Original Research

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

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Running Head: **Effect of Chronic Bronchitis on COPD Burden**

Keywords: chronic bronchitis; electronic health records; real-world evidence

Abbreviations: BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; CPT, current procedural terminology; EHR, electronic health record; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; HCPCS, healthcare common procedure coding system; HCRU, healthcare resource utilization; ICD-10-CM, International Classification of Diseases 10th Revision, clinical modification; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; Optum® EHR, Optum® de-identified Electronic Health Record data set; PDE4, phosphodiesterase type 4 inhibitor

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Abstract (240/250 words)

Chronic bronchitis (CB), classically defined as having cough and sputum production for at least three months per year for two consecutive years, is frequently associated with COPD. This retrospective cohort study using the Optum® de-identified Electronic Health Record data set (Optum® EHR) aimed to identify patients with CB, COPD and both CB and COPD through application of the classical definition of CB, and to compare the characteristics of these populations, timing of diagnosis as well as their healthcare resource utilization (HCRU). Scanning of the EHRs was performed electronically using a specially developed algorithm.

Of 104,633,876 patients in the study period between January 2007 to September 2020, 628,545 patients had CB only (i.e., non-obstructive disease),129,084 had COPD only (COPD cohort) and 77,749 had both COPD and CB (COPD-CB cohort). 75.9% of patients (59,009/77,749) fulfilled the criteria for CB diagnosis before their first diagnosis with COPD, compared with 24.1% who had COPD before being diagnosed with CB. HCRU over five years was highest in the COPD-CB cohort, whereas the COPD cohort and CB cohorts had similar HCRU over five years. The COPD-CB cohort had a greater percentage of common COPD comorbidities and exposure to more drug classes than the other cohorts.

These results highlight the importance of increased attention to CB. CB often precedes the diagnosis of COPD and subsequently leads to high HCRU. Interventions to better manage CB and prevent progression of CB to COPD could improve morbidity in this population.

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Introduction

Chronic bronchitis (CB) is classically defined as having cough and sputum production for at least three months per year for two consecutive years and is commonly associated with a history of smoking.[1,2] CB occurs in up to three quarters of patients with COPD[3] and also in individuals with normal lung function (non-obstructive CB, hereafter termed CB), with prevalence estimates varying widely among both categories.,[4] CB has a higher prevalence generally among those with smoking exposure.[3] Due to variability in CB definitions, estimation of the true burden of CB remains challenging. Compared to patients who do not have CB, those with CB have a higher risk of developing incident COPD, respiratory mortality, and all-cause mortality.[4] The COPDGene® observational study revealed that among patients with COPD, those with CB have worse respiratory symptoms, quality of life, and higher exacerbation risk than those without CB.[5]

Despite the existing literature describing the impact of CB on prognosis, the prevalence of patients with CB or COPD alone, compared to those who have both conditions, and their respective healthcare resource utilization (HCRU) has not been estimated before in a real-world population. In this analysis, our primary aim was to identify patients with CB, COPD and both CB and COPD through application of the classical definition of CB to real-world clinical notes in electronic health records and to compare the characteristics of these populations as well as their HCRU. We also examined medication use patterns in these populations and the distribution of timing of CB versus COPD onset for patients who eventually have both. Additionally, patients who develop COPD are at risk for several other comorbidities due to complex genetic and environmental exposure interactions. These comorbidities have been shown to cluster, potentially due to common underlying mechanisms.[6] One potential underlying mechanism that may contribute to comorbidity clustering is smoking related acquired cystic fibrosis transmembrane conductance regulator (CFTR).[7,8] Acquired systemic CFTR dysfunction is associated with CB, gastroesophageal reflux disease, and osteoporosis. [6,9] [10] Therefore, a final aim of this analysis was to determine if comorbidities that are associated with CFTR dysfunction are more prevalent in patients with both COPD and CB using real-world data.

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Methods

Study design

This was a retrospective cohort study based on the secondary use of data from Optum® de-identified Electronic Health Record data set. Optum® de-identified Electronic Health Record data set (Optum® EHR) is a longitudinal electronic health record repository derived from dozens of healthcare provider organizations in the United States. Administrative medical data is obtained from both inpatient and ambulatory electronic health records (EHRs), practice management systems and other internal systems and is processed, normalized, and standardized across the continuum of care from both acute inpatient stays and outpatient visits. The Optum data has been de-identified pursuant to HIPAA and Optum, using the expert determination method, has documented the methods and results of the analysis that justify such determination as set forth in 45 C.F.R. 164.514 and the "Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule".[11,12] As this study is a secondary analysis of fully anonymized data, institutional review board or additional informed consent was not required.[13]

The study period was from 01 January 2007 to 30 September 2020. Patients were studied from two years prior to first diagnosis with a post-diagnosis follow-up period for each patient of five years.

EHR review process

Patients' EHRs were electronically reviewed using an algorithm, which "read" each record, searching for particular terms that were used to define CB. The rules for searching within the EHRs are outlined in more detail in the Online Data Supplement. Manual chart reviews were not performed.

Definitions of CB and COPD

Cohorts were defined based on the contents of Optum® EHR using two sources: clinical notes for CB, and the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes for COPD. Both sources were then combined to derive a definition of the COPD and CB (COPD-CB) cohort (**Figure 1**).

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Definition of patients with CB cohort using Optum® EHR clinical notes (CB+)

CB is defined clinically as cough with sputum production for at least three months a year during a period of two consecutive years.[1,2] To apply this definition, records in Optum® EHR were scanned for documentation of both sputum and cough in the medical encounter notes, within two consecutive 3-month periods, two years in a row. For these analyses, "symptoms for two consecutive 3-month periods" was interpreted as the equivalent of symptoms reported in the clinical notes during two quarters in a row, i.e., at least 90 days apart and no more than 180 days apart". These 3-month periods had to be identified in each of two consecutive years to meet the definition of CB. See **Online Data Supplement** for further details on symptom scanning in clinical notes.

Definition of patients with COPD cohort using ICD-10-CM codes (COPD+)

The ICD-10-CM codes J43 (emphysema)-J44 (other chronic obstructive pulmonary disease) were used to identify patients with COPD. Patients had to have at least two diagnoses of COPD with these codes in their EHRs, at least 30 days apart. Patients with ICD-10-CM codes J41 (simple and mucopurulent CB) and J42 (unspecified CB), which are frequently included for COPD, in their EHR were not used to identify patients in this cohort as these codes are used for CB.

Definition of CB, COPD and COPD-CB cohorts

The CB cohort was defined as patients who had CB (as per the above definition) only without COPD. Index day for this cohort was defined as the date of their first record of "cough and sputum" symptoms. Patients were included in the cohort if they had two years of Optum® EHR data prior to index day and five years of follow-up Optum® EHR data after index day, all within the study period defined above. The COPD cohort was defined as patients who had COPD only without CB. Index day for this cohort was defined as the date of their first record of COPD diagnosis. Patients were included in the cohort if they had two years of Optum® EHR data prior to index day and five years of follow-up Optum® EHR data after index day, all included within the study period. The COPD-CB cohort was identified as patients with both CB and COPD as defined above at any time during the study period. For the COPD-CB cohort, index day was the later of the index days for CB and COPD, i.e., the first time a patient qualified for inclusion in

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both cohorts. Note that due to the large sample size, all results with numerical differences between different cohorts had p-values < 0.05.

Definition of smoking status

Clinical notes on smoking status recorded in Optum® EHR were reviewed to determine smoking status as outlined in the **Online Data Supplement**.

Spirometry

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) percentage predicted were computed from the FEV_1 and FVC measurements recorded in the Optum® EHR, and where available, in the follow-up window as per previously published calculations.[14] Averages over the five-year period were calculated for patients who had more than one measurement in their EHR.

Time to diagnosis within the COPD-CB cohort

For patients in the COPD-CB cohort, the time between their first CB diagnosis and their first diagnosis with COPD was assessed. Patients diagnosed with COPD first followed by CB had a negative value.

Healthcare resource utilization

Data were used to assess the clinical characteristics of the cohorts and their HCRU. For the purpose of the study, HCRU encompasses the following data: number of medical encounters, the number of pulmonologist visits, number of imaging referrals, number of hospitalizations and number of days in the hospital. Medical encounters are defined by the following activities recorded in the EHRs: visits to hospital, specialists, and in-person, written or telephone contact with a doctor. The mean number of medical encounters in each cohort was calculated for each year. All medical encounters are counted individually regardless of whether they relate to the same issue on the same day. Encounters are not restricted to those related to COPD or CB only.

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For each patient, lists of admission dates of distinct hospital visits in the follow-up period were extracted and grouped by the year of the follow-up window. The frequency for each patient was calculated by dividing the total number of hospital visits in the follow-up window by the number of years of the follow-up window. Number of days spent in hospital was computed using the visit start and end dates from the EHRs. Specialist visits and oxygen therapy were computed using the definitions in the **Online Data Supplement**.

Medication use

The number of drug prescriptions for the following medications in the follow-up period were extracted from the EHR: mucolytics and phosphodiesterase type 4 inhibitors (PDE4) inhibitors, macrolides, long-acting muscarinic antagonist (LAMA), long-acting β2-agonist (LABA) and inhaled corticosteroids (ICS). See **Online Data Supplement** for further details.

Analysis of common COPD comorbidities

The prevalence of GERD, diabetes, osteoporosis, bronchiectasis, lung cancer, and chronic rhinosinusitis, which are potentially associated with CFTR dysfunction[10,15-17], was evaluated in all three cohorts. These comorbidities were identified using ICD-10-CM codes, which is further described in the **Online Data Supplement.**

Results

The total population of Optum® EHR for the study period was 104,633,876 individual patients. The analysis revealed that there were 628,545 patients in the CB cohort, 129,084 in the COPD cohort and 77,749 in the COPD-CB cohort (**Figure 1**). Of the three cohorts, the COPD-CB cohort had the lowest proportion of patients who had never smoked, as expected since both COPD and CB are associated with smoking (**Table 1**). Where spirometry data were available, the CB cohort patients had a higher mean FEV1 and mean FEV_1/FVC ratio compared with the COPD and COPD-CB cohorts, with the latter two having broadly similar spirometry results to each other (**Table 1**). A greater proportion of patients with CB only or with both CB and COPD were women, whereas the numbers of men and women were almost balanced across patients with COPD only (**Table 1**).

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Time to diagnosis within the COPD-CB cohort

More patients fulfilled the criteria for CB diagnosis before their first diagnosis with COPD (59009 patients [75.9%]), than had COPD before being diagnosed with CB (18740 patients [24.1%], **Figure 2**).

Healthcare resource utilization

The COPD-CB cohort had the greatest number of interactions with healthcare (**Table 1**). Further, the COPD-CB cohort had the greatest HCRU in terms of the five metrics analyzed (medical encounters, interaction with pulmonologist, referral to imaging, all cause hospitalizations, and days in hospital, **Table 2, Figure 3**) and received the highest number of drug classes (**Table S1**) among the three cohorts. Among patients with COPD or CB only, HCRU (represented by the five metrics described above) was similar over five years.

Medication use

Macrolide prescriptions were more common in patients in the CB and COPD-CB cohorts than in the COPD cohort (**Table S1**). In particular, individuals in the COPD-CB cohort experienced more frequent changes in classes of inhaled therapy, compared to patients with COPD alone, who did not have CB symptoms. This is illustrated in the more complex flow pattern observed for the COPD-CB cohort compared to the COPD only cohort in **Figure S2**.

Analysis of common COPD comorbidities

The COPD-CB cohort had a greater percentage of common COPD comorbidities than the COPD cohort and the CB cohort (**Table S2**).

Discussion

Real-world data on the prevalence of CB phenotype in patients with COPD are scarce.[18] Similarly, clinical trials frequently focus on COPD as a whole rather than different clinical phenotypes.[19] Additionally, the definition of CB varies significantly, in epidemiologic studies.[3] While the use of algorithms to interrogate EHRs is becoming more common,[20,21] this study used a novel method of applying the classical definition of CB directly to physician notes in EHRs to determine the proportions of patients with COPD-CB or CB alone within the Optum® EHR. In

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clinical practice, physicians are unlikely to separate COPD and CB, therefore the application of the CB definition to patient EHRs is a valuable tool to differentiate patients.

The proportion of patients with CB in our analysis is aligned with previously reported studies[19,22] and the spirometry results for the patients at baseline also reflect previous reported distributions of phenotypes based on pulmonary function.[23] A greater proportion of patients with CB only or with both CB and COPD were women, whereas men and women were of almost equal proportion in patients with COPD only. Although it is frequently reported that CB is more common in men than women,[24] some studies have shown that CB predominantly affects women, in line with our results.[25,26]

Treatment and HCRU burden are important in COPD, particularly as disease severity increases.[27-32] Patients with COPD often have multiple comorbidities, which can also affect HCRU burden.[15] Compared to both the COPD cohort and the CB cohort, the COPD-CB cohort exhibited greater HCRU, including specialist visits. In addition, the COPD-CB cohort was exposed to a greater number of drug classes than the other cohorts (**Table S2** and **Figure S2**), suggesting that multiple medications were tried to improve control of burdensome patient symptoms. The frequent medication class changes in the COPD-CB cohort suggest that a a clear treatment pathway was not available. Most patients in the COPD-CB cohort fulfilled the criteria for CB diagnosis before COPD diagnosis, and while persistent cough and sputum symptoms may have driven healthcare contact and diagnosis more rapidly than other COPD symptoms, it also suggests that halting progression of CB to COPD-CB could reduce future HCRU burden. This reflects what has been previously described in other studies on a smaller scale[33,34] and in a recent systematic review, where CB increased all-cause and respiratory disease-related mortality; and was associated with additional decline in FEV_1.[35]

Our results demonstrate the large HCRU burden for COPD-CB patients and confirm that most patients in this cohort initially had CB only, experiencing symptoms of cough and sputum which were reported in healthcare encounters, highlighting the importance of finding efficacious early interventions. This may also reflect the presence of cough and sputum symptoms driving patients to seek medical attention which then leads to the diagnosis of COPD. Interestingly, the HCRU of

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patients with CB alone was comparable or higher than in patients with COPD alone. Currently, there is uncertainty for clinicians and investigators about how to manage patients who present with CB and/or COPD-like symptoms and normal spirometric measurements.[36] There have been suggestions to reintroduce the term "pre-COPD" to identify patients in whom spirometry is unable to detect airflow obstruction but who are at risk of subsequently developing COPD with a reduced FEV_1/FVC ratio.[37] Our study demonstrates that this severe progression path can be identified in the real world by asking patients whether they persistently experience symptoms of cough and sputum.

The longitudinal data presented here show that this patient population, across all cohorts, experiences a constant HCRU burden without clear improvement overtime; finding a treatment tailored to CB and/or COPD-CB would be instrumental to reducing this burden. There remains a need to improve treatment available, both to improve symptom control and to address underlying causes. New targets investigated for CB and COPD include the cystic fibrosis transmembrane conductance regulator (CFTR),[7] interleukins (IL-5, IL-4, IL-13, IL-33) or their receptors and anti-thymic stromal lymphopoietin (TSLP).[38,39]

A major strength of this study is that it is the first to report on CB and COPD in a broad, real-world US population. The Optum EHR database captures data from mostly commercially insured patients (44%), but also Medicaid, Medicare and uninsured patients (12%, 12% and 14 %, respectively) at over 700 hospitals and 140,000 healthcare providers and contains data from over 113 million patients. These patients are distributed across the Midwest, Northeast, South and West US census regions, with the Midwest region over-represented as compared to US census numbers. There are also some limitations in that patients >65 years of age are overrepresented compared to their proportion of the population. African American, Hispanic and Asian patients are underrepresented when compared to their proportion of the US population according to US census data.[40]

The study has several limitations: HCRU and prescription data can be under-counted in Optum® EHR. However, as these data are likely missing at random, this limitation in the EHRs will affect all cohorts equally. The novel method of applying the classical definition of CB to EHRs to

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diagnose CB presents some limitations: firstly, the definition of CB was applied retrospectively and secondly, because the CB cohort definition is a translation of the WHO definition adapted to the EHR format (i.e., clinical notes), there is the possibility of false positive diagnoses e.g. some of patients diagnosed with CB may have had bronchiectasis instead, which is common in patients with COPD and CB and is also associated with high HCRU.[41,42] Review of symptoms in Optum® EHR did not exclude negative descriptions (e.g., not detected, not confirmed, etc.). For CB diagnosis, it was assumed that "symptoms for two consecutive 3-month periods" from a patient's perspective were the equivalent of symptoms reported at least 90 days apart and no more than 180 days apart, but they could possibly constitute two episodes of acute bronchitis over a 3-month period. However, this spacing was necessary to minimize the risk of solely capturing one acute episode that was managed with two encounters. Data on smoking status were often missing, so only those patients where there was clear evidence of never smoking were categorized as "never smoker". This group may therefore be underestimated, but this should affect all cohorts equally. Furthermore, the cause of CB remains unknown in those without a history of smoking or diagnosis of COPD. Oxygen use was determined by a one-time listing of HCPCS code and these data were limited in the dataset. Potential limitations also arise from the real-world nature of the clinical notes of the EHRs. For example, imaging may have been ordered but may not have been documented in the medical note as being ordered by a pulmonologist. Furthermore, any medical encounter on the same day is labelled as an individual medical encounter, i.e., there is no grouping in relation to a particular event or query, therefore medical encounter data may appear higher than expected. More complete spirometric data could have provided more context for diagnosis within the COPD cohort and reduced the likelihood for misclassification. Furthermore, spirometry data would have enabled more detailed characterization of the CB cohort and especially the COPD-CB cohort which has the highest HCRU.

Notwithstanding the limitations of this study, these results demonstrate the prevalence of CB, both on its own and in patients with COPD. Furthermore, our study highlights the importance of a CB diagnosis, not only for patients with COPD where the disease may be more severe with worse clinical outcomes, but also for those patients with CB only, who experience a high burden of disease and have few treatment options. Patients with COPD, with or without CB, have many

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unmet needs. Beside the need to improve therapies available to patients, it is important to note that CB is not just a subtype of COPD, but rather CB and COPD are two separate conditions that can overlap and there is a pressing requirement to detect CB at an earlier stage, before the onset of airway obstruction, to potentially alter the course of disease progression.

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Data sharing

The data used were licensed from Optum and are not publicly available.

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Declaration of interest

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Tables

Table 1. Demographic characteristics of cohorts up to five years post-index date

	CB cohort	COPD cohort	COPD-CB cohort
Number of patients, N	628545	129084	77749
Female (n, %)	413583 (65.8%)	68931 (53.4%)	46727 (60.1%)
Never smoked* (n, %)	25142 (4%)	1549 (1.2%)	233 (0.3%)
Age in years at index date, mean (SD)	59.5 (18.4)	72.0 (10.7)	71.7 (10.9)
BMI†, mean (SD)	31.0 (7.7)	29.9 (7.9)	30.9 (8.2)
Emphysema diagnosis, n (%) ‡**	0.0 (0%)	29689 (23%)	26435 (34%)
Pneumonia, n (%)**	31427 (5%)	14199 (11%)	19437 (25%)
Lung Function (where available, over the five year follow up)			
FEV_1 Available , n (%)	16352 (2.60%)	7827 (6.06%)	8213 (10.56%)
FEV_1 (L), mean (SD)	2.02 (1.05)	1.69 (0.75)	1.55 (0.71)
Available FEV_1 (%-pred), n (%)	14678 (2.34%)	5188 (4.02%)	8035 (10.33%)
FEV_1 (%-pred), mean (SD)	77.6 (0.4)	65.5 (0.6)	61.7 (0.5)
FVC Available , n (%)	16967 (2.70%)	8274 (6.41%)	9172 (11.80%)
FVC (L), mean (SD)	2.58 (1.28)	2.73 (0.98)	2.44 (0.92)
FVC Available , n (%)	15307 (2.44%)	5749 (4.45%)	8993 (11.57%)

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FVC (%-pred), mean (SD)	80.1 (0.4)	83.5 (0.6)	77.7 (0.4)
FEV_1/FVC Available, n (%)	13452 (2.14%)	6946 (5.38%)	6926 (8.91%)
FEV_1/FVC, mean (SD)	0.77 (0.11)	0.61 (0.22)	0.63 (0.15)

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

*Measured at any time in the two years prior to and five years after index date

†Average in follow-up period per patient

‡Emphysema diagnosis based on two occurrences of ICD-10-CM code J43

¥Defined as hospital visits with primary diagnosis of ICD-10-CM code J43 or J44

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Table 2. Healthcare resource use over five-year follow-up period

	CB cohort	COPD cohort	COPD-CB cohort
Number of patients, N	628545	129084	77749
All medical encounters* per year, mean (SD) per patient	53.6 (47.4)	44.8 (58.4)	85.3 (78.1)
Hospital visits per year, mean (SD)	0.9 (1.9)	0.6 (1.1)	1.5 (2.6)
Hospital visits with COPD as primary diagnosis, per year, mean (SD)¥	0.0 (0.0)	0.32 (0.2)	0.77 (0.63)
Hospital days per year, mean (SD)	1.8 (5.0)	1.6 (4.7)	3.7 (7.8)
Number of medical encounters* per year, n (%)			
0 to 10	25142 (4%)	18072 (14%)	1555 (2%)
10 to 30	188564 (30%)	46470 (36%)	11662 (15%)
> 30	414840 (66%)	64542 (50%)	64532 (83%)
Appointment with pulmonologist, n (%)	219991 (35%)	72287 (56%)	57534 (74%)
Pulmonologist referral to imaging, n (%)**	18856 (3%)	7745 (6%)	8552 (11%)
All-cause hospitalizations per year, n (%)			
0	238847 (38%)	52924 (41%)	23325 (30%)
>0 & ≤1	232562 (37%)	49052 (38%)	21770 (28%)

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>1 & ≤2	75425 (12%)	18072 (14%)	13217 (17%)
> 2	81711 (13%)	10327 (8%)	18660 (24%)
Days in hospital per year, n (%)			
0	238847 (38%)	52924 (41%)	23325 (30%)
> 0 to 3	295416 (47%)	56797 (44%)	28767 (37%)
> 3	94282 (15%)	20653 (16%)	24880 (32%)
Patients on oxygen therapy, n (%)	1571 (0.25%)	1936 (1.5%)	5131 (6.6%)

*Medical encounters: all activities recorded in the database undertaken by patients regarding their health (this includes visits to hospital, specialists, written or telephone contact with a doctor). All medical encounters are counted individually regardless of whether they relate to the same issue on the same day. Encounters are not restricted to those related to COPD or CB only.

** Encounters of type “imaging” where the provider was a pulmonologist.

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Figure titles and Legends

Figure 1. Patient selection flow chart

COPD+ indicates patients fulfilling definition criteria for COPD; CB+ indicates patients fulfilling definition criteria for chronic bronchitis (CB).

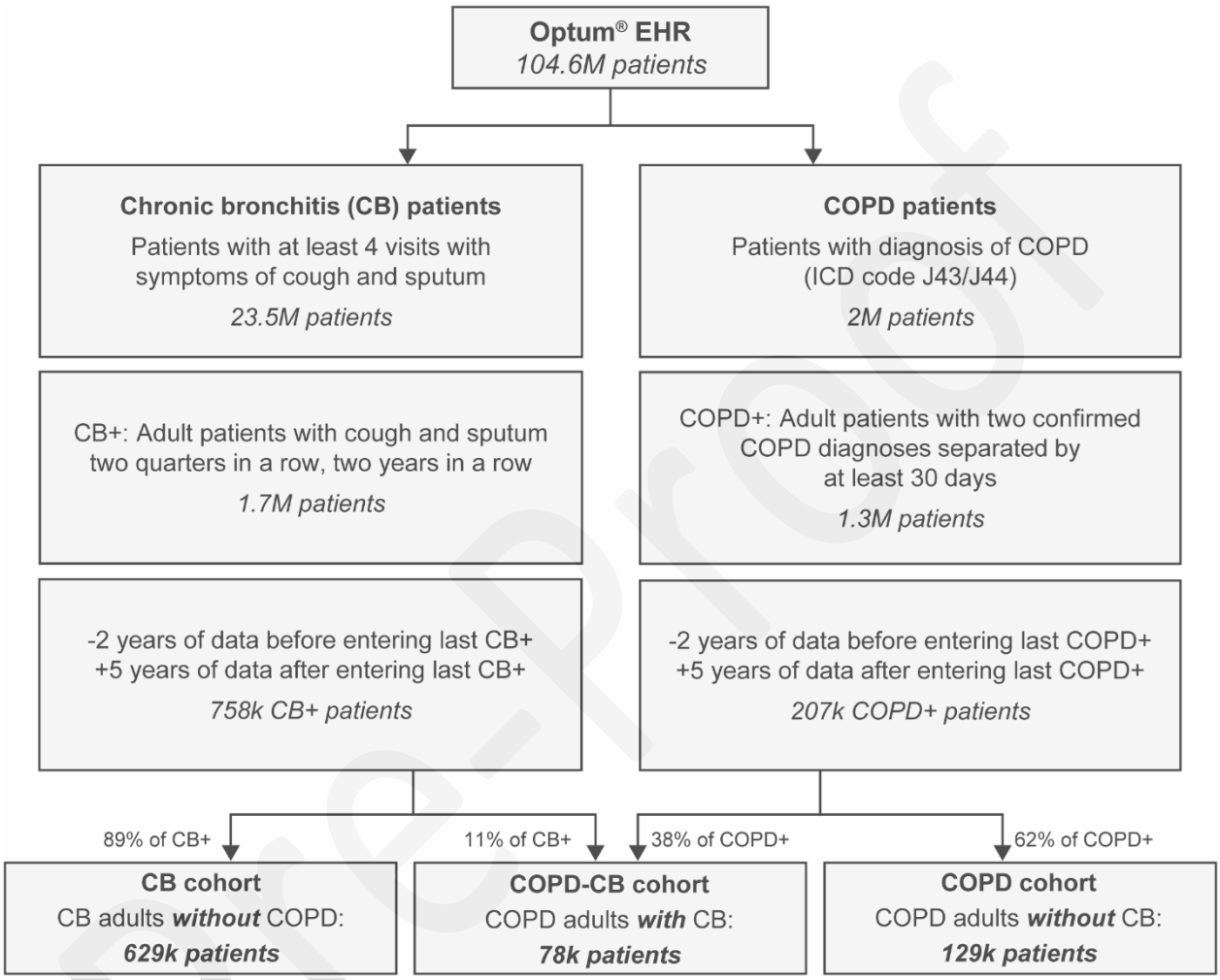

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Figure 2. Number of years between diagnoses of CB and COPD in the CB-COPD cohort
Grey = CB diagnosed before COPD and orange = COPD diagnosed before CB

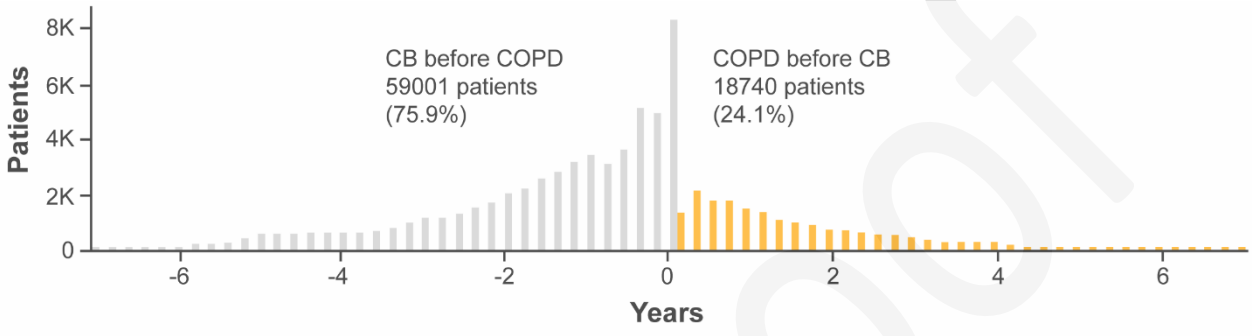

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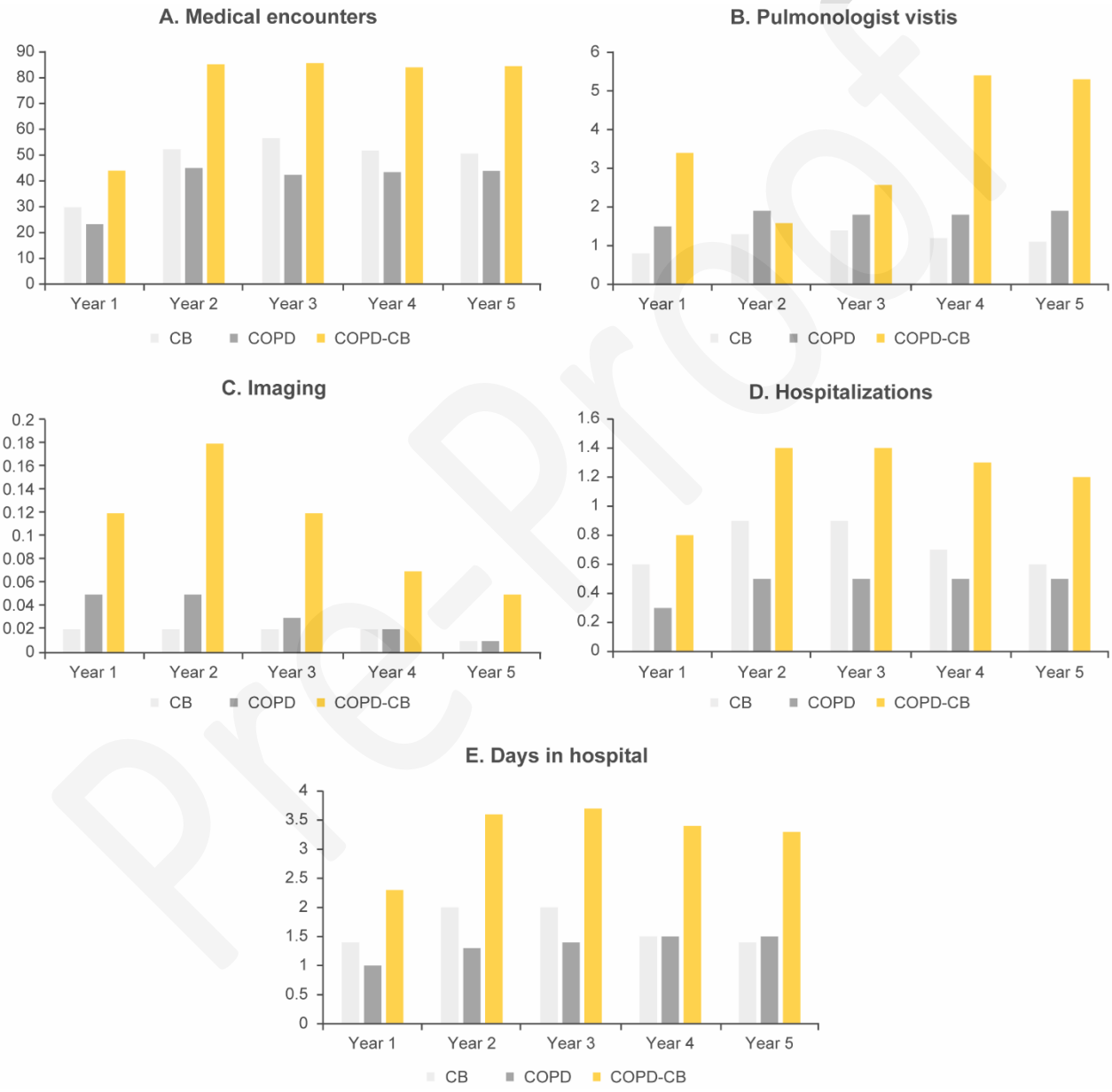
Figure 3. Five-year healthcare resource use among cohorts

Number of (a) medical encounters; (b) pulmonologist visits; (c) imaging (referral by pulmonologist); (d) hospitalizations; and (e) days in hospital over five-year follow-up shown.



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Online data supplement

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

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β2-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

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

Supplementary Figures

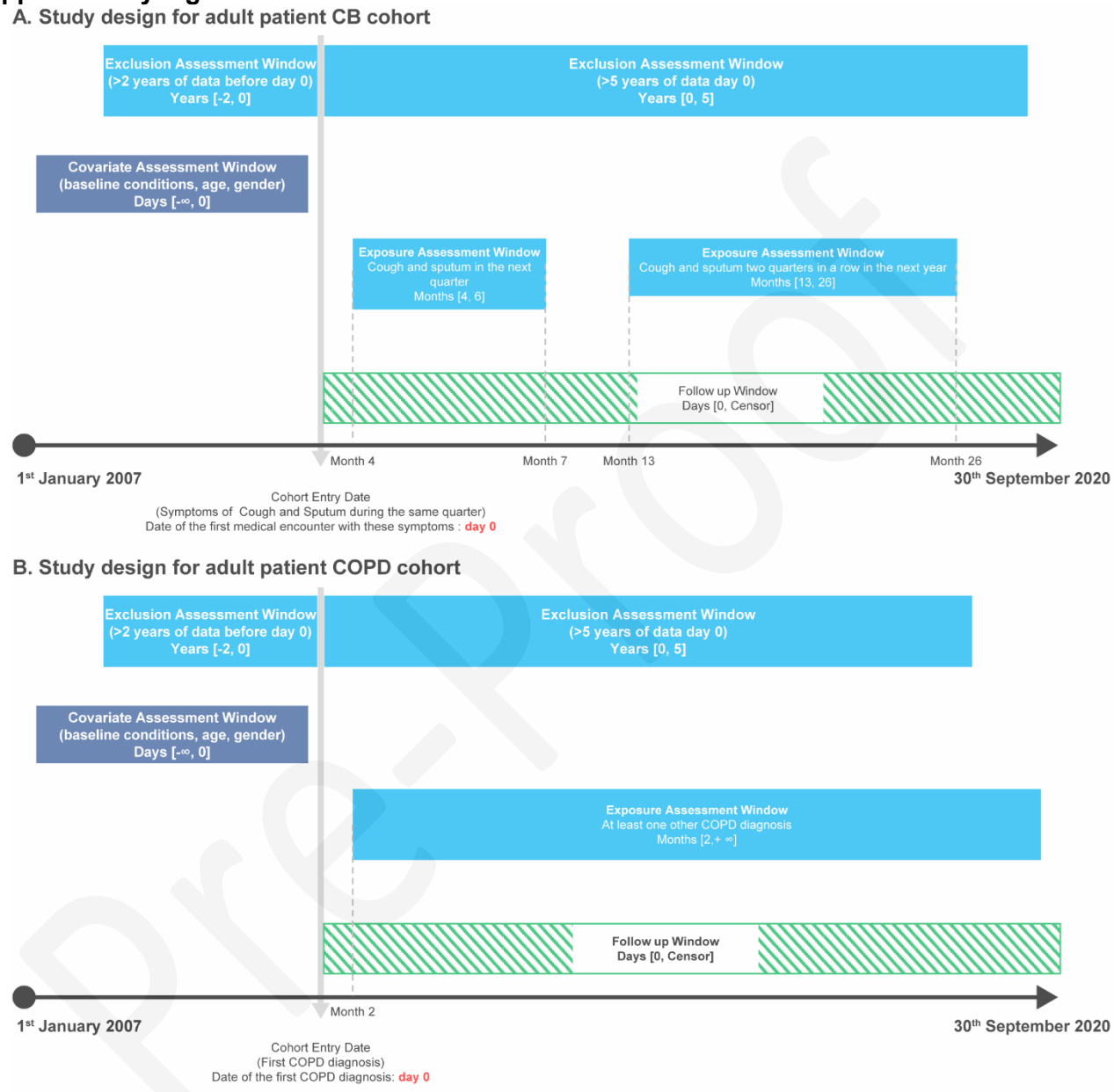

Figure S1. Study design for CB and COPD cohorts

CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease

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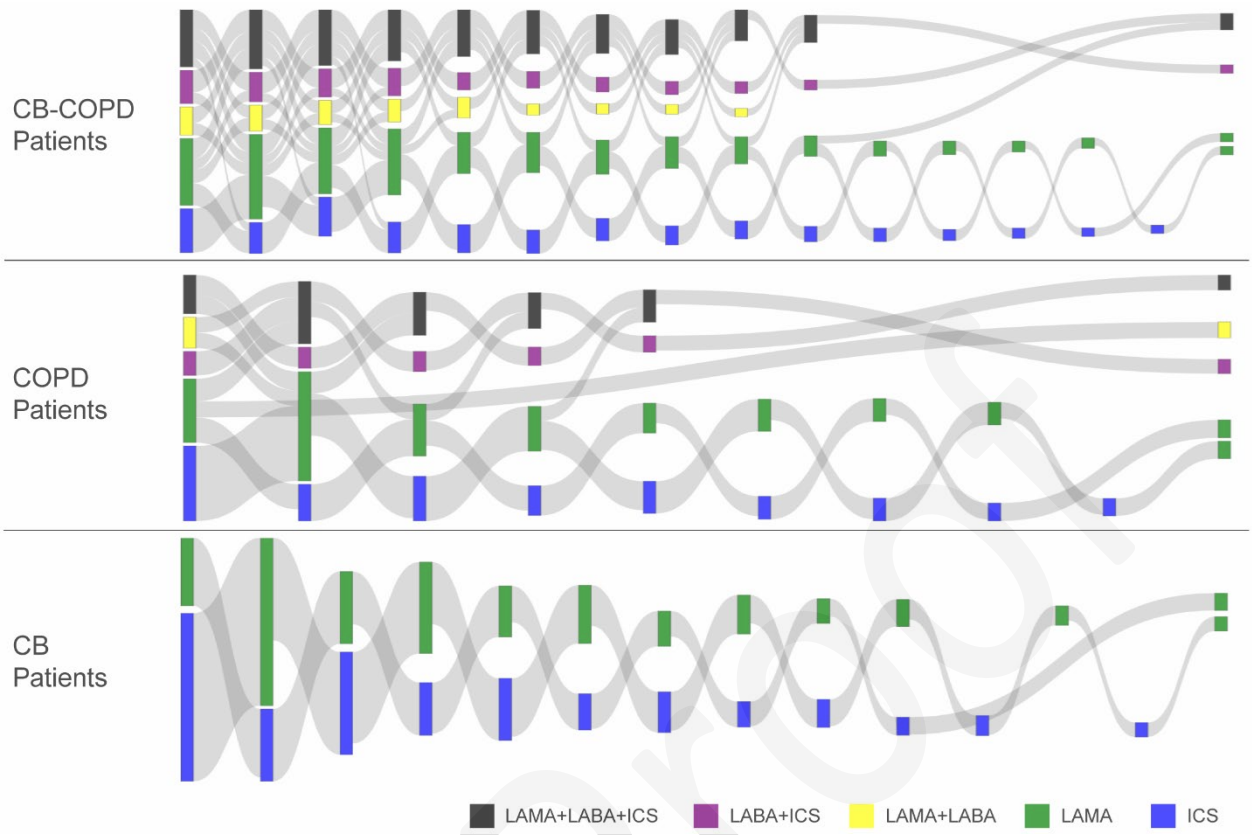

Figure S2. Sankey diagram of inhaled medication transitions over five years

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 β2-agonist; LAMA, long-acting muscarinic antagonist

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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

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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 β2-agonist; LAMA: long-acting muscarinic antagonist; PDE4, phosphodiesterase type 4 inhibitor

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

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

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