Use of sodium-glucose co-transporter-2 inhibitors to decrease the risk of dementia among patients with type 2 diabetes: A population-based cohort study

Zarin Abdullah

Department of Epidemiology, Biostatistics and Occupational Health

McGill University, Montreal

June 2024

A thesis submitted to McGill University in partial fulfilment of the requirements of the degree of

Master of Science in Epidemiology

Contents

Abstract

Background: Type 2 diabetes is a worldwide public health concern and is associated with various complications. There is emerging evidence that type 2 diabetes is also associated with an increased risk of cognitive decline, leading to dementia. The pathophysiology of cognitive impairment attributable to type 2 diabetes is still not completely understood. Sodium-glucose co-transporter-2 inhibitors (SGLT-2is) are a new class of antidiabetic drugs, recommended as second or third line of treatment for type 2 diabetes. Evidence on the association between SGLT-2is and the risk of dementia in patients with type 2 diabetes are sparse and needs further investigation.

Objective: This was a population-based retrospective cohort study aimed to evaluate the association between SGLT-2i use and the risk of incident dementia compared to dipeptidyl peptidase-4 inhibitors (DPP-4is) use among patients with type 2 diabetes.

Methods: We conducted the study using the Clinical Practice Research Datalink (CPRD) Aurum database, from the United Kingdom. Patients with type 2 diabetes, aged 40 years or older, were eligible to enter the cohort if they were newly prescribed with SGLT-2i or DPP-4i on or after 2013 to 2021. The primary outcome was incident dementia, and the secondary outcome was incident mild cognitive impairment (MCI). Cox proportional hazard models were used to estimate the hazard ratio and corresponding 95% confidence interval for the primary and secondary outcomes. Propensity score fine stratification weights were used to adjust for confounding. We conducted secondary analyses based on subtypes of dementia, age, sex, prior history of cardiovascular diseases and renal insufficiency, SGLT-2i molecule-specific outcomes and use of sulfonylurea as an alternative comparator. Sensitivity analyses were conducted to test the robustness of our findings.

Results: Among a cohort of 118,006 individuals, the incident rate of dementia was 0.56/1000 person-years over a median follow-up period of 1.54 years among SGLT-2i users whereas 2.67/1000 person-years in DPP-4i users, over a median follow-up period of 1.79 years. The adjusted hazard ratio for SGLT-2i use compared to DPP-4i use for dementia was 0.78 (95% CI: 0.55-1.12), while for MCI was 0.86 (95% CI: 0.80-0.92). The age-specific stratified analysis demonstrated the adjusted hazard ratio for SGLT-2i use compared to DPP-4i use for dementia

among elderly, aged 65 years or older, was 0.50 (95% CI: 0.31-0.80). We did not find any difference between the risk of dementia among SGLT-2i users and DPP-4i users based on their subtypes of dementia, sex, prior history of cardiovascular disease or renal insufficiency or their prescription of varying molecules of SGLT-2i (i.e. canagliflozin, dapagliflozin or empagliflozin). In sensitivity analyses, the primary findings were robust demonstrating the lack of reduction in dementia risk among SGLT-2i users aged 40 years or more.

Discussion: In our population-based retrospective cohort study of patients with type 2 diabetes, aged more than 40 years, we observed fewer events of incident dementia among SGLT-2i users compared to DPP-4i users. However, after adjusting for covariates, the observed association between SGLT-2i use and reduced risk of dementia no longer remained statistically significant. Despite that, the point estimate was substantial, with a hazard ratio of 0.78 indicating a trend towards a lower risk of dementia among SGLT-2i users. In secondary analysis, SGLT-2i use was associated with reduced risk of dementia among individuals aged 65 years or older. We rigorously adjusted for 34 potential confounders, including factors such as frailty, smoking status, BMI and HbA1c to balance the two groups which made our findings robust compared to previous studies. Despite adjustment for confounding, there remains a possibility of residual confounding. Also, shorter follow-up period and relatively younger cohort might have led to fewer events which limits us to infer a conclusive association between SGLT-2i use and incident dementia.

Conclusion: Our primary findings did not yield conclusive evidence to infer any association between SGLT-2i use and the risk of incident dementia; however, the secondary findings revealed that the use of SGLT-2is was significantly associated with a reduced risk of dementia among patients with type 2 diabetes, aged 65 years or older. Also, SGLT-2i use was associated with significant risk reduction for MCI in our secondary analysis. Due to the observational nature of our study, it is important to interpret the result with caution. Future prospective studies are warranted to confirm our findings.

Résumé

Contexte : Le diabète de type 2 est un problème de santé publique mondial et est associé à diverses complications. De nouvelles preuves suggèrent que le diabète de type 2 est également associé à un risque accru de déclin cognitif, conduisant à la démence. La physiopathologie des troubles cognitifs attribuables au diabète de type 2 n'est pas encore complètement comprise. Les inhibiteurs du co-transporteur 2 sodium-glucose (SGLT-2is) constituent une nouvelle classe de médicaments antidiabétiques, recommandés comme traitement de deuxième ou troisième intention du diabète de type 2. Les preuves de l'association entre le SGLT-2is et le risque de démence chez les patients atteints de diabète de type 2 sont rares et nécessitent des recherches plus approfondies.

Objectif : Il s'agissait d'une étude de cohorte rétrospective basée sur la population visant à évaluer l'association entre l'utilisation du SGLT-2i et le risque de démence incidente par rapport à l'utilisation des inhibiteurs de la dipeptidyl peptidase-4 (DPP-4is) chez les patients atteints de diabète de type 2.

Méthodes : Nous avons mené l'étude en utilisant la base de données du Aurum Clinical Practice Research Datalink (CPRD), du Royaume-Uni. Les personnes atteintes de diabète de type 2, âgées de 40 ans ou plus, étaient éligibles pour entrer dans la cohorte si elles avaient reçu une nouvelle prescription de SGLT-2i ou de DPP-4i en 2013 ou après. Le résultat de jugement principal était une démence incidente et les résultats secondaire était un incident léger Déficience cognitive (MCI). Des modèles de risque proportionnel de Cox ont été utilisés pour estimer le rapport de risque et l'intervalle de confiance correspondant à 95 % pour les résultats de jugement primaires et secondaires. Des poids de stratification fine du score de propension ont été utilisés pour ajuster la confusion. Nous avons effectué des analyses secondaires basées sur les sous-types de démence, l'âge, le sexe, les antécédents de maladies cardiovasculaires et d'insuffisance rénale, les résultats spécifiques à la molécule SGLT-2i et l'utilisation de la sulfonylurée comme comparateur alternatif. Des analyses de sensibilité ont été menées pour tester la robustesse de nos résultats.

Résultats : Parmi une cohorte de 118 006 individus, le taux d'incidence de démence était de 0,56/1 000 années-personnes sur une période de suivi médiane de 1,54 ans chez les utilisateurs du SGLT-2is, contre 2,67/1 000 années-personnes chez les utilisateurs du DPP-4is. sur une période de suivi médiane de 1,79 ans. Le rapport de risque ajusté pour l'utilisation du SGLT-2i par rapport à l'utilisation du DPP-4i pour la démence était de 0,78 (IC à 95 % : 0,55-1,12), tandis que pour le MCI était de 0,86 (IC à 95 % : 0,80-0,92). L'analyse stratifiée par âge a démontré que le rapport de risque ajusté pour l'utilisation du SGLT-2i par rapport à l'utilisation du DPP-4i pour la démence chez les personnes âgées de 65 ans ou plus était de 0,50 (IC à 95 % : 0,31-0,80). Nous n'avons trouvé aucune différence entre le risque de la démence chez les utilisateurs de SGLT-2is et les utilisateurs de DPP-4is en fonction de leur sous-type de démence, de leur sexe, de leurs antécédents de maladie cardiovasculaire ou d'insuffisance rénale ou de la prescription de différentes molécules de SGLT-2i (c.-à-d. canagliflozine, dapagliflozine ou empagliflozine). Dans l'analyse de sensibilité, les principaux résultats étaient solides, démontrant l'absence de la réduction du risque de démence chez les utilisateurs du SGLT-2i âgés de 40 ans ou plus.

Discussion : Discussion: In our population-based retrospective cohort study of patients with type 2 diabetes, aged more than 40 years, we observed fewer events of incident dementia among SGLT-2i users compared to DPP-4is users. However, after adjusting for covariates, the observed association between SGLT-2i use and reduced risk of dementia no longer remained statistically significant. Despite that, the point estimate was substantial, with a hazard ratio of 0.78 indicating a trend towards a lower risk of dementia among SGLT-2i users. In secondary analysis, SGLT-2is use was associated with reduced risk of dementia among individuals aged 65 years or older. We rigorously adjusted for 34 potential confounders, including factors such as frailty, smoking status, BMI and HbA1c to balance the two groups which made our findings robust compared to previous studies. Despite adjustment for confounding, there remains a possibility of residual confounding. Also, shorter follow-up period and relatively younger cohort might have led to fewer events which limits us to infer conclusive association between SGLT-2is use and incident dementia.

Conclusion: Nos principaux résultats n'ont pas fourni de preuves concluantes permettant de déduire une association entre l'utilisation du SGLT-2i et le risque de démence incidente ; cependant, les résultats secondaires ont révélé que l'utilisation du SGLT-2is était associée de

manière significative à un risque réduit de démence chez les patients atteints de diabète de type 2, âgés de 65 ans ou plus. En outre, l'utilisation du SGLT-2is était associée à une réduction significative du risque de MCI dans notre analyse secondaire. En raison de la nature observationnelle de notre étude, il est important d'interpréter les résultats avec prudence. De futures études prospectives sont nécessaires pour confirmer nos résultats.

Acknowledgements

I wish to extend my sincere appreciation to Dr. Robert William Platt, my supervisor, for the opportunity to contribute to this project and for his consistent guidance throughout. His expertise has been invaluable, and I am grateful for the numerous learning opportunities provided.

I would also like to express my deep gratitude to Dr. Hoi Yun Oriana Yu, my co-supervisor, for her expert advice on epidemiological methodology and invaluable contributions at every stage of the project. Her availability to address my queries has been immensely appreciated.

I am thankful to Dr. Christel Renoux, a member of my supervisory committee, for her constructive feedback and support during this endeavor.

Special thanks go to Ying Cui for her indispensable assistance with data analysis.

Lastly, I am profoundly grateful for the unwavering support of my family and friends. My parents' dedication to hard work serves as an inspiration, and I am thankful to my husband for accompanying me on this journey.

Contribution of Authors

Dr. Zarin Abdullah: Statistical analyses, interpretation of the data, writing, review, and revision of the manuscript and administrative, technical, or material support

Ying Cui: Statistical analyses and interpretation of the data

Dr. Christel Renoux: Methodology, revision of the manuscript

Dr. Robert William Platt: Development of methodology, revision of the manuscript and study supervisor

Dr. Oriana Hoi Yun Yu: Study conception and design, statistical analyses, and review of the manuscript and administrative, technical, or material support and study supervisor

Dr. Zarin Abdullah performed the literature review and wrote all parts of this manuscript-based thesis. Dr. Robert William Platt and Dr. Christel Renoux reviewed and provided feedback on all thesis chapters. Ying Cui analysed the data and Dr. Zarin Abdullah provided support in the data analysis. Dr. Oriana Hoi Yun Yu critically revised all the drafts of the thesis as study supervisor.

List of Tables

List of Figures

List of Abbreviations and Acronyms

aHR	Adjusted hazard ratio
CANVAS	Canagliflozin cardiovascular assessment study
CANVAS-R	Canvas–renal
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CIHI	Canadian Institute for Health Information
CPRD	Clinical practice research datalink
DECLARE–TIMI 58	Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58
DPP-4 inhibitors	Dipeptidyl peptidase-4 inhibitors
DPP-4is	Dipeptidyl peptidase-4 inhibitors
EMA	European medicines agency
EMPA-REG OUTCOME trial	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
FDA	U.S. Food and Drug Administration
HbA1c	Hemoglobin a1c
HES	Hospital episode statistics
HR	Hazard ratio
IMD	Indices of multiple deprivation
IPCW	Inverse probability of censoring weighting
IR	Incident rate
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
NMDA	N-methyl-D-aspartate
PS fine stratification	Propensity score fine stratification
SGLT-2 inhibitors	Sodium-glucose co-transporter-2 inhibitors
SGLT-2is	Sodium-glucose co-transporter-2 inhibitors
SMDs	Standardized mean differences
SNOMED CT	Systemized Nomenclature of Medicine Clinical Terms
U.S.	United states
UK	United Kingdom

Chapter 1: Introduction

1.1 Background

Global burden of type 2 diabetes and dementia

Diabetes is a major public health concern that impacts approximately one in every ten individuals globally. In 2021, there were approximately 537 million adults, aged 20 to 79 years, living with diabetes (1). Most of these individuals were suffering from type 2 diabetes, which affects over 462 million people worldwide. This equates to 6.28% of the global population, with older individuals being more susceptible to the disease (1-3). Over the last three decades, the global prevalence of type 2 diabetes is increasing. The trend showed that from 1990 to 2017, the age-standardized incidence rate of type 2 diabetes rose from 228.5 to 279.1 per 100,000 people and prevalence has increased significantly from 4,577 to 5,722 per 100,000 people (4). The global prevalence of type 2 diabetes is projected to increase to 7,079 individuals per 100,000 by 2030, reflecting a continued rise across all regions of the world which poses a significant threat to public health (5). Patients with type 2 diabetes are at an increased risk of developing microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (myocardial infarction, stroke, and peripheral arterial disease) complications (6). In addition, type 2 diabetes is a risk factor for cognitive decline, resulting in dementia such as Alzheimer's disease and vascular dementia, which are also increasing due to the ageing population.

Globally, dementia is the seventh most common cause of mortality and is associated with significant disability and dependency among the elderly population (7). Every year, nearly 10 million new cases of dementia emerge (7). In 2019, more than 50 million people were living with dementia (7). It is projected that the number of cases will go up to 152.8 million by 2050 (8). The social and economic burden of dementia is also a grave matter of concern. In March 2023, the World Health Organization reported, globally, 1.3 trillion United States (U.S.) dollars were spent to manage patients with dementia and approximately 50% of that cost was contributed by informal caregivers (e.g., family members and close friends) equating about five hours of care and supervision per day, on average (7). The economic burden of dementia has been reported to have increased by 4.5% from 2000 to 2019 and will continue to rise to 17% of all expected health spending by 2050 (9).

Type 2 diabetes and dementia, both impose a substantial global burden; and the trends showed the burden will eventually increase to a greater extent. This calls for addressing this issue from different aspects of research, service delivery and caregiving. Furthermore, the pathophysiology of dementia exhibits a strong correlation with diabetes, adding complexity to the task to alleviate the situation.

Pathophysiology and risk estimation of cognitive impairment among patients with type 2 diabetes

Cognitive impairment, such as dementia is a general term that refers to a decline in cognitive ability severe enough to interfere with activities of daily living. Types of dementia include Alzheimer's disease, vascular dementia, frontotemporal dementia, Lewy body dementia and mixed dementia. Alzheimer's disease is the most common type of dementia, accounting for at least two-thirds of cases of dementia in people aged 65 years and older (10).

The pathophysiology of cognitive impairment attributable to type 2 diabetes is still not completely understood. Type 2 diabetes has been associated with increased the risk for cognitive decline such as Alzheimer's disease and vascular dementia in several studies (11, 12). Studies show multifaceted risk factors responsible for cognitive impairment among patients with type 2 diabetes. Some of these potential factors were obesity, age, mid-, and late-life diabetes, duration of diabetes, concurrent vascular or associated co-morbidities, and hyper- and hypoglycemia (13-16).

Glycaemic control plays an important role in the risk of developing cognitive impairment. Hyperglycemia can cause vascular injury and affect blood flow (17). A recent cohort study conducted on more than 200,000 patients with type 2 diabetes, aged 50 years or older, revealed that patients with a higher (≥9%) glycated hemoglobin A1c (HbA1c) concentration had significantly increased risk of dementia compared to normal range (<5.7%) of HbA1c (18). Another systematic review, that included 86 studies, showed that increasing glycemia, elevated HbA1c concentration, and glucose variability, were negatively associated with cognitive function in patients with type 2 diabetes without dementia (19).

Diabetes duration has also been a risk factor leading to cognitive impairment. A prospective analysis of 5,099 participants from the Atherosclerosis Risk in Communities (ARIC) study reported, for participants who had longer diabetes duration (>5 years), the incidence rate of cognitive impairment increased by 59% [hazard ratio (HR) 1.59, 95% confidence interval (CI): 1.23, 2.07] compared to those who had a shorter duration (≤5 years) of type 2 diabetes (20).

Co-existing conditions such as metabolic syndrome and vascular disease also contribute to the progression of cognitive impairment. A systematic review was conducted to quantify the relative risk of progression from mild cognitive impairment (MCI) to dementia in people with and without type 2 diabetes, and with and without the metabolic syndrome. The authors reported with the presence of MCI, both type 2 diabetes and metabolic syndrome were associated with an increased risk of developing dementia. Patients with type 2 diabetes and MCI had 1.53 times [pooled odds ratio: 1.53 (95% CI: 1.20–1.97)] higher likelihood of progressing to dementia compared to those without diabetes. Patients with metabolic syndrome and MCI also had a high likelihood [pooled odds ratio: 2.95 (95% CI: 1.23–7.05)] of developing dementia compared to those without metabolic syndrome. A longer duration of diabetes and the presence of retinopathy were potential modifiers with an increased risk of progression from MCI to dementia among patients with type 2 diabetes. Having multiple cardiovascular risk factors was also a significant modifier for the progression from MCI to dementia in people with metabolic syndrome (21).

Type 2 diabetes and cognitive impairment are closely linked health issues which are highly prevalent among the elderly population. When these conditions happen together, they result in considerable morbidity and mortality, emphasizing the importance of studying the pathways to effectively manage both conditions using pharmacological treatments.

Exploring available pharmacotherapy for dementia

At present, there is a lack of comprehensive information on the use of medication for preventing the progression of or treating dementia. Commonly, acetylcholinesterase inhibitors and memantine are used along with other therapeutic tools to alleviate the detrimental cognitive and behavioural consequences of dementia.

Acetylcholine is an important factor in memory and attention. The basal forebrain, which is the primary source of cortical cholinergic input, is affected by pathological changes in Alzheimer's disease (22). Cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine are approved by the U.S. Food and Drug Administration (FDA) and commonly used to increase acetylcholine levels, treating mild to moderate Alzheimer's disease (23). However, cholinesterase inhibitors are not effective in frontotemporal dementia and may cause agitation (24). Also, the common side effects of acetylcholine inhibitors include nausea, vomiting, and diarrhoea which may lead to discontinuation of this therapy. Moreover, these medications may cause severe but rare side effects such as syncope, bradycardia, and falls (25).

The N-methyl-D-aspartate (NMDA)-receptor antagonist, memantine, is also an FDA approved drug for moderate to severe dementia (23). Memantine acts to prevent the pathologic overactivation of the NMDA receptor. It has not been shown to be of benefit in mild Alzheimer's disease (26). General practice is to combine memantine and a cholinesterase inhibitors in moderate to severe Alzheimer's disease, although there is no good evidence to demonstrate an added benefit (27). These agents (i.e. donepezil, rivastigmine, galantamine and memantine) are also approved by the Canadian Institute for Health Information (CIHI) to improve cognition in patients with dementia. However, these drugs do not cure or slow the progression of the disease. Rather, they improve cognition (including memory, orientation, and language) and function (including performance of daily activities) among individuals who are already suffering from cognitive impairment (28).

The preventive potential of oral anti-diabetic agents

Antidiabetic agents are becoming progressively important in minimizing symptoms of diabetes and potentially preventing complications of diabetes such as cardiovascular diseases, inflammation, cognitive impairment, or renal diseases. These complications are often associated with each other and addressing one may alleviate others. Studies have suggested that oral anti-diabetic agents may enhance cognitive performance in patients with type 2 diabetes by addressing both vascular and neurodegenerative complications, or through direct drug properties such as anti-inflammatory effects. It is proven in clinical trials that improved glycaemic control can result in enhancements in both self-reported and objective measures of cognitive functioning

(29-31). However, evidence on preventive potential of any specific anti-diabetic agents for preventing cognitive impairment is still limited.

Common oral anti-diabetic agents, such as metformin, an insulin sensitizer and the first line therapy for type 2 diabetes, have shown a positive effect on cognitive function in a prospective observational study (the Sydney Memory and Ageing Study)(32). The study was conducted on 1,037 community-dwelling older patients with diabetes, aged 70-90 years, without dementia at baseline. The objective of this study was to determine the association between use of metformin with incident dementia and cognitive decline over the follow-up period of 6 years. The authors reported metformin use was associated with an 81% lower risk of incident dementia (HR: 0.19 [95% CI 0.04–0.85]; P=0.030) compared to patients not receiving metformin. However, the authors reported, people with declining cognition, might have been prescribed to stop metformin to simplify their therapeutic regimen, which may have led to a spurious increase in the number of incident dementia among patients not receiving metformin, suggesting a possible limitation of this findings (32). Another study investigated how treating diabetes impacts the development of cognitive abilities in certain domains over a follow-up period of 4 years (33). A total of 211 participants with diabetes, between the ages of 65-69 years were included in the study. Participants who used metformin alone had a better cognitive function at baseline for the domains of verbal learning, working memory, and executive function compared to participants on other forms of antidiabetic treatment (such as diet, or metformin with other oral antidiabetic agents or insulin, or other oral antidiabetic agents only, or insulin alone, or in combination). The limitations of this study include not being able to adjust for variables like glycaemic control, plasma insulin level, type of diabetes, duration of diabetes, and level of renal function. Since, metformin is a first line therapy for uncomplicated diabetes, there was a possibility that the participants who were prescribed metformin did not have diabetes for long enough duration to develop any cognitive imparement (33).

These studies indicate, though, that there could be a potential role of first line therapy for diabetes in reducing the risk of developing cognitive impairment; other anti-diabetic agents, prescribed as 2nd or 3rd line of therapy, may play a stronger role in preventing cognitive

impairment among individuals who are suffering from type 2 diabetes for longer duration and have other related complications.

The preventive potential of 2nd or 3rd line oral anti-diabetic agents

Dipeptidyl peptidase-IV inhibitors

Dipeptidyl peptidase-4 inhibitors (DPP-4is), known as gliptins, are a class of 2nd or 3rd line oral anti-diabetic agents. DPP-4i molecules, sitagliptin, saxagliptin, linagliptin, and alogliptin have been approved by the FDA. Vildagliptin has not been approved by the FDA but has approval from the European Medicines Agency (EMA) (34).

The evidence on cognitive benefits of DPP-4is is rather few. In a pre-clinical study, Pipatpiboon and colleagues (2013) reported, vildagliptin, a DPP-4 receptor inhibitor, improved the neuronal insulin receptor function and brain mitochondrial function; and prevented brain mitochondrial dysfunction in rats with insulin resistance (35). Since, preclinical studies of DPP-4is for dementia have yielded promising results, observational studies were also conducted to investigate the association of DPP-4is use and risk of dementia when compared to other common antidiabetic medication. In 2019, Kim et al., conducted a 1:1 propensity-score matched population-based cohort study with health insurance services data to compare the risk of dementia in elderly patients with type 2 diabetes on DPP-4is and sulfonylureas. The authors reported that DPP-4i use was associated with a lower risk of dementia (HR: 0.66; 95% CI: 0.56–0.78; $p < 0.001$) in elderly patients with type 2 diabetes when compared to the use of sulfonylurea (36). However, this study was limited by not accounting for diabetes duration which is a potential risk factor of cognitive impairment among patients with type 2 diabetes. Also, it was unclear if the study findings reflected an increased risk of dementia with sulfonylurea use due to its potential link with hypoglycaemia (37), rather than a protective effect of DPP-4is use.

To assess the effect of an individual DPP-4i molecule, sitagliptin, on cognitive function, Isik et al. (2017) conducted a prospective study on elderly patients with diabetes, with or without cognitive impairment. A total of 253 elderly patients with type 2 diabetes were enrolled and those who could not tolerate metformin or had medical contraindication were prescribed with sitagliptin. Sitagliptin was also prescribed for patients with poor glycaemic control along with insulin and/or metformin. Those who took sitagliptin (100 mg/day) with insulin and/or metformin

defined as the case group, while those who did not take sitagliptin defined as the control group. Comprehensive geriatric assessment (CGA) which includes Mini-Mental State Examination (MMSE), was conducted at the baseline and after 6 months. They found that after six months, sitagliptin therapy was associated with an increase in the MMSE scores ($p = 0.034$) (38). However, in the CARMELINA trial, the effect of another DPP-4i molecule, linagliptin treatment was not associated with improved cognitive function. The trial involved 1,545 participants with cardiorenal disease and randomized participants to receiving linagliptin 5 mg or placebo once daily (1:1), in addition to standard of care for type 2 diabetes management. The authors assessed accelerated cognitive decline using the MMSE over a median follow-up period of 2.5 years. The findings showed that there was no difference in accelerated cognitive decline among participants treated with linagliptin versus placebo (28.4% (linagliptin) vs. 29.3% (placebo) (odds ratio 0.96 [95% CI 0.77, 1.19]) (39). Similar findings were obtained in the CAROLINA COGNITION trial, where participants were randomized to linagliptin and glimepiride (i.e. a sulfonylurea drug). The authors reported over a median of 6.1 years of follow up, accelerated cognitive decline did not differ between participants treated with linagliptin versus glimepiride (OR: 1.01; 95% C: 0.86- 1.18) (40). In summary, though some preclinical and observational studies suggested a beneficial effect of DPP-4is on cognitive ability of patients with type 2 diabetes, the findings from those studies were not validated in randomized controlled trials.

Sodium-glucose co-transporter-2 inhibitors

Sodium-glucose co-transporter-2 inhibitors (SGLT-2is), also called gliflozins, (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) are newer antidiabetic agents and recommended as a 2nd or 3rd line of treatment after metformin and are usually prescribed at the same level in the treatment paradigm as DPP-4is in the management of type 2 diabetes. At present, there are four SGLT-2is that are approved by the EMA in 2013 and the FDA 2014 and available for type 2 diabetes management: canagliflozin, dapagliflozin, empagliflozin and ertugliflozin (41, 42).

Their main mechanism of action is inhibiting SGLT-2 receptors in the proximal tubules of the kidneys, thus lowering blood glucose levels by blocking its reabsorption from the urine (43). There are two particular features of SGLT-2is which stands out: (i) Their mechanism of action is not tied to insulin secretion, which decreases the likelihood of hypoglycaemia compared to other

anti-diabetic agents; and (ii) They exhibit protective effects for cardiovascular and renal outcomes that are independent of glycemic control and these effects were observed early after treatment initiation, indicating their mechanisms of action beyond blood glucose lowering (41, 44).

The CANVAS Program, comprising two sister trials [Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS–Renal (CANVAS-R)], was conducted on 10,142 patients with type 2 diabetes with an elevated risk of cardiovascular disease. The findings showed that the risk for adverse cardiovascular outcome was 14% lower (HR: 0.86; 95% CI: 0.75 to 0.97) among patients who received canagliflozin, an SGLT-2i, compared to those who received placebo. In this trial, canagliflozin was also found to be associated with reduced progression of adverse renal outcomes such as albuminuria by 27% (HR: 0.73; 95% CI, 0.67 to 0.79) (45). The "Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients" (EMPA-REG OUTCOME trial) was conducted on the efficacy of empagliflozin, a SGLT-2i. A sub study from that trial showed there was significant decrease in the rates of death from cardiovascular causes among empagliflozin group compared to placebo (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction) (46).

The "Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58" (DECLARE–TIMI 58) trial investigated the effects of dapagliflozin, another SGLT-2i on cardiovascular outcomes in a large number of patients. The DECLARE–TIMI 58 trial had 17,160 participants with type 2 diabetes and with an increased risk for atherosclerotic cardiovascular disease, randomized to either receiving dapagliflozin or placebo. Upon followed up for a median of 4.2 years, patients receiving dapagliflozin did not have a higher or lower rate of major adverse cardiovascular events than placebo (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR: 0.93; 95% CI, 0.84 to 1.03; P=0.17) but they had a lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs. 5.8%; HR: 0.83; 95% CI, 0.73 to 0.95; P=0.005) (47). Given that there is evidence that SGLT-2is provide cardiovascular benefits and there is an established correlation between cardiovascular disease and cognitive decline (48), further research is needed to investigate the potential neuroprotective effect of SGLT-2is in patients with type 2 diabetes.

There is growing evidence that SGLT-2is have a neuroprotective potential, improving both cerebral microvascular and cognitive impairment (49). Hierro-Bujalance et al., 2020, discussed about the correlation between Alzheimer's disease and type 2 diabetes; and rationalized the pre-clinical study of the potential of antidiabetic drugs to limit or slow down brain pathology in Alzheimer's disease due to the common pathological features of these two diseases such as inflammation, insulin signaling alterations, and vascular damage (50). They investigated the role of empagliflozin on alleviating the complication of these diseases in diabetic mice. They found that the use of empagliflozin aided to maintain insulin levels in diabetic mice, limited cortical thinning and reduced neuronal loss in treated mice (50). Pawlos et al., (2021) reviewed preclinical studies and summarized neuroprotective effects of SGLT-2is. Their summary indicated that SGLT-2is can cross the blood-brain barrier due to their lipid solubility and achieve a brain to serum ratio ranging from 0.3 to 0.5 (51). Therefore, these agents might have positive effects on the brain, potentially reducing the risk of dementia in people with type 2 diabetes by addressing metabolic dysfunction (52). As SGLT-2is are not entirely specific to SGLT-2 receptors, they can also interact with the SGLT1 receptor, which is associated with shielding against brain damage caused by ischemia/reperfusion (53). SGLT-2is exhibit anti-inflammatory and anti-atherosclerotic effects, alleviate oxidative stress, enhance endothelial function, prevent remodelling, and provide protection to various components of the neurovascular unit, such as the blood-brain barrier, pericytes, astrocytes, microglia, and oligodendrocytes (54). SGLT-2is may also offer potential benefits for patients with Alzheimer's Disease through several mechanisms described earlier, such as anti-inflammatory, anti-oxidative, and athero-protective effects. Moreover, they may provide direct neuroprotective effects by increasing brain-derived neurotrophic factor levels and inhibiting acetylcholinesterase. Additionally, SGLT2is could be beneficial for Alzheimer's patients by enhancing brain insulin sensitivity (49, 55).

With the recent discoveries on effectiveness and advantages of SGLT-2is in pre-clinical studies, these medications are promptly becoming recognized for their usefulness in treating diabetes and preventing cognitive decline. Particularly for patients who have type 2 diabetes but are unwilling or unprepared to begin insulin treatment, SGLT-2is could be an alternative for those who need more glucose reduction and who have cardiovascular and renal co-morbidities. The

evidence generated on the positive impacts on cognitive outcomes warrants for further research to determine the long-term effects of SGLT-2is.

1.2 Rationale

With the increasing prevalence of type 2 diabetes in the aging population, it is important to identify treatments that can prevent cognitive decline. Previous studies have shown that good glycemic control and low rate of diabetic complications are associated with a low risk of dementia. Since type 2 diabetes and dementia share common risk factors and underlying pathology, studying the effects of antidiabetic drugs on cognitive function could be a promising approach to finding effective treatments.

SGLT-2is are versatile antidiabetic agents and the use of SGLT-2is results in good glycemic control with cardiovascular and metabolic benefits (56). Though cognitive impairment is a known complication for patients with type 2 diabetes, the association between SGLT-2i use and cognitive function remained uncertain. Therefore, we conducted a retrospective cohort study to explore the relationship between SGLT2is and incident dementia. The aim of this study was to investigate the association between SGLT-2is use and risk of developing dementia in patients with type 2 diabetes. We planned to compare with DPP-4is since both drugs are typically prescribed at the same stage of treatment for type 2 diabetes (57, 58). Furthermore, DPP-4is have similar effects when compared to SGLT-2is on weight loss, hypoglycemia risk, and cost (59). Past trials like the CARMELINA and CAROLINA-COGNITION trials have indicated that DPP-4is have no impact on cognitive decline (40, 60). Therefore, DPP-4i users were the most clinically relevant comparator to SGLT-2i users. DPP-4is have also been used as a comparator for SGLT-2is in previous studies (61, 62) . The evidence generated from this study will enhance the understanding of role of SGLT-2is in improving cognitive function among patients with type 2 diabetes in clinical settings.

1.3 Objectives

Primary objective: To determine if SGLT-2i use is associated with a decreased risk of incident dementia compared to DPP-4i use among patients with type 2 diabetes.

Secondary objectives:

a) To determine if SGLT-2i use is associated with a decreased risk of MCI compared to DPP-4i use.

b) To determine the association between SGLT-2i use and dementia stratified into vascular and Alzheimer's disease dementia compared to DPP-4i use among patients with type 2 diabetes.

c) To determine if the association between SGLT-2i use and risk of incident dementia compared to DPP-4i use among patients with type 2 diabetes differs by age initiation at <65 and ≥65 years, and sex.

c) To determine if the association between SGLT-2i use and the risk of incident dementia compared to DPP-4i use among patients with type 2 diabetes differs by prior history of cardiovascular disease (i.e., myocardial infarction and stroke) and prior history of renal insufficiency.

e) To determine if SGLT-2i use is associated with a decreased risk of incident dementia compared to sulfonylurea use among patients with type 2 diabetes.

f) To determine the association between individual SGLT-2i molecule use and the risk of incident dementia among patients with type 2 diabetes.

Chapter 2: Literature Review

Evidence generated from pre-clinical and observational studies suggest there could be an association between the use of SGLT-2is and risk of incident dementia among patients with type 2 diabetes when compared to other anti-diabetic agents; though there were limitations of these findings (63-65). In our literature review, we summarized, the existing evidence on the effect of SGLT-2is on the risk of incident dementia and listed the limitations which we planned to address in our study.

A recent population-based retrospective cohort study was conducted among 106,903 Ontario residents, aged ≥66 years, initiating SGLT-2is or DPP-4is (63). The authors found that SGLT-2i use was associated with a 20% lower risk of dementia (adjusted hazard ratio, aHR: 0.80 [95% CI: 0.71-0.89]) compared to the DPP-4is use. The authors also reported that, not all molecules of SGLT-2is were associated with lower risk of dementia, neither the risk estimation was the same for all. When they conducted stratified analysis by different SGLT-2is, dapagliflozin was associated with the lowest risk of incident dementia (aHR 0.67 [95% CI 0.53–0.84]), followed by empagliflozin (aHR 0.78 [95% CI 0.69–0.89]). Canagliflozin was not found to be associated with incident dementia (aHR 0.96 [95% CI 0.80–1.16]). This study only considered older patients, ≥66 years (63). Previous research has indicated that individuals who experienced diabetes at an early age, also tend to develop dementia at a younger age (64). Also, the authors acknowledged, the study was limited by considering only one year of lag period. Dementia is a chronic process, and the advancement of cognitive decline and subsequent diagnosis may take longer than one year. Therefore, considering only a one-year lag may have led to including cases of dementia, that may not be attributed to the use of SGLT-2is or DPP-4is. Also, they did not exclude patients with a history of MCI which may have led to higher numbers of dementia identified (i.e., people with possibly early onset of dementia were included in the study).

Siao and colleagues in 2022, conducted a similar population-based retrospective cohort study comparing SGLT-2is users with other anti-diabetic agents (65). Data from insurance claims of 976,972 patients diagnosed with type 2 diabetes from Taiwan were used. The authors found the use of SGLT-2is was associated with a decreased risk of developing dementia (HR: 0.88, 95% CI: 0.81–0.97; P value =0 .0015) compared to those who were prescribed any other anti-diabetic

agents in real-world practice. After adjusting for age, sex, duration of type 2 diabetes, comorbidities, and drug index date of the patients, the use of SGLT-2is was observed to be associated with 11% lower risk of incident dementia compared to use of non-SGLT-2i anti-diabetic medications (aHR: 0.89, 95% CI: 0.82-0.96; P value = 0.0021). The researchers performed sensitivity analysis with 1:2 matching of the patients, and the observed effect estimate remained consistent with the main findings (aHR 0.92; 95% CI 0.85–0.99; p = 0.0460) (65). However, the important limitation of this study was comparing the use of SGLT-2is to varying degree of anti-diabetic agents' usage. Since, there are an array of anti-diabetic agents, both oral and injectables, comparing SGLT-2is users with all other anti-diabetic agents' users may not be an appropriate comparison in terms of glucose lowering ability, mode of administration or considering effects on other co-morbidities. Also, the users might not be at the same stage of disease and certainly not at the same baseline risk of dementia.

Mui et al. (2021) conducted a 1:2 propensity score-matched population-based cohort study to investigate the effects of SGLT-2i and DPP-4i use on cognitive impairment among 51,460 patients with type 2 diabetes mellitus in Hong Kong (66). This study also showed that SGLT-2is use was associated with lower risks of dementia compared to DPP-4is use (HR: 0.41, 95% CI: 0.27–0.61, P value < 0.0001); however, lack of adjustment for drug exposure duration and unavailability of information on lifestyle risk factors (e.g. smoking) limits the validity of the result reported (66).

Other than the observational studies, there are evidence from animal studies on the effect of SGLT-2is on dementia. Pang and colleagues, (2023) investigated the impact of ertugliflozin, an SGLT-2i, on Alzheimer's disease using a rat model. In this study, intracerebroventricular injection of streptozotocin was used to induce cognitive deficits in rats, and ertugliflozin were administered for 20 days. The results showed that ertugliflozin treatment improved cognitive function, reduced acetylcholinesterase activity in the hippocampus, decreased markers of neuronal apoptosis, improved mitochondrial function, and protected synaptic plasticity in the streptozotocin-induced rats. Additionally, the study found that ertugliflozin reduced tau hyperphosphorylation in the hippocampus, potentially by regulating insulin signalling pathways. These findings suggest that ertugliflozin may have a positive impact on pathology of dementia development (67).

Systematic reviews and meta-analysis on the association between SGLT-2is and the risk of dementia were few with potential limitations. Tang et al., 2023 conducted a meta-analysis to investigate the association between newer glucose-lowering drugs and the risk of dementia in people with type 2 diabetes (68). To evaluate the association between SGLT-2is and the risk of dementia, the authors considered three observational studies. Their analysis of the three observational studies revealed that SGLT-2i use was significantly associated with a lower risk of all-cause dementia, when compared to non-SGLT2 inhibitor users (RR, 0.62; 95% CI, 0.39–0.97). However, the authors reported a high level of heterogeneity (I-squared=82.5%, p=0.003) between the findings of these studies in this meta-analysis (68).

From the above discussion, we summarized a number of limitations which we planned to address in our study to add to the evidence of the effect of SGLT-2is on the cognitive function of patients with type 2 diabetes. In previous studies, the comparison group encompassed a wide range of anti-diabetic drugs which may not be prescribed at the same level of treatment with SGLT-2is. In our study, we planned to use DPP-4is users as our comparison group because these anti-diabetic agents are prescribed in same level of treatment as SGLT-2is and has similar glucose lowering properties. Another limitation which we observed in previous studies was only to include older age group. We planned to include younger individuals to investigate the association of SGLT-2i use with dementia risk. Since having a history of MCI may lead to confounding whereby people with MCI are less likely prescribed SGLT-2is compared to DPP-4is, we planned to exclude patients with a history of MCI. Moreover, we planned to include a wide range of relevant modifiers such as smoking, HbA1c and measures of frailty that previous studies may not have considered.

Table 2-1: Overview of limitations and proposed study approaches

Limitations in previous studies	Proposed approach
Various anti-diabetic agents were compared with SGLT-2is in terms of their link to cognitive decline, which may not be in the same level of treatment or have similar glucose lowering ability (65)	Planned to compare SGLT-2is with DPP-4is which are generally prescribed on same level of treatment and has similar glucose lowering ability
Older individuals were included in the cohort (63)	Planned to include individuals, ≥40 years, in our study
Some previous studies did not exclude patients with history of MCI (63)	Planned to exclude patients with history of MCI by using the approach documented by Ford et al. 2021 (69)
May not have considered important modifiers and confounders (63, 66)	Planned to account for a broad spectrum of factors including behavioral, pharmaco-therapeutic, and comorbid conditions during the adjustment process
Used only one year of lag period (63)	Repeating the primary analyses using a lag period of 1.5 and 2 years

Chapter 3: Manuscript

Preface to manuscript

In chapter 2, we summarized the existing evidence of the effect of SGLT-2is on the cognitive function of patients with type 2 diabetes. Our review indicated that the use of SGLT-2is is significantly associated with a reduced risk of dementia and an improvement in cognitive function, however, the number of studies conducted was limited and the findings were not homogenous. We observed a number of limitations such as comparison with varying anti-diabetic agents, the inclusion of only older participants, the failure to exclude patients with history of MCI, the adjustment for a limited number of confounders and the consideration of only one-year of lag period. We planned to address these limitations in our study and report in our manuscript. In our manuscript, we set out to evaluate the association between SGLT-2is use and risk of dementia among patients with type 2 diabetes compared to DPP-4is.

This manuscript has been prepared for submission at the *British Medical Journal (BMJ) Open*.

The association between use of sodium-glucose co-transporter-2 inhibitor and the risk of incident dementia: a population-based cohort study

Zarin Abdullah[1,4], Ying Cui[4], Robert Platt[1,3], Christel Renoux[2,4], Laurent Azoulay[1,4], Chenjie Xia[2], Oriana Hoi Yun Yu[3,4, £]

[1]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada.
[2]Department of Neurology and Neurosurgery, McGill University, Montreal, Canada.
[3]Department of Medicine, McGill University, Montreal, Canada.
[4]Lady Davis Institute, Centre for Clinical Epidemiology Jewish General Hospital, Montreal, Canada.

Keywords: Type 2 diabetes, Dementia, SGLT-2i, DPP-4i, Cognitive Impairment

Funding: This research project supported by grants from the Canadian Foundation for Innovation, the Canadian Institutes of Health Research (CIHR)

£Corresponding author: Dr. Oriana Hoi Yun Yu
Address: McGill University, Montreal, Canada
Email address: hoi.yu@mcgill.ca

E-mail addresses of authors:
Dr. Zarin Abdullah: zarin.abdullah@mail.mcgill.ca
Ms. Ying Cui: ying.cui@ladydavis.ca
Dr. Robert Platt: robert.platt@mcgill.ca
Dr. Christel Renoux: christel.renoux@mcgill.ca
Dr. Laurent Azoulay: laurent.azoulay@mcgill.ca
Dr. Chenjie Xia: chenjie.xia@mcgill.ca

Word count:
Abstract: 532
Main text: 4,998

Tables and figures:
Tables: 3
Figures: 2
Supplementary Table: 1

Abstract

Objectives: Type 2 diabetes is a worldwide public health concern and is associated with various complications. There is emerging evidence that type 2 diabetes is also associated with an increased risk of cognitive decline, leading to dementia. The pathophysiology of cognitive dysfunction attributable to type 2 diabetes is still not completely understood. Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) are a new class of antidiabetic drugs, recommended as second or third-line treatment for type 2 diabetes. Evidence on the association between SGLT-2i and the reduced risk of dementia in people with type 2 diabetes are sparse and needs further investigation. This was a population-based retrospective cohort study aimed to assess the association between SGLT-2i use and the reduction of risk of incident dementia compared to dipeptidyl peptidase-4 inhibitors (DPP-4i) use among patients with type 2 diabetes.

Design and methods: We conducted the study using the Clinical Practice Research Datalink (CPRD) Aurum database, from the United Kingdom. Patients with type 2 diabetes, aged 40 years or older, were eligible to enter the cohort if they were newly prescribed SGLT-2i or DPP-4i on or after 2013 to 2021. The primary outcome was incident dementia, and the secondary outcome was incident mild cognitive impairment (MCI). Cox proportional hazard models were used to estimate the hazard ratio and corresponding 95% confidence interval for the primary and secondary outcomes. Propensity score fine stratification weights were used to adjust for confounding. We conducted secondary analyses based on subtypes of dementia, age, sex, prior history of cardiovascular diseases and renal insufficiency, SGLT-2i molecule-specific outcomes and use of sulfonylurea as an alternative comparator. Sensitivity analyses were conducted to test the robustness of our findings.

Results: Among a cohort of 118,006 individuals, the incident rate of dementia was 0.56/1000 person-years over a median follow-up period of 1.54 years among SGLT-2i users compared to 2.67/1000 person-years in DPP-4i users, over a median follow-up period of 1.79 years. The adjusted hazard ratio for SGLT-2i use compared to DPP-4i use for dementia was 0.78 (95% CI: 0.55-1.12), while for MCI was 0.86 (95% CI: 0.80-0.92). Age-specific stratified analysis demonstrated the adjusted hazard ratio for SGLT-2i use compared to DPP-4i use for the risk of incident dementia among elderly, aged 65 years or older, was 0.50 (95% CI: 0.31-0.80). We did not find any difference

between the risk of dementia among SGLT-2i users and DPP-4i users based on their subtypes of dementia, sex, prior history of cardiovascular disease or renal insufficiency or varying molecules of SGLT-2i (i.e. canagliflozin, dapagliflozin or empagliflozin). In sensitivity analyses, the primary findings were robust demonstrating the lack of reduction in dementia risk among SGLT-2i users aged 40 years or more.

Conclusion: Our primary findings did not yield conclusive evidence to infer any association between SGLT-2i use and the risk of incident dementia; however, the secondary findings revealed that the use of SGLT-2is was significantly associated with a reduced risk of dementia among patients with type 2 diabetes, aged 65 years or older. Also, SGLT-2is use was associated with significant risk reduction for MCI in our secondary analysis. Due to the observational nature of our study, it is important to interpret the result with caution. Future prospective studies are warranted to confirm our findings.

Strengths and limitations of this study:

- This was a population-based retrospective cohort study that investigated the risk of incident dementia associated with the use of SGLT-2i compared to the use of DPP-4i
- We used cox proportional hazards models to estimate the hazard ratio and corresponding 95% confidence interval for the primary and secondary outcomes. Propensity score fine stratification weights were used to adjust for multiple potential confounding factors
- Given our study's relatively short follow up, there were fewer incident dementia events. Further studies with longer duration of follow-up are needed
- Even though we chose an active comparator drug, DPP-4i and we adjusted for multiple potential confounders with propensity score fine stratification, there remains a possibility of residual confounding and the need for future prospective studies remains.

Introduction

The global prevalence of type 2 diabetes is projected to be more than 7,000 patients per 100,000 by 2030, reflecting a continued rise across all regions of the world (1). Patients with type 2 diabetes are at an increased risk of developing microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (myocardial infarction, stroke, and peripheral arterial disease) complications (2). Type 2 diabetes is also a recognised risk factor for cognitive decline, such as Alzheimer's disease and vascular dementia, which are increasing due to the ageing population (3). Globally, dementia is the seventh most common cause of mortality and is associated with significant disability and dependency among the elderly population (4). Every year, nearly 10 million new cases of dementia emerge (4) and it is projected that the number of cases will go up to 152.8 million by 2050 (5).

The pathophysiology of cognitive dysfunction attributable to type 2 diabetes is still not completely understood. Some potential factors are age, glycaemic control, duration of diabetes, obesity, and associated vascular or other co-morbidities (6-9). Previous evidence indicated that better glycemic control, lower HbA1c levels, and use of anti-diabetic medication are associated with a decreased risk of cognitive dysfunction (10-13). These findings have generated interest in the potential role of anti-diabetic agents in reducing the risk of cognitive dysfunction among patients with type 2 diabetes. However, previous studies that have been conducted with first-line therapy such as metformin, were inconclusive and insulin was associated with a detrimental effect on cognitive function (14, 15). Sodium-glucose co-transporter-2 inhibitors (SGLT-2is) are the newest class of antidiabetic agents recommended as second or third-line of treatments after metformin in the management of type 2 diabetes. They provide effective glycemic control and have been shown to have cardiovascular and metabolic benefits (16). Pre-clinical studies have shown that SGLT-2is prevent ischemia-related cerebral damage, and confer anti-inflammatory and anti-oxidative properties, preventing neuronal loss and enhancing neurogenesis (17, 18). Several observational studies showed evidence of beneficial effects of SGLT-2i on cognitive function; however, these studies were limited by sample size, shorter follow-up periods, inclusion of people with history cognitive dysfunction and using a range of comparators not suitable for SGLT-2is (19-22).

The objective of our study was to assess the association between SGLT-2i and risk of dementia among patients with type 2 diabetes compared with another second-line oral anti-diabetic agent, dipeptidyl peptidase-4 inhibitors (DPP-4i) which have similar effects on weight loss, hypoglycemia risk, and cost as SGLT-2i (23). Also, in large, randomized control trials, DPP-4i was found to be not associated with improved cognitive function (24, 25). Therefore, DPP-4i was the pertinent comparator in our study. The evidence generated from this study will enhance the understanding of role of SGLT-2i s in improving cognitive function among patients with type 2 diabetes in clinical settings.

Methods

Research Design and Data Source

This was a population-based retrospective cohort study. The Clinical Practice Research Datalink (CPRD) Aurum was used as the data source. CPRD is a large primary care database of electronic medical records from a network of general practices across the United Kingdom (UK). This primary care dataset is linked to a range of health-related data which provides a longitudinal and representative database of the UK population. The dataset contains records of around 60 million patients (26).

For the last three decades, the CPRD database has been used to generate evidence to inform clinicians on drug safety, use of medicines, effectiveness of health policy, health care delivery and disease risk factors (27). The database contains Read and SNOMED CT (Systemized Nomenclature of Medicine Clinical Terms) codes to identify patients with specific diagnoses such as type 2 diabetes and their other medical history. Prescription drugs are coded using the Dictionary of Medicines and Devices (dm+d) codes which are a subset of the SNOMED CT terminology and are assigned a “Product Code” for each prescribed medication (28, 29). There have been several studies conducted on the validity of the CPRD database. Jick et al. (2020), assessed the quality and completeness of diagnoses recorded in the CPRD Aurum database by cross-checking with another database, named Hospital Episode Statistics (HES). They reported 76.8% correctness and 79.1% completeness in the diagnosis of their selected medical condition (i.e., pulmonary embolism) (30). Khan, Harrison and Rose (2010) conducted a systematic review of the validity of diagnostic coding within a UK-based General Practice Research Database and

found most of the diagnoses were accurately recorded in the patient electronic record system (31).

The protocol of this study (Number: 1-22_001834 ISAC) was approved by the ethics committee at the Jewish General Hospital and the Independent Scientific Advisory Committee from the CPRD.

Study Cohort

The study cohort was compiled using the CPRD Aurum database. We identified individuals who initiated treatment with a non-insulin antidiabetic agent between January 1, 1998, and December 31, 2021. From these identified individuals, we assembled a cohort by restricting the entry period between 2013 and 2021 (Figure 3-1).

Inclusion and exclusion criteria

In the next step, we included only those patients with at least one new prescription of DPP-4is or SGLT-2is starting from 2013, because this was the year in which SGLT-2is were approved in the UK (32, 33). By using these inclusion criteria, we identified patients with at least one prescription of DPP-4i or SGLT-2i on or after 2013. The first prescription for each patient was set as the cohort entry date. We excluded patients who had prescriptions for both DPP-4i and SGLT-2i on the cohort entry date, and those with prior use of either drug before the cohort entry date. Individuals in the DPP-4i group were excluded for prior prescriptions of DPP-4i or SGLT-2i, and individuals in the SGLT-2i group were excluded for the same reason. These exclusion criteria ensured that the cohort entry date was the first-ever prescription of DPP-4i for the DPP-4i group and SGLT-2i for the SGLT-2i group.

Patients who met any of the following criteria were excluded from the study cohort: patients who were given a combination of both DPP-4i and SGLT-2i at cohort entry or had a prior use of study drugs; were < 40 years of age; had a diagnosis of dementia or MCI at any time before cohort entry; prescribed anti-dementia medications such as acetylcholinesterase inhibitors or memantine at any time before entering the study cohort; on dialysis during the year preceding their entry into the study cohort, as SGLT-2is are not recommended for patients with end-stage

renal disease; and if the prescription was discontinued before one year. A one-year lag period was used to account for potential exposure effects of study drugs on dementia.

All individuals meeting the inclusion criteria were followed up until an event or censoring due to death from any cause, end of study date (December 31, 2022), or end of registration with the general practice in the CPRD, whichever came first.

Exposure Definition

For the exposure variable, we divided the study cohort based on their prescribed drugs into SGLT-2i initiators and DPP-4i initiators between 2013 and 2021, followed until December 31, 2022. Exposure to SGLT-2is and DPP-4is were assumed to be "as-treated", meaning individuals were followed while they were continuously exposed to SGLT-2is or DPP-4is until an event occurred or censored due to death from any cause, end of study date (December 31, 2022), or end of registration with the general practice in the CPRD, whichever came first. The follow-up period was defined by the prescription duration plus a 30-day time interval as grace period. Patients are considered continuously exposed to the study drugs if the duration of one prescription overlaps with the date of the next prescription. . We considered one year of lag period in our analysis, assuming that it is unlikely to observe any association between exposures and dementia risk within a period of one year after initiating the drug. Therefore, if the outcome of dementia was identified within one year of initiating SGLT-2is or DPP-4is, individuals were excluded. Duration of exposure was calculated as the duration of their prescription (at least one year) plus a 30-day grace period following discontinuation or modification of their treatment. Individuals were censored if they had been prescribed a DPP-4i while on SGLT-2i treatment or if they stopped treatment beyond the grace period.

Outcome Definition

The primary outcome variable was incident dementia, which was defined by Read and SNOMED codes in the CPRD Aurum dataset. We included all forms of dementia diagnoses as mixed and unspecified dementia have also been associated with type 2 diabetes in addition to Alzheimer's disease and vascular dementia (34, 35). The primary outcome of the study was also defined by the record of prescribed medications for the treatment of dementia in the CPRD Aurum dataset. These medications include acetylcholinesterase inhibitors such as donepezil,

galantamine, and rivastigmine, which are used to treat mild to moderate dementia, and memantine, which is prescribed for patients with severe dementia or those who are intolerant to acetylcholinesterase inhibitors (36). The CPRD data base has been used successfully in studies assessing dementia as an outcome (37-41) and diagnosis of dementia using Read codes and prescription medications (i.e. acetylcholinesterase inhibitors and memantine) has been shown to be reliable and valid in the CPRD (37, 38, 41). Furthermore, the diagnosis of dementia using the CPRD has been shown to have a positive predictive value (PPV) ranging from 0.83 to 1.0 (42).

Our secondary outcome was MCI. To define MCI, we used Read and SNOMED codes for MCI in the CPRD Aurum database. However, MCI usually occurs before dementia diagnosis and the physicians may not document MCI as a diagnosis. Therefore, in addition to using Read codes for MCI diagnosis, we included Read codes for cognitive impairment, cognitive function cognitive screening tests such as MMSE and others, diagnosis of memory loss or referral to memory clinic, referral to psychiatrist, neurologist, or geriatrician to identify MCI. This approach has been used by Ford et al. (2020) to identify patients with MCI. They reported a high degree of accuracy when above mentioned codes were used to identify patients with MCI in the CPRD with the area under the curve (AUC) values ranging from 0.87 to 0.90 (43).

Covariates

In this study, several potential confounders were considered at the time of cohort entry, including age, sex, year of entry, duration of treated type 2 diabetes in years, history of alcohol-related illnesses, smoking status, glycated haemoglobin A1c (HbA1c) and body mass index (BMI) and the number of physician visits. Since, we used a database from UK, the index of multiple deprivation was used to assess socioeconomic status. Indices of multiple deprivation (IMD) are based on UK locations and used as a proxy measure of poverty of certain locations within UK (44).

Additionally, the history of microvascular complications from diabetes, history of cardiovascular disease, peripheral arterial disease, heart failure, atrial fibrillation, depression, chronic renal insufficiency, use of lipid-lowering, anticoagulation, antihypertensive therapies, frailty indicator such as falls, housebound, tremor and Parkinson's disease were identified at any time before cohort entry, and use of other anti-diabetic medications (i.e., metformin,

sulfonylureas, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, glucagon-like peptide 1 receptor agonists, and insulin) were considered in our analyses.

Statistical Analysis

Primary Analyses

Descriptive statistics were used to describe the baseline characteristics of two exposure groups, "before and after" propensity score weighting. To determine if covariates in both exposure groups were balanced, we calculated the standardized mean differences (SMDs), with a difference of <0.1 as an indicator of good balance. We used the cut-off of 0.1 to assess the balance and observed that most of unadjusted the SMDs > 0.1. To balance these two groups, propensity score (PS) fine stratification weights were used. Fine stratification was used for our analyses rather than using PS matching to ensure that there will be sufficient sample size and statistical power, especially in subgroups with low events. It also allowed better balance of 34 covariates compared to PS matching, improving control of confounding variables. We also considered Inverse probability of treatment weighting (IPTW), however, extreme propensity scores in the DPP-4i group created large weights in IPTW, leading to unstable estimates. Fine stratification offered a more stable and reliable control of confounding.

To estimate the propensity score, a logistic regression model was built to predict the probability of receiving SGLT-2is vs. DPP-4is, as a function of the potential covariates listed above. For fine stratification, instead of using the propensity scores as continuous values, a range of propensity scores was used for dividing the population into 50 fine strata or intervals. Each stratum represented a specific range of propensity scores and patients with similar propensity scores were grouped together to ensure a better balance between the treatment and comparator groups within each stratum. After propensity score fine stratification weighting, we again calculated SMDs and observed the differences between two groups were <0.1 indicating good balance between study and comparator groups.

The Cox-proportional hazard model was used to estimate the hazard ratio and corresponding 95% CI for the risk of dementia associated with SGLT-2i use compared to DPP-4i use.

Secondary Analyses

We conducted eight secondary analyses. First, we used cox proportional hazards model to estimate the HR and 95% CI for the association between SGLT-2i and the risk of MCI. Second, dementia is more common in those over the age of 65 years (2), therefore, we conducted our analysis separately in strata by age (< 65 and ≥65 years). Third, patients with a history of cardiovascular disease are at higher risk of developing dementia (45, 46). To ascertain whether SGLT-2i use has differential effects in reducing the risk of dementia among patients with cardiovascular disease, we conducted an analysis, stratifying for a history of cardiovascular disease. Fourth, people with renal insufficiency are at higher risk of developing dementia (47, 48). As SGLT-2i s use have been shown to reduce renal outcomes among patients with type 2 diabetes, we conducted the primary analysis stratified by a history of chronic renal insufficiency (49). Fifth, to determine whether SGLT-2i use decreases the risk of vascular dementia more than that of Alzheimer's disease, we repeated our primary analysis, stratifying the primary outcome into Alzheimer's disease and vascular dementia. Sixth, we repeated the primary analysis stratified by sex to assess whether the association between SGLT-2i use and the risk of incident dementia differs by sex. Seventh, Due to uncertainty regarding the comparator group for SGLT-2i users, we repeated our primary analysis, using sulfonylurea users as the comparator group. Finally, to determine if individual SGLT-2i molecules have an effect on the risk of incident dementia, we repeated the primary analysis, stratifying by individual SGLT-2i molecule (dapagliflozin, empagliflozin, and canagliflozin).

Sensitivity Analyses

We carried out five sensitivity analyses to assess the robustness of our findings. First, to investigate the impact of the grace period, we repeated our primary analysis using grace periods of 0 and 90 days. Second, to account for the possibility of death occurring before developing dementia, we utilized a proportional hazard model for competing risk developed by Fine and Gray in our primary analysis (50). Third, considering the uncertainties related to the duration of the latency period, we varied the one-year lag period of our exposure definition by repeating the analyses using a lag period of 1.5 and 2 years. Fourth, we conducted a modified intention to treat analysis whereby we had a maximum follow up of three years. Finally, we used time varying inverse probability of censoring weighting (IPCW) to address individuals lost to follow-up due to

seven time-dependant covariates including reduced renal function, falls, peripheral neuropathy, foot ulceration, diabetic ketoacidosis, urinary tract infection, and vaginitis.

Results

Study Population and Baseline Characteristics

A total of 1,331,056 eligible individuals, newly treated with a non-insulin antidiabetic agent between January 1, 1998, and December 31, 2021, were identified in the CPRD Aurum database. To create the initial study cohort, 359,985 patients, prescribed with at least one new prescription of DPP-4i or SGLT-2i on or after 2013, were identified. The study cohort entry date was defined as the date when the prescription of the new antidiabetic agent, DPP-4i or SGLT-2i, was given. We excluded 3,532 patients who had prescriptions for both DPP-4i and SGLT-2i on the cohort entry date, and those with prior use of either drug before the cohort entry date. Specifically, 43,371 individuals in the DPP-4i group were excluded for prior prescriptions of DPP-4i or SGLT-2i, and 4,553 individuals in the SGLT-2i group were excluded for the same reason. These exclusion criteria ensured that the cohort entry date corresponded to the first prescription of DPP-4i for the DPP-4i group and SGLT-2i group. After excluding people on combination treatment with SGLT-2i and DPP-4i; 258,379 DPP-4i users and 98,074 SGLT-2i users remained in the study cohort. In the next step, more individuals were excluded based upon the exclusion criteria such as date inconsistencies, < 1 year of medical history, < 40 years of age, prior use of DPP-4i or SGLT-2i, history of dialysis during the year prior to study cohort entry, prior history dementia/MCI, or prescribed an anti-dementia medication or <1 year follow-up period. We also excluded those individuals who have been diagnosed with dementia, MCI or prescribed an anti-dementia medication within one year of cohort entry (Figure 3-1).

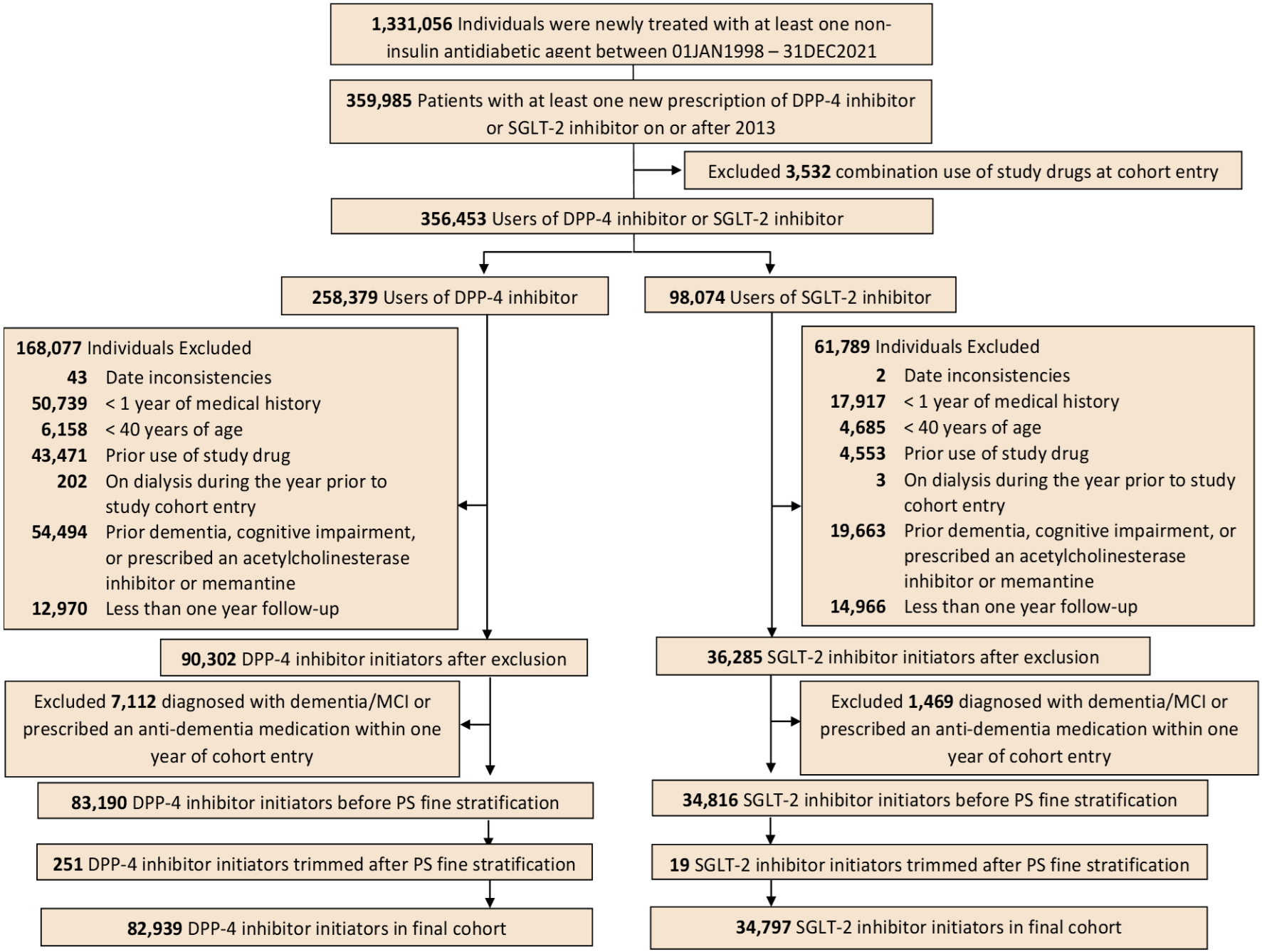

Figure 3-1: Study Flow chart.

Before PS fine stratification, a total of 118,006 patients with a history of type 2 diabetes, aged 40 years or older, who began treatment with an SGLT-2i (n = 34,816; with 61% male participants) or a DPP-4i (n = 83,190; 60% male participants) between 2013 to 2021 comprised the study cohort. Individuals prescribed with SGLT-2is were younger (mean [SD] age, 56.83 [8.96] years vs 62.34 [11.71] years), more likely to be obese (58.99% vs 45.26%), had a higher HbA1c level of >8% (70.65% vs 62.36%), were less likely to have a diagnosis of chronic renal insufficiency (4.84% vs 16.7%) and had been treated with more than one glucose-lowering medication, particularly glucagon-like peptide-1 receptor agonists (12.78% vs 2.23%) and insulin (13.54% vs 5.56%), and less likely to be treated with anticoagulation therapy (34.54% vs 44.85%) when compared to Individuals prescribed with DPP-4is (Table 3-1).

After PS fine stratification, the final cohort consisted of 34,797 SGLT-2i users and 82,939 DPP-4i users; all baseline characteristics were well balanced between two groups with less than <0.1 of SMDs (Table 3-2). Since, most of the SGLT-2i users were matchable, this indicates a high level of overlap of characteristics of patients using SGLT-2i users with DPP-4i users. Therefore, the PS fine stratification estimand, which we conducted to adjust for confounding variables by stratifying patients into groups based on their scores, was very close to the average treatment effect on the treated.

Table 3-1: Selected baseline characteristics, before and after propensity score (PS) fine stratification, among patients initiating SGLT-2is vs DPP-4is.

	Before weighting					After weighting*				
Variables	**SGLT-2i (n=34,816)**		**DPP-4i (n=83,190)**		**SMD**	**SGLT-2i (n=34,797)**		**DPP-4i n=82,939)**		**SMD**
Age (years)										
Mean (SD)	56.83	8.96	62.34	11.71	-0.528	56.83	8.96	56.91	9.06	-0.009
40-45, n (%)	3,590	10.31	5,785	6.95	0.120	3,589	10.31	8,854	10.68	-0.012
46-55, n (%)	12,683	36.43	20,495	24.64	0.258	12,675	36.43	29,507	35.58	0.018
56-65, n (%)	12,376	35.55	24,347	29.27	0.134	12,366	35.54	29,876	36.02	-0.010
66-75, n (%)	5,315	15.27	19,828	23.83	-0.217	5,315	15.27	12,474	15.04	0.006
76-85, n (%)	804	2.31	10,696	12.86	-0.407	804	2.31	2,061	2.48	-0.011
>85, n (%)	48	0.14	2,039	2.45	-0.205	48	0.14	167	0.20	-0.015
Sex, n (%)										
Females	13,684	39.30	33,584	40.37	-0.022	13,681	39.32	33,226	40.06	-0.015
Males	21,132	60.70	49,606	59.63	0.022	21,116	60.68	49,713	59.94	0.015
Index of multiple deprivation 2010, n (%)										
1st	2,447	7.03	5,432	6.53	0.020	2,446	7.03	5,629	6.79	0.009
2nd	2,767	7.95	6,252	7.52	0.016	2,764	7.94	6,446	7.77	0.006
3rd	2,427	6.97	5,968	7.17	-0.008	2,425	6.97	5,600	6.75	0.009
4th	2,937	8.44	6,611	7.95	0.018	2,934	8.43	7,104	8.57	-0.005
5th	3,317	9.53	7,305	8.78	0.026	3,315	9.53	7,819	9.43	0.003
6th	4,439	12.75	8,783	10.56	0.068	4,432	12.74	10,575	12.75	<0.001
7th	3,922	11.26	9,564	11.5	-0.008	3,922	11.27	9,367	11.29	-0.001
8th	3,917	11.25	9,990	12.01	-0.024	3,916	11.25	9,362	11.29	-0.001
9th	4,155	11.93	11,582	13.92	-0.059	4,155	11.94	10,083	12.16	-0.007
10th	4,488	12.89	11,703	14.07	-0.035	4,488	12.9	10,953	13.21	-0.009
Calendar year of cohort entry date, n (%)										
2013	464	1.33	11,306	13.59	-0.480	464	1.33	1,189	1.43	-0.009
2014	1,944	5.58	10,149	12.20	-0.234	1,944	5.59	4,320	5.21	0.017
2015	3,529	10.14	10,701	12.86	-0.085	3,529	10.14	8,095	9.76	0.013

2016	3,915	11.24	11,519	13.85	-0.079	3,915	11.25	8,949	10.79	0.015
2017	4,501	12.93	11,435	13.75	-0.024	4,501	12.94	10,686	12.88	0.002
2018	5,399	15.51	10,830	13.02	0.071	5,399	15.52	13,118	15.82	-0.008
2019	6,844	19.66	9,270	11.14	0.238	6,844	19.67	16,413	19.79	-0.003
2020	6,386	18.34	6,612	7.95	0.311	6,379	18.33	15,531	18.73	-0.010
2021	1,834	5.27	1,368	1.64	0.200	1,822	5.24	4,638	5.59	-0.015
Diabetes duration (years)										
Mean (SD)	5.70	4.67	5.73	4.50	-0.007	5.59	4.72	5.64	4.84	-0.010
Median (IQR)	5	(2-9)	5	(2-9)		4	(2-7)	4	(2-7)	
<1 year, n (%)	3,177	9.13	7,412	8.91	0.008	3,177	9.13	7,563	9.12	<0.001
1-4.9 years, n (%)	14,171	40.70	32,263	38.78	0.039	14,171	40.72	33,969	40.96	-0.005
5-9.9 years, n (%)	10,101	29.01	26,396	31.73	-0.059	10,096	29.01	23,891	28.81	0.004
>=10 years, n (%)	7,367	21.16	17,119	20.58	0.014	7,353	21.13	17,516	21.12	<0.001
Healthcare use, n (%)										
Number of physician visits in the 365 days prior to t0										
0-2	8,864	25.46	19,516	23.46	0.047	8,860	25.46	21,238	25.61	-0.003
3-5	12,307	35.35	28,479	34.23	0.024	12,301	35.35	29,150	35.15	0.004
6+	13,645	39.19	35,195	42.31	-0.064	13,636	39.19	32,551	39.25	-0.001
Comorbidities, n (%)										
Retinopathy	4,926	14.15	13,842	16.64	-0.069	4,922	14.14	11,682	14.08	0.002
Nephropathy	11	0.03	85	0.10	-0.027	11	0.03	25	0.03	<0.001
Neuropathy	552	1.59	1,495	1.80	-0.016	552	1.59	1,379	1.66	-0.006
Non -fatal MI**	930	2.67	3,134	3.77	-0.062	929	2.67	2,180	2.63	0.002
Stroke	902	2.59	3,177	3.82	-0.070	901	2.59	2,170	2.62	-0.002
Peripheral arterial disease	415	1.19	1,738	2.09	-0.071	415	1.19	1,049	1.26	-0.006
Heart failure	641	1.84	2,003	2.41	-0.040	641	1.84	1,556	1.88	-0.003
Atrial fibrillation	1,073	3.08	4,513	5.42	-0.116	1,073	3.08	2,538	3.06	0.001
Depression	5,240	15.05	10,152	12.20	0.083	5,236	15.05	12,558	15.14	-0.003
Chronic renal insufficiency	1,686	4.84	13,895	16.70	-0.390	1,686	4.85	4,434	5.35	-0.023

Falls	378	1.09	1,617	1.94	-0.070	378	1.09	961	1.16	-0.007
Housebound	96	0.28	753	0.91	-0.082	96	0.28	254	0.31	-0.006
Tremor	233	0.67	791	0.95	-0.031	233	0.67	559	0.67	<0.001
Parkinson's disease	10	0.03	58	0.07	-0.018	10	0.03	18	0.02	0.006
Medications, n (%)										
metformin	33,541	96.34	78,960	94.92	0.070	33,522	96.34	79,976	96.43	-0.005
sulfonylureas	15,789	45.35	40,937	49.21	-0.077	15,773	45.33	37,287	44.96	0.007
meglitinides	353	1.01	686	0.82	0.020	351	1.01	873	1.05	-0.004
thiazolidinediones	4,681	13.44	9,762	11.73	0.052	4,666	13.41	11,103	13.39	0.001
alpha-glucosidase inhibitors	202	0.58	369	0.44	0.020	202	0.58	507	0.61	-0.004
GLP1 receptor agonists[δ]	4,450	12.78	1,858	2.23	0.409	4,431	12.73	10,008	12.07	0.020
insulin	4,715	13.54	4,623	5.56	0.274	4,696	13.50	11,120	13.41	0.003
lipid lowering therapy	27,564	79.17	69,220	83.21	-0.104	27,548	79.17	65,173	78.58	0.014
anticoagulation therapy	12,027	34.54	37,313	44.85	-0.212	12,019	34.54	28,513	34.38	0.003
antihypertensive therapy	24,649	70.80	61,697	74.16	-0.075	24,632	70.79	58,601	70.65	0.003
Other covariates, n (%)										
Body Mass Index (kg/m^2)										
< 30	7,299	20.96	27,929	33.57	-0.286	7,299	20.98	17,524	21.13	-0.004
≥ 30	20,538	58.99	37,651	45.26	0.277	20,521	58.97	48,592	58.59	0.008
Unknown	6,979	20.05	17,610	21.17	-0.028	6,977	20.05	16,823	20.28	-0.006
Smoking										
Never	8,303	23.85	18,755	22.54	0.031	8,296	23.84	19,663	23.71	0.003
Ever	26,449	75.97	64,179	77.15	-0.028	26,437	75.97	63,126	76.11	-0.003
Unknown	64	0.18	256	0.31	-0.026	64	0.18	150	0.18	<0.001
HbA1c level (mmol/mol)										
≤ 7	2,026	5.82	6,454	7.76	-0.077	2,026	5.82	4,987	6.01	-0.008
7.1-8	7,538	21.65	23,270	27.97	-0.147	7,538	21.66	18,180	21.92	-0.006
> 8	24,599	70.65	51,874	62.36	0.176	24,580	70.64	58,233	70.21	0.009
Unknown	653	1.88	1,592	1.91	-0.002	653	1.88	1,539	1.86	0.001
Excessive alcohol use	508	1.46	1,138	1.37	0.008	508	1.46	1,277	1.54	-0.007

Abbreviations: SMD, standardized mean difference; SD, standard deviation; IQR, interquartile range; MI, myocardial infarction; GLP1 , glucagon-like peptide-1

* PS fine stratification

Primary and secondary outcome analyses

Over a median follow-up period of around 1.54 years, 40 patients developed dementia among 34,816 SGLT-2i users. In comparison, 533 patients among 83,190 DPP-4i users had dementia over a median follow-up period of 1.79 years. The incident rate (IR) per 1000 person-years for dementia was overall 0.56 in SGLT-2i users vs 2.67 in DPP-4i users. Before adjusting for co-variates shown in Table 3-2, SGLT-2i use was associated with the lower risk of incident dementia compared to DPP-4i use (HR: 0.26; 95% CI: 0.19-0.35); In the adjusted analysis, the effect estimate on the association of SGLT-2i use with the risk of incident dementia compared to DPP-4i use demonstrated no effect, but the CI was compatible with a range of protective effects (aHR: 0.78; 95% CI: 0.55-1.12) (Table 3-3).

Table 3-2: Incidence and risk of dementia among SGLT-2is users vs DPP-4is users

Primary Analysis with "As-treated approach"	**SGLT-2i**	**DPP-4i**
	N=34,816	N=83,190
Total follow up period (person-years)	70,942	199,618
Median follow up period (years)	1.54	1.79
Dementia cases	40	533
Incidence rate (per 1,000 person-years)	0.56	2.67
Crude HR (95%CI)	0.26 (0.19-0.35)	1.00 (reference)
Adjusted HR* (95%CI)	0.78 (0.55-1.12)	1.00 (reference)

Note: Primary outcome was defined by both medical codes and product codes for anti-dementia medication, *PS fine stratification
Abbreviations: SGLT-2i, SGLT-2is; DPP-4i, DPP-4is.

In secondary analyses, the use of SGLT-2i was associated with 14% lower risk of MCI when compared to DPP-4i use (aHR: 0.86; 95% CI: 0.80-0.92). There was no difference in the associated risk among SGLT-2i users and DPP-4 users when other subtypes of dementia such as Alzheimer Dementia (aHR: 1.34; 95% CI: 0.39-4.66) or vascular dementia (aHR: 0.45; 95% CI: 0.17-1.17) were considered. When stratifying the patients by age, the use of SGLT-2i was associated with a lower risk of dementia among patients with 65 years or more (aHR: 0.50; 95% CI: 0.31-0.80) compared to the use of DPP-4i. This effect was not observed among younger patients, <65 years (aHR: 1.23; 95% CI: 0.70-2.14), which likely to be a false indication of heterogeneity caused by the small number of cases. Stratification by sex did not yield any difference in risk between SGLT-2i or DPP-4is users. We also did not observe any difference in adjusted hazard ratio among patients with

cardiovascular disease or chronic renal insufficiency receiving either SGLT-2i or DPP-4i. We conducted molecule specific analysis, and we did not observe any significant difference between following groups: canagliflozin vs DPP-4is (aHR: 1.49; 95% CI: 0.87-2.55), dapagliflozin vs DPP-4is (aHR: 0.66; 95% CI: 0.39-1.11) and empagliflozin vs DPP-4is (aHR: 0.58; 95% CI: 0.28-1.20). When we compared the risk of dementia among SGLT-2i users with sulfonylurea users, instead of DPP-4i users, we observed the SGLT-2i use was associated with a decreased risk of dementia (aHR: 0.74; 95% CI: 0.57-0.96) (Table 3-3).

Table 3-3: Secondary analyses

Secondary analyses	Before propensity score weighting				After propensity score weighting			
	N	Crude events/at-risk person-years	Incidence rate	Crude HR (95%CI)	N	Adjusted events/at-risk person-years	Incidence rate	Adjusted HR (95%CI)
Association between SGLT-2i use and risk of MCI								
Mild cognitive impairment								
SGLT-2i	34,816	951/69,729	13.64	0.50 (0.46-0.53)	34,797	950/69,707	13.63	0.86 (0.80-0.92)
DPP-4i	83,190	5,690/190,340	29.89	1.00 (reference)	82,939	2,607/164,621	15.84	1.00 (reference)
Association between SGLT-2i use and risk of subtypes of dementia								
Alzheimer dementia								
SGLT-2i	34,816	S	S	S	34,797	S	S	S
DPP-4i	83,190	53/200,245	0.26	1.00 (reference)	82,939	7/167,939	0.04	1.00 (reference)
Vascular dementia								
SGLT-2i	34,816	5/70,990	0.07	0.11 (0.05-0.27)	34,797	5/70,968	0.07	0.45 (0.17-1.17)
DPP-4i	83,190	156/200,139	0.78	1.00 (reference)	82,939	25/167,919	0.15	1.00 (reference)
Stratified analysis to examine the risk of incident dementia in different groups								
Age-stratified analyses								
Age <65								
SGLT-2i	27,866	22/57,019	0.39	0.81 (0.50-1.33)	27,843	22/56,990	0.39	1.23 (0.70-2.14)
DPP-4i	48,560	61/111,765	0.55	1.00 (reference)	48,516	29/97,096	0.30	1.00 (reference)
Age ≥65								
SGLT-2i	6,950	18/13,924	1.29	0.31 (0.19-0.50)	6,949	18/13,923	1.29	0.50 (0.31-0.80)
DPP-4i	34,630	472/87,853	5.37	1.00 (reference)	34,431	209/73,306	2.85	1.00 (reference)
Sex-stratified analyses								
Female								
SGLT-2i	13,684	15/27,582	0.54	0.21 (0.12-0.35)	13,671	15/27,564	0.54	0.67 (0.38-1.19)
DPP-4i	33,584	262/79,596	3.29	1.00 (reference)	33,189	53/66,790	0.79	1.00 (reference)
Male								

SGLT-2i	21,132	25/43,360	0.58	0.31 (0.20-0.46)	21,121	25/43,348	0.58	0.89 (0.56-1.41)
DPP-4i	49,606	271/120,022	2.26	1.00 (reference)	49,498	63/100,367	0.63	1.00 (reference)
Stratified by prior history of cardiovascular disease								
Without prior history of cardiovascular disease								
SGLT-2i	33,039	35/67,433	0.52	0.27 (0.19-0.38)	33,020	35/67,410	0.52	0.77 (0.52-1.13)
DPP-4i	77,121	439/184,447	2.38	1.00 (reference)	76,946	101/155,463	0.65	1.00 (reference)
With prior history of cardiovascular disease								
SGLT-2i	1,777	5/3,509	1.42	0.28 (0.11-0.69)	1,759	5/3,480	1.44	1.04 (0.38-2.81)
DPP-4i	6,069	94/15,171	6.20	1.00 (reference)	5,455	16/11,352	1.41	1.00 (reference)
Stratified by prior history of renal insufficiency								
Without prior history of chronic renal insufficiency								
SGLT-2i	33,130	35/67,527	0.52	0.33 (0.23-0.47)	33,111	35/67,505	0.52	0.84 (0.57-1.25)
DPP-4i	69,295	319/164,103	1.94	1.00 (reference)	68,781	82/138,564	0.59	1.00 (reference)
With prior history of chronic renal insufficiency								
SGLT-2i	1,686	5/3,415	1.46	0.30 (0.12-0.73)	1,683	5/3,412	1.47	0.85 (0.34-2.11)
DPP-4i	13,895	214/35,515	6.03	1.00 (reference)	13,697	57/29,859	1.91	1.00 (reference)
Stratified by molecules of SGLT-2is								
Canagliflozin	5,400	15/11,823	1.27	0.53 (0.31-0.88)	5,398	15/11,821	1.27	1.49 (0.87-2.55)
DPP-4i	83,190	533/199,618	2.67	1.00 (reference)	71,274	119/149,670	0.80	1.00 (reference)
Dapagliflozin	15,045	16/31,568	0.51	0.22 (0.13-0.36)	15,038	16/31,561	0.51	0.66 (0.39-1.11)
DPP-4i	83,190	533/199,618	2.67	1.00 (reference)	82,899	133/174,898	0.76	1.00 (reference)
Empagliflozin	14,298	8/26,755	0.30	0.16 (0.08-0.31)	14,292	8/26,747	0.30	0.58 (0.28-1.20)
DPP-4i	83,190	533/199,618	2.67	1.00 (reference)	69,898	70/133,484	0.52	1.00 (reference)
Ertugliflozin	65	S	S	S				
DPP-4i	83,190	533/199,618	2.67	1.00 (reference)				
Sulfonylurea use as a comparator								
SGLT-2i	31,279	78/63,541	1.23	0.25 (0.20-0.32)	31,275	78/63,534	1.23	0.74 (0.57-0.96)
Sulfonylurea	64,945	717/144,724	4.95	1.00 (reference)	64,873	199/122,106	1.63	1.00 (reference)

Note: Cardiovascular disease is defined by diagnosed with non-fatal myocardial infarction and/or stroke.

Abbreviations: SGLT-2i, SGLT-2 inhibitors; DPP-4i, DPP-4is; S, as per Clinical Practice Research Datalink requirement, <5 events were replaced with "S".

Findings from sensitivity analyses

In our study, we conducted a sensitivity analysis to explore the impact of SGLT-2i use on incident dementia with two different grace period of 0 days, and 90 days. We observed, with a 90-day grace period, the association between SGLT-2i and incident dementia was statistically significant (aHR: 0.72; 95% CI: 0.54-0.95) in our adjusted dataset compared to DPP-4i use but did not observe any difference with grace period of 0 days. The point estimates were similar when we varied the grace period (Figure 3-2). When we considered death as a competing risk in our analysis, we did not observe any difference between the SGLT-2i users and DPP-4i users (aHR: 0.79; 95% CI: 0.55-1.14). Furthermore, repeating primary analysis with 1.5 years (aHR: 0.80; 95% CI: 0.55-1.16) and 2 years (aHR: 0.93; 95% CI: 0.63-1.37) lag period, demonstrated the lack of association between SGLT-2i and incident dementia compared to DPP-4is. We used IPCW to address individuals lost to follow-up due to seven time-dependant covariates including reduced renal function, falls, peripheral neuropathy, foot ulceration, diabetic ketoacidosis, urinary tract infection, and vaginitis. We observed the risk of dementia did not vary between SGLT-2i and DPP-4is users (aHR: 0.79; 95% CI: 0.56-1.11) and were consistent with our primary findings. We conducted an intention-to-treat analysis, which demonstrated results consistent with our primary analysis (aHR: 0.83; 95% CI: 0.61-1.14) (Figure 3-2, Supplementary Table 3-1).

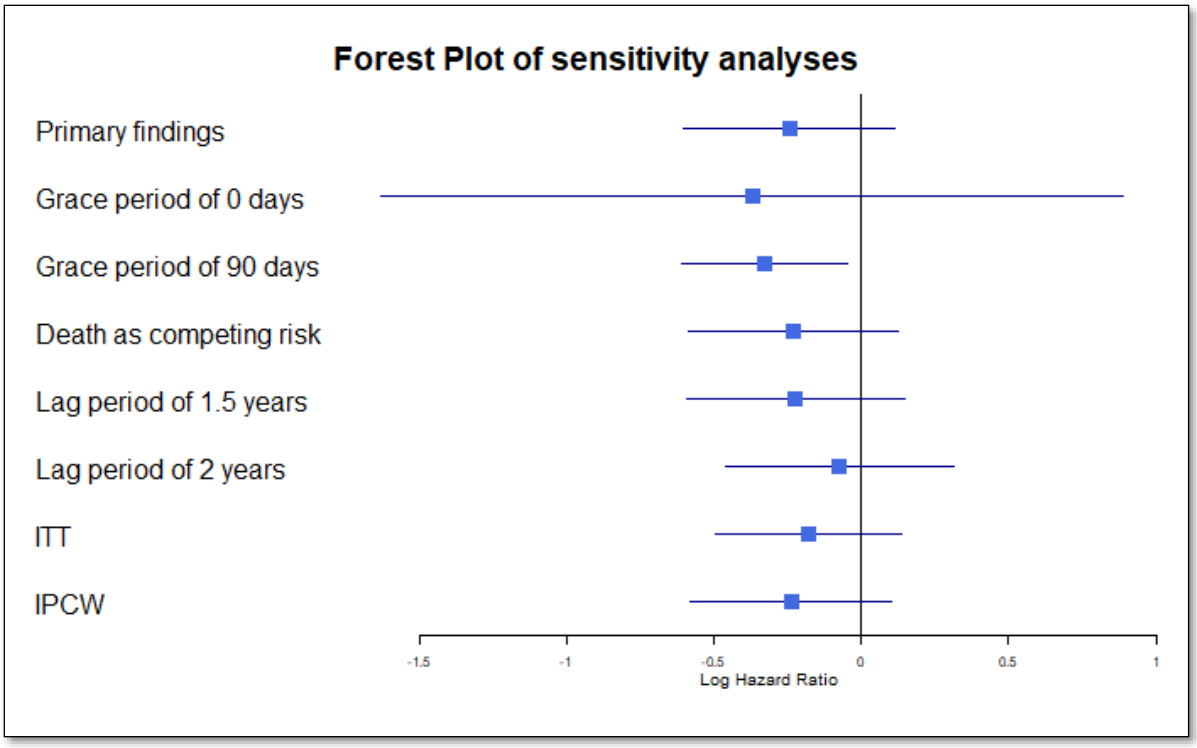

Figure 3-2: Forest plot displaying the log hazard ratios and confidence intervals for various sensitivity analyses.

Abbreviations: ITT, intention to treat; IPCW, inverse probability of censoring weighting.

Supplementary Table 3-1: Sensitivity analyses

Exposures	Before propensity score weighting				propensity score weighting			
	N	Crude events/at-risk person-years	Incidence rate	Crude HR (95%CI)	N	Adjusted events/at-risk person-years	Incidence rate	Adjusted HR (95%CI)
Grace period								
Grace period of 0 days								
SGLT-2i	34,816	S	S	S	34,797	S	S	S
DPP-4i	83,190	59/103,088	0.57	1.00 (reference)	82,939	13/101,448	0.13	1.00 (reference)
Grace period of 90 days								
SGLT-2i	34,816	66/91,027	0.73	0.25 (0.19-0.32)	34,797	66/91,003	0.73	0.72 (0.54-0.95)
DPP-4i	83,190	862/255,477	3.37	1.00 (reference)	82,939	189/204,129	0.93	1.00 (reference)
Competing risk								
SGLT-2i	34,816	40/70,942	0.56	0.26 (0.19-0.36)	34797	40/70,920	0.56	0.79 (0.55-1.14)
DPP-4i	83,190	533/199,618	2.67	1.00 (reference)	82939	117/167,811	0.70	1.00 (reference)
Lag Period								
Lag period of 1.5 years								
SGLT-2i	29,529	37/74,369	0.50	0.29 (0.21-0.41)	29,515	37/74,343	0.50	0.80 (0.55-1.16)
DPP-4i	75,050	451/213,758	2.11	1.00 (reference)	74,946	114/188,070	0.61	1.00 (reference)
Lag period of 2 years								
SGLT-2i	26,140	35/77,255	0.45	0.37 (0.26-0.53)	26,140	35/77,255	0.45	0.93 (0.63-1.37)
DPP-4i	68,139	352/224,025	1.57	1.00 (reference)	68,052	96/200,866	0.48	1.00 (reference)
Intention to treat analysis								
SGLT-2i	34,816	52/87,804	0.59	0.25 (0.19-0.33)	34,797	52/87,804	0.59	0.83 (0.61-1.14)
DPP-4i	83,190	566/226,658	2.50	1.00 (reference)	82,939	148/208,604	0.71	1.00 (reference)
IPCW								HR (95%CI)
SGLT-2i								0.79 (0.56-1.11)
DPP-4i								1.00 (reference)

Abbreviations: S, as per Clinical Practice Research Datalink requirement, <5 events were replaced with "S"; IPCW: inverse probability of censoring weighting

Discussion

Diabetes and its associated complications are topics of significant attention in both public health research and clinical practice worldwide. Hence, several studies were conducted to investigate the additional beneficial effects of anti-diabetic agents beyond their primary role in glycaemic control to alleviate the associated complications, such as cognitive dysfunctions (51-54). Among various anti-diabetic agents, the role of SGLT-2is in preserving cognitive function has emerged as a point of interest along with their established beneficial effect on cardiovascular and renal outcomes. In our large population-based retrospective cohort study of patients with type 2 diabetes, 40 years of age and older, we observed fewer events of incident dementia among SGLT-2i users compared to DPP-4i users. Our secondary analysis revealed that SGLT-2i use was associated with a reduced risk of dementia among patients aged 65 years or older. Our study findings also demonstrated SGLT-2i use was associated with a lower risk of MCI. These findings were consistent with previously published studies and are also logical in the context of clinical settings. Because people who are 65 and older are at a higher risk of developing dementia than those who are younger that 65 years, assessing older individuals increases the likelihood of detecting a difference in dementia risk attributable to SGLT-2i. Previously conducted studies also demonstrated this association.

Proietti et al. (2023) compared the risk of dementia among SGLT-2i users with non-users among elderly patients with mean age of 66.7 years in a retrospective cohort study. They found a 66% elevated risk of incident dementia among non-users of SGLT-2is compared to users of SGLT-2is (22). The recent retrospective cohort study, with the most comparable sample size to our study conducted by Wu et al., 2022, found the use of SGLT-2is compared to use of DPP-4is was associated with a 20% reduction in risk of dementia among elderly Ontario residents aged ≥66 years over a mean follow-up of 2.8 years with an intention-to-treat approach (21). Their secondary analysis with an as-treated approach revealed a stronger association of SGLT-2is with lower dementia risk (aHR: 0.66, 95% CI: 0.57–0.76) (21). However, this study did not exclude patients with prior history of MCI, which could lead to elevated number of events in the analysis, given people with MCI may be less likely given a SGLT-2i. In two other retrospective cohort studies, Siao et al. (2022) and Mui et al. (2021) reported the use of SGLT-2i was associated with

lower risks of dementia, though their comparator group and age of the cohort were different (19, 20). Similar to our study population, in Siao et al. (2022), the average age of participants was lower compared to other studies, which could have potentially influenced the study outcomes including the relatively low hazard ratio reported when compared to Mui et al. (2021) and Wu et al., (2022). Mui et al. (2021) observed a much larger reduction in the risk of dementia (HR: 0.41, 95% CI: 0.27–0.61, P < 0.0001) associated with SGLT-2i use when compared to DPP-4i use among elderly individuals in a Chinese population cohort (i.e., average age of 61 years) (20). None of these studies considered to exclude patients with the history of MCI. The low number of incident dementia cases in our study could be attributed to this exclusion of patients with history of MCI, along with relatively short follow up.

There were a handful of prospective studies conducted on the association between SGLT-2is and cognitive function. In studies in which patients MCI and dementia were included, the use of SGLT-2is was strongly associated with improvements in cognitive function measured by Montreal Cognitive Assessment (MoCA) score (55-57). In contrast, studies conducted with patients with normal baseline cognitive function, no significant associations were observed between the use of SGLT-2is and changes in cognitive function scores (58, 59). This corresponds with our study findings since we excluded patients with any prior history of MCI or dementia before starting the follow-up. This inconsistency might also be due to relatively younger age of participants in our study (58, 59) compared to other studies in which only older patients were included (55, 56). This observation also aligned with the results of the subgroup analysis for dementia onset in our study, whereby we stratified patients by of age <65 and ≥65 years and observed that SGLT-2i use was associated with a reduced risk of incident dementia among patients age ≥65 years. Moreover, SGLT-2i has been shown to be beneficial in frail older adults with diabetes to improve their cognitive impairment (56). Randomized controlled trials (RCTs) conducted on the association of SGLT-2i s use and cognitive function were rather few with short duration of follow up, smaller sample size and often with a specific SGLT-2i molecule (57, 58, 60). The population examined were elderly and SGLT-2i use showed improvement in cognitive function for elderly patients with type 2 diabetes with a follow-up period of 12 months in a RCT

conducted by Perna et al. (2018) (60). Other studies had a shorter follow-up period, 16 weeks (58) and 6 months (57) and did not show any significant association.

Our study has several strengths which contributes significance and reliability to our findings. A key strength of our study was that our cohort comprised of patients without any prior history of dementia and MCI, which allowed us to accurately assess the true effect size of the risk of developing dementia in a population with type 2 diabetes and no prior history of cognitive impairment. Another strength was our selection of DPP-4i as a comparator. By selecting DPP-4is, the baseline characteristics between the two user groups of these anti-diabetic agents were more similar in terms of duration of diabetes, co-morbidities, and other aspects. We also rigorously adjusted for 34 potential confounders. These covariates were balanced between the two groups after adjustment with propensity score fine stratification.

Our study has several limitations. The relatively short follow up period in our study might have led to less incident dementia events. Unmeasured confounding is a known limitation of observational studies. However, we used an active comparator at the design stage to make subjects in the exposure and reference groups as comparable as possible. Additionally, we conducted an extensive literature search to identify and adjust for 34 relevant confounders, achieving good balance between SGLT-2i and DPP-4i users. Another limitation of our study was the low number of events of dementia subtypes, because most subtypes of dementia were coded as “dementia” in the database unless otherwise specified. The low number of events documented for Alzheimer’s disease and vascular dementia precluded us to infer any association. However, the total number of dementia events was very low for the SGLT-2i users anyway in the primary analysis, so any stratified analysis by type of dementia, even if all dementias had been specified in term of subtype would have been challenging and the number would still be limited. Also, most patients have mixed forms of dementia, which includes both forms; therefore, it was difficult to study the effect on one subtype.

Conclusion

In summary, this large population-based retrospective cohort study was conducted to explore the association between SGLT-2i use and the risk of dementia. Our primary findings did not yield conclusive evidence to infer any association between SGLT-2i use and the risk of incident dementia. Our secondary findings revealed that the use of SGLT-2is was associated with a reduced risk of dementia among elderly patients aged 65 years or older. Also, SGLT-2i use showed potential beneficial effect in reducing the risk of MCI. Considering the observational nature of the study with a relatively short follow-up period, we acknowledge that residual confounding might still be present, despite our effort to mitigate potential biases. Therefore, further large-scale prospective studies with longer follow-up period are needed to confirm whether SGLT-2i use affects dementia risk and other cognitive outcomes.

References

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Kaabi JA. Epidemiology of Type 2 diabetes - Global burden of disease and forecasted trends. Journal of Epidemiology and Global Health. 2020;10(1):107-11.
2. Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GEHM, Biessels GJ. Cognitive function in patients with diabetes mellitus: Guidance for daily care. The Lancet Neurology2015.
3. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: A systematic review. Lancet Neurology2006.
4. World Health O. Dementia. 2023.
5. Nichols E, Steinmetz JD, Vollset SE, Fukutaki K, Chalek J, Abd-Allah F, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. The Lancet Public Health. 2022;7(2):e105-e25.
6. Profenno LA, Porsteinsson AP, Faraone SV. Meta-Analysis of Alzheimer's Disease Risk with Obesity, Diabetes, and Related Disorders. Biological Psychiatry. 2010;67(6):505-12.
7. Xu W, Qiu C, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Mid- And late-life diabetes in relation to the risk of dementia: A population-based twin study. Diabetes. 2009;58(1):71-7.
8. Dao L, Choi S, Freeby M. Type 2 diabetes mellitus and cognitive function: Understanding the connections. Current Opinion in Endocrinology, Diabetes and Obesity2023.
9. Lyu F, Wu D, Wei C, Wu A. Vascular cognitive impairment and dementia in type 2 diabetes mellitus: An overview. Life Sciences: Elsevier Inc.; 2020.
10. Kielstein JT. Glucose levels and risk of dementia. N Engl J Med. 2013;369(19):1863.
11. Liu S, Lu Y, Cai X, Cong R, Li J, Jiang H, et al. Glycemic Control is Related to Cognitive Dysfunction in Elderly People with Type 2 Diabetes Mellitus in a Rural Chinese Population. Curr Alzheimer Res. 2019;16(10):950-62.
12. Kim JY, Ku YS, Kim HJ, Trinh NT, Kim W, Jeong B, et al. Oral diabetes medication and risk of dementia in elderly patients with type 2 diabetes. Diabetes Res Clin Pract. 2019;154:116-23.
13. Zheng F, Yan L, Yang Z, Zhong B, Xie W. HbA1c, diabetes and cognitive decline: the English Longitudinal Study of Ageing. Diabetologia. 2018;61(4):839-48.
14. Samaras K, Makkar S, Crawford JD, Kochan NA, Wen W, Draper B, et al. Metformin use is associated with slowed cognitive decline and reduced incident dementia in older adults with type 2 diabetes: The Sydney memory and ageing study. Diabetes Care. 2020;43(11):2691-701.
15. Xue M, Xu W, Ou YN, Cao XP, Tan MS, Tan L, et al. Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies. Ageing Res Rev. 2019;55:100944.
16. Tsushima Y, Lansang MC, Makin V. The role of SGLT-2 inhibitors in managing type 2 diabetes. Cleve Clin J Med. 2021;88(1):47-58.
17. Wiciński M, Wódkiewicz E, Górski K, Walczak M, Malinowski B. Perspective of SGLT2 Inhibition in Treatment of Conditions Connected to Neuronal Loss: Focus on Alzheimer's Disease and Ischemia-Related Brain Injury. Pharmaceuticals. 2020;13:379.

18. Al Hamed FA, Elewa H. Potential Therapeutic Effects of Sodium Glucose-linked Cotransporter 2 Inhibitors in Stroke. Clinical Therapeutics. 2020;42(11):e242-e9.
19. Siao WZ, Lin TK, Huang JY, Tsai CF, Jong GP. The association between sodium-glucose cotransporter 2 inhibitors and incident dementia: A nationwide population-based longitudinal cohort study. Diabetes and Vascular Disease Research. 2022;19(2).
20. Mui JV, Zhou J, Lee S, Leung KSK, Lee TTL, Chou OHI, et al. Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors vs. Dipeptidyl Peptidase-4 (DPP4) Inhibitors for New-Onset Dementia: A Propensity Score-Matched Population-Based Study With Competing Risk Analysis. Frontiers in Cardiovascular Medicine. 2021;8.
21. Wu CY, Iskander C, Wang C, Xiong LY, Shah BR, Edwards JD, et al. Association of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors with time to dementia: a population-based cohort study. Alzheimer's & Dementia. 2022;18(S10).
22. Proietti R, Rivera-Caravaca JM, López-Gálvez R, Harrison SL, Marín F, Underhill P, et al. 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. 2023;12(8).
23. Harper W, Clement M, Goldenberg R, Hanna A, Main A, Retnakaran R, et al. Policies, Guidelines and Consensus Statements: Pharmacologic Management of Type 2 Diabetes-2015 Interim Update. Canadian Journal of Diabetes: Elsevier B.V.; 2015. p. 250-2.
24. Biessels GJ, Verhagen C, Janssen J, van den Berg E, Wallenstein G, Zinman B, et al. Effects of linagliptin vs glimepiride on cognitive performance in type 2 diabetes: results of the randomised double-blind, active-controlled CAROLINA-COGNITION study. Diabetologia. 2021;64(6):1235-45.
25. Biessels GJ, Verhagen C, Janssen J, van den Berg E, Zinman B, Rosenstock J, et al. Effect of Linagliptin on Cognitive Performance in Patients With Type 2 Diabetes and Cardiorenal Comorbidities: The CARMELINA Randomized Trial. Diabetes Care. 2019;42(10):1930-8.
26. Research NIfHaC. Primary care data for public health research [cited 2024 05/01]. Available from: https://www.cprd.com/.
27. Lookups Other Updates CPRD Aurum Data Specification [Available from: https://www.cprd.com/primary-care.
28. England N. SNOMED CT [updated 22 January 2024. Available from: https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct.
29. CPRD Code Browser quick user guide. 2022.
30. Jick SS, Hagberg KW, Persson R, Vasilakis-Scaramozza C, Williams T, Crellin E, et al. Quality and completeness of diagnoses recorded in the new CPRD Aurum Database: evaluation of pulmonary embolism. Pharmacoepidemiol Drug Saf. 2020;29(9):1134-40.
31. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract. 2010;60(572):e128-36.
32. Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet. 2021;398(10296):262-76.
33. Agency EM. Forxiga [Digital]. European Union; 2012 [updated 06/03/2023. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga.

34. Jan Biessels G, Verhagen C, Janssen J, van den Berg E, Wallenstein G, Zinman B, et al. Effects of linagliptin vs glimepiride on cognitive performance in type 2 diabetes: results of the randomised double-blind, active-controlled CAROLINA-COGNITION study.
35. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. Journal of Diabetes Investigation. 2013;4(6):640-50.
36. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. JAMA - Journal of the American Medical Association. 2019;322(16):1589-99.
37. Dunn N MM, Perry VH, Holmes C. Association between dementia and infectious disease: evidence from a case-control study. Alzheimer Dis Assoc Disord. 2005;19(2):91-4. doi: 10.1097/01.wad.0000165511.52746.1f.
38. Dell'Agnello G, Desai U, Kirson NY, Wen J, Meiselbach MK, Reed CC, et al. Reliability of coded data to identify earliest indications of cognitive decline, cognitive evaluation and Alzheimer's disease diagnosis: a pilot study in England. BMJ Open. 2018;8(3):e019684.
39. Donegan K, Fox N, Black N, Livingston G, Banerjee S, Burns A. Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study. Lancet Public Health. 2017;2(3):e149-e56.
40. Khosrow-Khavar F, Rej S, Yin H, Aprikian A, Azoulay L. Androgen Deprivation Therapy and the Risk of Dementia in Patients With Prostate Cancer. Journal of Clinical Oncology. 2016;35(2):201-7.
41. Seshadri S ZG, Derby LE, Myers MW, Jick H, Drachman DA. Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease. Arch Neurol. 2001;58(3):435-40. doi: 10.1001/archneur.58.3.435.
42. McGuinness LA, Warren-Gash C, Moorhouse LR, Thomas SL. The validity of dementia diagnoses in routinely collected electronic health records in the United Kingdom: A systematic review. Pharmacoepidemiol Drug Saf. 2019;28(2):244-55.
43. Ford E, Sheppard J, Oliver S, Rooney P, Banerjee S, Cassell JA. Automated detection of patients with dementia whose symptoms have been identified in primary care but have no formal diagnosis: a retrospective case-control study using electronic primary care records. BMJ Open. 2021;11(1):e039248.
44. McLennan D, Barnes H, Noble M, Davies J, Garratt E, Dibben C. The English Indices of Deprivation 20102011.
45. Bursi F, Rocca WA, Killian JM, Weston SA, Knopman DS, Jacobsen SJ, et al. Heart disease and dementia: a population-based study. Am J Epidemiol. 2006;163(2):135-41.
46. Breteler MM, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. Bmj. 1994;308(6944):1604-8.
47. Barzilay JI, Fitzpatrick AL, Luchsinger J, Yasar S, Bernick C, Jenny NS, et al. Albuminuria and dementia in the elderly: a community study. Am J Kidney Dis. 2008;52(2):216-26.
48. Kurella M, Chertow GM, Luan J, Yaffe K. Cognitive impairment in chronic kidney disease. J Am Geriatr Soc. 2004;52(11):1863-9.
49. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-306.

50. He P, Eriksson F, Scheike TH, Zhang MJ. A Proportional Hazards Regression Model for the Sub-distribution with Covariates Adjusted Censoring Weight for Competing Risks Data. Scand Stat Theory Appl. 2016;43(1):103-22.
51. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 13. Older Adults: Standards of Care in Diabetes—2023. Diabetes Care. 2022;46(Supplement_1):S216-S29.
52. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. Nature Reviews Endocrinology. 2022;18(9):525-39.
53. Jin Y, Zhao H, Hou Y, Song G. 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 Diabetologica. 2020;57(10):1129-44.
54. Tang H, Shao H, Shaaban CE, Yang K, Brown J, Anton S, et al. Newer glucose-lowering drugs and risk of dementia: A systematic review and meta-analysis of observational studies. Journal of the American Geriatrics Society. 2023;71(7):2096-106.
55. Mone P, Lombardi A, Gambardella J, Pansini A, Macina G, Morgante M, et al. Empagliflozin Improves Cognitive Impairment in Frail Older Adults With Type 2 Diabetes and Heart Failure With Preserved Ejection Fraction. Diabetes Care. 2022;45(5):1247-51.
56. Mone P, Varzideh F, Jankauskas SS, Pansini A, Lombardi A, Frullone S, et al. SGLT2 Inhibition via Empagliflozin Improves Endothelial Function and Reduces Mitochondrial Oxidative Stress: Insights From Frail Hypertensive and Diabetic Patients. Hypertension. 2022;79(8):1633-43.
57. Zhao Y, Zhang R, Wang S. 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. 2022;51(6):1251-8.
58. Cheng H, Zhang Z, Zhang B, Zhang W, Wang J, Ni W, et al. 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. 2022;45(5):1201-10.
59. Low S, Goh KS, Ng TP, Moh A, Ang SF, Wang J, et al. Association Between Use of Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibitors and Cognitive Function in a Longitudinal Study of Patients with Type 2 Diabetes. Journal of Alzheimer's Disease. 2022;87:635-42.
60. Perna S, Mainardi M, Astrone P, Gozzer C, Biava A, Bacchio R, et al. 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. 2018;10:141-51.

Chapter 4: Discussion

4.1 Summary of findings

The primary objective of our study was to assess the association between SGLT-2is and dementia among patients with type 2 diabetes, aged 40 years and older. Previous observational studies investigating this association implied SGLT-2i use was linked to a reduced risk of developing dementia compared to other anti-diabetic agents (65, 70). In our study, we did not find a statistically significant association between SGLT-2i use and the risk of incident dementia compared to DPP-4i use (aHR: 0.78; 95% CI: 0.55-1.12).

In our secondary age-specific stratified analysis, SGLT-2i use was linked with a lower risk of incident dementia compared to DPP-4i users among patients aged 65 years or older with type 2 diabetes (aHR:0.50; 95% CI: 0.31-0.80). We did not find an association between SGLT-2i use and the risk of incident dementia among people younger than 65 years. We also observed a 14% lower risk of MCI among SGLT-2i users when compared to DPP-4i users (aHR: 0.86; 95% CI: 0.80-0.92). We did not find any difference between SGLT-2i users and DPP-4i users based on their subtypes of dementia, sex, prior history of cardiovascular disease or renal insufficiency or their prescription of varying molecules of SGLT-2is (i.e. canagliflozin, dapagliflozin or empagliflozin). However, with sulfonylurea use as a comparator, instead of DPP-4is, we observed that SGLT-2i use was associated with a decreased risk of dementia (aHR: 0.74; 95% CI: 0.57-0.96). The number of events in the SGLT-2i exposure groups was low in this stratified analysis, which may have led to high uncertainty. However, this was anticipated given the small number of events overall in the primary analysis for this group. In sensitivity analyses, the findings were aligned with our primary findings.

4.2 Comparison of the findings with previous studies on association between SGLT-2is and dementia

Diabetes and its associated complications are topics of significant attention in both public health research and clinical practice worldwide. Hence, a number of studies were conducted to investigate the additional beneficial effects of anti-diabetic agents beyond their primary role in glycaemic control to alleviate the associated complications, such as potential neuroprotective effects of glucose-lowering agents (68, 71-73). Among various anti-diabetic agents, the role of SGLT-2is in preserving cognitive function has emerged as a point of interest along with their

established beneficial effect on cardiovascular and renal outcomes. In preclinical studies, SGLT-2is showed a decreased risk in Alzheimer's disease indicators like amyloidosis and improvement in both cerebral microvascular health and cognitive impairment (50, 74). Meta-analysis conducted including five randomized control trials on the effects of SGLT-2is on stroke and its subtypes revealed SGLT-2is have a potential protective effect specifically against hemorrhagic stroke (RR = 0.49, 95% CI 0.30–0.82, P = 0.007), though risk of other subtypes such as fatal stroke, non-fatal stroke, ischemic stroke or transient ischemic attack was not associated with SGLT-2i use (75). Beside the potential protective effect of SGLT-2is on the brain or cerebral vessels, SGLT-2is have also been linked to a reduced risk of heart failure (61, 76) and renal protection (77, 78), which may ultimately lead to better brain health. Research on the association of SGLT-2is and dementia are currently being studied (63, 66, 79), and our study contributes to this growing body of evidence on this association.

In our large population-based retrospective cohort study of patients, aged 40 years or older, with type 2 diabetes, we observed fewer events of incident dementia among SGLT-2i users compared to DPP-4i users. However, after adjusting for covariates in our analysis, the observed association between SGLT-2i use and reduced risk of dementia no longer remained statistically significant. Despite this, the point estimate was substantial, with a hazard ratio of 0.78 indicating a trend towards a lower risk of dementia among SGLT-2i users. In our secondary analysis, we observed SGLT-2i use was associated with a reduced risk of dementia among individuals aged 65 years or older. This finding was consistent with previously published retrospective cohort studies. Proietti et al. (2023), examined cardiovascular, cerebrovascular and cognitive outcomes of SGLT-2is use among patients with atrial fibrillation and type 2 diabetes. They compared the risk of dementia among SGLT-2i users with a mean age of 66.7 years with individuals receiving other anti-diabetic agents except SGLT-2is. It was a retrospective cohort study with a follow-up period of three years until the primary or secondary outcomes occurred. They found a 66% elevated risk of incident dementia (HR: 1.66, 95% CI: 1.30–2.12) among non-users of SGLT-2is compared to SGLT-2i users (70). The recent retrospective cohort study conducted by Wu et al., 2022, with the most comparable sample size to our study, found the use of SGLT-2is compared to use of DPP-4is was associated with a 20% reduction in risk of dementia among Ontario residents aged ≥66 years

over a mean follow-up of 2.8 years with an intention-to-treat approach. Their secondary analysis with an as-treated approach revealed a stronger association of SGLT-2is with lower dementia risk (aHR: 0.66, 95% CI: 0.57–0.76) (63). However, this study did not exclude patients with prior history of MCI, which could lead to elevated number of events in the analysis, given people with MCI may be less likely given a SGLT-2i. Though the authors attempted to proxy MCI by excluding residents of long-term care on cohort entry, the possibility of inclusion of patients with MCI remains. In two other retrospective cohort studies, Siao et al. (2022) and Mui et al. (2021) also found that the use of SGLT-2i was associated with a lower risk of dementia, though their comparator group and age of the cohort were different. Siao et al. (2022) compared with SGLT-2i users with patients who were using other anti-diabetic agents except SGLT-2is defined as non-SGLT-2is user, in the general Taiwanese population. The authors reported an 11% lower risk of incident dementia (aHR: 0.89, 95% CI: 0.82–0.96; p = .0021) after matching with propensity scores (65). Similar to our study population, in Siao et al. (2022), the authors included a higher proportion of younger patients, with 53.1% being under 60 years older, compared to other studies. This demographic difference could have impacted the study outcomes, contributing to the relatively low hazard ratio observed in Siao et al. (2022) compared to the findings of Mui et al. (2021) and Wu et al., (2022). Mui et al. (2021) observed a much larger reduction in the risk of dementia associated with SGLT-2i use when compared to DPP-4i use (HR: 0.41, 95% CI: 0.27–0.61, P < 0.0001) among elderly individuals in a Chinese population cohort (i.e., average age of 61 years). They conducted their analyses using propensity score matching using a 1:2 ratio (66). None of these studies considered to exclude patients with the history of MCI. The low number of incident dementia cases in our study could be attributed to this exclusion of patients with history of MCI. Also, given the relatively shorter follow up of our study with younger cohort with median age around 57 years after PS stratification weighting, may also attributed to fewer incident dementia events.

There were a handful of prospective studies conducted on the association between SGLT-2is and cognitive function. In studies in which patients MCI and dementia were included, the use of SGLT-2is was strongly associated with improvements in cognitive function measured by Montreal Cognitive Assessment (MoCA) score (80, 81). In contrast, studies conducted with patients with normal baseline cognitive function showed no significant associations between the

use of SGLT-2is and changes in cognitive function scores (82, 83). This corresponds with our study findings since we excluded patients with any prior history of MCI or dementia before starting the follow-up. This inconsistency might also be due to relatively younger age of participants in our study (82, 83) compared to other studies in which only older individuals were included (80, 81). This observation is also aligned with the results of the subgroup analysis for dementia onset in our study, whereby we stratified individuals age <65 or ≥65 years of age and observed that SGLT-2i use was associated with a reduced risk of incident dementia among individuals age ≥65 years. Moreover, SGLT-2i was shown to be beneficial in frail older adults with diabetes to improve their cognitive impairment (81). Thus, although our results highlight the potential benefits of SGLT-2is in elderly patients without dementia or MCI, further research is necessary to explore the benefits SGLT-2is use in reducing the risk of developing or progression of cognitive impairment.

Randomized controlled trials (RCTs) conducted on the association of SGLT-2is use and cognitive function were rather few with short duration of follow up, smaller sample size and often with a specific SGLT-2i molecule (82, 84, 85). One RCT carried out on 39 elderly participants with type 2 diabetes with a follow-up period of 12 months conducted by Perna et al. (2018) showed that, patients treated with SGLT-2is did not suffer any reduction in cognitive performance when compared to incretins use (84). Other studies had a shorter follow-up period of 16 weeks (82) and 6 months (85) and did not show any significant effect of SGLT-2is on cognitive function.

4.3 Strengths and Limitations

Our study has several strengths. It was a large-scale population-based cohort study that investigated the risk of dementia associated with SGLT-2i use. Though our primary analysis did not demonstrate a reduction in dementia risk, our secondary analysis indicated a potential reduction in the risk of dementia among older age group of SGLT-2is users. A key strength of our study was that our cohort comprised of individuals without any prior history of dementia and MCI, which allowed us to assess the association between the risk of developing dementia and SGLT-2i use in a population with type 2 diabetes and no prior history of cognitive impairment. Another strength was our selection of DPP-4i as a comparator. This was important because most previous evidence compared SGLT-2is with a wide array of anti-diabetic agents. By selecting DPP-4is, which is generally prescribed at a similar level in type 2 diabetes management, the baseline

characteristics between the two user groups of these anti-diabetic agents were more similar in terms of duration of diabetes, co-morbidities, and other aspects. Furthermore, in our study, we rigorously adjusted for 34 potential confounders, including factors such as frailty, smoking status, BMI and Hba1c. These covariates were balanced between the two groups after adjustment with PS fine stratification.

Our study has several limitations. The relatively short follow up period in our study might have led to less incident dementia events. Unmeasured confounding is a known limitation of observational studies. However, we used an active comparator at the design stage to make subjects in the exposure and reference groups as comparable as possible. Additionally, we conducted an extensive literature search to identify and adjust for 34 relevant confounders, achieving good balance between SGLT-2i and DPP-4i users. In our study, diagnosis of dementia and MCI was determined through linkage to electronic health records rather than an in-person screening, and as such milder cases of dementia were not identified. However, this method is unlikely to introduce differential bias between two exposure groups. Moreover, by incorporating variables like cognitive function tests, prescription for anti-dementia drugs, referral to psychiatrist, neurologist, geriatrician, or memory clinic which minimized the possibility, we were able to capture more instances of MCI. Another limitation of our study was the low number of events of dementia subtypes, because most subtypes of dementia were coded as “dementia” in the database unless otherwise specified. This low number of events documented for Alzheimer’s disease and vascular dementia precluded us to infer any association. However, the total number of dementia events was very low for the SGLT-2i users anyway in the primary analysis, so any stratified analysis by type of dementia, even if all dementias had been specified in term of subtype would have been challenging and the number would still be limited. Also, most patients have mixed forms of dementia, which includes both forms; therefore, it was difficult to study the effect on one subtype.

Chapter 5: Conclusion

In summary, our literature review suggested that type 2 diabetes has been linked with increased risk of dementia in multiple studies and anti-diabetic agents are new point of interest to manage the complications of diabetes like cognitive dysfunctions along with glycaemic control. Till now a handful of observational studies has shown positive effect of anti-diabetic agents on cognitive function though the evidence were varied. In our study we set out to determine if SGLT-2i use was associated with a decreased risk of incident dementia compared to DPP-4i use among patients with type 2 diabetes using data from CPRD Aurum database from UK.

Our large population-based retrospective cohort study was conducted to explore the association between SGLT-2i use and the risk of dementia. Our primary findings did not yield conclusive evidence to infer any association between SGLT-2i use and the risk of incident dementia. Our secondary findings revealed that the use of SGLT-2is was associated with a reduced risk of dementia among elderly patients aged 65 years or older. Also, SGLT-2i use showed potential beneficial effect in reducing the risk of MCI. Considering the observational nature of the study with relatively shorter follow-up period, we acknowledge that residual confounding might still be present, despite our effort to mitigate potential biases. Therefore, further large-scale prospective studies with longer follow-up period are needed to confirm whether SGLT-2i use affects dementia risk and other cognitive outcomes.

References

1. Magliano DJ, Boyko EJ, committee IDFDAtes. IDF Diabetes Atlas. Idf diabetes atlas. Brussels: International Diabetes Federation© International Diabetes Federation, 2021.; 2021.

2. Gregory GA, Robinson TIG, Linklater SE, Wang F, Colagiuri S, de Beaufort C, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. The lancet Diabetes & endocrinology. 2022;10(10):741-60.
3. Organization WH. Diabetes 2023 [updated 5 April 2023; cited 2024 2 February]. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes.
4. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Scientific Reports. 2020;10(1).
5. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Kaabi JA. Epidemiology of Type 2 diabetes - Global burden of disease and forecasted trends. Journal of Epidemiology and Global Health. 2020;10(1):107-11.
6. Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GEHM, Biessels GJ. Cognitive function in patients with diabetes mellitus: Guidance for daily care. The Lancet Neurology2015.
7. Organization WH. Dementia 2023 [updated 15 March 2023; cited 2023 2 November]. Available from: https://www.who.int/news-room/fact-sheets/detail/dementia.
8. Nichols E, Steinmetz JD, Vollset SE, Fukutaki K, Chalek J, Abd-Allah F, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. The Lancet Public Health. 2022;7(2):e105-e25.
9. Pedroza P, Miller-Petrie MK, Chen C, Chakrabarti S, Chapin A, Hay S, et al. Global and regional spending on dementia care from 2000–2019 and expected future health spending scenarios from 2020–2050: An economic modelling exercise.
10. Kumar A SJGATJW. Alzheimer Disease: StatPearls Publishing; 2022.
11. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: A systematic review. Lancet Neurology2006.
12. Kopf D, Frölich L. Risk of incident Alzheimer's disease in diabetic patients: A systematic review of prospective trials. Journal of Alzheimer's Disease. 2009;16(4):677-85.
13. Profenno LA, Porsteinsson AP, Faraone SV. Meta-Analysis of Alzheimer's Disease Risk with Obesity, Diabetes, and Related Disorders. Biological Psychiatry. 2010;67(6):505-12.
14. Xu W, Qiu C, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Mid- And late-life diabetes in relation to the risk of dementia: A population-based twin study. Diabetes. 2009;58(1):71-7.
15. Dao L, Choi S, Freeby M. Type 2 diabetes mellitus and cognitive function: Understanding the connections. Current Opinion in Endocrinology, Diabetes and Obesity2023.
16. Lyu F, Wu D, Wei C, Wu A. Vascular cognitive impairment and dementia in type 2 diabetes mellitus: An overview. Life Sciences: Elsevier Inc.; 2020.
17. Aronson D. Hyperglycemia and the pathobiology of diabetic complications. Adv Cardiol. 2008;45:1-16.
18. Moran C, Lacy ME, Whitmer RA, Tsai A-L, Quesenberry CP, Karter AJ, et al. Glycemic Control Over Multiple Decades and Dementia Risk in People With Type 2 Diabetes. JAMA Neurology. 2023.

19. Geijselaers SLC, Sep SJS, Stehouwer CDA, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: A systematic review. The Lancet Diabetes and Endocrinology: Lancet Publishing Group; 2015. p. 75-89.
20. Rawlings AM, Sharrett AR, Albert MS, Coresh J, Windham BG, Power MC, et al. The association of late-life diabetes status and hyperglycemia with incident mild cognitive impairment and dementia: The ARIC study. Diabetes Care. 2019;42(7):1248-64.
21. Pal K, Mukadam N, Petersen I, Cooper C. Mild cognitive impairment and progression to dementia in people with diabetes, prediabetes and metabolic syndrome: a systematic review and meta-analysis. Social Psychiatry and Psychiatric Epidemiology: Dr. Dietrich Steinkopff Verlag GmbH and Co. KG; 2018. p. 1149-60.
22. Yakel JHaJL. Cholinergic modulation of the hippocampal region and memory function. Journal of Neurochemistry. 2017;142 [Suppl. 2].
23. Association As. FDA-approved treatments for Alzheimer's 2024 [cited 2023 5 December]. Available from: https://alz.org/media/documents/alzheimers-dementia-fda-approved-treatments-for-alzheimers-ts.pdf.
24. O'Brien JT, Holmes C, Jones M, Jones R, Livingston G, McKeith I, et al. Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology. Journal of Psychopharmacology2017.
25. Hildreth KL, Church S. Evaluation and Management of the Elderly Patient Presenting with Cognitive Complaints. Medical Clinics of North America: W.B. Saunders; 2015. p. 311-35.
26. Areosa SA, Sherriff F. Memantine for dementia. The Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2003.
27. Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, et al. Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: Secondary and post-hoc analyses. The Lancet Neurology. 2015;14(12):1171-81.
28. Information CIfH. Dementia prevention and treatment 2024 [cited 2023 4 October]. Available from: https://www.cihi.ca/en/dementia-in-canada/spotlight-on-dementia-issues/dementia-prevention-and-treatment#:~:text=Drugs%20in%20dementia%20treatment%201%20There%20is%20currently,the%20progression%20of%20the%20disease.%20...%20More%20items.
29. Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. Jama. 1998;280(17):1490-6.
30. Gradman TJ, Laws A, Thompson LW, Reaven GM. Verbal learning and/or memory improves with glycemic control in older subjects with non-insulin-dependent diabetes mellitus. J Am Geriatr Soc. 1993;41(12):1305-12.
31. Meneilly GS, Cheung E, Tessier D, Yakura C, Tuokko H. The effect of improved glycemic control on cognitive functions in the elderly patient with diabetes. J Gerontol. 1993;48(4):M117-21.
32. Samaras K, Makkar S, Crawford JD, Kochan NA, Wen W, Draper B, et al. Metformin use is associated with slowed cognitive decline and reduced incident dementia in older adults with type 2 diabetes: The Sydney memory and ageing study. Diabetes Care. 2020;43(11):2691-701.

33. Herath PM, Cherbuin N, Eramudugolla R, Anstey KJ. The Effect of Diabetes Medication on Cognitive Function: Evidence from the PATH Through Life Study. BioMed Research International. 2016;2016.
34. Baradhi SVSKKKM. Dipeptidyl Peptidase IV (DPP IV) Inhibitors2023.
35. Pipatpiboon N, Pintana H, Pratchayasakul W, Chattipakorn N, Chattipakorn SC. DPP4-inhibitor improves neuronal insulin receptor function, Brain mitochondrial function and cognitive function in rats with insulin resistance induced by high-fat diet consumption. European Journal of Neuroscience. 2013;37(5):839-49.
36. Kim YG, Jeon JY, Kim HJ, Kim DJ, Lee KW, Moon SY, et al. Risk of dementia in older patients with type 2 diabetes on dipeptidyl-peptidase IV inhibitors versus sulfonylureas: A real-world population-based cohort study. Journal of Clinical Medicine. 2019;8(1).
37. Lipscombe L, Booth G, Butalia S, Dasgupta K, Eurich DT, Goldenberg R, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults. Can J Diabetes. 2018;42 Suppl 1:S88-s103.
38. Isik AT, Soysal P, Yay A, Usarel C. The effects of sitagliptin, a DPP-4 inhibitor, on cognitive functions in elderly diabetic patients with or without Alzheimer's disease. Diabetes Research and Clinical Practice. 2017;123:192-8.
39. Biessels GJ, Verhagen C, Janssen J, van den Berg E, Zinman B, Rosenstock J, et al. Effect of Linagliptin on Cognitive Performance in Patients With Type 2 Diabetes and Cardiorenal Comorbidities: The CARMELINA Randomized Trial. Diabetes Care. 2019;42(10):1930-8.
40. Biessels GJ, Verhagen C, Janssen J, van den Berg E, Wallenstein G, Zinman B, et al. Effects of linagliptin vs glimepiride on cognitive performance in type 2 diabetes: results of the randomised double-blind, active-controlled CAROLINA-COGNITION study. Diabetologia. 2021;64(6):1235-45.
41. Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet. 2021;398(10296):262-76.
42. Agency EM. Forxiga [Digital]. European Union; 2012 [updated 6 March 2023. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga.
43. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2017;24(1):73-9.
44. Fathi A, Vickneson K, Singh JS. SGLT2-inhibitors; more than just glycosuria and diuresis. Heart Fail Rev. 2021;26(3):623-42.
45. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017;377(7):644-57.
46. Steiner S. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. Zeitschrift fur Gefassmedizin: Krause und Pachernegg GmbH; 2016. p. 17-8.
47. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-57.
48. Jia R, Wang Q, Huang H, Yang Y, Chung YF, Liang T. Cardiovascular disease risk models and dementia or cognitive decline: a systematic review. Front Aging Neurosci. 2023;15:1257367.
49. Pawlos A, Broncel M, Woźniak E, Gorzelak-Pabiś P. Neuroprotective effect of SGLT2 inhibitors. Molecules: MDPI; 2021.

50. Hierro-Bujalance C, Infante-Garcia C, Del Marco A, Herrera M, Carranza-Naval MJ, Suarez J, et al. Empagliflozin reduces vascular damage and cognitive impairment in a mixed murine model of Alzheimer's disease and type 2 diabetes. Alzheimer's Research and Therapy. 2020;12(1).
51. Tahara A, Takasu T, Yokono M, Imamura M, Kurosaki E. Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects. J Pharmacol Sci. 2016;130(3):159-69.
52. Wiciński M, Wódkiewicz E, Górski K, Walczak M, Malinowski B. Perspective of SGLT2 Inhibition in Treatment of Conditions Connected to Neuronal Loss: Focus on Alzheimer's Disease and Ischemia-Related Brain Injury. Pharmaceuticals (Basel). 2020;13(11).
53. Cinti F, Moffa S, Impronta F, Cefalo CM, Sun VA, Sorice GP, et al. Spotlight on ertugliflozin and its potential in the treatment of type 2 diabetes: evidence to date. Drug Des Devel Ther. 2017;11:2905-19.
54. Hayden MR, Grant DG, Aroor AR, DeMarco VG. Empagliflozin Ameliorates Type 2 Diabetes-Induced Ultrastructural Remodeling of the Neurovascular Unit and Neuroglia in the Female db/db Mouse. Brain Sci. 2019;9(3).
55. Sa-Nguanmoo P, Tanajak P, Kerdphoo S, Jaiwongkam T, Pratchayasakul W, Chattipakorn N, et al. SGLT2-inhibitor and DPP-4 inhibitor improve brain function via attenuating mitochondrial dysfunction, insulin resistance, inflammation, and apoptosis in HFD-induced obese rats. Toxicol Appl Pharmacol. 2017;333:43-50.
56. Tsushima Y, Lansang MC, Makin V. The role of SGLT-2 inhibitors in managing type 2 diabetes. Cleve Clin J Med. 2021;88(1):47-58.
57. Wium-Andersen IK, Osler M, Jørgensen MB, Rungby J, Wium-Andersen MK. Antidiabetic medication and risk of dementia in patients with type 2 diabetes: A nested case-control study. European Journal of Endocrinology. 2019;181(5):499-507.
58. Donegan K, Fox N, Black N, Livingston G, Banerjee S, Burns A. Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study. The Lancet Public Health. 2017;2(3):e149-e56.
59. Harper W, Clement M, Goldenberg R, Hanna A, Main A, Retnakaran R, et al. Policies, Guidelines and Consensus Statements: Pharmacologic Management of Type 2 Diabetes-2015 Interim Update. Canadian Journal of Diabetes: Elsevier B.V.; 2015. p. 250-2.
60. Biessels GJ, Verhagen C, Janssen J, Van Den Berg E, Zinman B, Rosenstock J, et al., editors. Effect of linagliptin on cognitive performance in patients with type 2 diabetes and cardiorenal comorbidities: The CARMELINA randomized trial. Diabetes Care; 2019 2019/10//: American Diabetes Association Inc.
61. Filion KB, Lix LM, Yu OH, Dell'Aniello S, Douros A, Shah BR, et al. Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events: multi-database retrospective cohort study. Bmj. 2020;370:m3342.
62. Yu OHY, Dell'aniello S, Shah BR, Brunetti VC, Daigle JM, Fralick M, et al. Sodium–glucose cotransporter 2 inhibitors and the risk of belowknee amputation: A multicenter observational study. Diabetes Care. 2020;43(10):2444-52.
63. Wu CY, Iskander C, Wang C, Xiong LY, Shah BR, Edwards JD, et al. Association of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors with time to dementia: a population-based cohort study. Alzheimer's & Dementia. 2022;18(S10).

64. Barbiellini Amidei C, Fayosse A, Dumurgier J, MacHado-Fragua MD, Tabak AG, Van Sloten T, et al. Association between Age at Diabetes Onset and Subsequent Risk of Dementia. JAMA - Journal of the American Medical Association. 2021;325(16):1640-9.
65. Siao WZ, Lin TK, Huang JY, Tsai CF, Jong GP. The association between sodium-glucose cotransporter 2 inhibitors and incident dementia: A nationwide population-based longitudinal cohort study. Diabetes and Vascular Disease Research. 2022;19(2).
66. Mui JV, Zhou J, Lee S, Leung KSK, Lee TTL, Chou OHI, et al. Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors vs. Dipeptidyl Peptidase-4 (DPP4) Inhibitors for New-Onset Dementia: A Propensity Score-Matched Population-Based Study With Competing Risk Analysis. Frontiers in Cardiovascular Medicine. 2021;8.
67. Pang B, Zhang LL, Li B, Sun FX, Wang ZD. The sodium glucose co-transporter 2 inhibitor ertugliflozin for Alzheimer's disease: Inhibition of brain insulin signaling disruption-induced tau hyperphosphorylation. Physiology and Behavior. 2023;263.
68. Tang H, Shao H, Shaaban CE, Yang K, Brown J, Anton S, et al. Newer glucose-lowering drugs and risk of dementia: A systematic review and meta-analysis of observational studies. Journal of the American Geriatrics Society. 2023;71(7):2096-106.
69. Ford E, Sheppard J, Oliver S, Rooney P, Banerjee S, Cassell JA. Automated detection of patients with dementia whose symptoms have been identified in primary care but have no formal diagnosis: a retrospective case-control study using electronic primary care records. BMJ Open. 2021;11(1):e039248.
70. Proietti R, Rivera-Caravaca JM, López-Gálvez R, Harrison SL, Marín F, Underhill P, et al. 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. 2023;12(8).
71. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 13. Older Adults: Standards of Care in Diabetes—2023. Diabetes Care. 2022;46(Supplement_1):S216-S29.
72. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. Nature Reviews Endocrinology. 2022;18(9):525-39.
73. Jin Y, Zhao H, Hou Y, Song G. 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 Diabetologica. 2020;57(10):1129-44.
74. Rizzo MR, Di Meo I, Polito R, Auriemma MC, Gambardella A, di Mauro G, et al. Cognitive impairment and type 2 diabetes mellitus: Focus of SGLT2 inhibitors treatment. Pharmacol Res. 2022;176:106062.
75. Tsai W-H, Chuang S-M, Liu S-C, Lee C-C, Chien M-N, Leung C-H, et al. Effects of SGLT2 inhibitors on stroke and its subtypes in patients with type 2 diabetes: a systematic review and meta-analysis. Scientific Reports. 2021;11(1):15364.
76. Han SJ, Ha KH, Lee N, Kim DJ. Effectiveness and safety of sodium-glucose co-transporter-2 inhibitors compared with dipeptidyl peptidase-4 inhibitors in older adults with type 2 diabetes: A nationwide population-based study. Diabetes Obes Metab. 2021;23(3):682-91.
77. Zhuo M, Paik JM, Wexler DJ, Bonventre JV, Kim SC, Patorno E. SGLT2 Inhibitors and the Risk of Acute Kidney Injury in Older Adults With Type 2 Diabetes. Am J Kidney Dis. 2022;79(6):858-67.e1.

78. Iskander C, Cherney DZ, Clemens KK, Dixon SN, Harel Z, Jeyakumar N, et al. Use of sodium-glucose cotransporter-2 inhibitors and risk of acute kidney injury in older adults with diabetes: a population-based cohort study. Cmaj. 2020;192(14):E351-e60.
79. Youn YJ, Kim S, Jeong HJ, Ah YM, Yu YM. Sodium-glucose cotransporter-2 inhibitors and their potential role in dementia onset and cognitive function in patients with diabetes mellitus: a systematic review and meta-analysis. Front Neuroendocrinol. 2024;73:101131.
80. Mone P, Lombardi A, Gambardella J, Pansini A, Macina G, Morgante M, et al. Empagliflozin Improves Cognitive Impairment in Frail Older Adults With Type 2 Diabetes and Heart Failure With Preserved Ejection Fraction. Diabetes Care. 2022;45(5):1247-51.
81. Mone P, Varzideh F, Jankauskas SS, Pansini A, Lombardi A, Frullone S, et al. SGLT2 Inhibition via Empagliflozin Improves Endothelial Function and Reduces Mitochondrial Oxidative Stress: Insights From Frail Hypertensive and Diabetic Patients. Hypertension. 2022;79(8):1633-43.
82. Cheng H, Zhang Z, Zhang B, Zhang W, Wang J, Ni W, et al. 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. 2022;45(5):1201-10.
83. Low S, Goh KS, Ng TP, Moh A, Ang SF, Wang J, et al. Association Between Use of Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibitors and Cognitive Function in a Longitudinal Study of Patients with Type 2 Diabetes. Journal of Alzheimer's Disease. 2022;87:635-42.
84. Perna S, Mainardi M, Astrone P, Gozzer C, Biava A, Bacchio R, et al. 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. 2018;10:141-51.
85. Zhao Y, Zhang R, Wang S. 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. 2022;51(6):1251-8.