TYPE 2 DIABETES AND COGNITIVE IMPAIRMENT: ASSESSING THE ASSOCIATION BETWEEN THE USE OF SODIUM GLUCOSE CO-TRANSPORTER-2 INHIBITORS AND THE RISK OF INCIDENT DEMENTIA.

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JANUARY 2025

DISCLOSURES

- None

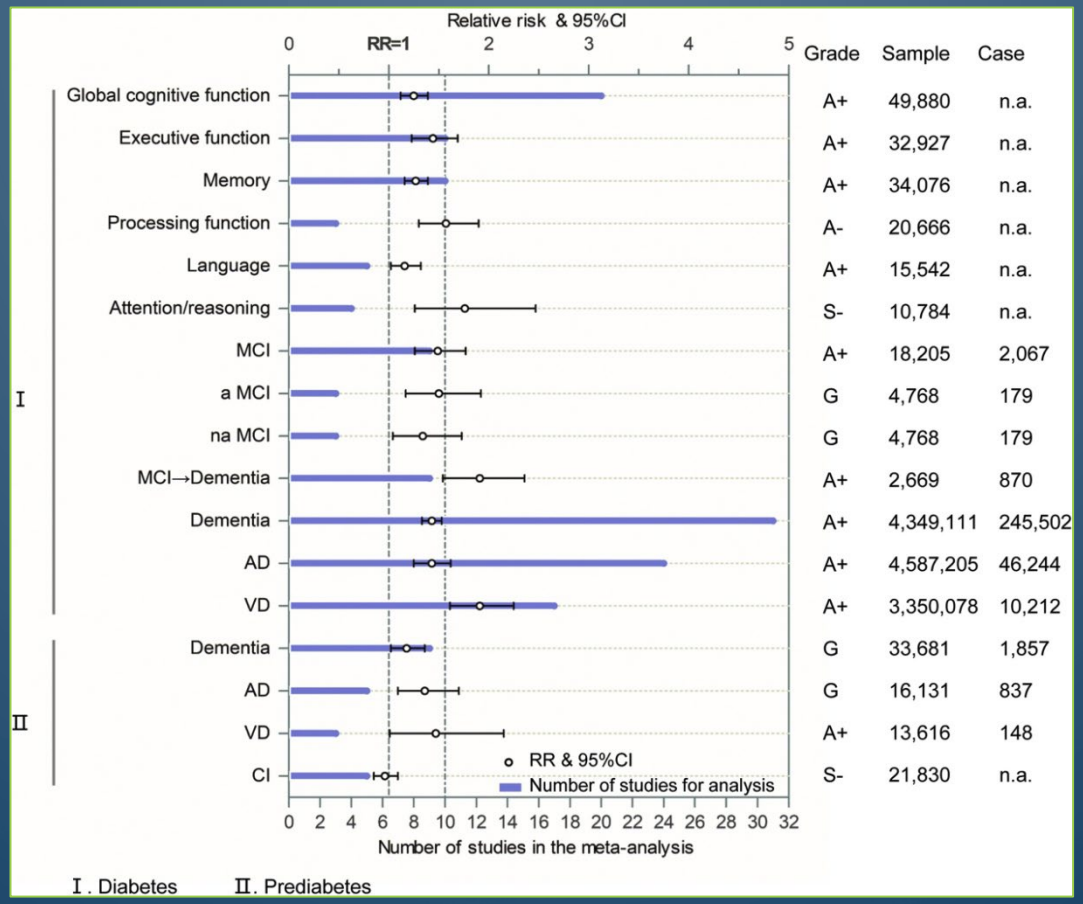
OUTLINE

- Review type 2 diabetes and cognitive impairment
- Present findings from a population-based cohort study assessing the association between sodium glucose co-transporter-2 inhibitor use and the risk of incident dementia among people with type 2 diabetes

COGNITIVE DECLINE-A NEW COMPLICATION OF DIABETES

- Cognitive impairment-type 1 and type 2 diabetes
- All ages-increased risk among individuals>60 years of age

Individuals with diabetes have a higher risk of dementia



Diabetes and risk of dementia (31 studies)
RR:1.43, 95%CI:1.33–1.53

Xue et al. Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies, Ageing Research Reviews 2019; 55: 1568-1637.

DEMENTIA

• Neurodegenerative conditions	• Non-neurodegenerative dementia
• Alzheimer disease (AD) • Dementia with Lewy bodies • Frontotemporal dementia • Parkinson disease dementia	• Vascular dementia

Mixed dementia

ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA

	Reference	Quality rating	Results (95% CI)	Additional adjustment for vascular risk factors
Any dementia	Ott[18]	9	1·9 (1·3–2·8)	
	Brayne[17]	7	OR 2·6 (0·9–7·8)	
	Peila[22]	7	1·5 (1·0–2·2)	1·5 (1·0–2·2)
	MacKnight[23]	7	1·2 (0·9–1·7)	1·3 (0·9–1·8)
	Xu[27]	7	HR 1·5 (1·1–2·1)	HR 1·5 (1·0–2·1)
	Leibson[16]	6	SMR 1·6 (1·3–2·0)	
	Hassing[21]	4		1·2 (0·8–1·7)
Alzheimer's disease	Ott[18]	9	1·9 (1·2–3·1)	
	Brayne[17]	7	OR 1·4 (1·1–17·0)	
	Yoshitake[15]	7	2·2 (1·0–4·9)	
	Peila[22]	7	1·7 (1·0–2·8)	1·8 (1·1–2·9)
	MacKnight[23]	7	1·2 (0·8–1·8)	1·3 (0·8–2·0)
	Xu[27]	7	HR 1·3 (0·8–1·9)	HR 1·3 (0·9–2·1)
	Leibson[16]	6	SMR 1·6 (1·3–2·0)	
	Luchsinger[28]	6	HR 2·4 (1·8–3·2)	HR 2·0 (1·4–2·9)
	Arvanitakis[25]	6	HR 1·7 (1·1–2·5)	
	Katzman[14]	5	OR 0·5 (0·1–2·3)	
	Hassing[21]	4		0·8 (0·5–1·5)
Vascular dementia	Ott[18]	9	2·0 (0·7–5·6)	
	Yoshitake[15]	7	2·8 (2·6–3·0)	
	Peila[22]	7	2·2 (1·1–4·7)	2·3 (1·1–5·0)
	MacKnight[23]	7	2·2 (1·3–3·6)	2·0 (1·2–3·6)
	Xu[27]	7	HR 2·2 (1·1–5·0)	HR 2·6 (1·2–6·1)
	Luchsinger[20]	6	HR 4·2 (2·2–8·3)	HR 3·4 (1·7–6·9)
	Hassing[21]	4		2·5 (1·4–4·8)

Risk of dementia in people with diabetes relative to those without diabetes. Results were adjusted for age and sex (except the Katzman study), mostly for education, and vascular risk factors (eg, history of stroke, hypertension, and heart disease). Diagnoses were made using DSM III[40] (dementias), NINCDS-ADRDA[42] (Alzheimer's disease), and NINCDS-AIREN[43] or California criteria[47] (vascular dementia). All results are expressed as relative risks unless otherwise stated. OR=odds ratio; HR=hazard ratio; SMR=standard morbidity ratio.

Table 2: **Risk of incident dementia in patients with diabetes mellitus—longitudinal studies with late-life assessment**

Biessels et al. Lancet Neurology. 2006; 5:64-74.

FACTORS CONTRIBUTING TO DEVELOPMENT OF COGNITIVE IMPAIRMENT IN DIABETES

Metabolic factors
- Chronic hyperglycemia
- Acute/recurrent hypoglycemia
- Protein glycation
- Changes in fuel metabolism and transport

Vascular disease
- Micro and macrovascular disease
- Endothelial dysfunction
- Inflammation
- Blood-brain permeability
- Dyslipidemia

Endocrine factors
- Decreased insulin sensitivity
- Hyperinsulinemia
- Hyperleptinaemia
- Hypothalamic-pituitary-adrenal axis dysregulation

CNS factors
- Genetic predisposition
- Amyloid disposition
- Oxidative stress
- Depression
- Changes in neuronal calcium homeostasis

McCrimmon et al. 2012 Lancet; 379: 2291-99.

TYPE 2 DIABETES AND COGNITIVE IMPAIRMENT

- Areas of impairment
  - Information processing speed
  - Attention and concentration
  - Executive functions
  - Working memory

RISK FACTORS FOR COGNITIVE IMPAIRMENT

- Hypertension
- Hypercholesterolemia
- Obesity
- Retinopathy

MANAGEMENT OF DIABETES AND COGNITIVE IMPAIRMENT

- In older adults at increased risk of hypoglycemia, medication classes with low risk of hypoglycemia are preferred
- Avoid overtreatment of diabetes
- Deintensification of complex regimens to reduce the risk of hypoglycemia if it can be achieved with individualized A1c target

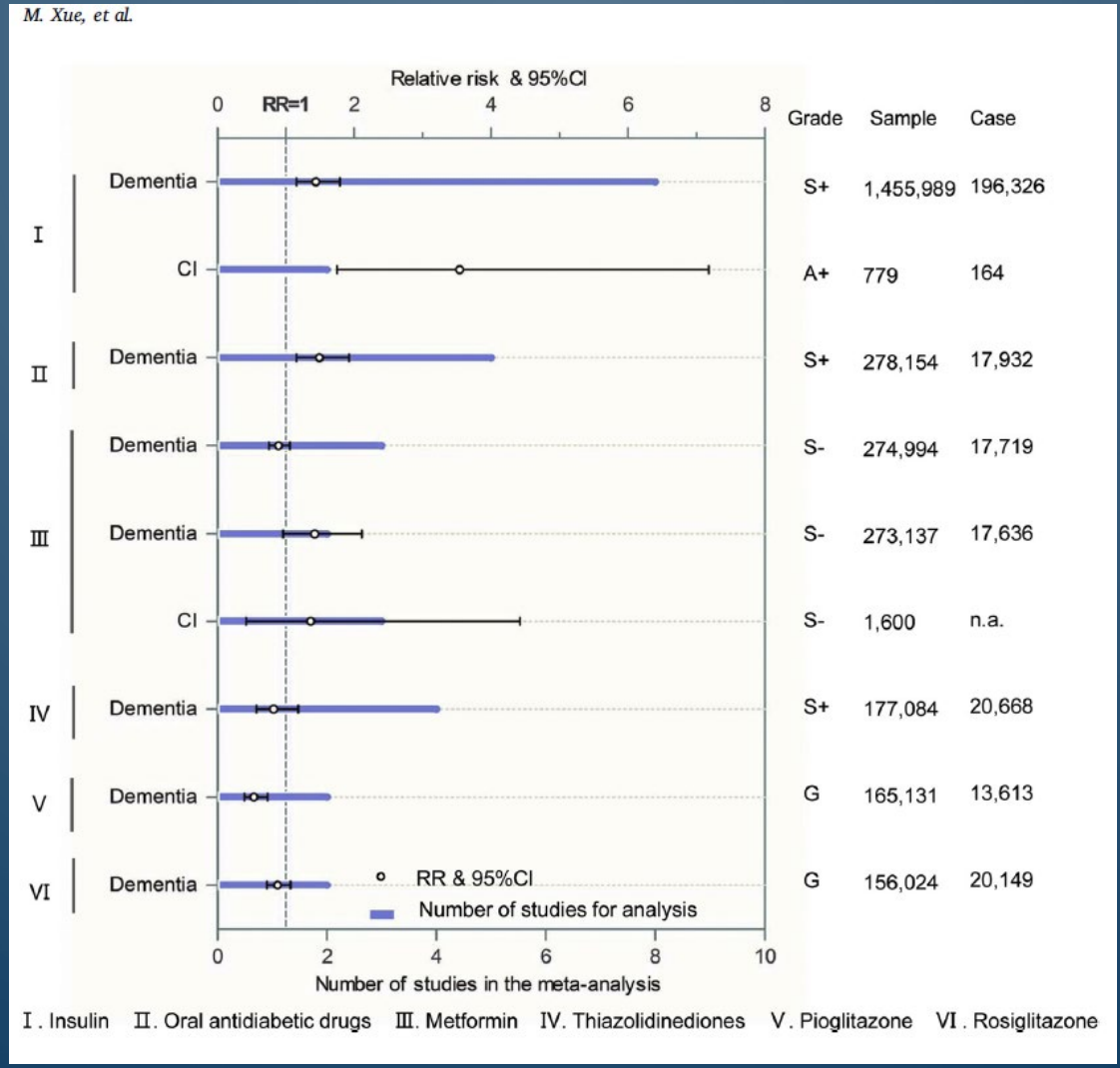
Diabetes Care 2019;42(Supplement_1):S139–S147

MANAGEMENT OF DIABETES AND COGNITIVE IMPAIRMENT

- Diabetes Canada
  - HbA1c<8.5%
  - Lifestyle modification
  - Metformin
  - DPP-4 inhibitors, GLP-1 RA
  - Avoid TZDs and sulfonylureas
  - To use DPP-4 inhibitors prior to SGLT2 inhibitors
  - Insulin-clock drawing test+cognitive test

Graydon S. Meneilly AK, David B. Miller, Diana Sherifali, Daniel Tessier, Afshan Zahedi Diabetes in Older People. Canadian journal of diabetes. 2018; **42**(Suppl 1): S1-S325.

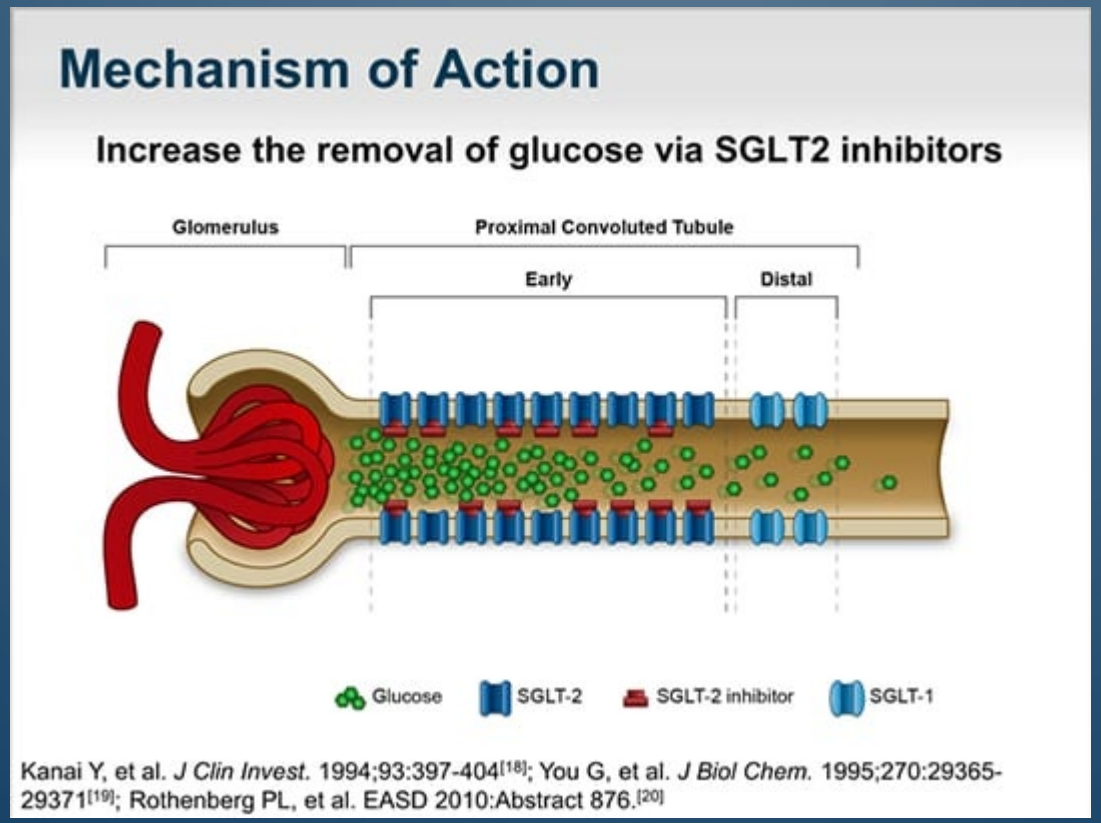
PHARMACOLOGICAL THERAPIES



Xue et al. Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies, Ageing Research Reviews 2019; 55: 1568-1637.

ASSESSING THE ASSOCIATION BETWEEN THE USE OF SODIUM GLUCOSE CO-TRANSPORTER-2 INHIBITORS AND THE RISK OF INCIDENT DEMENTIA AMONG PEOPLE WITH TYPE 2 DIABETES

SGLT-2 INHIBITORS: MECHANISM OF ACTION



SGLT-2 INHIBITORS AND POTENTIAL EFFECTS ON BRAIN HEALTH

- Vascular health
- Animal studies-SGLT-2 inhibitors have anti-inflammatory, anti-oxidant and anti-apoptotic effects
- Ketosis-additional fuel for brain when glucose insufficient
- Anti-cholinesterase activity
- Small clinical trials initiated to assess SGLT-2 inhibitors and cognitive effects (2 pilot studies in US, 1 RCT in Mexico in patients with history of cardiovascular disease)

PRIMARY STUDY OBJECTIVES

- To determine if SGLT-2 inhibitor use is associated with a decreased risk of incident dementia compared to DPP-4 inhibitor use among individuals with type 2 diabetes.

SECONDARY STUDY OBJECTIVES

- To determine if SGLT-2 inhibitor use is associated with a decreased risk of mild cognitive impairment (MCI).
- To determine if the association between SGLT-2 inhibitor use and risk of incident dementia compared to DPP-4 inhibitor use among individuals with type 2 diabetes differs by age <65 and ≥65 years, and sex.
- To determine if the association between SGLT-2 inhibitor use and the risk of incident dementia compared to DPP-4 inhibitor use among individuals with type 2 diabetes differs by prior history of cardiovascular disease (i.e., myocardial infarction and stroke) and prior history of renal insufficiency.
- To determine the association between SGLT-2 inhibitor use and dementia stratified into vascular and AD dementia compared to DPP-4 inhibitor use.

SGLT-2 INHIBITOR USE AND RISK OF INCIDENT DEMENTIA

- A population-based cohort study
- Clinical Practice Research Datalink
  - 40 million individuals from 1,700 practices
  - Demographic characteristics
  - Diagnoses
  - Laboratory test results
  - Procedures
  - Prescriptions
  - Immunizations
  - Administrative information
- Index of multiple deprivation

CPRD
MORE DIMENSIONS TO DATA

METHODS

- Individuals aged ≥40 years with type 2 diabetes (newly treated with at least one non-insulin antidiabetic agent) between 2013 and 2021.
- SGLT-2 inhibitor or DPP-4 inhibitor
  - Exclusions:
    - Combination use of SGLT-2 inhibitor and DPP-4 inhibitor
    - <1 year of medical history
    - Initiation of treatment with insulin
    - Dialysis during the year prior to study cohort entry
    - Prior history of dementia and MCI

EXPOSURES

- Initiation of SGLT-2 inhibitors or initiation of DPP-4 inhibitors
- Grace period of 30 days

Antidiabetic agent	Mode of administration	Decrease in HbA1c	Weight changes	Risk of hypoglycemia	Cost
SGLT-2 inhibitor	Oral	-0.5 to -0.7%	-2 to -3kg	Rare	$$$
DPP-4 inhibitor	Oral	-0.5 to -0.7%	Neutral	Rare	$$$
Metformin	Oral	-1.0%	Neutral	Rare	$
GLP-1 receptor agonist	Subcutaneous injection	-06-1.4%	-1.1 to -4.4kg	Rare	$$$$
Sulfonylurea	Oral	-0.6-1.2%	+1.3 to +3.2kg	Elevated	$
Thiazolidinedione	Oral	-0.7-0.9%	+2.0 to +2.5kg	Rare	$$$

Abbreviations: DPP=dipeptidyl peptidase-4; GLP=Glucagon-like peptide; HbA1c= glycated hemoglobin A1c; SGLT-2=sodium glucose co-transporter-2

PRIMARY OUTCOME

- Incident dementia
  - Diagnoses using Read codes
  - Initiation of acetylcholinesterase inhibitors or memantine

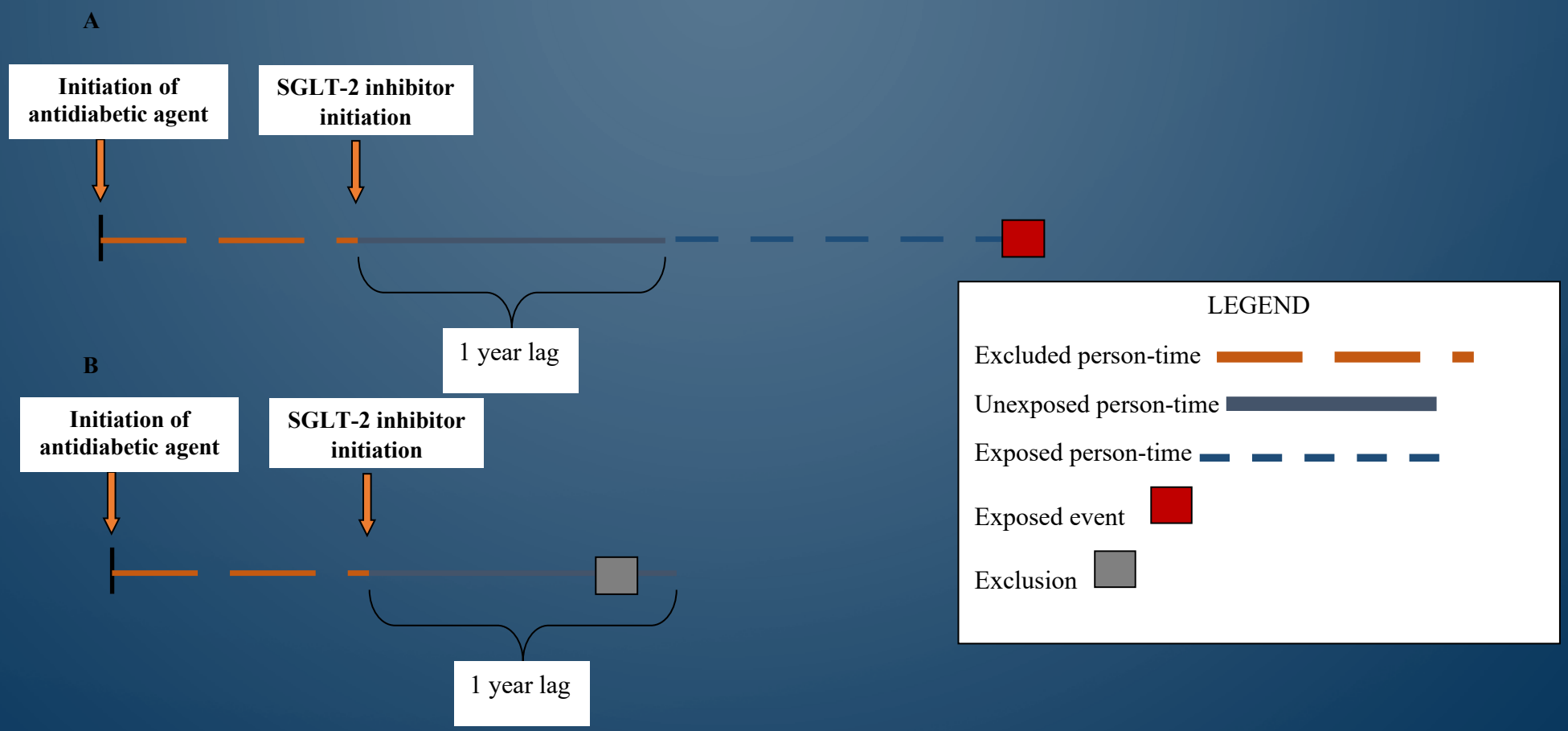
SECONDARY OUTCOME

- Secondary outcome
  - Mild cognitive impairment
    - Memory loss
    - Administration of the MMSE
    - Administration of Addenbrooke's cognitive examination
    - Administration of Montreal cognitive assessment
    - Referral to memory assessment
    - Referral to Psychiatry
    - Referral to Neurology
    - Referral to Geriatrics

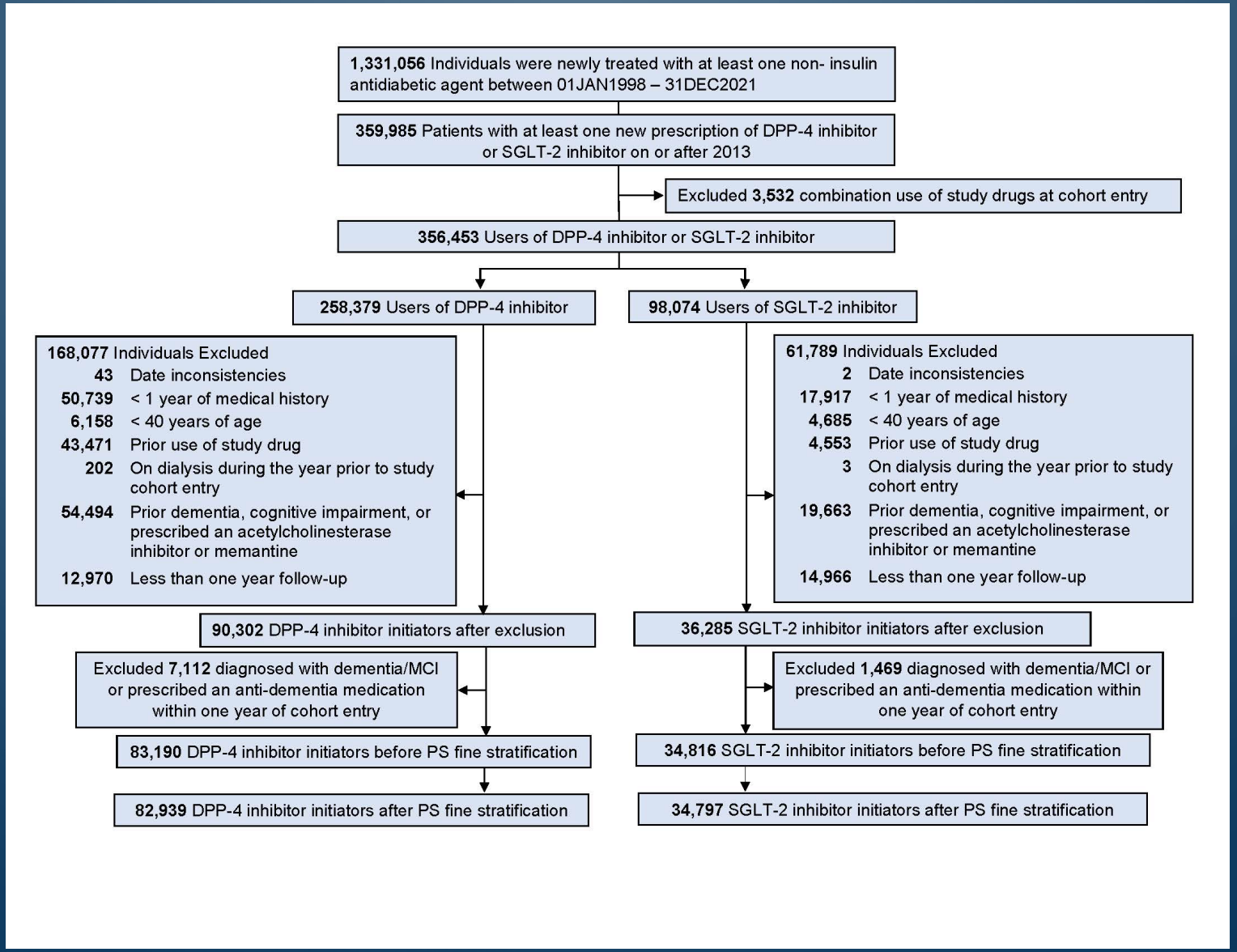
STATISTICAL ANALYSES

- Cox proportional hazards models with propensity score fine stratification weighting
- A one-year lag period was used to account for a potential latent exposure effect on the outcome, dementia

Exposure definition using a time-dependent approach with a 1 year lag period



STUDY FLOWCHART



DIFFERENCES BETWEEN THE TWO GROUPS PRIOR TO USING FINE PS WEIGHTING

- SGLT-2 inhibitor users were younger compared to DPP-4 inhibitor users (56.8 years (9.0) vs. 62.3 years (11.7)
- Calendar year of cohort entry-more DPP-4 inhibitors users entered in the study cohort years 2013 and 2014 compared to SGLT-2 inhibitor users
- DPP-4 inhibitor users more likely to have a history of atrial fibrillation and chronic kidney disease
- SGLT-2 inhibitors more likely to be treated with GLP-1 RA and insulin; DPP-4 inhibitor users more likely to be on lipid lowering therapy and anticoagulation therapy
- SGLT-2 inhibitor users more likely to have a BMI$\geq$ 30kg/m^2 and higher baseline HbA1c>8%

TABLE 1

	After weighting*				
	SGLT2 inhibitors		DPP-4 inhibitors		Standardized mean difference
	N or mean	% or SD	N or mean	% or SD	
Number of patients	34,797		82,939		
Age (years)					
Mean (SD)	56.83	8.96	56.91	9.06	-0.009
40-45, n (%)	3,589	10.31	8,854	10.68	-0.012
46-55, n (%)	12,675	36.43	29,507	35.58	0.018
56-65, n (%)	12,366	35.54	29,876	36.02	-0.010
66-75, n (%)	5,315	15.27	12,474	15.04	0.006
76-85, n (%)	804	2.31	2,061	2.48	-0.011
>85, n (%)	48	0.14	167	0.20	-0.015
Sex, n (%)					
Females	13,681	39.32	33,226	40.06	-0.015
Males	21,116	60.68	49,713	59.94	0.015

TABLE 1

	After weighting*				
	SGLT2 inhibitors		DPP-4 inhibitors		Standardized mean difference
	N or mean	% or SD	N or mean	% or SD	
Number of patients	34,797		82,939		
Index of multiple deprivation 2010, n (%)					
1st	2,446	7.03	5,629	6.79	0.009
2nd	2,764	7.94	6,446	7.77	0.006
3rd	2,425	6.97	5,600	6.75	0.009
4th	2,934	8.43	7,104	8.57	-0.005
5th	3,315	9.53	7,819	9.43	0.003
6th	4,432	12.7	10,575	12.75	0.000
7th	3,922	11.3	9,367	11.29	-0.001
8th	3,916	11.3	9,362	11.29	-0.001
9th	4,155	11.9	10,083	12.16	-0.007
10th	4,488	12.9	10,953	13.21	-0.009

TABLE 1

	After weighting*				
	SGLT2 inhibitors		DPP-4 inhibitors		Standardized mean difference
	N or mean	% or SD	N or mean	% or SD	
Number of patients	34,797		82,939		
Calendar year of cohort entry date, n (%)					
2013	464	1.33	1,189	1.43	-0.009
2014	1,944	5.59	4,320	5.21	0.017
2015	3,529	10.14	8,095	9.76	0.013
2016	3,915	11.25	8,949	10.79	0.015
2017	4,501	12.94	10,686	12.88	0.002
2018	5,399	15.52	13,118	15.82	-0.008
2019	6,844	19.67	16,413	19.79	-0.003
2020	6,379	18.33	15,531	18.73	-0.010
2021	1,822	5.24	4,638	5.59	-0.015

	After weighting*				
	SGLT2 inhibitors		DPP-4 inhibitors		Standardized mean difference
	N or mean	% or SD	N or mean	% or SD	
Number of patients	34,797		82,939		
Comorbidities, n (%)					
Retinopathy	4,922	14.14	11,682	14.08	0.002
Nephropathy	11	0.03	25	0.03	0.000
Neuropathy	552	1.59	1,379	1.66	-0.006
Non -fatal myocardial infarction	929	2.67	2,180	2.63	0.002
Stroke	901	2.59	2,170	2.62	-0.002
Peripheral arterial disease	415	1.19	1,049	1.26	-0.006
Heart failure	641	1.84	1,556	1.88	-0.003
Atrial fibrillation	1,073	3.08	2,538	3.06	0.001
Depression	5,236	15.05	12,558	15.14	-0.003
Chronic renal insufficiency	1,686	4.85	4,434	5.35	-0.023
Falls	378	1.09	961	1.16	-0.007
Housebound	96	0.28	254	0.31	-0.006
Tremor	233	0.67	559	0.67	0.000
Parkinson's disease	10	0.03	18	0.02	0.006

	After weighting*				
	SGLT2 inhibitors		DPP-4 inhibitors		Standardized mean difference
	N or mean	% or SD	N or mean	% or SD	
Medications, n (%)					
Metformin	33,522	96.34	79,976	96.43	-0.005
Sulfonylureas	15,773	45.33	37,287	44.96	0.007
Meglitinides	351	1.01	873	1.05	-0.004
Thiazolidinediones	4,666	13.41	11,103	13.39	0.001
Alpha-glucosidase inhibitors	202	0.58	507	0.61	-0.004
Glucagon-like peptide 1 receptor agonists	4,431	12.73	10,008	12.07	0.020
Insulin	4,696	13.50	11,120	13.41	0.003
Lipid lowering therapy	27,548	79.17	65,173	78.58	0.014
Anticoagulation therapy	12,019	34.54	28,513	34.38	0.003
Antihypertensive therapy	24,632	70.79	58,601	70.65	0.003
Number of physician visits in the 365 days prior to study cohort entry					
0-2	8,860	25.46	21,238	25.61	-0.003
3-5	12,301	35.35	29,150	35.15	0.004
6+	13,636	39.19	32,551	39.25	-0.001

	After weighting*				
	SGLT2 inhibitors		DPP-4 inhibitors		Standardized mean difference
	N or mean	% or SD	N or mean	% or SD	
Body Mass Index					
< 30	7,299	20.98	17,524	21.13	-0.004
≥ 30	20,521	58.97	48,592	58.59	0.008
Unknown	6,977	20.05	16,823	20.28	-0.006
Smoking					
Never	8,296	23.84	19,663	23.71	0.003
Ever	26,437	75.97	63,126	76.11	-0.003
Unknown	64	0.18	150	0.18	0.000
HbA1c level					
≤ 7	2,026	5.82	4,987	6.01	-0.008
7.1-8	7,538	21.66	18,180	21.92	-0.006
> 8	24,580	70.64	58,233	70.21	0.009
Unknown	653	1.88	1,539	1.86	0.001
Excessive alcohol use	508	1.46	1,277	1.54	-0.007

DURATION OF FOLLOW UP

- Median follow-up: 1.5 years

ASSOCIATION BETWEEN SGLT-2 INHIBITOR USE AND RISK OF INCIDENT DEMENTIA

Exposure	Number of patients	Number of events	Person-years	Incidence rate (per 1,000 person-years)	Crude HR (95%CI)	Adjusted HR[a] (95%CI)
SGLT-2i	34,816	40	70,942	0.56	0.26 (0.19-0.35)	0.78 (0.55-1.12)
DPP-4i	83,190	533	199,618	2.67	1.00 (reference)	1.00 (reference)

[a]Adjustment with fine propensity score stratification

ASSOCIATION BETWEEN SGLT-2 INHIBITOR USE AND THE RISK OF MILD COGNITIVE IMPAIRMENT

Exposure	Number of patients	Number of events	Person-years	Incidence rate (per 1,000 person-years)	Crude HR (95%CI)	Adjusted HR[a] (95%CI)
SGLT-2i	34,816	951	69,729	13.64	0.50 (0.46-0.53)	0.86 (0.80-0.92)
DPP-4i	83,190	5,690	190,340	29.89	1.00 (reference)	1.00 (reference)

[a]Adjustment with fine propensity score stratification

ASSOCIATION BETWEEN SGLT-2 INHIBITOR USE AND THE RISK OF INCIDENT DEMENTIA STRATIFIED BY AGE

	Number of patients	Number of events	Person-years	Incidence rate[a]	Crude HR (95%CI)	Adjusted HR[b] (95%CI)
Age <65						
SGLT-2i	27,866	22	57,019	0.39	0.81 (0.50-1.33)	1.23 (0.70-2.14)
DPP-4i	48,560	61	111,765	0.55	1.00 (reference)	1.00 (reference)
Age ≥65						
SGLT-2i	6,950	18	13,924	1.29	0.31 (0.19-0.50)	0.50 (0.31-0.80)
DPP-4i	34,630	472	87,853	5.37	1.00 (reference)	1.00 (reference)

[a]per 1,000 person-years

[b]Adjustment with fine propensity score stratification

ASSOCIATION BETWEEN SGLT-2 INHIBITOR USE AND THE RISK OF INCIDENT DEMENTIA STRATIFIED BY SEX

	Number of patients	Number of events	Person-years	Incidence rate[a]	Crude HR (95%CI)	Adjusted HR[b] (95%CI)
Females						
SGLT-2i	13,684	15	27,582	0.54	0.21 (0.12-0.35)	0.67 (0.38-1.19)
DPP-4i	33,584	262	79,596	3.29	1.00 (reference)	1.00 (reference)
Males						
SGLT-2i	21,132	25	43,360	0.58	0.31 (0.20-0.46)	0.89 (0.56-1.41)
DPP-4i	49,606	271	120,022	2.26	1.00 (reference)	1.00 (reference)

[a]per 1,000 person-years

[b]Adjustment with fine propensity score stratification

ASSOCIATION BETWEEN SGLT-2 INHIBITOR USE AND THE RISK OF INCIDENT DEMENTIA STRATIFIED BY HISTORY OF CARDIOVASCULAR DISEASE

	Number of patients	Number of events	Person-years	Incidence rate[a]	Crude HR (95%CI)	Adjusted HR[b] (95%CI)
No prior history of cardiovascular disease[c]						
SGLT-2i	33,039	35	67,433	0.52	0.27 (0.19-0.38)	0.77 (0.52-1.13)
DPP-4i	77,121	439	184,447	2.38	1.00 (reference)	1.00 (reference)
History of cardiovascular disease						
SGLT-2i	1,777	5	3,509	1.42	0.28 (0.11-0.69)	1.04 (0.38-2.81)
DPP-4i	6,069	94	15,171	6.20	1.00 (reference)	1.00 (reference)

[a]per 1,000 person-years

[b]Adjustment with fine propensity score stratification

[c] History of non-fatal myocardial infarction and/or non-fatal stroke

ASSOCIATION BETWEEN SGLT-2 INHIBITOR USE AND THE RISK OF INCIDENT DEMENTIA STRATIFIED BY HISTORY OF CHRONIC RENAL INSUFFICIENCY

	Number of patients	Number of events	Person-years	Incidence rate[a]	Crude HR (95%CI)	Adjusted HR[b] (95%CI)
No prior chronic renal insufficiency						
SGLT-2i	33,130	35	67,527	0.52	0.33 (0.23-0.47)	0.84 (0.57-1.25)
DPP-4i	69,295	319	164,103	1.94	1.00 (reference)	1.00 (reference)
Presence of chronic renal insufficiency						
SGLT-2i	1,686	5	3,415	1.46	0.30 (0.12-0.73)	0.85 (0.34-2.11)
DPP-4i	13,895	214	35,515	6.03	1.00 (reference)	1.00 (reference)

[a]per 1,000 person-years

[b]Adjustment with fine propensity score stratification

ASSOCIATION BETWEEN SGLT-2 INHIBITOR USE AND THE RISK OF ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA

	Number of patients	Number of events	Person-years[a]	Incidence rate	Crude HR (95%CI)	Adjusted HR[b] (95%CI)
Alzheimer dementia						
SGLT-2i	34,816	S[c]	S	S	S	S
DPP-4i	83,190	53	200,245	0.26	1.00 (reference)	1.00 (reference)
Vascular dementia						
SGLT-2i	34,816	5	70,990	0.07	0.11 (0.05-0.27)	0.45 (0.17-1.17)
DPP-4i	83,190	156	200,139	0.78	1.00 (reference)	1.00 (reference)

[a]per 1,000 person-years

[b]Adjustment with fine propensity score stratification

[c]S, as per Clinical Practice Research Datalink requirement, <5 events were replaced with "S"

SENSITIVITY ANALYSIS: VARYING GRACE PERIOD OF 0 AND 90 DAYS

	Number of patients	Number of events	Person-years[a]	Incidence rate	Crude HR (95%CI)	Adjusted HR[b] (95%CI)
Grace period 0 days						
SGLT-2i	34,816	S[c]	S	S	0.16 (0.05-0.51)	0.69 (0.20-2.43)
DPP-4i	83,190	59	103,088	0.57	1.00 (reference)	1.00 (reference)
Grace period 90 days						
SGLT-2i	34,816	66	91,027	0.73	0.25 (0.19-0.32)	0.72 (0.54-0.95)
DPP-4i	83,190	862	255,477	3.37	1.00 (reference)	1.00 (reference)

[a]per 1,000 person-years

[b]Adjustment with fine propensity score stratification

[c]S, as per Clinical Practice Research Datalink requirement, <5 events were replaced with "S"

SENSITIVITY ANALYSIS: VARYING LAG PERIOD

	Number of patients	Number of events	Person-years[a]	Incidence rate	Crude HR (95%CI)	Adjusted HR[b] (95%CI)
Lag period of 1.5 years						
SGLT-2i	29,529	37	74,369	0.50	0.29 (0.21-0.41)	0.80 (0.55-1.16)
DPP-4i	75,050	451	213,758	2.11	1.00 (reference)	1.00 (reference)
Lag period of 2.0 years						
SGLT-2i	26,140	35	77,255	0.45	0.37 (0.26-0.53)	0.93 (0.63-1.37)
DPP-4i	68,139	352	224,025	1.57	1.00 (reference)	1.00 (reference)

[a]per 1,000 person-years

[b]Adjustment with fine propensity score stratification

SENSITIVITY ANALYSIS: COMPETING RISK

	Number of patients	Number of events	Person-years[a]	Incidence rate	Crude HR (95%CI)	Adjusted HR (95%CI)
SGLT-2i	34 816	40	70 942	0,56	0.26 (0.19-0.36)	0.79 (0.55-1.14)
DPP-4i	83 190	533	199 618	2,67	1.00 (reference)	1.00 (reference)

[a]per 1,000 person-years

SENSITIVITY ANALYSIS: NEGATIVE CONTROL ANALYSIS (HEARING LOSS)

	Number of patients	Number of events	Person-years[a]	Incidence rate	Crude HR (95%CI)	Adjusted HR (95%CI)
SGLT-2i	31,598	353	40,718	8.67	0.61 (0.55-0.69)	0.92 (0.81-1.04)
DPP-4i	73,277	1,645	115,827	14.20	1.00 (reference)	1.00 (reference)

DISCUSSION

- SGLT-2 inhibitor use is associated with a reduced risk of dementia among individuals age ≥65 years compared to DPP-4 inhibitor use.
- SGLT-2 inhibitor use is associated with a decreased risk of MCI compared to DPP-4 inhibitor use among adults age ≥40 years.
- The association between SGLT-2 inhibitor use compared to DPP-4 inhibitor use and the risk of incident dementia did not differ when stratified by sex, presence of cardiovascular disease, and chronic kidney disease.

LIMITATIONS

- Relatively short duration of follow up
- Misclassification of outcome
- Residual confounding

ASSOCIATION OF SGLT-2 INHIBITORS WITH TIME TO DEMENTIA: A POPULATION-BASED COHORT STUDY

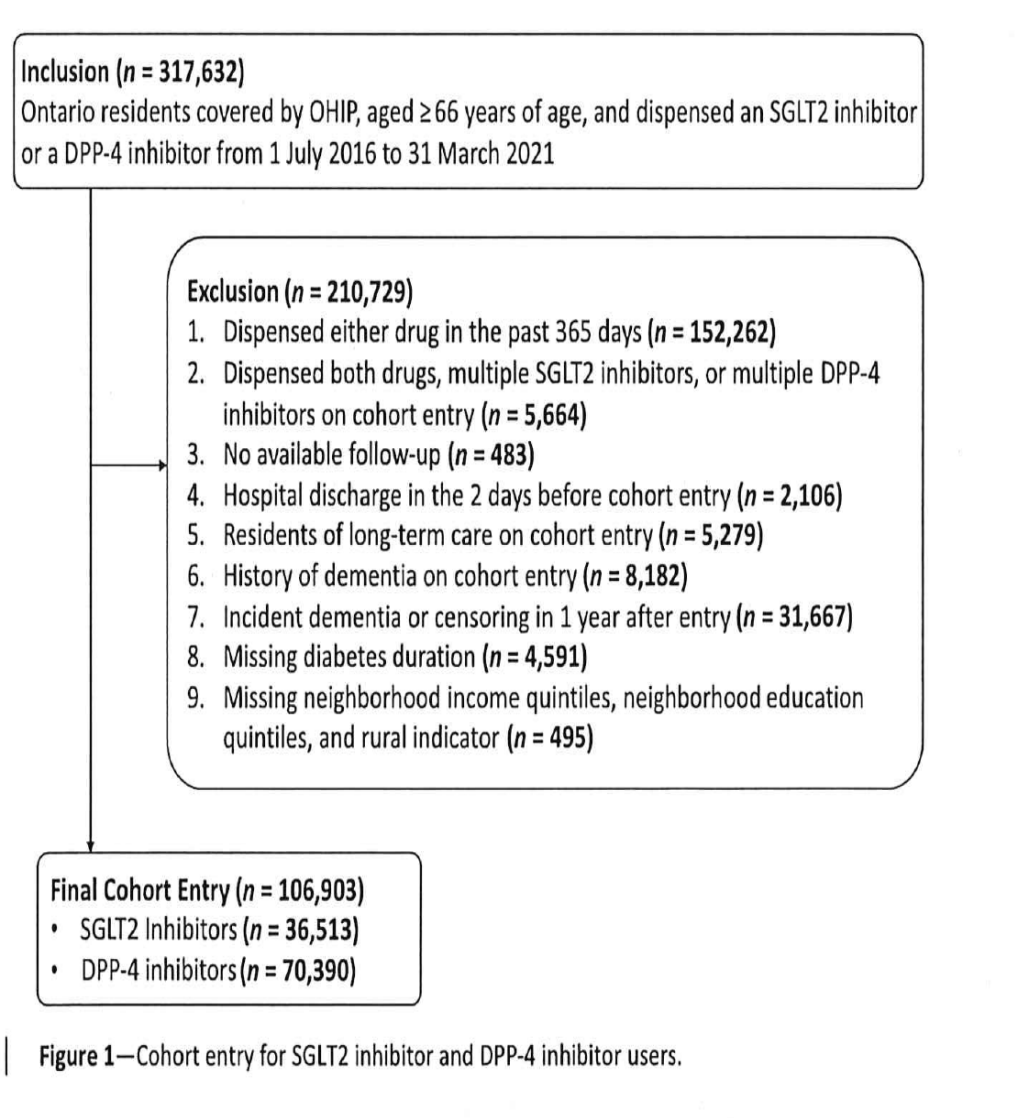


Figure 1—Cohort entry for SGLT2 inhibitor and DPP-4 inhibitor users.

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SGLT-2 INHIBITOR USE AND TIME TO DEMENTIA

Table 2—Associations of SGLT2 vs. DPP-4 inhibitors with time to dementia

	Before weighting			After weighting		
Exposures	*N*	Crude events/at-risk person-years	Crude HR (95% CI)	Weighted *N*	Adjusted events/at-risk person-years	Adjusted HR (95% CI)
Primary analysis with the "intention-to-treat" approach						
SGLT2 inhibitors	36,513	560/59,642.93	0.57 (0.52–0.63)	36,513	560/59,642.93	0.80 (0.71–0.89)
DPP-4 inhibitors	70,390	2,171/132,810.40	Reference	36,545	696/59,057.34	Reference
Molecule-specific analyses						
Canagliflozin	6,293	130/11,643.02	0.69 (0.58–0.83)	6,293	130/11,643.02	0.96 (0.80–1.16)
Dapagliflozin	5,757	81/10,250.48	0.48 (0.39–0.60)	5,757	81/10,250.48	0.67 (0.53–0.84)
Empagliflozin	24,463	349/37,749.44	0.56 (0.63–0.50)	24,463	349/37,749.44	0.78 (0.69–0.89)
DPP-4 inhibitors	70,390	2,171/132,810.40	Reference	36,545	696/59,057.34	Reference
Age-stratified analyses (aged ≥75)						
SGLT2 inhibitors	10,934	300/15,777.76	0.63 (0.55–0.71)	10,934	300/15,777.76	0.78 (0.67–0.91)
DPP-4 inhibitors	29,630	1,570/52,219.75	Reference	10,767	395/16,234.70	Reference
Age-stratified analyses (aged <75)						
SGLT2 inhibitors	25,579	260/43,865.17	0.80 (0.69–0.92)	25,579	260/43,865.17	0.84 (0.72–0.996)
DPP-4 inhibitors	41,030	601/80,590.64	Reference	25,778	300/42,822.64	Reference
Sex-stratified analyses (males)						
SGLT2 inhibitors	22,349	339/35,924.64	0.62 (0.55–0.71)	22,349	339/35,924.64	0.85 (0.74–0.99)
DPP-4 inhibitors	37,270	1,061/70,432.62	Reference	22,308	399/36,112.18	Reference
Sex-stratified analyses (females)						
SGLT2 inhibitors	14,164	221/23,718.29	0.52 (0.45–0.60)	14,164	221/23,718.29	0.72 (0.61–0.86)
DPP-4 inhibitors	33,120	1,110/62,377.78	Reference	14,236	296/22,945.16	Reference
Secondary analysis with the "as-treated" approach						
SGLT2 inhibitors	36,513	363/43,291.40	0.47 (0.41–0.52)	36,513	363/43,291.40	0.66 (0.57–0.76)
DPP-4 inhibitors	70,390	1,333/73,732.14	Reference	36,545	426/33,490.83	Reference

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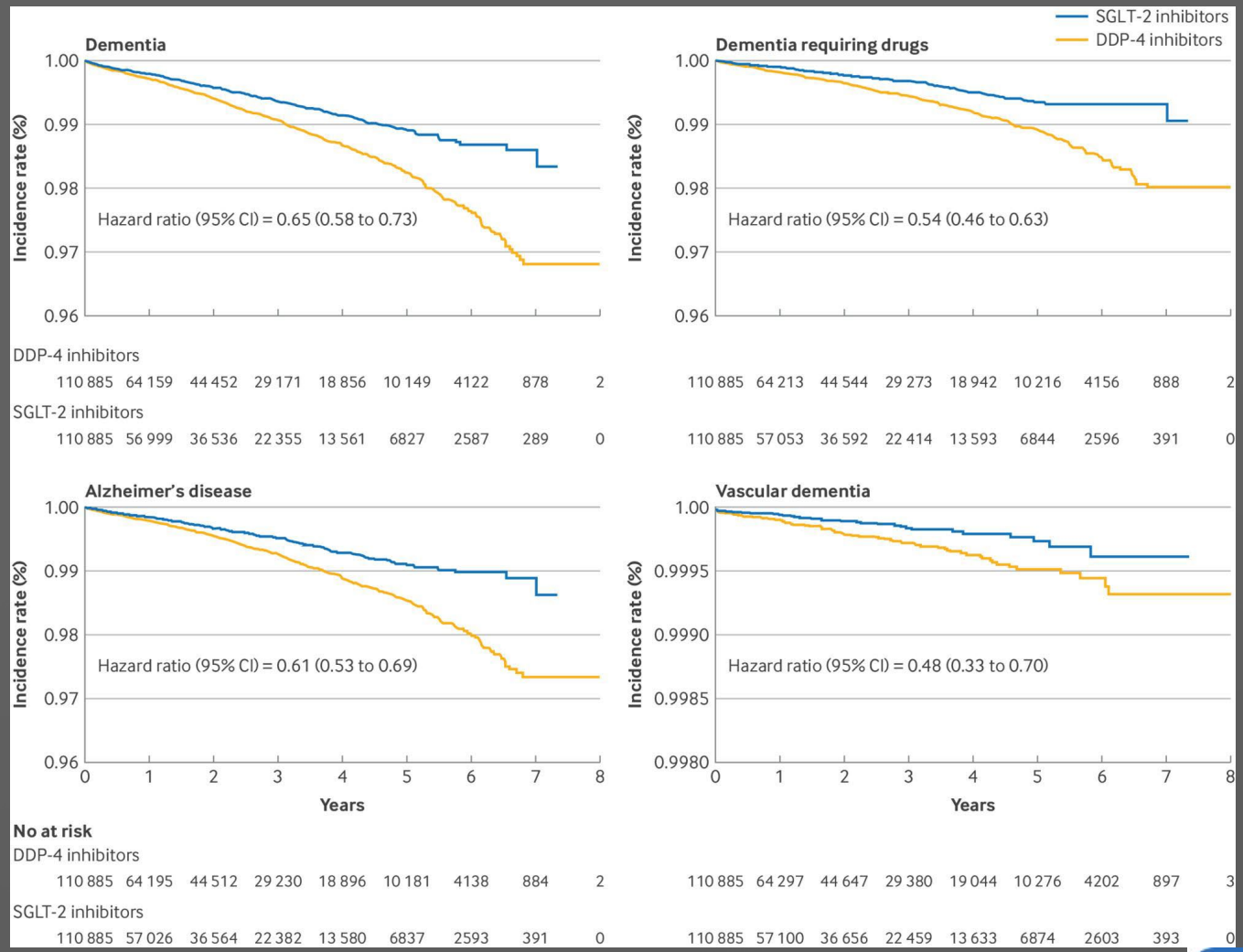
Kaplan-Meier curves for dementia-free survival comparing propensity score matched initiators of SGLT-2 inhibitors with initiators of DPP-4 inhibitors.



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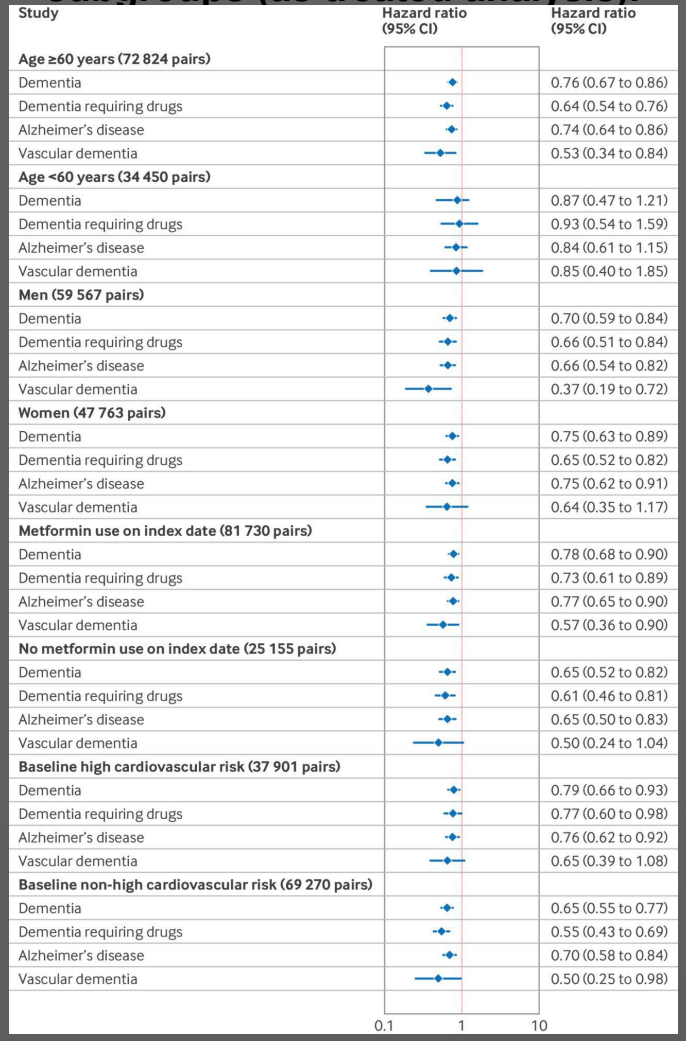
Comparative risk of dementia between initiators of sodium-glucose cotransporter-2 inhibitors and initiators of dipeptidyl peptidase-4 inhibitors in individual propensity score matched subgroups (as treated analysis).



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FUTURE STUDIES

- Clinical trials to determine if SGLT-2 inhibitor treatment affects cognitive function

ACKNOWLEDGEMENTS

- Ying Cui
- Zarin Abdullah
- Dr. Christel Renoux
- Dr. Laurent Azoulay
- Dr. Chenjie Xia
- Dr. Robert Platt

QUESTIONS