Data Analysis for Drug Repurposing for Effective Alzheimer's Medicines – Montelukast vs Fluticasone

NCT05457855

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1. Comparison Details

a. Intended aim(s)

To evaluate the comparative risk of dementia onset between patients treated with Montelukast versus Fluticasone for asthma.

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

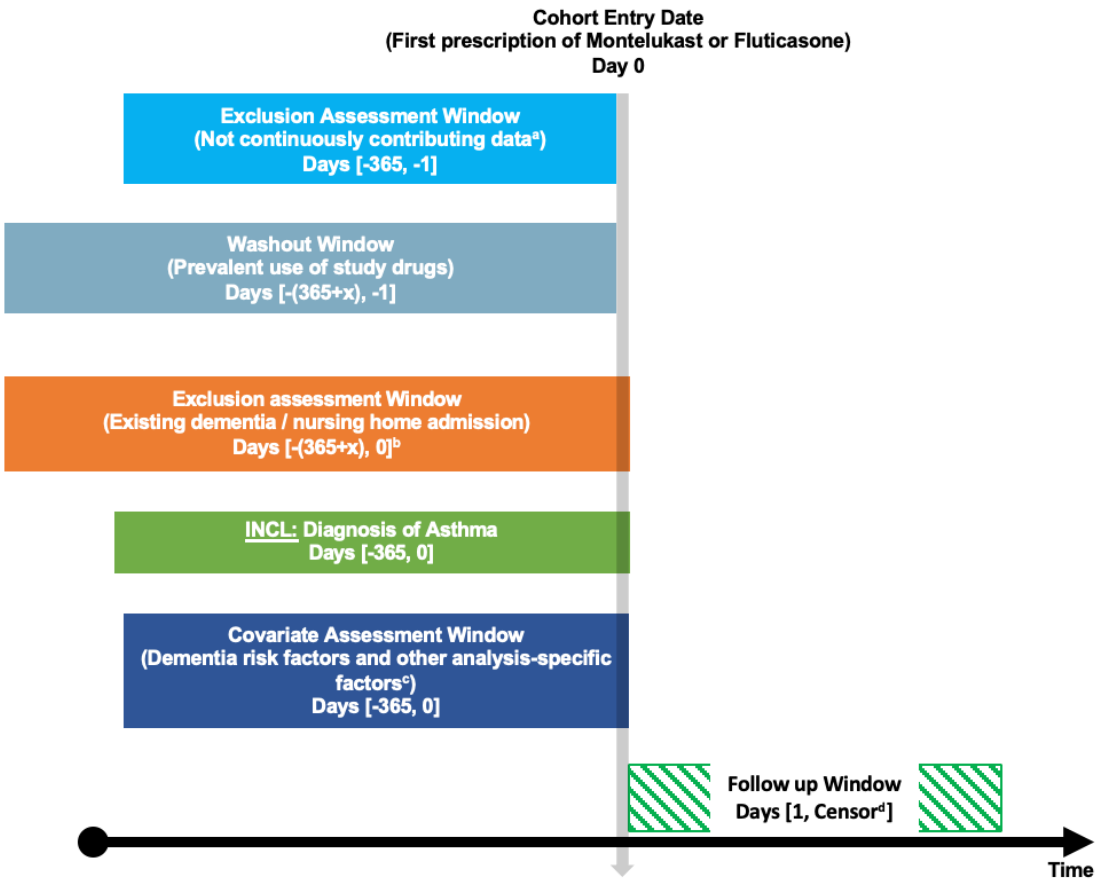
Seanna Vine

3. Data Source(s)

Medicare, 2008-2018

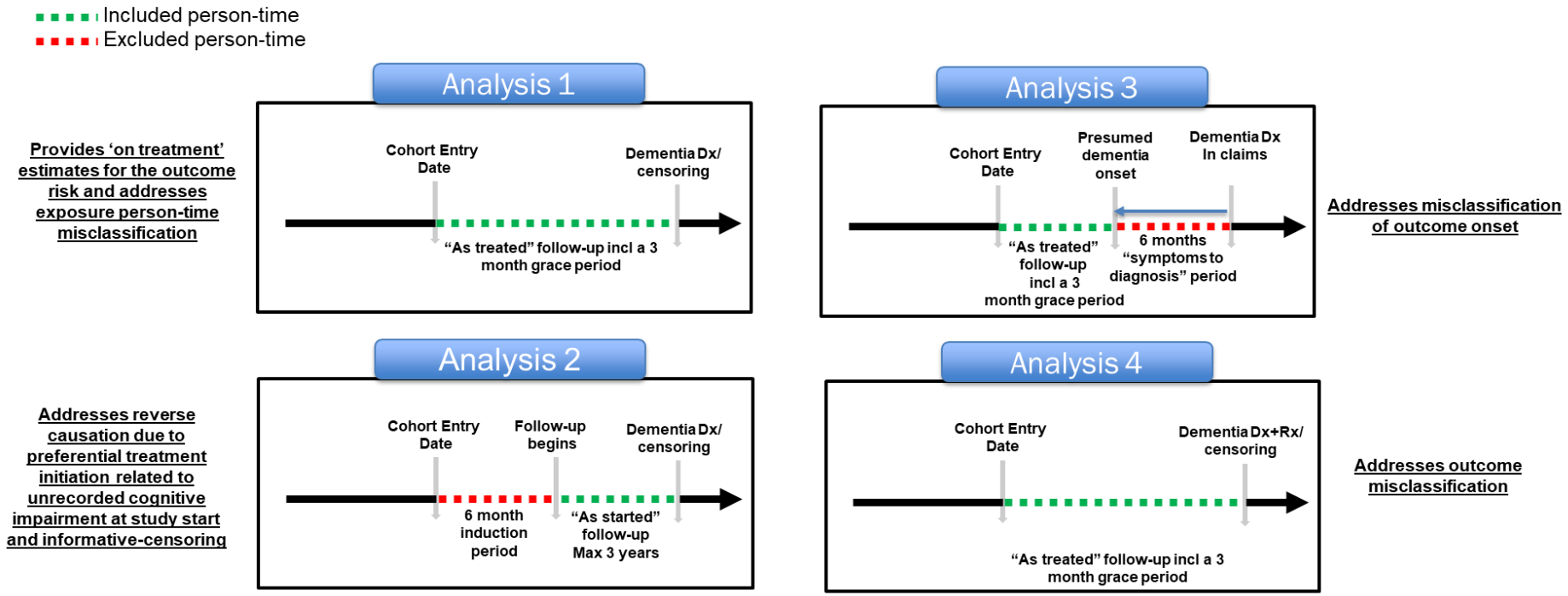
4. Study Design Diagrams

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 Montelukast versus Fluticasone. 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 Montelukast versus Fluticasone use

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 Montelukast versus Fluticasone, 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 asthma diagnosis recorded in 365 days prior to index date (ICD-9 493.0x, 493.1, 493.2x, 493.8x, 493.9x or ICD-10 J44.0, J44.1, J44.9, J45.2x, J45.3x, J45.4x, J45.5x, J45.9x)

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 Montelukast versus Fluticasone, 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 asthma diagnosis recorded in 365 days prior to index date (ICD-9 493.0x, 493.1,

493.2x, 493.8x, 493.9x or ICD-10 J44.0, J44.1, J44.9, J45.2x, J45.3x, J45.4x, J45.5x, J45.9x)

- 180-day continuous use of Montelukast versus Fluticasone 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	-21,749,739	1,716,436
Excluded due to insufficient enrollment	-1,010,844	705,592
Excluded based on Dementia Exclusion	-113,159	592,433
Excluded based on Nursing Home Admission	-62,588	529,845
Excluded based on Peripheral artery disease Diagnosis	-454,167	75,678
Excluded anyone aged <65 at index	-24,145	51,533
Patients in Montelukast group		12,575
Patients in Fluticasone group		38,958
Final cohort		51,533

6. Variables

a. Exposure-related variables:

Study drug:
The study exposure of interest is initiation of Montelukast
Comparator:
Fluticasone

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 outpatient visits
Mammography	Number of hospitalizations
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

Other Asthma treatments and Asthma severity indicators	
Respiratory failure	LABA
Asthma exacerbation	SABA
Tuberculosis	SAMA
Lung Cancer	LAMA
Bronchiectasis	ICS (excluding Fluticasone)
Sarcoidosis	Omalizumab, Mepolizumab, Reslizumab, Benralizumab, Dupilumab
Pulmonary Hypertension	Leukotriene receptor antagonist (excluding Montelukast)
Interstitial lung disease, lung fibrosis, ARDS	Number of Pulmonologist visits
Acute Upper/ Lower Respiratory Tract infection	Pulmonary function test
Pneumonia	Antibiotics
Corticosteroids	

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)

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

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 Montelukast and Fluticasone 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 (Montelukast and Fluticasone) 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 Montelukast and Fluticasone 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

	Unmatched			PS-Matched		
Variable	**Montelukast (N = 12,575)**	**Fluticasone (N = 38,958)**	**St. Diff**	**Montelukast (N = 12,572)**	**Fluticasone (N = 12,572)**	**St. Diff**
Demographics						
Age, mean (SD)	72.8 (6.1)	73.3 (6.4)	-8.20	72.8 (6.1)	72.8 (6.1)	-0.30
Gender, n (%)						
Male	3694 (29.4)	12706 (32.6)	-7.00	3694 (29.4)	3764 (29.9)	-1.20
Female	8881 (70.6)	26252 (67.4)	7.00	8878 (70.6)	8808 (70.1)	1.20
Race, n (%)						
White	10614 (84.4)	33028 (84.8)	-1.00	10613 (84.4)	10650 (84.7)	-0.80
Black	831 (6.6)	3055 (7.8)	-4.80	831 (6.6)	881 (7)	-1.60
Hispanic	218 (1.7)	639 (1.6)	0.70	218 (1.7)	203 (1.6)	0.90
Other	912 (7.3)	2236 (5.7)	6.10	910 (7.2)	838 (6.7)	2.30
Region, n (%)						
Northeast; n (%)	2271 (18.1)	8670 (22.3)	#####	2271 (18.1)	2335 (18.6)	-1.30
South; n (%)	5310 (42.2)	13528 (34.7)	15.50	5307 (42.2)	5179 (41.2)	2.10
Midwest; n (%)	2498 (19.9)	8288 (21.3)	-3.50	2498 (19.9)	2546 (20.3)	-1.00
West; n (%)	2484 (19.8)	8431 (21.6)	-4.70	2484 (19.8)	2501 (19.9)	-0.30
Other; n (%)	12 (0.1)	41 (0.1)	-0.30	12 (0.1)	11 (0.1)	0.30
Calendar year of index date, n (%)						
2014	3143 (25)	10567 (27.1)	-4.90	3142 (25)	3037 (24.2)	1.90
2015	2585 (20.6)	8299 (21.3)	-1.80	2585 (20.6)	2519 (20)	1.30
2016	2396 (19.1)	7305 (18.8)	0.80	2394 (19)	2425 (19.3)	-0.60
2017	2330 (18.5)	6986 (17.9)	1.50	2330 (18.5)	2408 (19.2)	-1.60
2018	2121 (16.9)	5801 (14.9)	5.40	2121 (16.9)	2183 (17.4)	-1.30

Low income subsidy, n (%)	1824 (14.5)	6953 (17.8)	-9.10	1823 (14.5)	1859 (14.8)	-0.80
Dementia risk factors, n (%)						
Diabetes	4101 (32.6)	13257 (34)	-3.00	4098 (32.6)	4087 (32.5)	0.20
Obesity	2804 (22.3)	9138 (23.5)	-2.80	2804 (22.3)	2808 (22.3)	-0.10
Coronary artery disease	3338 (26.5)	11429 (29.3)	-6.20	3338 (26.6)	3264 (26)	1.30
Hypertension	9870 (78.5)	30962 (79.5)	-2.40	9867 (78.5)	9909 (78.8)	-0.80
Depression	2029 (16.1)	6989 (17.9)	-4.80	2029 (16.1)	2013 (16)	0.30
Anxiety	2235 (17.8)	6921 (17.8)	0.00	2235 (17.8)	2234 (17.8)	0.00
Bipolar disorder	126 (1)	555 (1.4)	-3.90	126 (1)	120 (1)	0.50
Schizophrenia	8 (0.1)	70 (0.2)	-3.30	8 (0.1)	3 (0)	1.90
Markers for healthy behavior, frailty, healthcare use						
Smoking, n (%)	2803 (22.3)	10651 (27.3)	#####	2803 (22.3)	2833 (22.5)	-0.60
Mammography, n (%)	4285 (34.1)	12152 (31.2)	6.20	4283 (34.1)	4262 (33.9)	0.40
Colonoscopy, n (%)	1465 (11.7)	4797 (12.3)	-2.00	1464 (11.6)	1465 (11.7)	0.00
Fecal occult blood test, n (%)	1172 (9.3)	3374 (8.7)	2.30	1172 (9.3)	1172 (9.3)	0.00
Influenza vaccination, n (%)	8417 (66.9)	26819 (68.8)	-4.10	8416 (66.9)	8463 (67.3)	-0.80
Herpes zoster vaccination, n (%)	3 (0)	11 (0)	-0.30	3 (0)	2 (0)	0.60
Pneumococcal vaccination, n (%)	5584 (44.4)	17347 (44.5)	-0.20	5583 (44.4)	5680 (45.2)	-1.60
Bone mineral density test, n (%)	1743 (13.9)	5139 (13.2)	2.00	1743 (13.9)	1732 (13.8)	0.30
Number of distinct prescriptions, mean (SD)	12.3 (5.8)	12.5 (5.8)	-2.30	12.3 (5.8)	12.2 (5.7)	2.00
Number of emergency room visits, mean (SD)	0.7 (1.4)	0.8 (1.6)	-8.80	0.7 (1.4)	0.7 (1.2)	1.20
Number of outpatient visits, mean (SD)	12.5 (8.4)	12.4 (8.6)	1.10	12.5 (8.4)	12.5 (8.6)	0.90
Number of hospitalizations, mean (SD)	0.2 (0.6)	0.2 (0.6)	-6.60	0.2 (0.6)	0.2 (0.5)	1.40

Number of C-reactive protein tests ordered, mean (SD)	0.2 (0.8)	0.2 (0.9)	-1.20	0.2 (0.8)	0.2 (0.8)	0.40
Number of serum creatinine tests ordered, mean (SD)	0.9 (1.6)	1.1 (2)	#####	0.9 (1.6)	0.9 (1.5)	1.60
Composite frailty score, mean (SD)	0.2 (0.1)	0.2 (0.1)	#####	0.2 (0.1)	0.2 (0.1)	1.40
Osteoporosis, n (%)	1911 (15.2)	5814 (14.9)	0.80	1911 (15.2)	1912 (15.2)	0.00
Fractures, n (%)	877 (7)	2787 (7.2)	-0.70	877 (7)	893 (7.1)	-0.50
Falls, n (%)	641 (5.1)	2326 (6)	-3.80	641 (5.1)	656 (5.2)	-0.50
Use of supplemental oxygen, n (%)	260 (2.1)	1091 (2.8)	-4.80	260 (2.1)	279 (2.2)	-1.00
Combined comorbidity score, mean (SD)	2.2 (2.2)	2.4 (2.4)	#####	2.2 (2.2)	2.2 (2.2)	0.50
Comedication use, n (%)						
Lithium	17 (0.1)	50 (0.1)	0.20	17 (0.1)	12 (0.1)	1.20
Anti-epileptic mood stabilizers	142 (1.1)	562 (1.4)	-2.80	142 (1.1)	149 (1.2)	-0.50
Anti-epileptics (other than mood stabilizers)	1839 (14.6)	6087 (15.6)	-2.80	1837 (14.6)	1778 (14.1)	1.30
Atypical antipsychotics	170 (1.4)	719 (1.8)	-3.90	170 (1.4)	158 (1.3)	0.80
Benzodiazepines	2537 (20.2)	7878 (20.2)	-0.10	2537 (20.2)	2523 (20.1)	0.30
Serotonin-norepinephrine reuptake inhibitors	715 (5.7)	2343 (6)	-1.40	715 (5.7)	721 (5.7)	-0.20
Selective serotonin reuptake inhibitors	2265 (18)	7367 (18.9)	-2.30	2265 (18)	2205 (17.5)	1.20
Tricyclic antidepressants (TCAs)	434 (3.5)	1548 (4)	-2.80	434 (3.5)	425 (3.4)	0.40
Typical antipsychotics	20 (0.2)	105 (0.3)	-2.40	20 (0.2)	24 (0.2)	-0.80
Anticoagulants	1163 (9.2)	4342 (11.1)	-6.30	1163 (9.3)	1217 (9.7)	-1.50
Antiplatelet agents	947 (7.5)	3416 (8.8)	-4.50	947 (7.5)	916 (7.3)	0.90
Nitrates	915 (7.3)	3131 (8)	-2.90	915 (7.3)	881 (7)	1.10
Lipid lowering drugs	6790 (54)	22232 (57.1)	-6.20	6789 (54)	6819 (54.2)	-0.50
Non-insulin diabetes medications	2391 (19)	7537 (19.3)	-0.80	2388 (19)	2415 (19.2)	-0.50

Insulin	725 (5.8)	2740 (7)	-5.20	725 (5.8)	705 (5.6)	0.70
Antidepressants	3634 (28.9)	11842 (30.4)	-3.30	3634 (28.9)	3557 (28.3)	1.40
Angiotensin converting enzyme inhibitors (ACEi)	3269 (26)	10938 (28.1)	-4.70	3268 (26)	3300 (26.2)	-0.60
Angiotensin II receptor blockers (ARBs)	3599 (28.6)	10554 (27.1)	3.40	3598 (28.6)	3563 (28.3)	0.60
Beta blockers	4312 (34.3)	14499 (37.2)	-6.10	4312 (34.3)	4274 (34)	0.60
Calcium channel blockers	3182 (25.3)	10328 (26.5)	-2.80	3181 (25.3)	3192 (25.4)	-0.20
Disease-modifying antirheumatic drugs (DMARDs)	457 (3.6)	1522 (3.9)	-1.40	457 (3.6)	452 (3.6)	0.20
Diuretics	5260 (41.8)	17028 (43.7)	-3.80	5259 (41.8)	5306 (42.2)	-0.80
Biologics (Omalizumab, Mepolizumab, Reslizumab, Benralizumab, Dupilumab)	89 (0.7)	218 (0.6)	1.90	89 (0.7)	77 (0.6)	1.20
Comorbid conditions, n (%)						
Atrial fibrillation	1527 (12.1)	5492 (14.1)	-5.80	1527 (12.1)	1543 (12.3)	-0.40
Heart failure	1397 (11.1)	5145 (13.2)	-6.40	1397 (11.1)	1352 (10.8)	1.10
Stroke or transient ischemic attack	858 (6.8)	3209 (8.2)	-5.40	858 (6.8)	867 (6.9)	-0.30
Peripheral vascular disease	1056 (8.4)	3915 (10)	-5.70	1055 (8.4)	1055 (8.4)	0.00
Hyperlipidemia	8900 (70.8)	27637 (70.9)	-0.40	8898 (70.8)	8820 (70.2)	1.40
Renal dysfunction	1706 (13.6)	6279 (16.1)	-7.20	1705 (13.6)	1704 (13.6)	0.00
Chronic liver disease	810 (6.4)	2628 (6.7)	-1.20	809 (6.4)	807 (6.4)	0.10
Ischemic heart disease	3250 (25.8)	11107 (28.5)	-6.00	3250 (25.9)	3170 (25.2)	1.50
Chronic obstructive pulmonary disease	5222 (41.5)	16890 (43.4)	-3.70	5220 (41.5)	5213 (41.5)	0.10
Malignancy	3369 (26.8)	11073 (28.4)	-3.70	3369 (26.8)	3411 (27.1)	-0.80
Drug or alcohol abuse or dependence	944 (7.5)	4336 (11.1)	#####	944 (7.5)	936 (7.4)	0.20
Venous thromboembolism	425 (3.4)	1565 (4)	-3.40	425 (3.4)	423 (3.4)	0.10
Rheumatoid Arthritis	595 (4.7)	1994 (5.1)	-1.80	595 (4.7)	592 (4.7)	0.10

Other Asthma treatments and Asthma severity indicators						
Asthma exacerbation, n (%)	213 (1.7)	478 (1.2)	3.90	211 (1.7)	174 (1.4)	2.40
Bronchiectasis, n (%)	347 (2.8)	1006 (2.6)	1.10	346 (2.8)	357 (2.8)	-0.50
Interstitial lung disease, lung fibrosis, ARDS, n (%)	1220 (9.7)	3941 (10.1)	-1.40	1219 (9.7)	1205 (9.6)	0.40
Lung Cancer, n (%)	144 (1.1)	674 (1.7)	-4.90	144 (1.1)	137 (1.1)	0.50
Pneumonia, n (%)	694 (5.5)	2455 (6.3)	-3.30	693 (5.5)	670 (5.3)	0.80
Pulmonary Hypertension, n (%)	194 (1.5)	691 (1.8)	-1.80	194 (1.5)	182 (1.4)	0.80
Respiratory failure, n (%)	723 (5.7)	2725 (7)	-5.10	722 (5.7)	704 (5.6)	0.60
Sarcoidosis, n (%)	60 (0.5)	259 (0.7)	-2.50	60 (0.5)	68 (0.5)	-0.90
Tuberculosis, n (%)	2157 (17.2)	7552 (19.4)	-5.80	2155 (17.1)	2177 (17.3)	-0.50
Acute Upper/ Lower Respiratory Tract infection, n (%)	4789 (38.1)	14315 (36.7)	2.80	4788 (38.1)	4850 (38.6)	-1.00
Pulmonary function test, n (%)	4989 (39.7)	13566 (34.8)	10.00	4988 (39.7)	4943 (39.3)	0.70
Number of Pulmonologist visits, mean (SD)	1.1 (2.4)	1 (2.5)	3.50	1.1 (2.4)	1.1 (2.5)	0.90
Antibiotics, n (%)	9638 (76.6)	29724 (76.3)	0.80	9636 (76.6)	9601 (76.4)	0.70
Corticosteroids, n (%)	6750 (53.7)	18540 (47.6)	12.20	6748 (53.7)	6551 (52.1)	3.10
ICS (excluding Fluticasone), n (%)	3647 (29)	8369 (21.5)	17.40	3644 (29)	3386 (26.9)	4.60
LAMA, n (%)	884 (7)	3315 (8.5)	-5.50	884 (7)	883 (7)	0.00
LABA, n (%)	2532 (20.1)	12953 (33.2)	#####	2532 (20.1)	2143 (17)	8.00
Leukotriene receptor antagonist (excluding Montelukast), n (%)	93 (0.7)	150 (0.4)	4.70	91 (0.7)	68 (0.5)	2.30
SABA, n (%)	6687 (53.2)	21764 (55.9)	-5.40	6684 (53.2)	6657 (53)	0.40
SAMA, n (%)	656 (5.2)	2193 (5.6)	-1.80	656 (5.2)	629 (5)	1.00

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

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