Data Analysis for Drug Repurposing for Effective Alzheimer's Medicines – Salbutamol vs Long-acting Muscarinic Antagonists

NCT05457868

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1. Comparison Details

a. Intended aim(s)

To evaluate the comparative risk of dementia onset between patients treated with Salbutamol (albuterol) versus Long-acting muscarinic antagonists (LAMAs) – umeclidinium, aclidinium, tiotropium, glycopyrolate, glycopyrronium – for Chronic obstructive pulmonary disease (COPD).

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

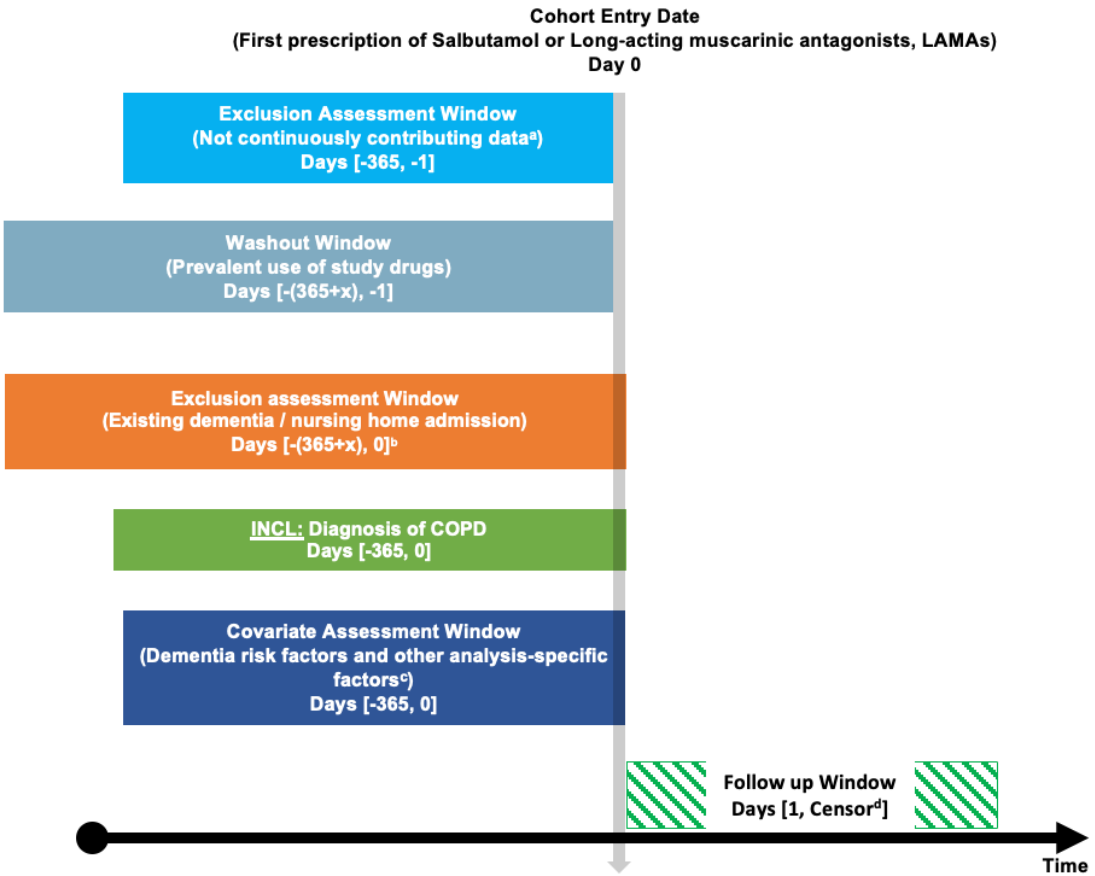
Seanna Vine

3. Data Source(s)

Medicare, 2014-2018

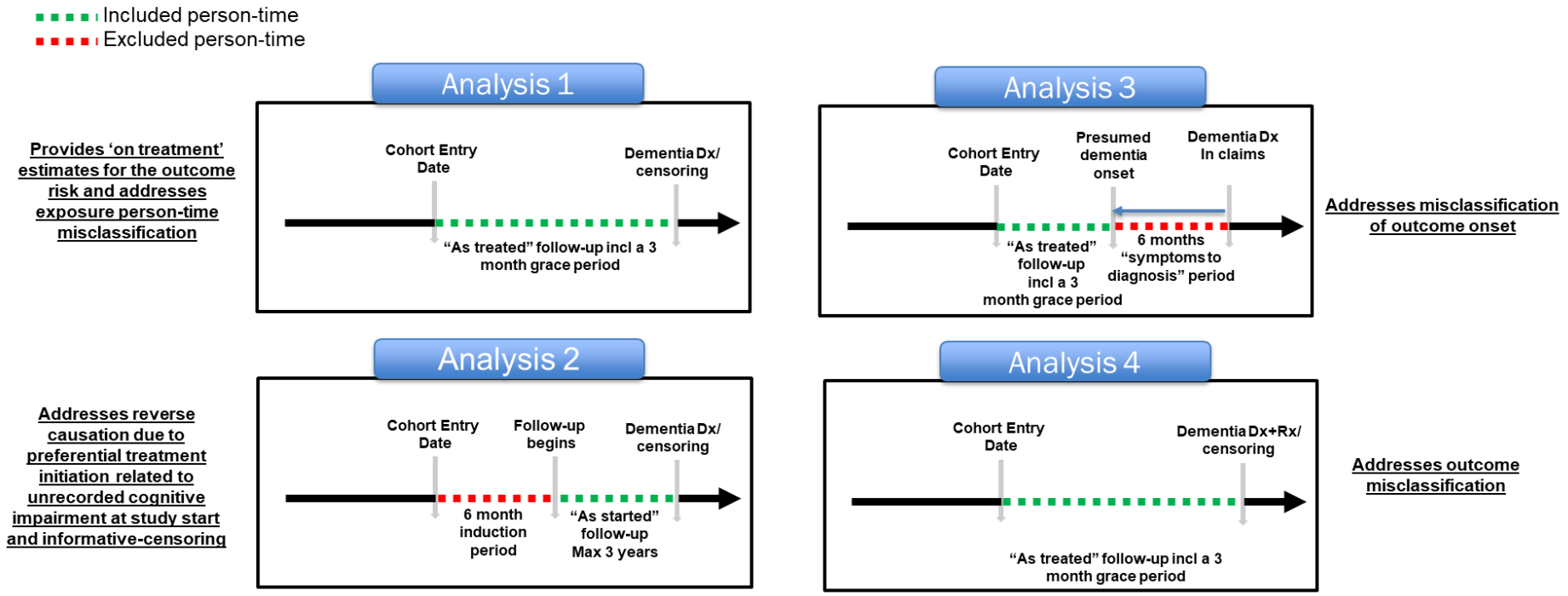
4. Study Design Diagrams

Figure – Basic study design



a. Continuous enrollment in Medicare parts A, B, D
b. Prior dementia diagnosis will be assessed using an 'all available lookback' approach where we will exclude patients will dementia recorded any time prior to the cohort entry date
c. Covariate list can be found in section 6b. on page 6
d. Earliest of dementia onset, death, disenrollment (and switching or discontinuation of study drugs when using an 'as treated' follow-up approach, 3 years when using an intent to treat follow-up approach)

Figure- Alternate analysis approaches



5. Cohort Identification

a. Cohort Summary

This study will employ a new user, active comparator, observational cohort study design comparing Salbutamol versus Long-acting muscarinic antagonists (LAMAs). The patients will be required to have continuous enrollment during the baseline period of 365 days before initiation of study drugs (cohort entry/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 Salbutamol versus Long-acting muscarinic antagonists (LAMAs)

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 Salbutamol versus Long-acting muscarinic antagonists (LAMAs) any time prior to index date (all available lookback approach with a minimum of 365 days)
- No diagnosis of dementia any time prior to and including index date
- No history of nursing home admission recorded in any time prior to and including index date
- At least two claims with COPD diagnosis recorded in 365 days prior to index date (ICD-9 490, 491.0, 491.1, 491.2x, 491.8, 491.9, 492.0, 492.8, 494.0, 494.1, 496 or ICD-10 J40, J41.0, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.9, J47.0, J47.1, J47.9)

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 or 365 days registration with a practice contributing data to CPRD prior to index date
- No use of Salbutamol versus Long-acting muscarinic antagonists (LAMAs), any time prior to index date (all available lookback approach with a minimum of 365 days)
- No diagnosis of dementia any time prior to and including index date

- No history of nursing home admission recorded in any time prior to and including index date
- At least two claims with COPD diagnosis recorded in 365 days prior to index date (ICD-9 490, 491.0, 491.1, 491.2x, 491.8, 491.9, 492.0, 492.8, 494.0, 494.1, 496 or ICD-10 J40, J41.0, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.9, J47.0, J47.1, J47.9)
- 180-day continuous use of Salbutamol versus Long-acting muscarinic antagonists (LAMAs) starting on the index date

c. Flowchart of the study cohort assembly

	Less Excluded Patients	Remaining Patients
All patients		23,466,175
Did not meet cohort entry criteria	-21,967,767	1,498,408
Excluded due to insufficient enrollment	-848,514	649,894
Excluded based on Dementia Exclusion	-122,364	527,530
Excluded based on Nursing Home Admission	-62,940	464,590
Excluded based on COPD Diagnosis	-340,473	124,117
Patients in Salbutamol group		101,279
Patients in Long-acting muscarinic antagonists (LAMAs) group		22,838
Final cohort		124,117

6. Variables

a. Exposure-related variables:

Study drug:
The study exposure of interest is initiation of Salbutamol
Comparator:
Long-acting muscarinic antagonists (LAMAs) – umeclidinium, aclidinium, tiotropium, glycopyrolate, glycopyrronium

b. Covariates:

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

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

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	

COPD specific and other pulmonary relevant covariates	
Respiratory failure	Pulmonary Hypertension
Moderate or Severe COPD exacerbation[1]	Interstitial lung disease, lung fibrosis, ARDS
Tuberculosis	Acute Upper/ Lower Respiratory Tract infection
Lung Cancer	Pneumonia
Bronchiectasis	Alpha-1-antitrypsin deficiency
Sarcoidosis	Number of Pulmonologist visits
Pulmonary function test	

COPD medication levels (a multi-category using hierarchical definition described below)[2]	
1. Monotherapy	Short acting muscarinic antagonist or short acting beta agonist (SAMA or SABA only): One or more from [Salbutamol, Fenoterol, Levalbuterol, Terbutaline, Ipratropium, Oxitropium] but not any from 2-6 below Long acting muscarinic antagonist or long acting beta agonist (LAMA or LABA only): One/more LABA [Arformoterol, Formoterol Indacaterol, Olodaterol, Salmeterol] OR one/more LAMA [Tiotropium, Aclidinium, Glycopyrronium, Umeclidinium] but not both
3. Dual therapy	LAMA+LABA: One/more LABA [Arformoterol, Formoterol Indacaterol, Olodaterol, Salmeterol] AND

	One/more LAMA [Tiotropium, Aclidinium, Glycopyrronium, Umeclidinium] but no inhaled corticosteroid ICS + LAMA: One/more inhaled corticosteroid [beclomethasone, budenoside, mometasone, fluticasone] AND One/more LAMA [Tiotropium, Aclidinium, Glycopyrronium, Umeclidinium] but no LABA ICS + LABA: One/more inhaled corticosteroid [beclomethasone, budenoside, mometasone, fluticasone] AND One/more LABA [Arformoterol, Formoterol Indacaterol, Olodaterol, Salmeterol] but no LAMA
4. Triple therapy (ICS + LAMA + LABA)	One/more inhaled corticosteroid [beclomethasone, budenoside, mometasone, fluticasone] AND One/more LAMA [Tiotropium, Aclidinium, Glycopyrronium, Umeclidinium] AND One/more LABA [Arformoterol, Formoterol Indacaterol, Olodaterol, Salmeterol]

Comedication use	
Lithium	Diuretics
Anti-epileptic mood stabilizers	Nitrates
Anti-epileptics (other than mood stabilizers)	Lipid lowering drugs
Atypical antipsychotics	Non-insulin diabetes medications
Benzodiazepines	Insulin
Serotonin-norepinephrine reuptake Inhibitors	Antidepressants

Selective serotonin reuptake inhibitors	Angiotensin II receptor blockers (ARBs)
Tricyclic antidepressants (TCAs)	Angiotensin converting enzyme inhibitors (ACEi)
Typical antipsychotics	Calcium channel blockers
Anticoagulants	Beta blockers
Antiplatelet agents	Disease-modifying antirheumatic drugs (DMARDs)
Corticosteroids	Antibiotics

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

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 Salbutamol and LAMAs 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 (Salbutamol and LAMAs) 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 Salbutamol and LAMAs 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)[3]-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.[4] 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,[5] and a caliper of 0.025 on the natural scale of the PS will be used to ensure similarity between the matched patients.[6]

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.[7] Next, balance in each individual covariate between two treatment groups is reported using standardized differences.[8]

8. Table for covariate balance

	Unmatched			PS-Matched		
Variable	**Salbutamol (N = 76,515)**	**LAMAs (N = 18,974)**	**St. Diff**	**Salbutamol (N = 18,633)**	**LAMAs (N = 18,633)**	**St. Diff**
Demographics						
Age, mean (SD)	74.4 (6.7)	74.9 (6.6)	-7	74.9 (6.8)	74.9 (6.6)	0.2
Gender, n (%)						
Male	34179 (44.7)	9622 (50.7)	-12.1	9399 (50.4)	9443 (50.7)	-0.5
Female	42336 (55.3)	9352 (49.3)	12.1	9234 (49.6)	9190 (49.3)	0.5
Race, n (%)						
White	68119 (89)	17022 (89.7)	-2.2	16740 (89.8)	16717 (89.7)	0.4
Black	4701 (6.1)	999 (5.3)	3.8	931 (5)	981 (5.3)	-1.2
Hispanic	895 (1.2)	197 (1)	1.3	209 (1.1)	195 (1)	0.7
Other	2800 (3.7)	756 (4)	-1.7	753 (4)	740 (4)	0.4
Region, n (%)						
Northeast; n (%)	12925 (16.9)	3858 (20.3)	-8.8	3901 (20.9)	3803 (20.4)	1.3
South; n (%)	30882 (40.4)	7738 (40.8)	-0.9	7470 (40.1)	7559 (40.6)	-1
Midwest; n (%)	19697 (25.7)	4337 (22.9)	6.7	4238 (22.7)	4281 (23)	-0.5
West; n (%)	12949 (16.9)	3028 (16)	2.6	3016 (16.2)	2978 (16)	0.6
Other; n (%)	62 (0.1)	13 (0.1)	0.5	8 (0)	12 (0.1)	-0.9
Calendar year of index date, n (%)						

2014	21088 (27.6)	5664 (29.9)	-5.1	5515 (29.6)	5603 (30.1)	-1
2015	16927 (22.1)	4117 (21.7)	1	4098 (22)	4080 (21.9)	0.2
2016	13486 (17.6)	3308 (17.4)	0.5	3372 (18.1)	3282 (17.6)	1.3
2017	13323 (17.4)	2979 (15.7)	4.6	2951 (15.8)	2958 (15.9)	-0.1
2018	11691 (15.3)	2906 (15.3)	-0.1	2697 (14.5)	2710 (14.5)	-0.2
Low income subsidy, n (%)	15429 (20.2)	3492 (18.4)	4.5	3416 (18.3)	3430 (18.4)	-0.2
Dementia risk factors, n (%)						
Diabetes	25989 (34)	6496 (34.2)	-0.6	6331 (34)	6370 (34.2)	-0.4
Obesity	14618 (19.1)	3559 (18.8)	0.9	3442 (18.5)	3486 (18.7)	-0.6
Hypertension	62676 (81.9)	15707 (82.8)	-2.3	15419 (82.8)	15430 (82.8)	-0.2
Coronary artery disease	29486 (38.5)	8138 (42.9)	-8.9	7942 (42.6)	7989 (42.9)	-0.5
Depression	13049 (17.1)	3139 (16.5)	1.4	3091 (16.6)	3071 (16.5)	0.3
Anxiety	13392 (17.5)	3112 (16.4)	2.9	3049 (16.4)	3041 (16.3)	0.1
Bipolar disorder	1089 (1.4)	260 (1.4)	0.5	277 (1.5)	254 (1.4)	1
Schizophrenia	162 (0.2)	30 (0.2)	1.2	28 (0.2)	29 (0.2)	-0.1
Markers for healthy behavior, frailty, healthcare use						
Smoking, n (%)	36477 (47.7)	10319 (54.4)	-13.5	10097 (54.2)	10136 (54.4)	-0.4
Mammography, n (%)	16014 (20.9)	3333 (17.6)	8.5	3263 (17.5)	3275 (17.6)	-0.2
Colonoscopy, n (%)	7990 (10.4)	1918 (10.1)	1.1	1819 (9.8)	1876 (10.1)	-1
Fecal occult blood test, n (%)	5563 (7.3)	1488 (7.8)	-2.2	1440 (7.7)	1461 (7.8)	-0.4

Influenza vaccination, n (%)	49288 (64.4)	12855 (67.8)	-7	12688 (68.1)	12622 (67.7)	0.8
Pneumococcal vaccination, n (%)	31232 (40.8)	8082 (42.6)	-3.6	7935 (42.6)	7896 (42.4)	0.4
Herpes zoster, n (%)	16 (0)	5 (0)	-0.4	7 (0)	4 (0)	0.9
Bone mineral density, n (%)	7356 (9.6)	1716 (9)	2	1753 (9.4)	1682 (9)	1.3
Number of distinct prescriptions, mean (SD)	12.1 (5.8)	12.1 (5.8)	0.9	12 (5.7)	12 (5.8)	-0.4
Number of emergency room visits, mean (SD)	0.9 (1.6)	0.8 (1.4)	9	0.8 (1.2)	0.8 (1.4)	-1
Number of outpatient visits, mean (SD)	11.6 (8.4)	12.2 (8.7)	-6.8	12.2 (8.7)	12.1 (8.7)	0.8
Number of hospitalizations, mean (SD)	0.3 (0.7)	0.4 (0.7)	-4.4	0.4 (0.7)	0.4 (0.7)	0
Number of physician office visits, mean (SD)	11.6 (8.4)	12.2 (8.7)	-6.8	12.2 (8.7)	12.1 (8.7)	0.8
Number of C-reactive protein tests ordered, mean (SD)	0.2 (0.8)	0.2 (0.8)	-1	0.2 (0.8)	0.2 (0.8)	0.1
Number of serum creatinine tests ordered, mean (SD)	1.2 (2.1)	1.2 (2.1)	-1.8	1.2 (2)	1.2 (2.1)	0.1
Composite frailty score, mean (SD)	0.2 (0.1)	0.2 (0.1)	-6	0.2 (0.1)	0.2 (0.1)	-0.6
Osteoporosis, n (%)	10519 (13.7)	2664 (14)	-0.8	2695 (14.5)	2622 (14.1)	1.1

Fractures, n (%)	5899 (7.7)	1347 (7.1)	2.3	1310 (7)	1314 (7.1)	-0.1
Falls, n (%)	4903 (6.4)	1101 (5.8)	2.5	1060 (5.7)	1071 (5.7)	-0.3
Use of supplemental oxygen, n (%)	2548 (3.3)	1124 (5.9)	-12.4	1083 (5.8)	1103 (5.9)	-0.5
Combined comorbidity score, mean (SD)	3 (2.6)	3.2 (2.7)	-8.8	3.2 (2.7)	3.2 (2.7)	-0.8
Comedication use, n (%)						
Lithium	104 (0.1)	31 (0.2)	-0.7	27 (0.1)	30 (0.2)	-0.4
Anti-epileptic mood stabilizers	962 (1.3)	233 (1.2)	0.3	230 (1.2)	226 (1.2)	0.2
Anti-epileptics (other than mood stabilizers)	12688 (16.6)	3012 (15.9)	1.9	2891 (15.5)	2939 (15.8)	-0.7
Atypical antipsychotics	1468 (1.9)	364 (1.9)	0	357 (1.9)	353 (1.9)	0.2
Benzodiazepines	15721 (20.5)	3774 (19.9)	1.6	3728 (20)	3694 (19.8)	0.5
Serotonin-norepinephrine reuptake inhibitors	4148 (5.4)	1090 (5.7)	-1.4	1056 (5.7)	1058 (5.7)	0
Selective serotonin reuptake inhibitors	14107 (18.4)	3371 (17.8)	1.7	3322 (17.8)	3310 (17.8)	0.2
Tricyclic antidepressants (TCAs)	2824 (3.7)	615 (3.2)	2.5	599 (3.2)	603 (3.2)	-0.1
Typical antipsychotics	280 (0.4)	55 (0.3)	1.3	46 (0.2)	55 (0.3)	-0.9
Anticoagulants	10269 (13.4)	3023 (15.9)	-7.1	2964 (15.9)	2971 (15.9)	-0.1
Antiplatelet agents	10147 (13.3)	2881 (15.2)	-5.5	2751 (14.8)	2827 (15.2)	-1.1
Nitrates	8214 (10.7)	2245 (11.8)	-3.5	2186 (11.7)	2202 (11.8)	-0.3
Lipid lowering drugs	45866 (59.9)	11884 (62.6)	-5.5	11554 (62)	11666 (62.6)	-1.2

Non-insulin diabetes medications	14767 (19.3)	3652 (19.2)	0.1	3513 (18.9)	3575 (19.2)	-0.8
Insulin	5629 (7.4)	1302 (6.9)	1.9	1313 (7)	1280 (6.9)	0.7
Antidepressants	22974 (30)	5581 (29.4)	1.3	5529 (29.7)	5469 (29.4)	0.7
Angiotensin II receptor blockers (ARBs)	17841 (23.3)	4732 (24.9)	-3.8	4669 (25.1)	4650 (25)	0.2
Angiotensin converting enzyme inhibitors (ACEi)	24902 (32.5)	6081 (32)	1.1	5892 (31.6)	5973 (32.1)	-0.9
Calcium channel blockers	21852 (28.6)	5684 (30)	-3.1	5476 (29.4)	5588 (30)	-1.3
Beta blockers	33549 (43.8)	8709 (45.9)	-4.1	8530 (45.8)	8547 (45.9)	-0.2
Disease-modifying antirheumatic drugs (DMARDs)	2824 (3.7)	691 (3.6)	0.3	650 (3.5)	674 (3.6)	-0.7
Diuretics	34617 (45.2)	8908 (46.9)	-3.4	8677 (46.6)	8751 (47)	-0.8
Corticosteroids	35722 (46.7)	7769 (40.9)	11.6	7603 (40.8)	7632 (41)	-0.3
Antibiotics	58260 (76.1)	12802 (67.5)	19.4	12572 (67.5)	12592 (67.6)	-0.2
COPD specific covariates						
Respiratory failure, n (%)	7994 (10.4)	2922 (15.4)	-14.8	2834 (15.2)	2865 (15.4)	-0.5
Moderate or Severe COPD exacerbation, n (%)	3341 (4.4)	1181 (6.2)	-8.3	1174 (6.3)	1175 (6.3)	0
Tuberculosis, n (%)	15389 (20.1)	4033 (21.3)	-2.8	3940 (21.1)	3992 (21.4)	-0.7
Lung Cancer, n (%)	3415 (4.5)	1150 (6.1)	-7.2	1133 (6.1)	1130 (6.1)	0.1
Bronchiectasis, n (%)	2207 (2.9)	820 (4.3)	-7.7	804 (4.3)	805 (4.3)	0
Sarcoidosis, n (%)	10967 (14.3)	3718 (19.6)	-14.1	3649 (19.6)	3659 (19.6)	-0.1

Pulmonary Hypertension, n (%)	1643 (2.1)	627 (3.3)	-7.1	610 (3.3)	607 (3.3)	0.1
Interstitial lung disease, lung fibrosis, ARDS, n (%)	10967 (14.3)	3718 (19.6)	-14.1	3649 (19.6)	3659 (19.6)	-0.1
Acute Upper/ Lower Respiratory Tract infection, n (%)	23603 (30.8)	4249 (22.4)	19.2	4103 (22)	4175 (22.4)	-0.9
Pneumonia, n (%)	6481 (8.5)	1734 (9.1)	-2.4	1703 (9.1)	1718 (9.2)	-0.3
Alpha-1-antitrypsin deficiency, n (%)	84 (0.1)	37 (0.2)	-2.2	35 (0.2)	36 (0.2)	-0.1
Number of Pulmonologist visits, mean (SD)	0.9 (2.2)	1.6 (2.6)	-27.2	1.6 (2.9)	1.6 (2.6)	0
Pulmonary function test, n (%)	22718 (29.7)	9742 (51.3)	-45.2	9806 (52.6)	9550 (51.3)	2.8
Hierarchical COPD Medication, n (%)						
Monotherapy	2536 (3.3)	1785 (9.4)	-25.2	1507 (8.1)	1726 (9.3)	-4.2
Dual therapy	55581 (72.6)	10873 (57.3)	32.6	10988 (59)	10873 (58.4)	1.3
Triple therapy	18398 (24)	6036 (31.8)	-17.4	6138 (32.9)	6034 (32.4)	1.2
Comorbid conditions, n (%)						
Atrial fibrillation	13416 (17.5)	3952 (20.8)	-8.4	3892 (20.9)	3892 (20.9)	0
Heart failure	14269 (18.6)	4218 (22.2)	-8.9	4137 (22.2)	4141 (22.2)	-0.1
Stroke or transient ischemic attack	7776 (10.2)	1943 (10.2)	-0.3	1900 (10.2)	1905 (10.2)	-0.1

Peripheral vascular disease	11563 (15.1)	3353 (17.7)	-6.9	3159 (17)	3299 (17.7)	-2
Hyperlipidemia	54201 (70.8)	13690 (72.2)	-2.9	13397 (71.9)	13443 (72.1)	-0.5
Renal dysfunction	15207 (19.9)	3997 (21.1)	-3	3849 (20.7)	3917 (21)	-0.9
Chronic liver disease	5263 (6.9)	1316 (6.9)	-0.2	1274 (6.8)	1287 (6.9)	-0.3
Asthma	45614 (59.6)	10854 (57.2)	4.9	10716 (57.5)	10630 (57)	0.9
Ischemic heart disease	28709 (37.5)	7935 (41.8)	-8.8	7759 (41.6)	7791 (41.8)	-0.3
Malignancy	22825 (29.8)	6008 (31.7)	-4	5830 (31.3)	5896 (31.6)	-0.8
Drug or alcohol abuse or dependence	19920 (26)	5549 (29.2)	-7.2	5436 (29.2)	5447 (29.2)	-0.1
Venous thromboembolism	3418 (4.5)	915 (4.8)	-1.7	889 (4.8)	899 (4.8)	-0.3
Rheumatoid Arthritis	3666 (4.8)	913 (4.8)	-0.1	876 (4.7)	897 (4.8)	-0.5

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[9] 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

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