

Online Supplement

Disease Onset and Burden in Patients With Chronic Bronchitis and COPD: A Real-World Evidence Study

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**at the time of the study*

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Supplemental methods

Definition of chronic bronchitis using Optum® EHR notes

Optum's clinical notes are pre-processed to generate keyword combinations (i.e. such as "moist cough" or "no cough"). For symptom scanning in clinical notes, the following rules were observed:

- Any clinical notes that used the term "bronchitis" were counted as cough and sputum
- "productive cough" and "moist cough" was counted as cough and sputum
- "nocturnal cough", "persistent cough" and "cough" were counted as cough only symptoms
- "rales", "rhonchi", "mucus cast", "sputum production", "phlegmy", "sputum", "phlegm" were counted as sputum only symptoms
- negative terms such as "no cough", "no sputum", **does not complain about cough** etc., were excluded

Definition of smoking status

Clinical notes on smoking status recorded by physicians in EHRs were reviewed to determine smoking status. Any patient whose notes contained "previously smoked", "current smoker", "not currently smoking" was categorized as "smoker or ex-smoker". Patients with no smoking status recorded or notes of "Invalid value", "Unknown smoking status", "Not recorded", "Other smoking status" were categorized as "unknown smoking status". Only patients where "Never smoked" was recorded at least once were categorized as "never smoked".

Healthcare resource utilization – definitions for specialist visits and oxygen therapy

The number of visits to a specialist was calculated by counting the encounters where the provider had the "Pulmonary Medicine" specialty.

Number of patients under oxygen therapy was extracted from the EHR using the oxygen therapy, Healthcare Common Procedure Coding System (HCPCS) codes "E0447", "E0467", "E1390", "E1391", "E1392", "E1354", "E1356", "E1357", "E1358", "E0443", "E0444", "E0447", "E0467", and "E1392".

Medication use

The number of drug prescriptions in the follow-up period were extracted from the EHR. For mucolytics and phosphodiesterase type 4 inhibitors (PDE4) inhibitors, the drugs administered or prescribed with drug class in "inhaled mucolytics" and "selective phosphodiesterase type 4 inhibitors", respectively were considered. Macrolide prescriptions were calculated from the drug class "macrolides". For respiratory drugs long-acting muscarinic antagonist (LAMA), long-acting

β 2-agonist (LABA) and inhaled corticosteroids (ICS), the following drug classes were considered "sympathomimetics", "inhaled anticholinergic agents", and "inhaled corticosteroids", respectively. For dual and triple therapy, ICS+LABA, LABA+LAMA, LABA+LAMA, and ICS+LABA+LAMA classes of drugs were considered. If a patient was prescribed each drug class separately within the same three-month period, this prescription was counted as multi-therapy prescription.

Sankey diagrams for medication

Sankey diagrams can be used to illustrate the flow of patients between states (e.g., being prescribed a certain medication type), with larger flow indicating greater numbers of patients making that transition.

Sankey diagrams were created to illustrate inhaled medication use by looking at every prescription every patient had during the five-year follow-up period, together with their respective dates. If a patient was prescribed each drug class separately in the same three-month period, this prescription was counted as multi-therapy prescription. Only inhaled medications were included in this analysis.

Prescription dates were ordered chronologically, and a number was appended to each prescription of the transition vector depending on what position they are in the list. The number of times each transition of prescription happened in each cohort was then computed. For visual clarity, transitions were not included if the number of patients in the transition was <1% of total patient numbers.

Analysis of common COPD comorbidities

The following COPD comorbidities were evaluated in all three cohorts: GERD; diabetes; osteoporosis or bone fractures; bronchiectasis; lung cancer and chronic rhinosinusitis.

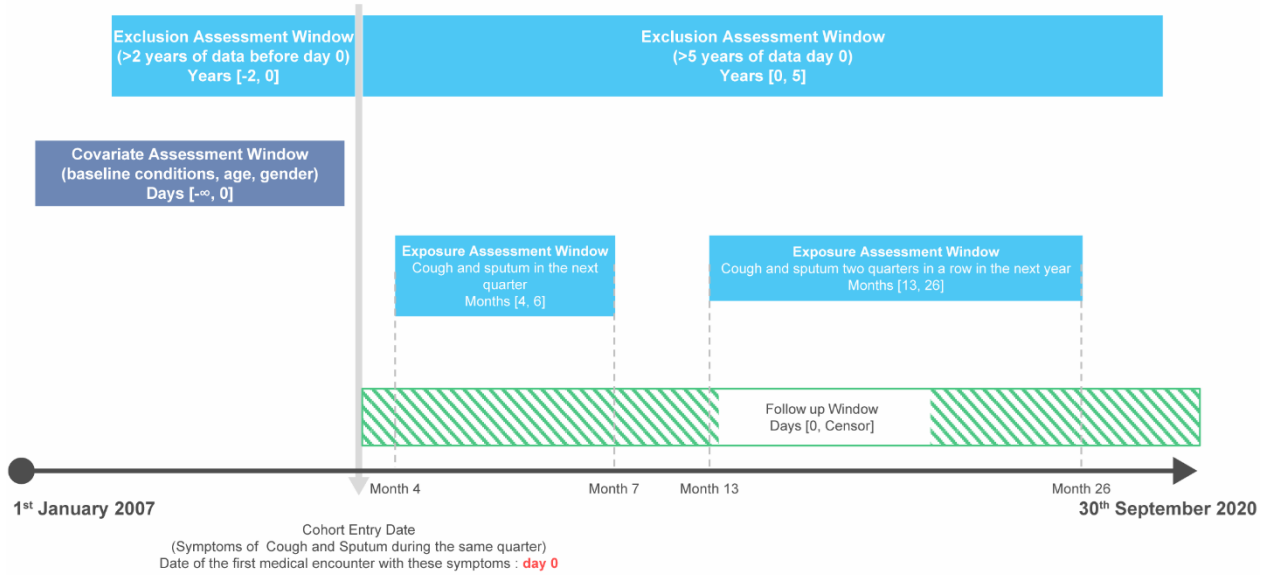
Comorbidities were detected using their ICD-10-CM code as follows: code K21 for GERD; E08, E09, E10, E11, E13 for diabetes; M80, M81, M83, M84 for osteoporosis, osteopenia, bone fractures; J47 for bronchiectasis; C34.90 for lung cancer and J32 for chronic rhinosinusitis.

Populations with BMI, age at index date, smoking status and gender covariates were matched using the Inverse Probability Weighting method whereby a pseudo-population was created where each patient was given an importance weight. If patients had more than one measurement of BMI, the average was taken of all measurements in the follow-up period. This weight is equal to the inverse of the probability that a patient is in its cohort given its covariates. This probability was approximated using a logistic regression on the covariates. The adjusted frequency of selected

common COPD morbidities was calculated using these weights to give a weighted average of patient counts for comparison of cohorts.

Supplementary Figures

A. Study design for adult patient CB cohort



B. Study design for adult patient COPD cohort

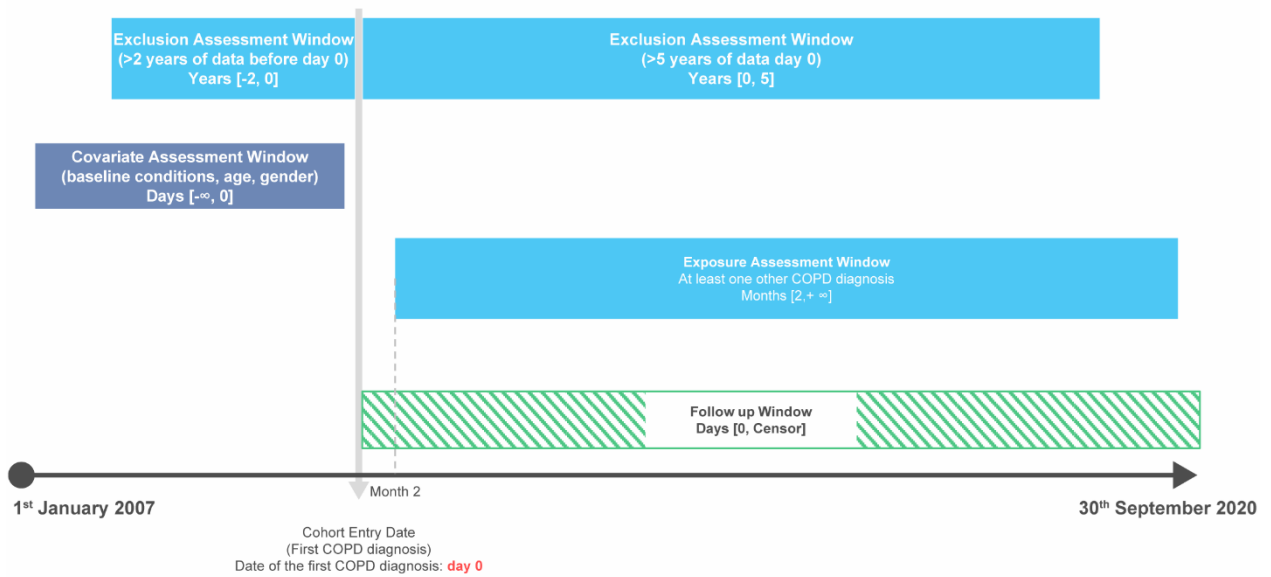


Figure S1. Study design for CB and COPD cohorts

CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease

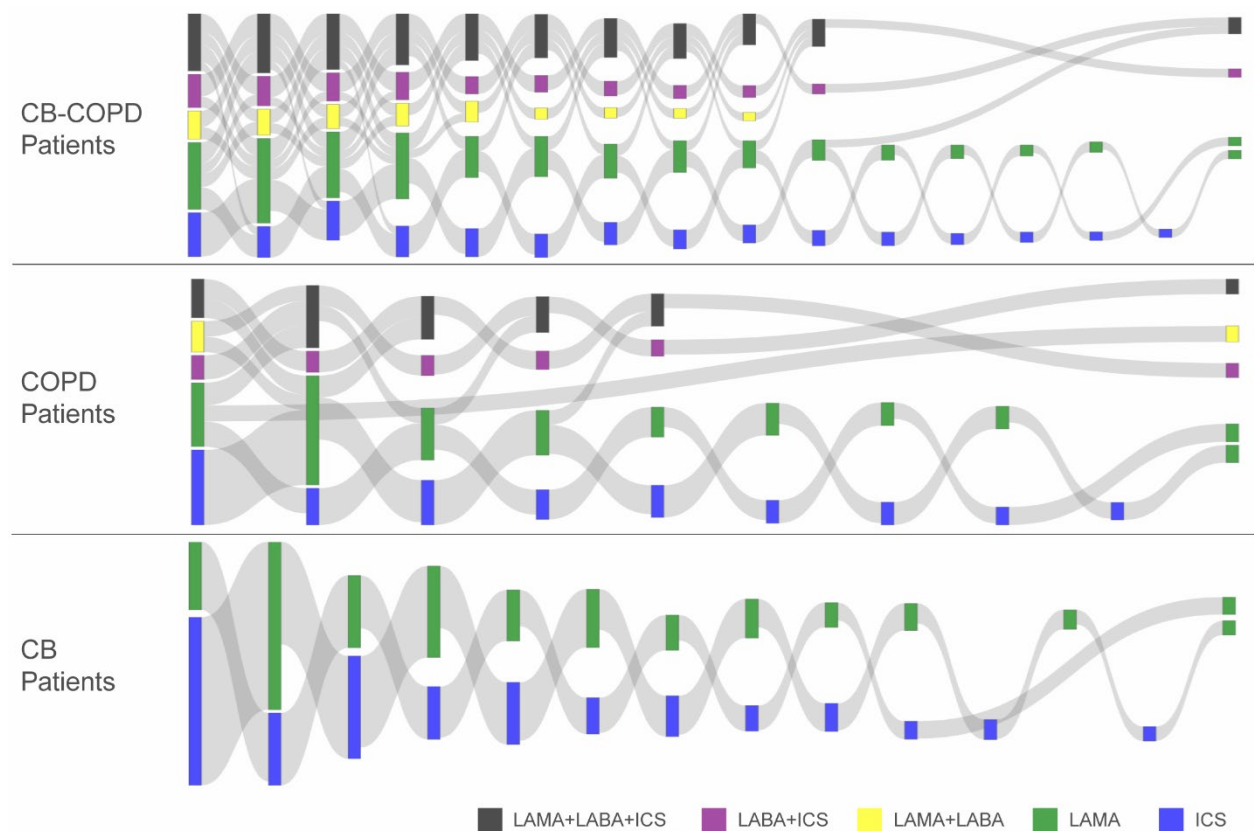


Figure S2. Sankey diagram of inhaled medication transitions over five years

Note 1% of the cohort has to make a given move in order to be represented in the Sankey diagram

CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β 2-agonist; LAMA, long-acting muscarinic antagonist

Supplementary Tables

Table S1. Respiratory medication records in Optum® EHR over five years

	CB	COPD	COPD-CB
Number of patients, N	628545	129084	77749
Respiratory medication and antibiotics prescribed, n (%)			
LAMA	326843 (52%)	58088 (45%)	48204 (62%)
LABA	18856 (3%)	18072 (14%)	15550 (20%)
ICS	295416 (47%)	30980 (24%)	28767 (37%)
LABA+ICS*	62855 (10%)	34853 (27%)	32655 (42%)
LAMA+LABA*	31427 (5%)	36144 (28%)	33432 (43%)
LAMA+LABA+ICS*	75425 (12%)	47761 (37%)	46649 (60%)
Inhaled mucolytics	0.0 (0%)	1291 (1%)	1555 (2%)
PDE4 inhibitors	0.0 (0%)	2582 (2%)	3887 (5%)
Macrolides (any)	370842 (59%)	50343 (39%)	50537 (65%)
Average respiratory drug classes per patient	1.29	1.75	2.64

Average prescriptions per year per patient			
LAMA	0.28	0.26	0.41
LABA	0.01	0.06	0.08
ICS	0.27	0.13	0.22
LABA+ICS*	0.05	0.16	0.27
LAMA+LABA*	0.01	0.16	0.28
LAMA+LABA+ICS*	0.01	0.43	0.88
Macrolides	0.27	0.17	0.43

*If a patient was prescribed each drug class separately in the three-month period, this prescription was counted as multi-therapy prescription.

CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA: long-acting β 2-agonist; LAMA: long-acting muscarinic antagonist; PDE4, phosphodiesterase type 4 inhibitor

Table S2. Analysis of common comorbidities with age, BMI, smoking status and gender matching

Comorbidity (\pm 95% CI)	CB	COPD	COPD-CB
Number of patients, N	628545	129084	77749
GERD	34% \pm 0.1%	36% \pm 0.11%	55% \pm 0.11%
Diabetes	27% \pm 0.1%	30% \pm 0.1%	38% \pm 0.11%
Osteoporosis or bone fractures	8% \pm 0.06%	9% \pm 0.06%	14% \pm 0.08%
Bronchiectasis	1% \pm 0.02%	1% \pm 0.02%	4% \pm 0.04%
Chronic rhinosinusitis	10% \pm 0.06%	5% \pm 0.05%	13% \pm 0.07%
Lung cancer	1% \pm 0.02%	4% \pm 0.04%	5% \pm 0.05%

CB, chronic bronchitis; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; COPD-CB, cohort with COPD and CB diagnosis; GERD, gastroesophageal reflux disease