Data Analysis for Drug Repurposing for Effective Alzheimer's Medicines – Semaglutide vs DPP4 Inhibitors

NCT05768945

July 7, 2023

1. Comparison Details

a. Intended aim(s)

To evaluate the comparative risk of dementia onset between patients treated with Semaglutide v DPP4 inhibitors in patients with diabetes

b. Primary endpoint

Incident dementia (i.e., Alzheimer's disease, vascular dementia, senile, presenile, or unspecified dementia, or dementia in other diseases classified elsewhere).

2. Person responsible for implementation of replication in Aetion

Mufaddal Mahesri

3. Data Source(s)

Medicare, 2008-2019

4. Study Design Diagrams

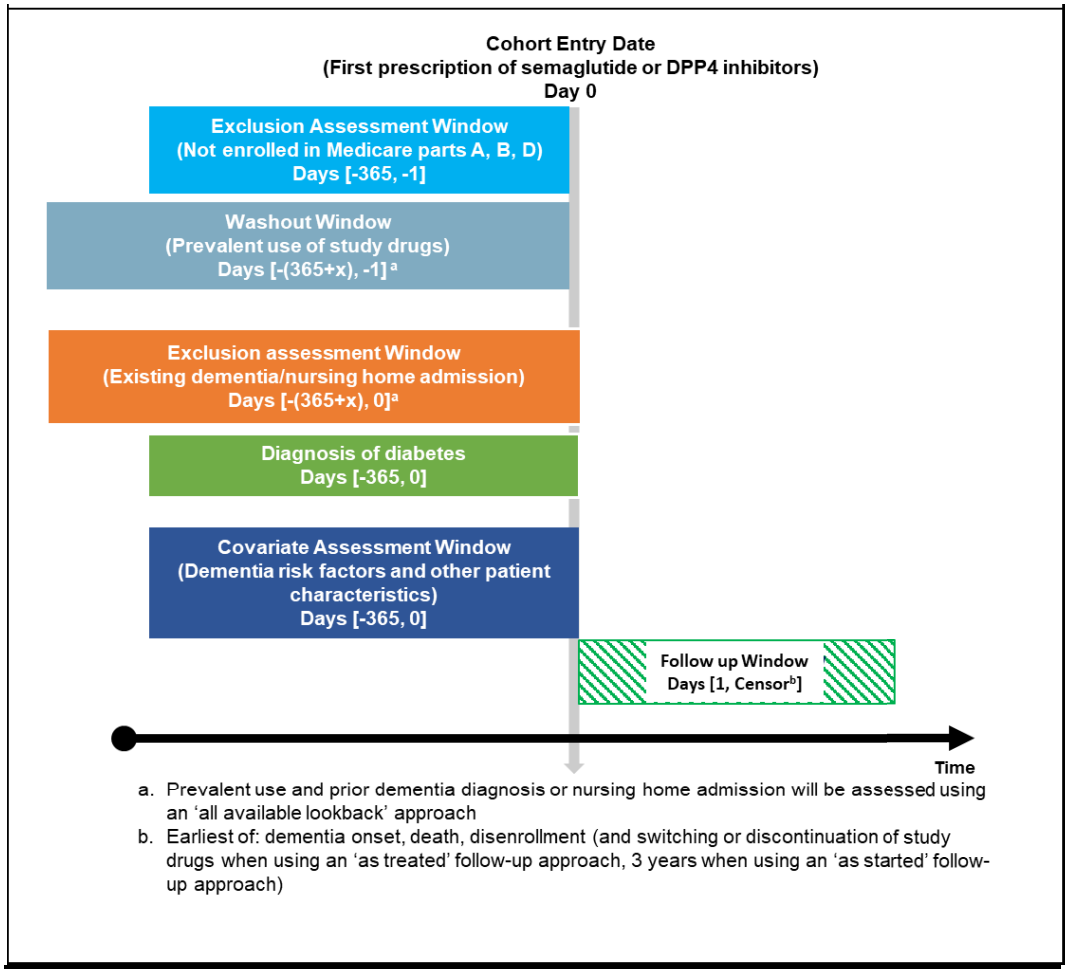
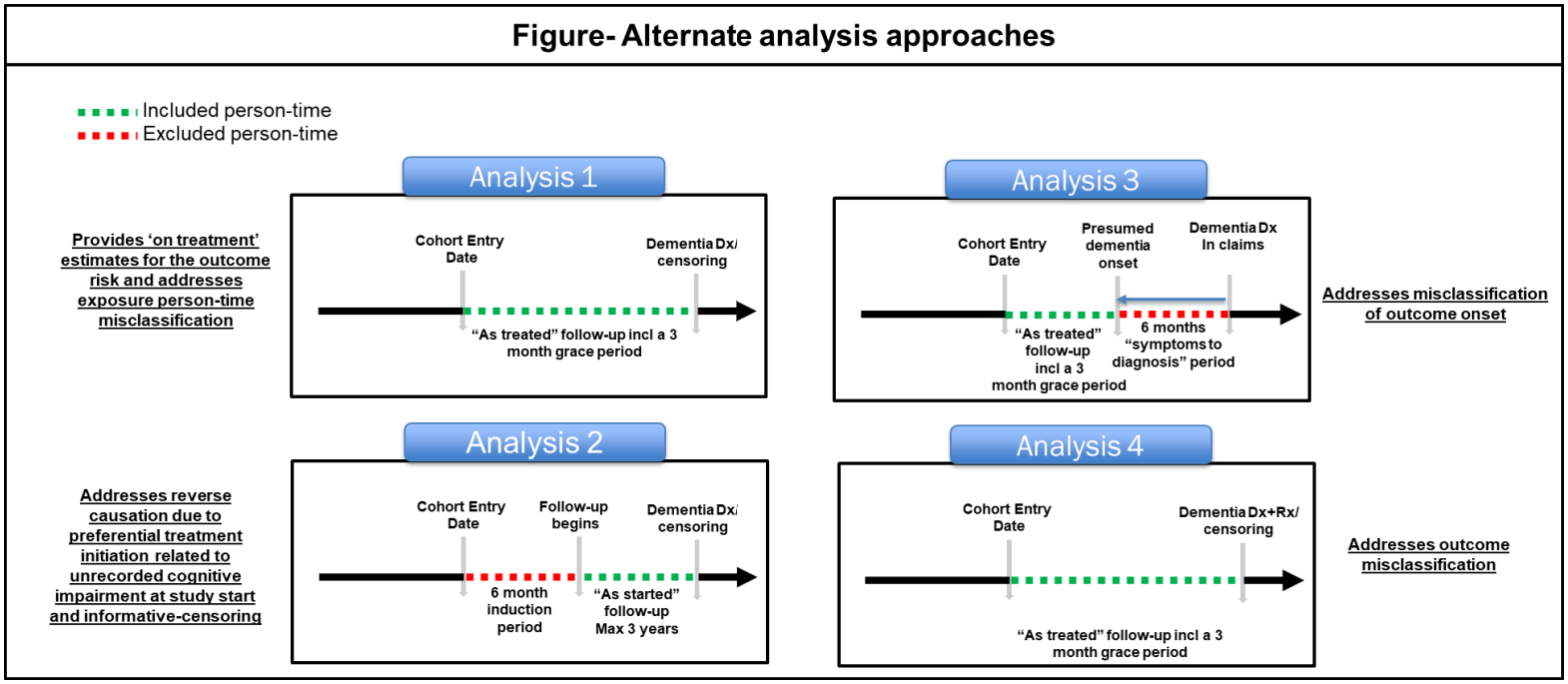


Figure- Alternate analysis approaches



5. Cohort Identification

a. Cohort Summary

This study will employ a new user, active comparator, observational cohort study design comparing Semaglutide v DPP4 inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin). The patients will be required to have continuous enrollment during the baseline period of 365 days before initiation of study drugs (index date). Follow-up for the outcome (dementia) differs between analyses. Follow-up begins the day after drug initiation (analysis 1, 3, 4); 180 days after drug initiation (analysis 2).

b. Key details regarding cohort creation

Index date:

- Day of initiation of new Semaglutide or DPP4 inhibitors

Inclusion criteria for analyses 1, 3, 4:

- Aged ≥ 65 years on the index date
- 365 days enrollment in Medicare Parts A, B, and D with no HMO coverage
- No use of any GLP receptor agonists (semaglutide, exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide) or DPP4 inhibitors
- No use of Semaglutide or DPP4 inhibitors concomitantly on index date
- No diagnosis of dementia any time prior to and including index date
- Diagnosis code for type 2 diabetes recorded in 365 days prior to index date

Inclusion criteria for analysis 2:

- Aged ≥ 65 years on the index date
- 365 days enrollment in Medicare Parts A, B, and D with no HMO coverage
- No use of any GLP receptor agonists (semaglutide, exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide) or DPP4 inhibitors
- No use of Semaglutide or DPP4 inhibitors concomitantly on index date
- No diagnosis of dementia any time prior to and including index date
- Diagnosis code for type 2 diabetes recorded in 365 days prior to index date
- 180-day continuous use of Semaglutide or DPP4 inhibitors starting on the index date

Flowchart of the study cohort assembly

	Less Excluded Patients	Remaining Patients
All patients		27,099,355
Did not meet cohort entry criteria	-24,529,389	2,569,966
Excluded due to insufficient enrollment	-900,367	1,669,599
Excluded due to prior use of referent	-828,655	840,944
Excluded due to prior use of exposure	-20,252	820,692
Excluded because patient qualified in >1 exposure category	-7	820,685
Excluded based on Dementia Exclusion	-26,498	794,187
Excluded based on Nursing home admission	-23,376	770,811
Excluded based on Semaglutide OR DPP4i	-15,281	755,530
Excluded based on Semaglutide AND DPP4i concomitantly on index date	0	755,530
Excluded based on GLP-1 RA (except Semaglutide)	-8,231	747,299
Excluded based on Diabetes	-3,306	743,993
Excluded based on Age <65	-1,323	742,670
Final cohort		742,670

6. Variables

a. Exposure-related variables:

Study drug:
The study exposure of interest is initiation of Semaglutide

Comparator:
Initiation of DPP4 inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin)

b. Covariates:

Demographics	
Age	Region
Gender	Calendar year of index date
Race	Low income subsidy

Dementia risk factors	
Diabetes	Anxiety
Obesity	Bipolar disorder
Coronary artery disease	Schizophrenia
Depression	

Markers for healthy behavior, frailty, healthcare use	
Smoking	Number of hospitalizations
Mammography	Number of physician office visits
Colonoscopy	Number of serum creatinine tests ordered
Fecal occult blood test	Composite frailty score
Influenza vaccination	Number of C-reactive protein tests ordered
Pneumococcal vaccination	Osteoporosis
Herpes zoster vaccination	Fractures

Bone mineral density test	Falls
Number of distinct generic agents	Use of supplemental oxygen
Number of emergency room visits	Combined comorbidity score
Number of outpatient visits	

Comedication use	
Lithium	Nitrates
Anti-epileptic mood stabilizers	Lipid lowering drugs
Anti-epileptics (other than mood stabilizers)	Non-insulin diabetes medications
Atypical antipsychotics	Insulin
Benzodiazepines	Antidepressants
Serotonin-norepinephrine reuptake Inhibitors	Typical antipsychotics
Selective serotonin reuptake inhibitors	Anticoagulants
Tricyclic antidepressants (TCAs)	Antiplatelet agents

Comorbid conditions	
Atrial fibrillation	Chronic liver disease
Coronary artery disease	Asthma
Heart failure	Ischemic heart disease
Stroke or transient ischemic attack	Chronic obstructive pulmonary disease
Peripheral vascular disease	Malignancy
Hyperlipidemia	Drug or alcohol abuse or dependence
Renal dysfunction	Venous thromboembolism

Diabetes-related conditions and treatments	
Diabetic nephropathy	Hyperglycemia
Diabetes with peripheral circulatory disorders	Hypoglycemia
Diabetic foot	Diabetes with other ophthalmic conditions or ophthalmic procedures
Diabetic neuropathy	Diabetic retinopathy
Insulin	Number of oral hypoglycemic agents
SGLT2 inhibitors	Metformin

Sulfonylureas	

ICD-9, ICD-10, HCPCS, and NDC codes used to define the covariates listed above are available in Appendix A.

c. Outcome variables and study follow-up:

- **Primary outcome**: incident dementia, i.e., Alzheimer's disease, vascular dementia, senile, presenile, or unspecified dementia, or dementia in other diseases classified elsewhere. Outcome will be defined by 1 inpatient claim or 2 outpatient claims in analysis 1, 2, 3. In analysis 4, the outcome will be defined by 1 inpatient or 1 outpatient claims and 1 prescription claim for a symptomatic treatment [donepezil, galantamine, rivastigmine, and memantine] within 6 months of each other with outcome date assigned to second event in the sequence.
- Secondary outcomes: Individual component:
  Alzheimer's disease

Condition	ICD-9 and ICD-10 codes
Alzheimer's disease	331.0*, F00*, G30*
Vascular dementia	290.4*, F01*
Senile, presenile, or unspecified dementia	290.0*, 290.1*. 290.3*, 797*, F03*
Dementia in other diseases classified elsewhere	331.1*, 331.2*, 331.7*, 294.1*, F02*

For analysis 1,3, and 4 the follow-up will start the day after initiation of Propranolol and Carvedilol and Atenolol, Bisoprolol, Sotalol and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest
- The date of end of continuous registration in the database,
- End of the study period,
- Measured death event occurs,
- The date of drug discontinuation, defined as the date of the last continuous treatment episode of the index drug (Propranolol and Carvedilol and hydrochlorothiazide) plus a defined grace period (i.e., 90 days after the end of the last prescription's days' supply in main analyses).

For analysis 2, the follow-up will start 180 days after initiation of Propranolol and Carvedilol and Atenolol, Bisoprolol, Sotalol and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest, unless otherwise specified for selected outcomes,

- The date of end of continuous registration in the database,
- End of the study period,
- Measured death event occurs,
- Maximum allowed follow-up time (1095 days) reached

7. Propensity score analysis

We will use a propensity-score (PS)[1]-based approach to account for measured confounding in this study. The PS will be calculated as the predicted probability of initiating the exposure of interest (i.e., the repurposing candidate) versus the reference drug conditional on baseline covariates using multivariable logistic regression constructed separately in each data source. On average, patients with similar PSs have similar distribution of potential confounders used to estimate the PS. Therefore, analyses conditioned on the PS provide effect estimates that are free from measured confounding. For all our analyses, initiators of each exposure of interest will be matched with initiators of the reference exposure based on their PS within each data source.[2] Pair matching will be conducted using a nearest-neighbor algorithm, which seeks to minimize the distance between propensity scores in each pair of treated and reference patients,[3] and a caliper of 0.025 on the natural scale of the PS will be used to ensure similarity between the matched patients.[4]

We report multiple diagnostics for PS analysis in this protocol. First, the PS distributional overlap is provided between two groups before and after matching to ensure comparability of these groups.[5] Next, balance in each individual covariate between two treatment groups is reported using standardized differences.[6]

8. Table for covariate balance

	Crude			PS-Matched		
Variable	**DPP4 inhibitors (N = 733,597)**	**Semaglutide (N = 9,073)**	**St. Diff**	**DPP4 inhibitors (N = 7,129)**	**Semaglutide (N = 7,129)**	**St. Diff**
Demographics						
Age, mean (SD)	73.86 (6.38)	70.64 (4.50)	0.58	70.70 (4.65)	70.71 (4.52)	0.00
Gender, n (%)						
Male	332,762 (45.4%)	4,626 (51.0%)	-0.11	3,787 (53.1%)	3,723 (52.2%)	0.02
Female	400,835 (54.6%)	4,447 (49.0%)	0.11	3,342 (46.9%)	3,406 (47.8%)	-0.02
Race, n (%)						
White	549,974 (75.0%)	7,530 (83.0%)	-0.20	5,968 (83.7%)	5,943 (83.4%)	0.01
Black	79,047 (10.8%)	754 (8.3%)	0.09	531 (7.4%)	547 (7.7%)	-0.01
Hispanic	34,368 (4.7%)	152 (1.7%)	0.17	116 (1.6%)	130 (1.8%)	-0.02
Asian	39,243 (5.3%)	166 (1.8%)	0.19	141 (2.0%)	131 (1.8%)	0.01
North American Native	4,451 (0.6%)	58 (0.6%)	0.00	44 (0.6%)	44 (0.6%)	0.00
Other	3,170 (42.4%)	8,009 (38.2%)	0.09	132 (1.9%)	139 (1.9%)	0.00
Unknown	6,409 (0.9%)	244 (2.7%)	-0.14	197 (2.8%)	195 (2.7%)	0.01
Region, n (%)						
Northeast; n (%)	145,176 (19.8%)	1,522 (16.8%)	0.08	1,166 (16.4%)	1,199 (16.8%)	-0.01
South; n (%)	304,574 (41.5%)	4,189 (46.2%)	-0.09	3,324 (46.6%)	3,276 (46.0%)	0.01
Midwest; n (%)	147,562 (20.1%)	2,017 (22.2%)	-0.05	1,579 (22.1%)	1,576 (22.1%)	0.00
West; n (%)	133,760 (18.2%)	1,338 (14.7%)	0.09	1,060 (14.9%)	1,078 (15.1%)	-0.01
Other; n (%)	2,525 (0.3%)	7 (0.1%)	0.04			
Calendar year of index date, n (%)						
2008	60,272 (8.2%)	0 (0.0%)	0.42			

2009	50,311 (6.9%)	0 (0.0%)	0.39			
2010	57,738 (7.9%)	0 (0.0%)	0.41			
2011	79,980 (10.9%)	0 (0.0%)	0.49			
2012	70,365 (9.6%)	0 (0.0%)	0.46			
2013	67,605 (9.2%)	0 (0.0%)	0.45			
2014	70,773 (9.6%)	0 (0.0%)	0.46			
2015	69,656 (9.5%)	0 (0.0%)	0.46			
2016	61,194 (8.3%)	0 (0.0%)	0.43			
2017	54,490 (7.4%)	0 (0.0%)	0.40			
2018	48,195 (6.6%)	1,425 (15.7%)	-0.29	1,138 (16.0%)	1,174 (16.5%)	-0.01
2019	43,018 (5.9%)	7,648 (84.3%)	-2.56	5,991 (84.0%)	5,955 (83.5%)	0.01
Low income subsidy, n (%)	242,009 (33.0%)	1,453 (16.0%)	0.40	1,091 (15.3%)	1,096 (15.4%)	0.00
Dementia risk factors, n (%)						
Anxiety	73,447 (10.0%)	1,442 (15.9%)	-0.18	1,073 (15.1%)	1,094 (15.3%)	-0.01
Bipolar disorder	7,036 (1.0%)	171 (1.9%)	-0.08	145 (2.0%)	131 (1.8%)	0.01
Coronary artery disease	247,844 (33.8%)	3,362 (37.1%)	-0.07	2,578 (36.2%)	2,527 (35.4%)	0.02
Depression	89,683 (12.2%)	1,708 (18.8%)	-0.18	1,362 (19.1%)	1,335 (18.7%)	0.01
Hypertension	685,085 (93.4%)	8,478 (93.4%)	0.00	6,618 (92.8%)	6,650 (93.3%)	-0.02
Obesity	151,074 (20.6%)	5,280 (58.2%)	-0.83	4,030 (56.5%)	4,005 (56.2%)	0.01
Schizophrenia	3,974 (0.5%)	22 (0.2%)	0.05	20 (0.3%)	15 (0.2%)	0.02
Markers for healthy behavior, frailty, healthcare use						
Bone mineral density test, n (%)	500 (0.1%)	3 (0.0%)	0.04			
Colonoscopy, n (%)	78,537 (10.7%)	1,150 (12.7%)	-0.06	918 (12.9%)	932 (13.1%)	-0.01
Fecal occult blood test, n (%)	61,356 (8.4%)	624 (6.9%)	0.06	504 (7.1%)	505 (7.1%)	0.00
Influenza vaccination, n (%)	451,885 (61.6%)	6,603 (72.8%)	-0.24	5,224 (73.3%)	5,207 (73.0%)	0.01

Mammography, n (%)	132,978 (18.1%)	2,410 (26.6%)	-0.21	1,843 (25.9%)	1,886 (26.5%)	-0.01
Pneumococcal vaccination, n (%)	195,654 (26.7%)	6,598 (72.7%)	-1.04	5,223 (73.3%)	5,204 (73.0%)	0.01
Smoking, n (%)	119,053 (16.2%)	2,419 (26.7%)	-0.26	1,979 (27.8%)	1,870 (26.2%)	0.04
Number of C-reactive protein tests ordered, mean (SD)	0.18 (0.72)	0.22 (0.77)	-0.05	0.23 (0.84)	0.21 (0.77)	0.02
Number of emergency room visits, mean (SD)	1.03 (2.27)	0.90 (1.92)	0.06	0.90 (1.83)	0.86 (1.87)	0.02
Number of distinct prescriptions, mean (SD)	13.30 (6.08)	14.31 (5.94)	-0.17	14.23 (6.01)	14.12 (5.78)	0.02
Number of hospitalizations, mean (SD)	0.33 (0.81)	0.22 (0.60)	0.15	0.21 (0.58)	0.20 (0.58)	0.02
Number of outpatient visits, mean (SD)	13.79 (18.06)	13.28 (12.00)	0.03	12.63 (10.86)	12.89 (11.82)	-0.02
Number of physician office visits, mean (SD)	5.71 (11.87)	4.19 (6.75)	0.16	4.02 (5.15)	4.16 (6.51)	-0.02
Number of serum creatinine tests ordered, mean (SD)	3.83 (3.16)	3.86 (3.10)	-0.01	3.76 (2.83)	3.73 (2.90)	0.01
Composite frailty score, mean (SD)	0.19 (0.06)	0.18 (0.05)	0.18	0.18 (0.05)	0.18 (0.05)	0.00
Falls, n (%)	27,171 (3.7%)	342 (3.8%)	-0.01	255 (3.6%)	255 (3.6%)	0.00
Fractures, n (%)	39,262 (5.4%)	425 (4.7%)	0.03	358 (5.0%)	330 (4.6%)	0.02
Osteoporosis, n (%)	79,507 (10.8%)	663 (7.3%)	0.12	490 (6.9%)	504 (7.1%)	-0.01
Use of supplemental oxygen, n (%)	9,663 (1.3%)	152 (1.7%)	-0.03	119 (1.7%)	106 (1.5%)	0.02
Combined comorbidity score, mean (SD)	3.84 (2.69)	3.94 (2.39)	-0.04	3.85 (2.42)	3.79 (2.32)	0.03
Comedication use, n (%)						
Antidepressants	176,510 (24.1%)	3,019 (33.3%)	-0.20	2,333 (32.7%)	2,327 (32.6%)	0.00

Insulin	115,136 (15.7%)	3,377 (37.2%)	-0.50	2,149 (30.1%)	2,150 (30.2%)	0.00
Lipid lowering drugs	588,438 (80.2%)	7,697 (84.8%)	-0.12	6,125 (85.9%)	6,125 (85.9%)	0.00
Nitrates	84,367 (11.5%)	903 (10.0%)	0.05	639 (9.0%)	639 (9.0%)	0.00
Non-insulin diabetes medications	733,349 (100.0%)	7,192 (79.3%)	0.72	7,008 (98.3%)	6,982 (97.9%)	0.03
Anticoagulants	81,608 (11.1%)	1,131 (12.5%)	-0.04	914 (12.8%)	850 (11.9%)	0.03
Anti-epileptic mood stabilizers	7,321 (1.0%)	109 (1.2%)	-0.02	98 (1.4%)	81 (1.1%)	0.03
Antiplatelet agents	113,790 (15.5%)	1,195 (13.2%)	0.07	888 (12.5%)	878 (12.3%)	0.01
Atypical antipsychotics	13,218 (1.8%)	162 (1.8%)	0.00	130 (1.8%)	126 (1.8%)	0.00
Benzodiazepines	60,389 (8.2%)	1,198 (13.2%)	-0.16	880 (12.3%)	898 (12.6%)	-0.01
Lithium	797 (0.1%)	11 (0.1%)	0.00	12 (0.2%)	7 (0.1%)	0.03
Anti-epileptics (other than mood stabilizers)	122,311 (16.7%)	2,188 (24.1%)	-0.18	1,629 (22.9%)	1,619 (22.7%)	0.00
Serotonin-norepinephrine reuptake inhibitors	34,437 (4.7%)	854 (9.4%)	-0.18	659 (9.2%)	640 (9.0%)	0.01
Selective serotonin reuptake inhibitors	106,415 (14.5%)	1,658 (18.3%)	-0.10	1,269 (17.8%)	1,291 (18.1%)	-0.01
Tricyclic antidepressants (TCAs)	30,159 (4.1%)	338 (3.7%)	0.02	262 (3.7%)	261 (3.7%)	0.00
Typical antipsychotics	3,027 (0.4%)	9 (0.1%)	0.06	8 (0.1%)	8 (0.1%)	0.00
Diabetes-related conditions and treatments						
Diabetic nephropathy, n(%)	100,928 (13.8%)	2,315 (25.5%)	-0.30	1,694 (23.8%)	1,631 (22.9%)	0.02
Diabetic foot, n (%)	27,182 (3.7%)	446 (4.9%)	-0.06	329 (4.6%)	324 (4.5%)	0.00
Diabetes with peripheral circulatory disorders, n (%)	72,825 (9.9%)	1,214 (13.4%)	-0.11	915 (12.8%)	894 (12.5%)	0.01
Diabetic neuropathy, n (%)	164,659 (22.4%)	3,201 (35.3%)	-0.29	2,318 (32.5%)	2,348 (32.9%)	-0.01

Diabetes with other ophthalmic manifestations, n(%)	41,657 (5.7%)	302 (3.3%)	0.12	225 (3.2%)	218 (3.1%)	0.01
Diabetic retinopathy, n (%)	88,446 (12.1%)	1,506 (16.6%)	-0.13	996 (14.0%)	1,040 (14.6%)	-0.02
Hypoglycemia, n(%)	38,577 (5.3%)	1,373 (15.1%)	-0.33	1,029 (14.4%)	1,031 (14.5%)	0.00
Hyperglycemia, n(%)	50,598 (6.9%)	785 (8.7%)	-0.07	575 (8.1%)	596 (8.4%)	-0.01
SGLT-2, n (%)	16,992 (2.3%)	1,721 (19.0%)	-0.56	1,386 (19.4%)	1,368 (19.2%)	0.01
Number of antidiabetic drugs, mean (SD)	2.68 (0.87)	2.77 (0.94)	-0.10	2.97 (0.91)	2.95 (0.84)	0.02
Number of Endocrinologist visits, mean (SD)	0.42 (1.34)	0.85 (1.81)	-0.27	0.72 (1.97)	0.73 (1.60)	-0.01
Comorbid conditions, n (%)						
Atrial fibrillation	99,884 (13.6%)	1,156 (12.7%)	0.03	929 (13.0%)	877 (12.3%)	0.02
Asthma	90,872 (12.4%)	1,936 (21.3%)	-0.24	1,467 (20.6%)	1,452 (20.4%)	0.00
Chronic obstructive pulmonary disease	140,603 (19.2%)	1,619 (17.8%)	0.04	1,242 (17.4%)	1,232 (17.3%)	0.00
Chronic liver disease	53,335 (7.3%)	1,035 (11.4%)	-0.14	829 (11.6%)	800 (11.2%)	0.01
Drug or alcohol abuse or dependence	52,626 (7.2%)	862 (9.5%)	-0.08	757 (10.6%)	664 (9.3%)	0.04
Heart failure	128,305 (17.5%)	1,364 (15.0%)	0.07	1,047 (14.7%)	952 (13.4%)	0.04
Hyperlipidemia	651,070 (88.8%)	8,284 (91.3%)	-0.08	6,475 (90.8%)	6,499 (91.2%)	-0.01
Ischemic heart disease	272,351 (37.1%)	3,292 (36.3%)	0.02	2,523 (35.4%)	2,475 (34.7%)	0.01
Malignancy	171,748 (23.4%)	2,269 (25.0%)	-0.04	1,797 (25.2%)	1,781 (25.0%)	0.00
Peripheral vascular disease	118,434 (16.1%)	1,212 (13.4%)	0.08	881 (12.4%)	877 (12.3%)	0.00
Renal dysfunction	201,317 (27.4%)	2,586 (28.5%)	-0.02	1,859 (26.1%)	1,816 (25.5%)	0.01
Stroke or transient ischemic attack	51,898 (7.1%)	452 (5.0%)	0.09	358 (5.0%)	337 (4.7%)	0.01
Venous thromboembolism	26,903 (3.7%)	304 (3.4%)	0.02	249 (3.5%)	229 (3.2%)	0.02

9. Statistical analysis plans

Incidence rates for the outcome will be estimated for the treatment and reference groups before and after PS matching. The competing risk of death could be of concern for the current set of analyses if mortality is frequent among patients included in the cohort and if differences in the risk of mortality between treatment and reference groups are substantial. In the PS-matched sample, we will use cause-specific hazard models[7] to provide hazard ratios averaged over the entire follow-up period as well as interval specific hazard ratios (1, 2, and 3 years) for the association between the treatment of interest and risk of ADRD after considering all-cause mortality as a competing event. Pre-specified subgroup analyses will be conducted based on age, sex, and baseline cardiovascular disease.

10. References

1. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70(1):41-55.
2. Rassen JA, Avorn J, Schneeweiss S. Multivariate-adjusted pharmacoepidemiologic analyses of confidential information pooled from multiple health care utilization databases. *Pharmacoepidemiology and drug safety.* 2010;19(8):848-857.
3. Rassen JA, Shelat AA, Myers J, Glynn RJ, Rothman KJ, Schneeweiss S. One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol Drug Saf.* May 2012;21 Suppl 2:69-80.
4. Austin PC. Some Methods of Propensity-Score Matching had Superior Performance to Others: Results of an Empirical Investigation and Monte Carlo simulations. *Biometrical Journal.* 2009;51(1):171-184.
5. AM Walker AM, Patrick A, Lauer M, et al. Tool for Assessing the Feasibility of Comparative Effectiveness Research. *Comp Effect Res* 2013;3:11-20.
6. Franklin JM, Rassen JA, Ackermann D, Bartels DB, Schneeweiss S. Metrics for covariate balance in cohort studies of causal effects. *Statistics in medicine.* May 10 2014;33(10):1685-1699.
7. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation.* 2016;133(6):601-609.