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Original Article

New-generation antidiabetic medications and dementia risk in older adults with type 2 diabetes: A retrospective cohort study

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ABSTRACT

Background: New-generation antidiabetic medications may have therapeutic potential for dementia, beyond their glycemic effects. However, information from observational studies exploring the association between new-generation antidiabetic use and dementia risk is limited.
Objectives: To examine the association between new-generation antidiabetic medication use and dementia risk.
Design: Retrospective cohort study using electronic health records of a large non-profit health maintenance organization.
Participants: 84,798 dementia-free individuals aged ≥65y with type 2 diabetes.
Measurements: Antidiabetic medication exposure was based on purchased prescriptions and was used as a time-varying variable. Exposure periods were defined as periods in which either dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose cotransporter-2 inhibitors (SGLT-2i), or glucagon-like peptide-1 analogs (GLP-1a) or their combinations were used, otherwise unexposed. Dementia classification was based on the International Classification of Diseases, Ninth Revision codes or antidementia medication prescriptions. Cox regression models were fitted to quantify the association between antidiabetic medication use and incident dementia. Models were adjusted for 13 potential sources of confounding using inverse-probability weighting.
Results: Among 84,798 individuals with a mean diabetes onset age of 66.4 ± 7.5 years, the median follow-up for dementia risk was 8.7 years (Q1-Q3: 5.4–12.8). Dementia was diagnosed in 11,642 (13.7%) individuals. New-generation medication use was associated with reduced dementia risk (HR = 0.69; 95% CI, 0.66–0.73) and by drug classes (DPP-4i, HR 0.67 [95% CI 0.63–0.71]; SGLT-2i, 0.63 [95% CI 0.56–0.70], GLP-1a, 0.61 [95% CI 0.54–0.69].
Conclusions: The results of this large-scale study suggest that new-generation antidiabetic medication use may be associated with lower dementia risk in older adults with T2D.

1. Introduction

Dementia refers to a group of disorders and diseases characterized by cognitive impairment that limits daily activities and often results in a decline in cognitive function [1,2]. An estimated 57 million individuals are currently living with dementia, and projections suggest that this number will reach 153 million globally by the year 2050 [1,2]. Current antidementia treatments are limited and can only alleviate symptoms or have modest benefit to cognition in patients at specific disease stages [2,3]). As a result, dementia prevention is acknowledged as a national and international priority, with efforts directed towards addressing potentially modifiable risk factors [2].

Type 2 diabetes (T2D) is an established risk factor for Alzheimer's disease (AD) and vascular dementia, the most common dementia subtypes [2,4]. In addition, T2D shares multiple signaling pathways and biological processes with AD [5–7] and vascular dementia [4,8], including central and peripheral insulin resistance, chronic inflammation, and cerebrovascular dysfunction.

Based on these common pathophysiologies, it is postulated that antidiabetic medications may benefit brain health even beyond their glycemic control effects. Indeed, decreased dementia incidence was observed in individuals exposed to some antidiabetic medications, such as metformin and pioglitazone, independently of glycemic control indices [9,10]. Yet, other antidiabetic medications, including insulin and sulfonylureas (SU), were associated with increased dementia risk [2,11,12] possibly due to their hypoglycemic effects [13], or showed no associations with dementia incidence [11,14].

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New-generation antidiabetic medications that were released to the market in recent years are dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 analogs (GLP-1a), and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) [15]. DPP-4i and GLP-1a indirectly reduce glucose levels by increasing incretin levels and enhancing insulin secretion, while SGLT-2i lowers glucose levels by promoting glucose renal excretion [15]. The new-generation antidiabetic medications also carry a low hypoglycemia risk and were found in preclinical studies to inhibit amyloid plaque formation and reduce tau phosphorylation [15]. Additionally, preclinical studies suggest that these medications improve synaptic plasticity, learning, and memory [16,17].

Systematic reviews and meta-analyses assessed observational studies that examined the association between new-generation antidiabetic medications and dementia risk [18–21]. Most studies showed that the new antidiabetes medications use is associated with dementia risk reduction [18–21]. However, the number of observational studies included in these systematic reviews was low (up to 10 overall), and their findings were inconsistent. In addition, the studies included were limited by their case-control design with a low matching ratio [9,12,22], the comparison of one medication use versus non-use [9,12,22], and a limited quantification of drug exposure. For example, exposure was determined at a single time point or based on the longest medication prescription, while not accounting for periods without medication and prescription renewal [9,12]. These types of exposure modeling might not reflect "real-world" medication use patterns and lead to possible misclassification of medication use as up to two-thirds of individuals with T2D tend to change dosage and switch or add antidiabetic prescriptions to their treatment routine [23,24].

To overcome some of the prior methodological limitations, we used a retrospective cohort study design, with comprehensive national-based data. We compared dementia risk between periods of new-generation medication use and non-use while adjusting for time-varying covariates. Our general aim was to examine the associations between cumulative use of DPP-4i, GLP-1a, and SGLT-2i and dementia risk in older adults with T2D.

2. Methods

2.1. Study sample and design

In this nationwide cohort study, we retrieved individual-level information from Maccabi Healthcare Services (Maccabi hereafter) members' detailed electronic health records (EHR), including information from centralized laboratories and pharmacies. Maccabi is the second largest non-profit health maintenance organization (HMO) in Israel and provides nationwide healthcare services to over 2.5 million individuals, nearly 27% of the total population [25]. By law, every citizen is covered by one of four HMOs and can switch between HMOs. Refusal to grant membership to a de jure resident by any HMO in Israel based on geographic location, demographic characteristics, health conditions, needs, or other characteristics is illegal. This legal feature minimizes selection bias in this study. Also, governmental subsidies cover copayments for those in need, and basic medical coverage costs are inexpensive. The HMO EHR at Maccabi is updated regularly based on predefined criteria and collected data [25], and has been published before in dementia and diabetes research [26,27]. Ethical approval was granted to conduct the present study by the Institutional Review Board at the University of Haifa and the Helsinki Institutional Review Board at Maccabi. Informed consent was waived as the study data were de-identified. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were followed in this study.

The source population consisted of individuals diagnosed with T2D from the age of 55 years or older in the interval from 0101-1998 to 01-01-2019 according to the HMO diabetes registry and were HMO members during that time interval. Inclusion in the registry is based on the American Diabetes Association's suggested criteria and additional criteria of the HMO to maximize its validity (**Supplementary Text 1**). The follow-up for incident dementia began when the individuals were aged between 65 and 95 years. To reduce reverse causality risk, a one-year lag was applied and individuals diagnosed with dementia or censored less than one year after diabetes diagnosis were excluded from the study. For the full exclusion criteria see Fig. 1 and **Supplementary Text 2.**

2.2. Dementia ascertainment

Dementia diagnosis was ascertained by the HMO dementia registry criteria as used in previous studies [27]. The dementia registry criteria include at least two visit diagnoses or one active diagnosis by a specialist (geriatrician, psychiatrist, or neurologist) using *International Classification of Diseases, Ninth Revision* (ICD-9) codes [28]. Similarly, a general practitioner can diagnose dementia, but the diagnosis must be accompanied by an updated Sweet 16 cognitive test score of 13 or lower [29]. Another criterion for inclusion in the dementia registry was the pre-

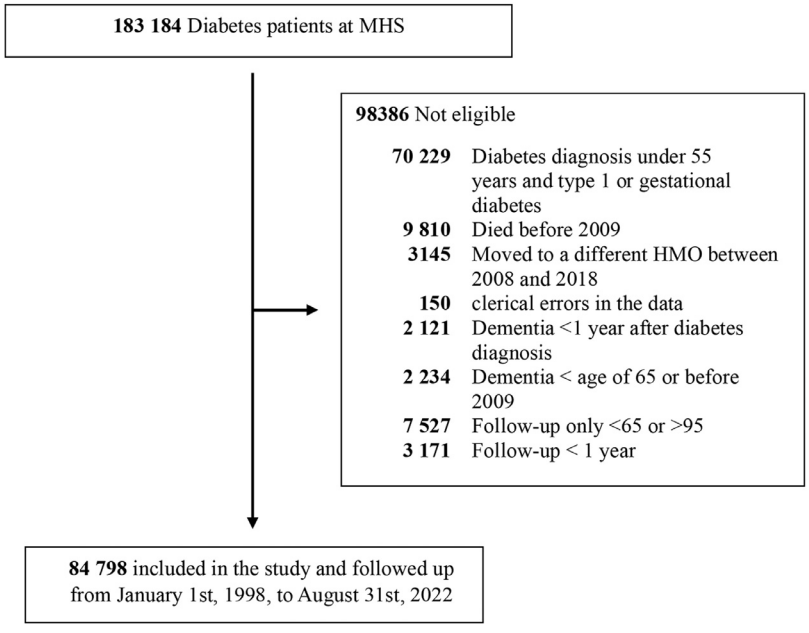

Fig. 1. Study sample flowchart.
Study flow diagram of cohort selection, inclusion, exclusion, and follow-up. Abbreviations: HMO, Health Maintenance Organization; MHS, Maccabi Health Services; T2D, Type 2 Diabetes.

scription of anti-dementia medications based on Anatomical Therapeutic Chemical 5 (ATC-5) codes (full ATC-5 codes list in **Supplementary Table 1** and full diagnosis criteria in **Supplementary Text 3**).

2.3. Definition of new-generation antidiabetic drug use

All antidiabetic medication data were extracted from the HMO prescription purchasing register. This data includes the ATC-5 code and description, purchase date, number of packages purchased, medication delivery method per prescription (e.g., tablets, vials, pens), and dosage. Diabetes medications were classified into nine drug classes based on ATC-5 codes. Three new-generation antidiabetic drug classes: dipeptidyl-peptidase-4 inhibitors (DPP-4i; A10BH*, A10BD*), glucagon-like peptide-1 analogs (GLP-1a; A10BJ*), and sodium-glucose cotransporter-2 inhibitors (SGLT-2i; A10BK*, A10BD*). DPP-4i and GLP-1a were introduced in Israel in January and May 2008, respectively, while SGLT-2i were introduced in April 2015. Six older antidiabetic drug classes: alpha-glucosidase inhibitors (A10BF*), biguanides (metformin; A10BA), insulin (A10A*), repaglinide (A10BX02), thiazolidinediones (TZDs; A10BG*), and sulfonylurea derivatives (SU; A10BB*) (complete ATC-5 codes listed in **Supplementary Table 2**).

Antidiabetic medication use was classified for each individual in the study and only for drug classes purchased more than once, based on the validated PRE2DUP (Prescriptions to Drug Use Periods) method [30]. This method considers dose changes, stockpiling, and purchase regularity and calculates use periods and average dosage in daily defined dose (DDD) units. Overlapping exposure periods to the same drug class were combined to generate the final exposure periods. Use of the new-generation antidiabetic drug class, either as a single drug or in combination, was implemented as a time-varying variable such that each individual could potentially contribute their time at risk as users or non-users, alternatively.

2.4. Covariates

There were 13 covariates in the study chosen based on the potential for confounding (i.e., an association with both receiving a specific T2D medication and with dementia risk). All covariates' information was retrieved from the participants' routinely collected HMO electronic health records. Sociodemographic covariates were: age, sex, and neighborhood socioeconomic status (SES). Age at cohort entry was entered as a linear and quadratic term [31]. Because education is not routinely recorded in HMO records, we used neighborhood socioeconomic status (SES) as a proxy for cognitive reserve, similarly to multiple studies that were based on HMO data [26,32]. Neighborhood SES was acknowledged as a possible risk factor for neurodegeneration [33]. In the current study, the SES used was developed and validated by Points Location Services Ltd (Points) on a scale from 1 to 10 and categorized into 3 groups (low [1–4], medium [5–6], and high [7–10]). The Points SES scale extends SES data from the Israeli Central Bureau of Statistics with additional updated socio-economic and demographic information [34]. It is regularly employed by the Israeli Ministry of Health, MHS, and all other HMOs in the country [35]. Health-related covariates were diabetes diagnosis onset age, and the following time-varying covariates: diabetes duration divided into quartiles, Hemoglobin A1C (HbA1C) (%), fasting blood glucose levels in mg/dL, Body Mass Index (BMI) classified into: underweight (<18.5), normal range (18.5–24.9), overweight (25.0–29.9), obese class 1 (30.0–34.9), obese class 2 (35.0–39.9), obese class 3 (≥40) [36], systolic blood pressure levels (mm Hg) [37], total cholesterol levels (mg/dL), triglycerides levels (mg/dL), chronic kidney disease (CKD) based on estimated glomerular filtration rate (eGFR) levels (mL/min) of less than 60 [38], and cardiovascular diseases (CVD) based on the HMO registry [39]. All these covariates were found to be associated with the risk of cognitive impairment and dementia among individuals with diabetes [40–42].

2.5. Statistical analyses

Missing data were imputed for SES, HbA1c levels, BMI, systolic blood pressure levels, total cholesterol levels, triglycerides levels, and eGFR using the Multivariate Imputation by Chained Equations (MICE) algorithm (**Supplementary Text 4, Supplementary Table 3**). The Little chi-squared test of missing-completely-at-random (MCAR) showed that missing data deviated from the MCAR assumption (Little MCAR test: $\chi^2_{1,472} = 18{,}716$; $P < 0.001$). Data was treated as missing at random, as in most clinical epidemiological data [43]. We calculated the sample characteristics at cohort entry, then incident dementia rates per 1000 person-years.

Cox proportional hazard regression models were employed to estimate hazard ratios (HRs) and 95% Confidence Intervals (CI) for dementia, using age as the time scale [44]. These models were fitted using the survival package in R, which accounts for truncation and left censoring [45]. The marginal structural method was used with stabilized and truncated inverse probability weights (IPW) calculated for each individual at each time point, following previous study procedures [46]. The calculated IPW account for time-varying covariates that could be affected by previous exposure, consider residual confounding, and allows an approximation of the causal effect [46–48]. The IPW included all the previously described time-varying and constant covariates (**Supplementary Text 5**). The Cox model proportional hazards assumption was tested for the primary model, where the corresponding scaled Schoenfeld residuals were correlated with time. Follow-up concluded for each individual at the earliest of the following: dementia diagnosis, death, leaving the HMO, or end of follow-up on the 31st of August 2022 (**Supplementary Fig. 1**).

An unadjusted Cox proportional hazard regression model was fitted without weights and only with antidiabetic medication use as a covariate. In the primary analysis, we compared the use periods with IPW and adjusted for unbalanced covariates with absolute standardized mean differences (SMD) higher than 0.1 between the exposed and unexposed groups [49]. This procedure can further minimize residual imbalance between the groups [50]. Individuals who did not purchase any antidiabetic medication throughout their entire follow-up period were classified as 'on lifestyle change only' and were excluded from the primary analysis.

2.6. Complementary analyses

To challenge the primary analysis robustness, we performed six complementary analyses. We fitted three models similar to our primary model where use of each of the new-generation antidiabetic medications (DPP-4i, model 1; GLP-1a, model 2; SGLT-2i, model 3) was compared with non-use (i.e., periods in which none of the new-generation medications were used). In the fourth complementary analysis (model 4), we included the time contributed by those who were on lifestyle change only throughout the follow-up to the no-use category. Next, we excluded from the comparison period times in which Insulin or SU were used, due to their potential to cause hypoglycemia, and hence increase dementia risk (model 5) [13]. An analysis accounting for the competing risk of mortality was computed for the primary model (model 6) (**Supplementary Text 6**). In this model, each individual was followed until the occurrence of the following outcomes: dementia or death, which were set as the terminal state [51]. All analyses were performed using R version 4.1.3 (March 2022) with the R packages Survival [45], IPW [52], and MICE [53] (**Supplementary texts 4–6**).

3. Results

3.1. Population characteristics

At baseline, the analytic sample consisted of 84,798 individuals (Fig. 1). The participants' mean age was 66.4 ± 7.5 years, 42,497

Table 1
Characteristics at cohort entry of the final sample.

Baseline Characteristics	Sample (n = 84,798)
Age of diabetes onset, mean ± SD	66.4 ± 7.5
Female, N (%)	42,497 (50.1)
Socio Economic Group, N (%)	
Low	13,800 (16.3)
Medium	23,408 (27.6)
High	47,590 (56.1)
BMI levels, N (%)	
Underweight (<18.5)	191 (0.2)
Normal range (18.5 – 24.9)	9785 (11.5)
Overweight (25.0 – 29.9)	31,809 (37.5)
Obese class 1 (30.0 – 34.9)	43,013 (50.7)
Obese class 2 (35.0 – 39.9)	11,356 (13.4)
Obese class 3 (≥40)	4933 (5.8)
eGFR ≥60, N (%)	26,723 (31.5)
Baseline Characteristics	**Sample (n = 84,798)**
Cardiovascular disease, N (%)	16,211 (19.1)
HbA1C levels (%), mean ± SD	6.71 ± 1.1
Systolic blood pressure, mm Hg, mean ± SD	135.36 ± 17.7
Total cholesterol levels, mg/dL, mean ± SD	186.52 ± 43.0
Triglycerides levels, mg/dL, mean ± SD	161.05 ± 88.7
Fasting blood glucose levels, mg/dL, mean ± SD	134.49 ± 38.9
Diabetes duration, mean ± SD	11.7 ± 5.6

Abbreviations: BMI, Body Mass Index; eGFR, Estimated Glomerular Filtration Rate; HbA1C, Hemoglobin A1C.

Table 2
Rate of dementia per 1000 person-years.

Exposure	Dementia cases	Event rate per 1000 person-years (95% CI)
Total	11,642	14.6 (14.3 - 14.9)
New-generation antidiabetic medications	2384	13.4 (12.9 - 14.0)
DPP-4i	1654	13.4 (12.8 - 14.1)
SGLT-2i	275	11.6 (10.2 - 13.0)
GLP-1a	455	12.6 (11.4 - 13.8)
Older antidiabetic medications	8318	14.3 (14.0 - 14.6)

Abbreviations: DPP-4i, dipeptidyl peptidase 4 inhibitors; SGLT-2i, sodium-glucose cotransporter inhibitor; GLP-1a, glucagon-like peptide-1 analogs.

(50.1%) were women, the mean HbA1C level was 6.71 ± 1.1%, and more than 38,000 used at least one of the new-generation antidiabetic medications with median use time of 3.5 years (Q1 – Q3: 1.3 – 6.5) (Table 1**, Supplementary Table 4**).

The median follow-up time was 8.7 years (Q1 – Q3: 5.4 – 12.8). During the study follow-up, 11,642 (13.7%) individuals were diagnosed with dementia over 798,003 person-years at-risk (Table 2). The dementia rate per 1000 person-years was 13.4 (95% CI 12.9 – 14.0) for all the new-generation antidiabetic medications combined compared to 14.3 (95% CI 14.0 – 14.6) for the older antidiabetic medications (Table 2).

3.2. Antidiabetic medication and the risk of dementia

In the unadjusted Cox model, the use of any of the new-generation antidiabetic medications was associated with a lower dementia risk compared to the older antidiabetic medications use (unadjusted HR = 0.94; 95% CI, 0.89–0.98). In the main model, adjustment for potential confounders with absolute SMD higher than 0.1 following the IPW implementation was made. This included confounders such as diabetes age, SES, and HbA1C levels (full list on **Supplementary Table 5**). In this model, the association showed 31% lower dementia risk comparing periods in which the new drug classes were used to those of non-use (adj. HR = 0.69; 95% CI, 0.66–0.73; Fig. 2, and all covariates: **Supplementary Table 6**).

3.3. Complementary analyses

Each of the new-generation antidiabetic medications separately was associated with a reduced risk of dementia (HR = 0.67; 95% CI, 0.63–0.71, HR = 0.63; 95% CI, 0.56–0.70, and HR = 0.61; 95% CI, 0.54–0.69 for DPP-4i (model 1), GLP-1a (model 2) and SGLT-2i (model 3), respectively) (Fig. 2). The associations remained similar when the use of Insulin and SU was excluded from the comparison group (HR = 0.53; 95% CI, 0.50–0.57) (Fig. 2, model 4) and when individuals who were on lifestyle change only were included in the comparison group (HR = 0.69; 95% CI, 0.65–0.72) (Fig. 2, model 5). Lastly, accounting for the competing risk of all-cause mortality did not attenuate the primary results (HR = 0.73; 95% CI 0.64 – 0.80) (Fig. 2, model 6). The proportional hazard assumption was not violated for the exposure in any of the analyses.

4. Discussion

In this nationwide retrospective cohort study, the use of new-generation antidiabetic medications was associated with a 31% reduced risk of incident dementia among individuals older than 65 years with T2D. Specifically, exposure to antidiabetic medications from the DPP-4i, GLP-1a, and SGLT-2i classes was associated with 33%, 37%, and 39% reduced dementia risk, respectively. The associations remained robust even after controlling for diabetes duration and time-varying glycemic control indices, and in several sensitivity analyses, including after accounting for competing risk of death.

To our knowledge, this is the first study to directly compare time-varying medication use of each new antidiabetic medication to older antidiabetic medications, while other studies compared primarily a single medication and its constant use [9,12,54,55]. Our study results are consistent with findings from some prior epidemiological studies, which show that new-generation antidiabetic medication use is associated with reduced dementia risk in older adults with T2D beyond their glycemic control effects [9,18–22,54–56]. However, some previous studies found no difference in dementia risk between newer and older antidiabetic medications [12,57]. This may stem from using a case-control design and matching with a low ratio between the exposure groups in those studies or the simplified drug modeling approaches used [12,54,57].

The current finding of a decreased dementia risk associated with the use of new antidiabetic medications compared to older antidiabetic medications is supported by previous preclinical studies. These studies show that DPP-4i and GLP-1a reduce oxidative stress and inflammation as well as amyloid beta deposits and tau protein phosphorylation in the brain [15]. Similarly, in animal models, SGLT-2i were found to reduce oxidative stress, protect synaptic plasticity, and improve brain insulin signaling [16].

The study results remained robust following six complementary analyses. The inclusion of individuals with T2D who were not using any antidiabetic medication (the lifestyle change group) in the comparison group resulted in similar effect sizes. However, after including them, we expected some attenuation from the association since this group may represent early T2D stages and milder disease presentation. One explanation for these unexpected findings may be that this group may also represent those who were non-adherent or failed to fill prescriptions, both could be due to patients' characteristics such as ischemic heart disease or polypharmacy [58]. In addition, excluding individuals who were exposed to SU and insulin from the unexposed group resulted in even lower dementia risk in those exposed to the new-generation antidiabetic medications. This finding contradicts our initial hypothesis that the effect size will change toward the null, since SU and insulin may increase dementia risk due to their hypoglycemic propensity. However, not all studies support the hypothesis that SU and insulin use are associated with increased dementia risk [11,59]. The complex associations between T2D medications and dementia risk need to be further analyzed in future studies.

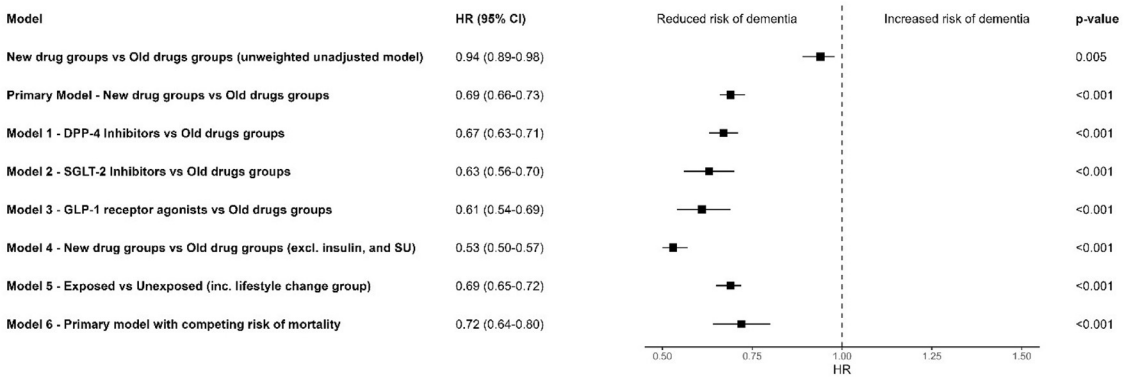

Fig. 2. Adjusted and weighted hazard ratio for dementia in the different models.
Abbreviations: HR, Hazard Ratio from the Cox regression model; CI, Wald two-sided 95% confidence interval; *P* value, *P* value for test of the hypothesis HR=1 vs the hypothesis HR≠1; DPP-4i, dipeptidyl peptidase 4 inhibitors; SGLT-2i, sodium-glucose cotransporter inhibitor; GLP-1a, glucagon-like peptide-1 analogs; SU, Sulfonylureas.

4.1. Strengths and limitations

This is the first study to examine antidiabetic medication exposure based on an advanced pharmacoepidemiological method combining detailed prescription purchase information. This method quantifies antidiabetic medication exposure periods with increased accuracy [30]. Additional strengths of our study include a large unselected sample of more than 84,000 older adults with T2D from a non-profit HMO in a country that provides affordable healthcare and restricts selection by law. Also, more than 11,000 dementia cases were reported using validated diagnosis criteria, which improves the exposure association estimation. Additionally, based on available information, this sample has the longest overall exposure time to date for the new-generation antidiabetic medications, increasing our faith in the association. All these sample characteristics minimize the threat of selection bias. A methodological strength of our study is the use of marginal structural Cox proportional hazards regression models that allow an approximation of a causal effect [46]. Moreover, we implemented a one-year lag reducing, but not eliminating, reverse causality risk. Finally, the IPW used in the current study can account for time-varying covariates that could be affected by previous exposure and are found to reduce residual confounding [48,49].

Our study has some notable limitations. Since this is an observational study, the current findings cannot imply causality. Also, new-generation antidiabetic medications, particularly SGLT-2i and GLP-1a, were available for a relatively short exposure time (median exposure of 3.5 years). Hence, we cannot rule out future dementia cases for individuals exposed to these drug classes, possibly leading to an increased protective association. Additionally, SGLT-2i were introduced only in 2015, meaning those who use them could be healthier and did not develop dementia at least until 2015. Despite the adjustments for multiple sources of residual confounding, we cannot eliminate the possibility of residual confounding. Specifically, factors such as level of education, smoking, depressive symptoms, *APOE ε4* genotype, ethnicity, contraindications, and dietary intake were not available and therefore not adjusted for in our study. In addition, the treatment and comparison groups may still have different distributions of disease severity indicators which we may have failed to adjust for, resulting in channeling bias.

Exposure in our study was measured by medication purchases, hence, we cannot confirm medication consumption. However, the modeling of antidiabetic medication exposure was based on a method that uses prescription purchasing durations over time and so provides a more reliable exposure estimation than standard methods such as a predefined exposure period or average DDD. Lastly, a possible under-ascertainment of dementia cases in our study may lead to non-differential misclassification and therefore attenuated associations [60]. Yet, dementia diagnosis in the HMO records is based on multiple criteria, including drug prescription for dementia and active diagnosis by experts, hence minimizing this potential bias. Finally, our findings may have limited generalizability as our large sample is of Israeli citizens only.

5. Conclusions

Based on a nationwide cohort study of 84,798 older individuals with T2D, the current findings showed that the use of new-generation compared to older antidiabetic medications was associated with an estimated 31% dementia risk reduction, after adjustment for multiple potential confounders. Before new-generation antidiabetics are used for dementia prevention, clinical trials are required to replicate our findings. Particularly, our results underscore the plausible therapeutic potential of SGLT-2i, a newer antidiabetic medication class, for dementia prevention, and encourage future investigations of these drugs with more protracted duration of use. Potentially, repurposing new-generation antidiabetic medications may serve as a promising strategy for dementia prevention in older adults with T2D.

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Ethics approval and consent to participate

Ethical approval was granted to conduct the present study by the Institutional Review Board at the University of Haifa and the Helsinki Institutional Review Board at Maccabi Healthcare Services. Informed consent was waived by the Institutional Review Board at the University of Haifa and the Helsinki Institutional Review Board at Maccabi Healthcare Services as the study data were de-identified.

Availability of data and materials

Individual-level data collected and retrieved from electronic health records can be made available on request from a qualified investigator. This request is subjected to internal review to ensure that participants' privacy is protected, and subject to completion of data sharing agreement, approval from the institutional review board of the Maccabi Healthcare Services and institutional guidelines, and in accordance with the current data sharing guidelines of Maccabi and the Israeli law.

Prior presentation

The research project's preliminary results were presented at the Alzheimer's Association International Conference 2023 in Amsterdam. The research project's complete report and full data were not presented at this conference or shared with conference attendees or journalists.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Avi Cohen reports financial support was provided by Alzheimer's Association. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Avi Cohen: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Stephen Z Levine:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation. **Gabriel Vainstein:** Resources, Data curation. **Michal Schnaider Beeri:** Writing – review & editing. **Galit Weinstein:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100199.

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