (0.51–1.09)	89	

Abbreviations: DPP4i, dipeptidyl peptidase IV inhibitor; HR, hazard ratio; NA, not applicable; MCI, mild cognitive impairment; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

[a] Wu (2023) and Siao (2022) were included. In Siao 2022, we extracted the HR values for individuals aged 60–80 years and pooled them for analysis.

2022a; Tomic et al., 2022). Considering this growing interest, several systematic reviews and meta-analyses have been conducted to evaluate the potential neuroprotective effects of glucose-lowering agents on dementia (Jin et al., 2020; Luan et al., 2022; Tang et al., 2023). Among these, the role of SGLT-2 inhibitors in cognitive function has emerged as a focal point. Although several meta-analyses assessing the potential of SGLT-2 inhibitors to reduce the risk of dementia have been published, inconsistent results have been reported, exacerbated by the inherent limitations of the included studies, such as the small number of studies and small sample sizes (Jin et al., 2020; Tang et al., 2023). In contrast to previous reviews, our study incorporated data from eight additional studies and established that SGLT-2 inhibitors are significantly associated with a reduced risk of dementia. This result remained consistent across different types of pooled estimations and subgroup analyses. Given that our systematic review and meta-analysis incorporated recently published research and restricted the included studies to those with valid and robust study designs, we assert that our findings enhance the existing literature and, provide a more comprehensive and rigorous overview of the current body of knowledge.

Our findings, derived from four retrospective cohort studies, demonstrated a significantly reduced risk of dementia associated with the SGLT-2 inhibitors use. This aligns with the result of a previous study by Tang et al. (2023), which incorporated three observational studies (one cohort study and two case-control studies); however, we added three more retrospective cohort studies and stratified the pooled estimates based on study designs, distinguishing between cohort and case-control studies. The HRs reported in four retrospective cohort studies consistently indicated a positive effect of SGLT-2 inhibitors on the onset of dementia, although there were differences in the study methodologies (Mui et al., 2021; Siao et al., 2022; Wu et al., 2023a). This suggests the potential of SGLT-2 inhibitors for dementia prevention despite the limited number of studies. In contrast, the pooled estimates from the two case-control studies did not show a significant association between SGLT-2 inhibitor use and the incidence of dementia. Although these estimates appear inconsistent, the potential neuroprotective effects of SGLT-2 inhibitors cannot be ignored. Additionally, these inconsistencies may be largely due to the considerable heterogeneity between the two cross-sectional studies, specifically regarding the look-back period, and the inherently lower strength of their study designs. Therefore, the non-significant results reported by Bohlken *et al.* may be attributable to the relatively short look-back period used in their study (Jens Bohlken and Kostev, 2018). Further analyses incorporating more robust data sources, such as RCTs, are required to elucidate the role of SGLT-2 inhibitors in the incidence of dementia.

The neuroprotective effects of SGLT-2 inhibitors have been proposed to occur via various mechanisms; however, these specific mechanisms have not yet been clearly defined. Although it is understood that cognitive impairment in DM results from a combination of vascular pathways and neurodegenerative damage, glycemic control by SGLT-2 inhibitors was previously considered a key mechanism for their cognitive effects. Recent studies have suggested plausible mechanisms linked to endothelial (Guo et al., 2023; Mone et al., 2023; Santulli et al., 2023; Youssef et al., 2023) and mitochondrial dysfunctions (Koyani et al., 2020; Moon et al., 2022; Zou et al., 2022; Zügner et al., 2022; Radlinger et al., 2023). Mitochondria are involved in endothelial mobilization, senescence, growth, and proliferation, and mitochondrial dysfunction is a crucial factor leading to abnormal endothelial function in the vascular lining (Kluge et al., 2013; Kirkman et al., 2021). Numerous studies have shown that SGLT-2 inhibitors, including canagliflozin and empagliflozin, provide vascular protection by ameliorating mitochondrial dysfunction (Koyani et al., 2020; Zou et al., 2022; Zügner et al., 2022). Moreover, given that SGLT-2 inhibitors are lipid-soluble and capable of penetrating the blood–brain barrier, they can affect the SGLT-1/SGLT-2 cotransporter widely expressed in the brain, which has been implicated in learning processes, long-term memory, and movement by reducing brain inflammation, apoptosis, and oxidative stress (Pawlos et al., 2021; Youssef et al., 2023). Additionally, SGLT-2 inhibitors have been shown to inhibit both acetylcholinesterase and SGLT-2 cotransporters and enhance the levels of brain-derived neurotrophic factors, which play pivotal roles in the growth, survival, and plasticity of neurons (Shaikh et al., 2016; Miranda et al., 2019; Pawlos et al., 2021).

In addition to evaluating the incidence of dementia, we assessed changes in cognitive function attributable to SGLT-2 inhibitors by integrating the results of RCTs (Cheng et al., 2022; Zhao and Wang, 2022) and a prospective cohort study (Low et al., 2022; Mone et al., 2022a; Mone et al., 2022b). In patients with MCI and dementia (Mone et al., 2022a; Mone et al., 2022b; Zhao and Wang, 2022), the use of SGLT-2 inhibitors was significantly associated with improvements in cognitive function scores. Conversely, in study populations with normal baseline cognitive function (Cheng et al., 2022; Low et al., 2022), no significant associations were observed between the use of SGLT-2 inhibitors and changes in cognitive function scores, which is in contrast to our findings on dementia incidence. This inconsistency might be attributed to the limited number of studies incorporating a population with normal cognitive function as a subgroup and the comparatively younger age of participants in these studies (Cheng et al., 2022; Low et al., 2022) compared to subgroup analyses in patients with dementia or MCI, which included only older individuals (Mone et al., 2022a; Mone

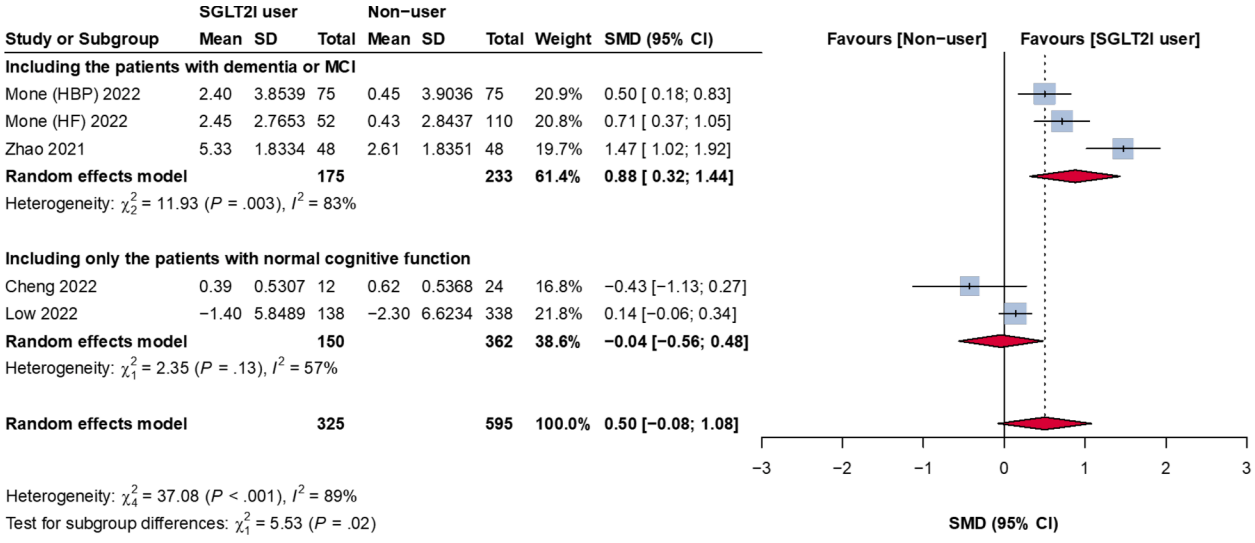

Fig. 3. Forest plot of cognitive function score changes with sodium-glucose cotransporter 2 inhibitors.

et al., 2022b; Zhao and Wang, 2022). This observation aligns with the results of the subgroup analysis for dementia onset in our study, which included patients aged ≥60 years at enrollment. Recent studies have demonstrated that the SGLT-2 inhibitor, empagliflozin, has beneficial effects on cognitive impairment in frail older adults with DM (Mone et al., 2022b; Santulli et al., 2023). However, the RCT by Perna et al. (2018), which was not included in our meta-analysis, indicated no significant association between SGLT-2 inhibitor use and changes in the cognitive status in patients with normal cognitive function. In addition, the SMD was larger in studies with longer follow-up periods (Low et al., 2022; Zhao and Wang, 2022) and smaller in a study using liraglutide as a control (Cheng et al., 2022). Considering these previous findings, the differences between subgroups could be correlated with study characteristics, such as age, follow-up periods, and choice of active control medication. Consequently, although our results highlight the potential benefits of SGLT-2 inhibitors in patients with dementia or MCI, further research is necessary to confirm these findings.

In our subgroup analysis, we could not identify specific factors, except for age, which contributed to the reduced risk of dementia attributed to SGLT-2 inhibitor use. In patients aged ≥60 years, the incidence of dementia was significantly reduced in SGLT-2 inhibitor users compared to non-users, although the point estimation was somewhat smaller than that in the entire population. However, caution is needed when interpreting this result, as it was based on only two studies with subgroup analysis of older patients. In the analysis of cognitive function score changes, the age of patients with MCI or dementia was higher than that of those with normal cognitive function (mean age of SGLT-2 users: 61.1–80.6 vs. 57.0–58.6 years). This suggests that SGLT-2 inhibitors may positively affect cognitive function in older patients. However, further research is required to confirm these findings.

Additionally, we differentiated the comparison groups between those who did not use SGLT-2 inhibitors and those who used another glucose-lowering agent, dipeptidyl peptidase-4 inhibitors (DPP-4i). However, no significant conclusions were drawn from subgroup analysis of the comparison groups. Previous studies demonstrated that DPP-4 inhibitors have significant protective effects on cognitive function (Bernstein et al., 2018; Kim et al., 2019; Chai et al., 2023), similar to those of SGLT-2 inhibitors. Incretin-based therapies, including DPP-4 inhibitors, may exert protective effects on the cognitive function in patients with type 2 DM. Recent meta-analyses have consistently reported the positive effects of incretins on cognitive function and the onset of dementia (Luan et al., 2022; Chai et al., 2023). Chai *et al.* observed an increase in cognitive scores in the incretin group (weighted mean difference: 1.20, 95 % CI: 0.39–2.01; based on MMSE scores) compared to the control group (Chai et al., 2023). However, a meta-analysis focusing on GLP-1 agonists reported a non-significant effect on the overall cognitive function. Notably, in subgroup analyses stratified by age and history of cardio-cerebrovascular disease, GLP-1 use had a positive effect on cognitive function in patients without cardio-cerebrovascular disease and in those younger than 65 years (Luan et al., 2022). The mechanisms underlying the positive effects of incretins on cognitive function are thought to involve anti-inflammatory and anti-oxidative properties, as well as reductions in Aβ levels and tau phosphorylation (Groeneveld et al., 2016).

Given that diabetes is a risk factor for cognitive impairment, other antidiabetic medications may also be associated with changes in cognitive function in patients with type 2 DM. In addition to SGLT-2 inhibitors and incretin-based therapies, thiazolidinediones and metformin may positively influence the risk of dementia (Zhou et al., 2020; Kuate Defo et al., 2024). However, a few studies have suggested that sulfonylureas and insulin may be risk factors (McMillan et al., 2018; Weinstein et al., 2019; Wu et al., 2023b), potentially owing to the adverse effects of hypoglycemia on cognitive function (Whitmer et al., 2009). Similarly, meglitinides have been reported to increase the risk of dementia in patients with diabetes (Kuate Defo et al., 2024). In real-world DM management, various glucose-lowering agents are often used in combination, which complicates the interpretation of observational study results. An inherent limitation of real-world data is that analyzing individual drug effects or comparisons between agents is not possible. Consequently, evidence for the selection of drugs for the adjunctive purpose of dementia prevention and their primary glucose-lowering effects in patients with DM remains limited. Further studies using robust methodologies for direct and indirect drug comparisons are essential.

Our study has several limitations that should be considered when interpreting the findings. First, although our systematic review and meta-analysis incorporated recently published articles, expanding the pool of studies beyond previous reviews (Tang et al., 2022; Tang et al., 2023; Tian et al., 2023), a maximum of five studies contributed to our pooled estimates. In addition, the participant count was notably low, especially in the RCTs, and the number of studies available for subgroup analyses remained limited. Moreover, providing integrated results was further complicated by varied outcome measures across studies, including dementia incidence and MMSE, MoCA, and RBANS scores. Nonetheless, we attempted to provide consolidated results for changes in cognitive function scores by calculating standardized mean differences. Second, the presence of substantial heterogeneity among the studies included in our analysis, spanning differences in study design, follow-up periods, and comparison groups, compromised the generalizability of our findings. The follow-up periods ranged from a few months to several years. Given that the changes in cognitive function and dementia development are chronic processes that occur over extended periods, a short follow-up period may cause an underestimation of the risk of dementia. To address this concern, we incorporated HRs, which are measurements that account for the follow-up period (Spruance et al., 2004), and conducted a sensitivity analysis. After excluding the study by Zhao and Wang (2022), which exhibited a relatively moderate bias, the pooled estimate remained significant, and the results from all other sensitivity analyses were consistent with the main findings. The control groups differed across studies, as non-users were compared with those using other anti-diabetic medications, such as DPP-4 inhibitors. The covariates adjusted for each study, including baseline comorbidities, cognitive function, and demographics, such as age and country, varied. To address these inconsistencies, we conducted subgroup analyses based on variables such as baseline cognitive function, age, country, and type of control group. However, deriving significant results is challenging owing to the limited number of studies available. In our meta-analysis, female participation in the included studies was generally lower than that of males; however, subgroup analysis considering sex ratio differences could not be performed. Given that dementia risk is reported to be higher in women than that in men (Gong et al., 2023; Lee et al., 2023), the influence of sex differences on the protective activity of SGLT-2 inhibitors remains uncertain. Meta-regression or funnel plot analyses could not be performed to confirm publication bias. Finally, although users of SGLT-2 inhibitors generally exhibited greater improvements in cognitive function scores than non-users, the non-user group also showed post-treatment improvements in cognitive function scores. This suggests that further studies are required to control for factors beyond the use of SGLT-2 inhibitors that might influence improvements in cognitive function.

5. Conclusions

We conducted a systematic review and meta-analysis of the studies investigating the effects of SGLT-2 inhibitor use on cognitive function by incorporating newly published research to provide a more comprehensive and rigorous overview. Our findings indicate that the use of SGLT-2 inhibitors is significantly associated with a reduced risk of dementia and an improvement in cognitive function. Due to the limited number of studies incorporated and the heterogeneity of the included studies, we could not identify specific factors contributing to the reduction in dementia risk attributed to SGLT-2 inhibitor use. Therefore, further large-

scale studies with stronger validity are needed to clarify the effects of SGLT-2 inhibitors on the risk of dementia.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Yea Jin Youn: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Seungyeon Kim:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hyun-Jeong Jeong:** Investigation, Formal analysis, Data curation, Conceptualization. **Young-Mi Ah:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Yun Mi Yu:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Acknowledgments

Not applicable

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2024.101131.

References

Bernstein, H.G., Dobrowolny, H., Keilhoff, G., Steiner, J., 2018. Dipeptidyl peptidase IV, which probably plays important roles in Alzheimer disease (AD) pathology, is upregulated in AD brain neurons and associates with amyloid plaques. Neurochem. Int. 114, 55–57. https://doi.org/10.1016/j.neuint.2018.01.005.

Chai, S., Liu, F., Yu, S., Yang, Z., Sun, F., 2023. Cognitive protection of incretin-based therapies in patients with type 2 diabetes mellitus: a systematic review and meta-analysis based on clinical studies. J Diabetes Investig 14, 864–873. https://doi.org/10.1111/jdi.14015.

Chen, S., Wang, Q., Christodoulou, A., Mylonas, N., Bakker, D., Nederlof, R., Hollmann, M.W., Weber, N.C., Coronel, R., Wakker, V., Christoffels, V.M., Andreadou, I., Zuurbier, C.J., 2023. Sodium glucose cotransporter-2 inhibitor empagliflozin reduces infarct size independently of sodium glucose cotransporter-2. Circulation 147, 276–279. https://doi.org/10.1161/circulationaha.122.061688.

Cheng, H., Zhang, Z., Zhang, B., Zhang, W., Wang, J., Ni, W., Miao, Y., Liu, J., Bi, Y., 2022. Enhancement of impaired olfactory neural activation and cognitive capacity by liraglutide, but not dapagliflozin or acarbose, in patients with type 2 diabetes: a 16-week randomized parallel comparative study. Diabetes Care 45, 1201–1210. https://doi.org/10.2337/dc21-2064.

Cho, Y., Park, H.S., Huh, B.W., Seo, S.H., Seo, D.H., Ahn, S.H., Hong, S., Suh, Y.J., Kim, S. H., 2022. Prevalence and risk of diabetic complications in young-onset versus late-onset type 2 diabetes mellitus. Diabetes Metab. 48 https://doi.org/10.1016/j.diabet.2022.101389.

Deeks, J.J.H., Altman, D.G., 2011. Chapter 10: Analysing data and undertaking meta-analyses. In Cochrane Handbook for Systematic Reviews of Interventions. In: The Cochrane Collaboration. Cochrane training.

Dunham, K.J., Shadi, S., Sofko, C.A., Denney, R.L., Calloway, J., 2014. Comparison of the repeatable battery for the assessment of neuropsychological status effort scale and effort index in a dementia sample. Arch. Clin. Neuropsychol. 29, 633–641. https://doi.org/10.1093/arclin/acu042.

Dyck, J.R.B., Sossalla, S., Hamdani, N., Coronel, R., Weber, N.C., Light, P.E., Zuurbier, C. J., 2022. Cardiac mechanisms of the beneficial effects of SGLT2 inhibitors in heart failure: evidence for potential off-target effects. J. Mol. Cell. Cardiol. 167, 17–31. https://doi.org/10.1016/j.yjmcc.2022.03.005.

Elsayed, N.A., Aleppo, G., Aroda, V.R., Bannuru, R.R., Brown, F.M., Bruemmer, D., Collins, B.S., Hilliard, M.E., Isaacs, D., Johnson, E.L., Kahan, S., Khunti, K., Leon, J., Lyons, S.K., Perry, M.L., Prahalad, P., Pratley, R.E., Jeffrie Seley, J., Stanton, R.C., Gabbay, R.A., on behalf of the American Diabetes Association, 2022a. 13. Older adults: standards of care in diabetes—2023. Diabetes Care 46, S216–S229. https://doi.org/10.2337/dc23-S013.

Elsayed, N.A., Aleppo, G., Aroda, V.R., Bannuru, R.R., Brown, F.M., Bruemmer, D., Collins, B.S., Hilliard, M.E., Isaacs, D., Johnson, E.L., Kahan, S., Khunti, K., Leon, J., Lyons, S.K., Perry, M.L., Prahalad, P., Pratley, R.E., Seley, J.J., Stanton, R.C., Gabbay, R.A., on behalf of the American Diabetes Association, 2022b. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023. Diabetes Care 46, S140–S157. https://doi.org/10.2337/dc23-S009.

Gong, J., Harris, K., Lipnicki, D.M., Castro-Costa, E., Lima-Costa, M.F., Diniz, B.S., Xiao, S., Lipton, R.B., Katz, M.J., Wang, C., Preux, P.M., Guerchet, M., Gbessemehlan, A., Ritchie, K., Ancelin, M.L., Skoog, I., Najar, J., Sterner, T.R., Scarmeas, N., Yannakoulia, M., Kosmidis, M.H., Guaita, A., Rolandi, E., Davin, A., Gureje, O., Trompet, S., Gussekloo, J., Riedel-Heller, S., Pabst, A., Röhr, S., Shahar, S., Singh, D.K.A., Rivan, N.F.M., Boxtel, M.V., Köhler, S., Ganguli, M., Chang, C.C., Jacobsen, E., Haan, M., Ding, D., Zhao, Q., Xiao, Z., Narazaki, K., Chen, T., Chen, S., Ng, T.P., Gwee, X., Numbers, K., Mather, K.A., Scazufca, M., Lobo, A., De-La-Cámara, C., Lobo, E., Sachdev, P.S., Brodaty, H., Hackett, M.L., Peters, S.E., Woodward, M., 2023. Sex differences in dementia risk and risk factors: individual-participant data analysis using 21 cohorts across six continents from the COSMIC consortium. Alzheimers Dement. 19, 3365–3378. https://doi.org/10.1002/alz.12962.

Groeneveld, O.N., Kappelle, L.J., Biessels, G.J., 2016. Potentials of incretin-based therapies in dementia and stroke in type 2 diabetes mellitus. J Diabetes Investig 7, 5–16. https://doi.org/10.1111/jdi.12420.

Guideline Adaptation Committee, 2016. Clinical Practice Guidelines and Principles of Care for People with Dementia. [Online]. Available at: https://cdpc.sydney.edu.au/wp-content/uploads/2019/06/CDPC-Dementia-Guidelines_WEB.pdf [Accessed Sep 2023].

Guo, H., Yu, X., Liu, Y., Paik, D.T., Justesen, J.M., Chandy, M., Jahng, J.W.S., Zhang, T., Wu, W., Rwere, F., Zhao, S.R., Pokhrel, S., Shivnaraine, R.V., Mukherjee, S., Simon, D.J., Manhas, A., Zhang, A., Chen, C.H., Rivas, M.A., Gross, E.R., Mochly-Rosen, D., Wu, J.C., 2023. SGLT2 inhibitor ameliorates endothelial dysfunction associated with the common ALDH2 alcohol flushing variant. Sci. Transl. Med. 15, eabp9952 https://doi.org/10.1126/scitranslmed.abp9952.

Hahn, J., Jo, Y., Yoo, S.H., Shin, J., Yu, Y.M., Ah, Y.M., 2022. Risk of major adverse events associated with gabapentinoid and opioid combination therapy: a systematic review and meta-analysis. Front. Pharmacol. 13, 1009950 https://doi.org/10.3389/fphar.2022.1009950.

Higgins, J.P., Li, T., Deeks, J.J., 2019. chapter 6: Choosing effect measures and computing estimates of effect. Cochrane handbook for systematic reviews of interventions. Cochrane Training 143–176.

International Diabetes Federation, 2021. International Diabetes Federation Diabetes Atlas 10th edition. [Online]. Available at: https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf [Accessed 5 Sep 2023].

Jenkins, B.J., Blagih, J., Ponce-Garcia, F.M., Canavan, M., Gudgeon, N., Eastham, S., Hill, D., Hanlon, M.M., Ma, E.H., Bishop, E.L., Rees, A., Cronin, J.G., Jury, E.C., Dimeloe, S.K., Veale, D.J., Thornton, C.A., Vousden, K.H., Finlay, D.K., Fearon, U., Jones, G.W., Sinclair, L.V., Vincent, E.E., Jones, N., 2023. Canagliflozin impairs T cell effector function via metabolic suppression in autoimmunity. Cell Metab. 35, 1132–1146.e1139. https://doi.org/10.1016/j.cmet.2023.05.001.

Jens Bohlken, L.J., Kostev, K., 2018. Association between the use of antihyperglycemic drugs and dementia risk: a case-control study. J. Alzheimers Dis. https://doi.org/10.3233/JAD-180808.

Jin, Y., Zhao, H., Hou, Y., Song, G., 2020. The effects of dipeptidyl peptidase-4 inhibitors and glucagon-like peptide 1 receptor agonists on cognitive functions in adults with type 2 diabetes mellitus: a systematic review and meta-analysis. Acta Diabetol. 57, 1129–1144. https://doi.org/10.1007/s00592-020-01529-1.

Kim, Y.G., Jeon, J.Y., Kim, H.J., Kim, D.J., Lee, K.W., Moon, S.Y., Han, S.J., 2019. Risk of dementia in older patients with type 2 diabetes on dipeptidyl-peptidase IV inhibitors versus sulfonylureas: a real-world population-based cohort study. J. Clin. Med. 8 https://doi.org/10.3390/jcm8010028.

Kirkman, D.L., Robinson, A.T., Rossman, M.J., Seals, D.R., Edwards, D.G., 2021. Mitochondrial contributions to vascular endothelial dysfunction, arterial stiffness, and cardiovascular diseases. Am. J. Phys. Heart Circ. Phys. 320, H2080–H2100. https://doi.org/10.1152/ajpheart.00917.2020.

Kluge, M.A., Fetterman, J.L., Vita, J.A., 2013. Mitochondria and endothelial function. Circ. Res. 112, 1171–1188. https://doi.org/10.1161/circresaha.111.300233.

Koyani, C.N., Plastira, I., Sourij, H., Hallström, S., Schmidt, A., Rainer, P.P., Bugger, H., Frank, S., Malle, E., Von Lewinski, D., 2020. Empagliflozin protects heart from inflammation and energy depletion via AMPK activation. Pharmacol. Res. 158, 104870 https://doi.org/10.1016/j.phrs.2020.104870.

Kuate Defo, A., Bakula, V., Pisaturo, A., Labos, C., Wing, S.S., Daskalopoulou, S.S., 2024. Diabetes, antidiabetic medications and risk of dementia: a systematic umbrella review and meta-analysis. Diabetes Obes. Metab. 26, 441–462. https://doi.org/10.1111/dom.15331.

Lee, H.W., Kim, S., Jo, Y., Kim, Y., Ye, B.S., Yu, Y.M., 2023. Neuroprotective effect of angiotensin II receptor blockers on the risk of incident Alzheimer's disease: a nationwide population-based cohort study. Front. Aging Neurosci. 15, 1137197 https://doi.org/10.3389/fnagi.2023.1137197.

Low, S., Goh, K.S., Ng, T.P., Moh, A., Ang, S.F., Wang, J., Ang, K., Tang, W.E., Lim, Z., Subramaniam, T., Sum, C.F., Lim, S.C., 2022. Association Between Use of Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibitors and Cognitive Function in a Longitudinal Study of Patients with Type 2 Diabetes. J. Alzheimers Dis. 87, 635–642. https://doi.org/10.3233/jad-215678.

Luan, S., Cheng, W., Wang, C., Gong, J., Zhou, J., 2022. Impact of glucagon-like peptide 1 analogs on cognitive function among patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 13, 1047883. https://doi.org/10.3389/fendo.2022.1047883.

Mcmillan, J.M., Mele, B.S., Hogan, D.B., Leung, A.A., 2018. Impact of pharmacological treatment of diabetes mellitus on dementia risk: systematic review and meta-analysis. BMJ Open Diabetes Res. Care 6. https://doi.org/10.1136/bmjdrc-2018-000563.

Miranda, M., Morici, J.F., Zanoni, M.B., Bekinschtein, P., 2019. Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. Front. Cell. Neurosci. 13 https://doi.org/10.3389/fncel.2019.00363.

Mone, P., Lombardi, A., Gambardella, J., Pansini, A., Macina, G., Morgante, M., Frullone, S., Santulli, G., 2022a. Empagliflozin improves cognitive impairment in frail older adults with type 2 diabetes and heart failure with preserved ejection fraction. Diabetes Care 45, 1247–1251. https://doi.org/10.2337/dc21-2434.

Mone, P., Varzideh, F., Jankauskas, S.S., Pansini, A., Lombardi, A., Frullone, S., Santulli, G., 2022b. SGLT2 inhibition via empagliflozin improves endothelial function and reduces mitochondrial oxidative stress: insights from frail hypertensive and diabetic patients. Hypertension 79, 1633–1643. https://doi.org/10.1161/hypertensionaha.122.19586.

Mone, P., Lombardi, A., Kansakar, U., Varzideh, F., Jankauskas, S.S., Pansini, A., Marzocco, S., De Gennaro, S., Famiglietti, M., Macina, G., Frullone, S., Santulli, G., 2023. Empagliflozin improves the microRNA signature of endothelial dysfunction in patients with heart failure with preserved ejection fraction and diabetes. J. Pharmacol. Exp. Ther. 384, 116–122. https://doi.org/10.1124/jpet.121.001251.

Moon, J.S., Hong, J.H., Jung, Y.J., Ferrannini, E., Nauck, M.A., Lim, S., 2022. SGLT-2 inhibitors and GLP-1 receptor agonists in metabolic dysfunction-associated fatty liver disease. Trends Endocrinol. Metab. 33, 424–442. https://doi.org/10.1016/j.tem.2022.03.005.

Mui, J.V., Zhou, J., Lee, S., Leung, K.S.K., Lee, T.T.L., Chou, O.H.I., Tsang, S.L., Wai, A.K.C., Liu, T., Wong, W.T., Chang, C., Tse, G., Zhang, Q., 2021. Sodium-glucose cotransporter 2 (SGLT2) inhibitors vs. dipeptidyl peptidase-4 (DPP4) inhibitors for new-onset dementia: a propensity score-matched population-based study with competing risk analysis. Front. Cardiovasc. Med. 8, 747620 https://doi.org/10.3389/fcvm.2021.747620.

Page, M.J., Mckenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., Mcdonald, S., Mcguinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71. https://doi.org/10.1136/bmj.n71.

Park, Y., Ah, Y.M., Yu, Y.M., 2023. Vitamin D supplementation for depression in older adults: a meta-analysis of randomized controlled trials. Front. Nutr. 10, 1169436 https://doi.org/10.3389/fnut.2023.1169436.

Pawlos, A., Broncel, M., Woźniak, E., Gorzelak-Pabiś, P., 2021. Neuroprotective effect of SGLT2 inhibitors. Molecules 26. https://doi.org/10.3390/molecules26237213.

Perna, S., Mainardi, M., Astrone, P., Gozzer, C., Biava, A., Bacchio, R., Spadaccini, D., Solerte, S.b., Rondanelli, M., 2018. 12-month effects of incretins versus SGLT2-inhibitors on cognitive performance and metabolic profile. A randomized clinical trial in the elderly with type-2 diabetes mellitus. Clin. Pharmacol.: Adv. Appl. 141–151.

Pezzotti, P., Scalmana, S., Mastromattei, A., Di Lallo, D., 2008. The accuracy of the MMSE in detecting cognitive impairment when administered by general practitioners: a prospective observational study. BMC Fam. Pract. 9, 29. https://doi.org/10.1186/1471-2296-9-29.

Proietti, R., Rivera-Caravaca, J.M., López-Gálvez, R., Harrison, S.L., Marín, F., Underhill, P., Shantsila, E., Mcdowell, G., Vinciguerra, M., Davies, R., Giebel, C., Lane, D.A., Lip, G.Y.H., 2023. Cerebrovascular, cognitive and cardiac benefits of SGLT2 inhibitors therapy in patients with atrial fibrillation and type 2 diabetes mellitus: results from a global federated health network analysis. J. Clin. Med. 12 https://doi.org/10.3390/jcm12082814.

Radlinger, B., Ress, C., Folie, S., Salzmann, K., Lechuga, A., Weiss, B., Salvenmoser, W., Graber, M., Hirsch, J., Holfeld, J., Kremser, C., Moser, P., Staudacher, G., Jelenik, T., Roden, M., Tilg, H., Kaser, S., 2023. Empagliflozin protects mice against diet-induced obesity, insulin resistance and hepatic steatosis. Diabetologia 66, 754–767. https://doi.org/10.1007/s00125-022-05851-x.

Rom, S., Heldt, N.A., Gajghate, S., Seliga, A., Reichenbach, N.L., Persidsky, Y., 2020. Hyperglycemia and advanced glycation end products disrupt BBB and promote occludin and claudin-5 protein secretion on extracellular microvesicles. Sci. Rep. 10, 7274. https://doi.org/10.1038/s41598-020-64349-x.

Santulli, G., Varzideh, F., Forzano, I., Wilson, S., Salemme, L., De Donato, A., Lombardi, A., Rainone, A., Nunziata, L., Jankauskas, S.S., Tesorio, T., Guerra, G., Kansakar, U., Mone, P., 2023. Functional and clinical importance of SGLT2-inhibitors in frailty: from the kidney to the heart. Hypertension 80, 1800–1809. https://doi.org/10.1161/hypertensionaha.123.20598.

Scheen, A.J., Bonnet, F., 2023. Efficacy and safety profile of SGLT2 inhibitors in the elderly: how is the benefit/risk balance? Diabetes Metab. 49, 101419 https://doi.org/10.1016/j.diabet.2023.101419.

Shaikh, S., Rizvi, S.M., Shakil, S., Riyaz, S., Biswas, D., Jahan, R., 2016. Forxiga (dapagliflozin): plausible role in the treatment of diabetes-associated neurological disorders. Biotechnol. Appl. Biochem. 63, 145–150. https://doi.org/10.1002/bab.1319.

Siao, W.Z., Lin, T.K., Huang, J.Y., Tsai, C.F., Jong, G.P., 2022. The association between sodium-glucose cotransporter 2 inhibitors and incident dementia: a nationwide population-based longitudinal cohort study. Diab. Vasc. Dis. Res. 19, 14791641221098168 https://doi.org/10.1177/14791641221098168.

Sinclair, A., Saeedi, P., Kaundal, A., Karuranga, S., Malanda, B., Williams, R., 2020. Diabetes and global ageing among 65–99-year-old adults: Findings from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res. Clin. Pract. 162, 108078 https://doi.org/10.1016/j.diabres.2020.108078.

Spruance, S.L., Reid, J.E., Grace, M., Samore, M., 2004. Hazard ratio in clinical trials. Antimicrob. Agents Chemother. 48, 2787–2792. https://doi.org/10.1128/AAC.48.8.2787-2792.2004.

Steen, E., Terry, B.M., Rivera, E.J., Cannon, J.L., Neely, T.R., Tavares, R., Xu, X.J., Wands, J.R., De La Monte, S.M., 2005. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease–is this type 3 diabetes? J. Alzheimers Dis. 7, 63–80. https://doi.org/10.3233/jad-2005-7107.

Sterne, J.C., Hernán, M.A., Reeves, B.C., Savović, J., Berkman, N.D., Viswanathan, M., Henry, D., Altman, D.G., Ansari, M.T., Boutron, I., Carpenter, J.R., Chan, A.-W., Churchill, R., Deeks, J.J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y.K., Pigott, T.D., Ramsay, C.R., Regidor, D., Rothstein, H.R., Sandhu, L., Santaguida, P.L., Schünemann, H.J., Shea, B., Shrier, I., Tugwell, P., Turner, L., Valentine, J.C., Waddington, H., Waters, E., Wells, G.A., Whiting, P.F., Higgins, J.P.T., 2016. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919. https://doi.org/10.1136/bmj.i4919.

Sterne, J.C., Savović, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., Cates, C.J., Cheng, H.-Y., Corbett, M.S., Eldridge, S.M., Emberson, J.R., Hernán, M.A., Hopewell, S., Hróbjartsson, A., Junqueira, D.R., Jüni, P., Kirkham, J.J., Lasserson, T., Li, T., Mcaleenan, A., Reeves, B.C., Shepperd, S., Shrier, I., Stewart, L.A., Tilling, K., White, I.R., Whiting, P.F., Higgins, J.P.T., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, l4898. https://doi.org/10.1136/bmj.l4898.

Tang, H., Niu, S., Brown, J., Wei, J., Shao, H., Bian, J., Guo, J., 2022. Newer glucose-lowering drugs and risk of dementia: a meta-analysis of cardiovascular outcome trials. J. Am. Geriatr. Soc. 70, 2719–2722. https://doi.org/10.1111/jgs.17895.

Tang, H., Shao, H., Shaaban, C.E., Yang, K., Brown, J., Anton, S., Wu, Y., Bress, A., Donahoo, W.T., Dekosky, S.T., Bian, J., Guo, J., 2023. Newer glucose-lowering drugs and risk of dementia: a systematic review and meta-analysis of observational studies. J. Am. Geriatr. Soc. 71, 2096–2106. https://doi.org/10.1111/jgs.18306.

Tian, S., Jiang, J., Wang, J., Zhang, Z., Miao, Y., Ji, X., Bi, Y., 2023. Comparison on cognitive outcomes of antidiabetic agents for type 2 diabetes: a systematic review and network meta-analysis. Diabetes Metab. Res. Rev., e3673 https://doi.org/10.1002/dmrr.3673.

Tomic, D., Shaw, J.E., Magliano, D.J., 2022. The burden and risks of emerging complications of diabetes mellitus. Nat. Rev. Endocrinol. 18, 525–539. https://doi.org/10.1038/s41574-022-00690-7.

Weinstein, G., Davis-Plourde, K.L., Conner, S., Himali, J.J., Beiser, A.S., Lee, A., Rawlings, A.M., Sedaghat, S., Ding, J., Moshier, E., Van Duijn, C.M., Beeri, M.S., Selvin, E., Ikram, M.A., Launer, L.J., Haan, M.N., Seshadri, S., 2019. Association of metformin, sulfonylurea and insulin use with brain structure and function and risk of dementia and Alzheimer's disease: pooled analysis from 5 cohorts. PLoS One 14, e0212293. https://doi.org/10.1371/journal.pone.0212293.

Whitmer, R.A., Karter, A.J., Yaffe, K., Quesenberry Jr., C.P., Selby, J.V., 2009. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. J. Am. Med. Assoc. 301, 1565–1572. https://doi.org/10.1001/jama.2009.460.

Wium-Andersen, I.K., Osler, M., Jørgensen, M.B., Rungby, J., Wium-Andersen, M.K., 2019. Antidiabetic medication and risk of dementia in patients with type 2 diabetes: a nested case-control study. Eur. J. Endocrinol. 181, 499–507. https://doi.org/10.1530/eje-19-0259.

Wu, C.Y., Iskander, C., Wang, C., Xiong, L.Y., Shah, B.R., Edwards, J.D., Kapral, M.K., Herrmann, N., Lanctôt, K.L., Masellis, M., Swartz, R.H., Cogo-Moreira, H., Macintosh, B.J., Rabin, J.S., Black, S.E., Saskin, R., Swardfager, W., 2023a. Association of sodium-glucose cotransporter 2 inhibitors with time to dementia: a population-based cohort study. Diabetes Care 46, 297–304. https://doi.org/10.2337/dc22-1705.

Wu, C.Y., Iskander, C., Wang, C., Xiong, L.Y., Shah, B.R., Edwards, J.D., Kapral, M.K., Herrmann, N., Lanctôt, K.L., Masellis, M., Swartz, R.H., Cogo-Moreira, H., Macintosh, B.J., Rabin, J.S., Black, S.E., Saskin, R., Swardfager, W., 2023b. Association of sulfonylureas with the risk of dementia: a population-based cohort study. J. Am. Geriatr. Soc. https://doi.org/10.1111/jgs.18397.

Yagiz, G., Akaras, E., Kubis, H.-P., Owen, J.A., 2022. The effects of resistance training on architecture and volume of the upper extremity muscles: a systematic review of randomised controlled trials and meta-analyses. Appl. Sci. [Online], 12.

Youssef, M.E., Yahya, G., Popoviciu, M.S., Cavalu, S., Abd-Eldayem, M.A., Saber, S., 2023. Unlocking the full potential of SGLT2 inhibitors: expanding applications beyond glycemic control. Int. J. Mol. Sci. 24 https://doi.org/10.3390/ijms24076039.

Zhao, Y., Wang, S., 2022. Effect of dapagliflozin combined with cognitive behavior training on quality of life and cognitive function in elderly patients with type 2 diabetes mellitus complicated with mild cognitive impairment. Iran. J. Public Health. https://doi.org/10.18502/ijph.v51i6.9668.

Zhou, J.B., Tang, X., Han, M., Yang, J., Simó, R., 2020. Impact of antidiabetic agents on dementia risk: a Bayesian network meta-analysis. Metabolism 109, 154265. https://doi.org/10.1016/j.metabol.2020.154265.

Zou, R., Shi, W., Qiu, J., Zhou, N., Du, N., Zhou, H., Chen, X., Ma, L., 2022. Empagliflozin attenuates cardiac microvascular ischemia/reperfusion injury through improving mitochondrial homeostasis. Cardiovasc. Diabetol. 21, 106. https://doi.org/10.1186/s12933-022-01532-6.

Zügner, E., Yang, H.C., Kotzbeck, P., Boulgaropoulos, B., Sourij, H., Hagvall, S., Elmore, C.S., Esterline, R., Moosmang, S., Oscarsson, J., Pieber, T.R., Peng, X.R., Magnes, C., 2022. Differential in vitro effects of SGLT2 inhibitors on mitochondrial oxidative phosphorylation, glucose uptake and cell metabolism. Int. J. Mol. Sci. 23 https://doi.org/10.3390/ijms23147966.