Online Supplement

Original Research
Multimorbidities in COPD are Associated With Increased Exacerbations and Health Care Resource Utilization in Real-World Patients from a U.S. Database

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**at the time the study was completed*

Supplementary methods

Optum's de-identified Clinformatics® Data Mart Database

Optum's Clinformatics® Data Mart (CDM) is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans. CDM administrative claims submitted for payment by providers and pharmacies are verified, adjudicated and de-identified prior to inclusion. This data, including patient-level enrollment information, is derived from claims submitted for all medical and pharmacy health care services with information related to health care costs and resource utilization. The population is geographically diverse, spanning all 50 states[1].

Matching

All cohorts were matched 1:1 with their comparator group (i.e., patients with COPD versus patients without COPD) in order to minimize bias within the comparison. All cohorts were matched to their comparator group using simple age-matching based on decades (to maximize the number of patients in each cohort). The following age groups were used: 40-49, 50-59, 60-69, 70-79, 80-89 years. Patients with COPD and diabetes were matched 1:1 with their comparator group based on the age groups and on weight status. The following weight categories were used based on ICD-10-CM diagnosis codes: Overweight (code E66.3), Obese (codes E66.09, E66.1, E66.8, and E66.9), Severely obese (codes E66.01 and E66.2), and Other (patients without any code for any of the above weight categories, including those with normal weight). Patients with COPD and osteoporosis/osteopenia were matched 1:1 with their comparator group based on the age groups and the presence of "underweight" status (ICD-10-CM codes R63.4, R64).

Exclusion criteria

Patients were excluded from the "without COPD" cohort if they had ≥1 medical claim with an ICD-10-CM diagnosis code for COPD at any time during the identification period. Patients were excluded from the "without GERD", "without diabetes" and "without" cohorts if they had ≥1 medical claim with an ICD-10-CM diagnosis code for the relevant condition at any time during the identification period.

Conditional logistic regression

For the conditional logistic regression models, the outcome variable was whether or not the event, i.e., diagnosis of GERD, diabetes or osteoporosis/osteopenia, COPD exacerbations and COPD-related HCRU occurred in the patient during the end of the defined five-year follow-up period. The independent variable was the cohort (e.g., with COPD vs without COPD; with COPD and diabetes vs with COPD without diabetes) and strata were the matched pairs (IDs) in each cohort.

Medication use

Descriptive statistics were reported for medication use for each index year at up to 5 years after and including the index date for the following treatment classes, in line with the GOLD 2022 report[2]. Number and proportion of patients using the following mediations were reported: short-acting beta-agonist (SABA); short-acting muscarinic antagonist (SAMA); long-acting muscarinic antagonist (LAMA); SABA/SAMA combination; Long-acting beta-agonist (LABA)/LAMA combination; methylxanthines; LABA/inhaled corticosteroid (ICS) combination; LABA/LAMA/ICS combination; and phosphodiesterase-4 (PDE4) inhibitors.

Treatments were identified by National Drug Codes (NDCs) and Healthcare Common Procedure Coding System (HCPCS) from the pharmacy claims table (for outpatient

prescriptions) and the medical claims table (for inpatient prescriptions) in CDM. Where claims for medications in the same treatment class overlap, claims were combined into continuous treatment windows. All HCPCS codes were assigned on day of supply.

Monotherapies were defined as ≥60 days or at least two separate ≥30 days of consecutive periods of prescriptions for the specified treatment within a 1-year time period at the class level. Consecutive periods of prescriptions may not have gaps of >7 days or ≥180 days of cumulative periods of prescription within the 1-year period at the class level.

Combinations included fixed doses (i.e. when both treatments are combined in a single inhaler) or when prescribed individually (loose combination) but taken concomitantly.

All concomitant treatments were counted as loose combinations if taken together for ≥60 days or at least two separate ≥30 days of consecutive periods of prescriptions for the specified treatment within a 1-year time period at the class level (consecutive periods of prescriptions may not have gaps of >7 days); or if taken together for ≥180 days of cumulative periods of prescription within the 1-year period at the class level. HCPCS (J) codes were included in loose combinations only if they were ≥1% of the total HCPCS treatment in either COPD or non-COPD cohort.

Supplementary References

1. Optum's de-identified Clinformatics® Data Mart Database [data on file] (accessed on January 4th, 2024).

2. Disease GIfCOL. GLOBAL STRATEGY FOR PREVENTION, DIAGNOSIS AND MANAGEMENT OF COPD: 2023 Report. 2022.

3. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. Mar 15 2011;173(6):676-82. doi:10.1093/aje/kwq433

4. Statistics NCfH. International Classification of Diseases, Tenth Revision. Centers for Disease Prevention and Control 2023. https://www.cdc.gov/nchs/icd/icd10.htm

Supplementary Results

Table S1 ICD-10-CM codes used for diagnosis

Condition	ICD-10-CM diagnosis codes/Source
COPD	J41.x, J42.x, J43.x, J44.x
Weight status: overweight	E66.3
Weight status: obese	E66.09, E66.1, E66.8, E66.9
Weight status: severely obese	E66.01, E66.2
Underweight status	R63.4, R64
Charlson comorbidities	Quan et al Am J Epidemiol. 2011;173(6):676-82.[3]
Diabetes	E08.x, E09.x, E10.x, E11.x, E13.x
GERD	K21.x
Osteoporosis, Osteopenia, bone fractures	M80.x, M81.x, M83.x, M84.x

ICD-10-CM is the tenth revision of the international classification of diseases.[4]

COPD, Chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; ICD, international classification of diseases

Table S2. Demographic characteristics at index date in match patient cohorts

Cohort (N)	Age, years, mean (SD)	Female[a], n (%)
Patients with COPD (N=158,106)	71.1 (8.95)	88,036 (55.7)
Patients without COPD (N=158,106)	70.9 (9.11)	92,506 (58.5)
COPD with GERD (N=71,150)	71.9 (8.63)	43,359 (60.9)
COPD without GERD (N=71,150)	72.1 (8.54)	35,947 (50.5)
COPD with diabetes (N=55,182)	71.9 (8.78)	28,558 (51.8)
COPD without diabetes (N=55,182)	71.9 (8.78)	32,150 (58.3)
COPD with osteoporosis/ osteopenia (N=32,895)	73.8 (7.98)	28,595 (86.9)
COPD with osteoporosis/ osteopenia (N=32,895)	73.6 (8.12)	14,587 (44.3)

[a]Sex was unknown for 2 patients each in the with COPD cohort, the without COPD cohort and the COPD without GERD cohort and for 1 patient in the COPD with diabetes cohort

Index date was defined as the date of the first diagnosis of COPD within the identification period.

COPD, Chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease

Table S3. CCI scores in matched patients with selected morbidities

	COPD with GERD (N=71150)		COPD without GERD (N=71150)		COPD with Diabetes (N=55182)		COPD without Diabetes (N=55182)		COPD with Osteoporosis/ Osteopenia (N=32895)		COPD without Osteoporosis/ Osteopenia (N=32895)	
Selected Comorbidities	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Chronic rhinosinusitus	5940	8.4	2578	3.6	3213	5.8	3386	6.1	2273	6.9	1745	5.3
Diabetes	31276	44.0	25982	36.5	55182	100.0	0	0.0	10541	32.0	13807	42.0%
GERD	71150	100.0	0	0.0	26164	47.4	23462	42.5	17538	53.3%	13450	40.9%
Inflammatory bowel disease	1340	1.9	671	0.9	782	1.4	789	1.4	642	2.0%	442	1.3%
Osteoporosis, osteopenia, bone fracture	16721	23.5	10919	15.4	8756	15.9	11472	20.8	32895	100.0%	0	0.0%
Pneumonia	17204	24.2	9497	13.4	11371	20.6	8969	16.3%	7627	23.2%	6101	18.6%
Quan-Charlson Comorbidity Index	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients with CCI	71150	100.0	71150	100.0	55182	100.0	55182	100.0	32895	100.0	32895	100.0
CCI score	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
	4.81	3.06	3.79	2.71	5.16	2.96	3.62	2.71	4.50	3.03	4.40	2.94
CCI disease groups	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Myocardial Infarction	18065	25.4	11658	16.4	14085	25.5	9362	17.0	6417	19.5	7197	21.9
Congestive Heart Failure	33457	47.0	24295	34.2	26710	48.4	18543	33.6	13576	41.3	13821	42.0
Peripheral Vascular Disease	46716	65.7	41459	58.3	36679	66.5	32026	58.0	21832	66.4	20919	63.6
Cerebrovascular Disease	30707	43.2	21521	30.3	23063	41.8	17788	32.2	13443	40.9	12149	36.9

	COPD with GERD (N=71150)		COPD without GERD (N=71150)		COPD with Diabetes (N=55182)		COPD without Diabetes (N=55182)		COPD with Osteoporosis/ Osteopenia (N=32895)		COPD without Osteoporosis/ Osteopenia (N=32895)	
Dementia	11849	16.7	8382	11.8	9167	16.6	6486	11.8	6000	18.2	4987	15.2
Chronic Pulmonary Disease	71150	100.0	71150	100.0	55182	100.0	55182	100.0	32895	100.0	32895	100.0
Rheumatic Disease	9426	13.3	5075	7.1	6063	11.0	5306	9.6	5595	17.0	2628	8.0
Peptic Ulcer Disease	7580	10.7	2049	2.9	4316	7.8	3329	6.0	2775	8.4	2186	6.7
Moderate Liver Disease	17615	24.8	10639	15.0	12612	22.9	9832	17.8	6624	20.1	6279	19.1
Diabetes Without Chronic Complications	34956	49.1	28963	40.7	54033	97.9	0	0.0	12272	37.3	15236	46.3
Diabetes With Chronic Complications	25384	35.7	20137	28.3	41079	74.4	0	0.0	8374	25.5	11110	33.8
Hemiplegia or Paraplegia	4003	5.6	2409	3.4	3062	5.6	1941	3.5	1595	4.9	1517	4.6
Renal Disease	33327	46.8	27717	39.0	29717	53.9	18990	34.4	14383	43.7	14951	45.5
Any Malignancy	18751	26.4	15605	21.9	13471	24.4	13234	24.0	8448	25.7	8394	25.5
Moderate or Severe Liver Disease	1595	2.2	723	1.0	1202	2.2	658	1.2	546	1.7	519	1.6
Metastatic Solid Tumor	4044	5.7	3204	4.5	2815	5.1	2841	5.2	1948	5.9	1763	5.4
AIDS/HIV	241	0.3	208	0.3	197	0.4	165	0.3	86	0.3	117	0.4

COPD, Chronic obstructive pulmonary disease; CCI, Quan-Charlson Comorbidity Index; GERD, gastroesophageal reflux disease; SD, standard deviation

Table S4. COPD-related HCRU after five years in age-matched patients with COPD with and without GERD (all patients)

	COPD with GERD (N=71,150)		COPD without GERD (N=71,150)		COPD with GERD vs COPD without GERD OR[2] (CI), p value
ER visits					
n (%)	31,008	(43.6)	19,970	(28.1)	
Mean (SD)	1.68	4.04	0.69	1.78	1.983 (1.939, 2.029), p<0.001
Hospitalization visits					
n (%)	41,623	(58.5)	27,628	(38.8)	
Mean (SD)	2.03	3.24	0.91	1.74	2.222 (2.174, 2.272), p<0.001

COPD, Chronic obstructive pulmonary disease; ER, emergency room; GERD, gastroesophageal reflux disease; HCRU, healthcare resource utilization; SD, standard deviation

Table S5. COPD-related HCRU after five years in age- and weight-matched patients with COPD with and without diabetes (all patients)

	COPD with diabetes (N=55,182)	COPD without diabetes (N=55,182)	COPD with diabetes vs COPD without diabetes OR[2] (CI), p value
ER visits			
N patients (%)	20,070 (36.4)	18,893 (34.2)	
Mean (SD)	1.30 (3.70)	0.98 (2.36)	1.098 (1.071, 1.125), p<0.001
Hospitalization visits			
N patients (%)	28,368 (51.4)	25,222 (45.7)	
Mean (SD)	1.69 (3.00)	1.18 (2.06)	1.26 (1.23, 1.291), p<0.001

COPD, Chronic obstructive pulmonary disease; ER, emergency room; HCRU, healthcare resource utilization; SD, standard deviation

Table S6. COPD-related HCRU after five years in age- and underweight status-matched patients with COPD with and without osteoporosis/osteopenia (all patients)

	COPD with osteoporosis/ osteopenia (N=32,895)	COPD without osteoporosis/ osteopenia (N=32,895)	COPD with osteoporosis/ osteopenia vs COPD without osteoporosis/ osteopenia OR[2] (CI), p value
ER visits			
N patients (%)	13,563 (41.2)	11,295 (34.3)	
Mean (SD)	1.46 (3.62)	1.06 (2.72)	1.343 (1.301, 1.387), p<0.001
Hospitalization visits			
N patients (%)	18,376 (55.9)	15,841 (48.2)	
Mean (SD)	1.91 (3.08)	1.38 (2.46)	1.368 (1.326, 1.411), p<0.001

COPD, Chronic obstructive pulmonary disease; ER, emergency room; HCRU, healthcare resource utilization; SD, standard deviation

Table S7. Medication use after 5 years in patients with COPD and GERD compared with age-matched patients with COPD without GERD

	COPD patients with GERD (N=71150)		COPD patients without GERD (N=71150)	
Treatment	**N**	**%**	**N**	**%**
SABA	3,510	4.9%	2,882	4.1%
SAMA	184	0.3%	142	0.2%
SABA/SAMA combination (fixed or loose)	1,554	2.2%	1,426	2.0%
LAMA	4,226	5.9%	3,720	5.2%
LABA/LAMA combination (fixed or loose)	553	0.8%	587	0.8%
LABA/ICS combination (fixed or loose)	5,805	8.2%	4,824	6.8%
LABA/LAMA/ICS combination (fixed or loose)	18	0.0%	11	0.0%
Methylxanthines	365	0.5%	265	0.4%
PDE4 Inhibitors	220	0.3%	111	0.2%

Single treatment/fixed combination: Patients who have at least one period of ≥60 days consecutive treatment or two separate periods of ≥30 days consecutive treatment with a maximum 7 days permitted between these two ≥30 day periods, or at least 180 days of cumulative treatment for each year within the corresponding follow-up period.

Loose combination: at least one ≥60 days consecutive overlap or two ≥30 days consecutive overlap considering 7 days as allowed gap for each year within the corresponding follow-up year

COPD, Chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, Long-acting beta-agonist; LAMA, Long-acting muscarinic antagonist ; PDE4, phosphodiesterase-4; SABA, Short-acting beta-agonist; SAMA, Short-acting muscarinic antagonist standard deviation

Table S8. Medication use after 5 years in patients with COPD and diabetes compared with age- and weight-matched patients with COPD without diabetes

	COPD with Diabetes (N=55182)		COPD without Diabetes (N=55182)	
Treatment	**N**	**%**	**N**	**%**
SABA	2,487	4.5%	2,443	4.4%
SAMA	1,15	0.2%	148	0.3%
SABA/SAMA combination (fixed or loose)	1,056	1.9%	1,163	2.1%
LAMA	2,642	4.8%	3,336	6.1%
LABA/LAMA combination (fixed or loose)	352	0.6%	496	0.9%
LABA/ICS combination (fixed or loose)	3,612	6.6%	4,460	8.1%
LABA/LAMA/ICS combination (fixed or loose)	6	0.0%	10	0.0%
Methylxanthines	261	0.5%	253	0.5%
PDE4 Inhibitors	137	0.3%	121	0.2%

Single treatment/fixed combination: Patients who have at least one period of ≥60 days consecutive treatment or two separate periods of ≥30 days consecutive treatment with a maximum 7 days permitted between these two ≥30 day periods, or at least 180 days of cumulative treatment for each year within the corresponding follow-up period.

Loose combination: at least one ≥60 days consecutive overlap or two ≥30 days consecutive overlap considering 7 days as allowed gap for each year within the corresponding follow-up year

COPD, Chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, Long-acting beta-agonist; LAMA, Long-acting muscarinic antagonist ; PDE4, phosphodiesterase-4; SABA, Short-acting beta-agonist; SAMA, Short-acting muscarinic antagonist standard deviation

Table S9. Medication use after 5 years in patients with COPD and osteoporosis/osteopenia compared with age- and underweight status-matched patients with COPD without osteoporosis/osteopenia

	COPD with osteoporosis/osteopenia (N=32895)		COPD without osteoporosis/osteopenia (N=32895)	
Treatment	**N**	**%**	**N**	**%**
SABA	1,606	4.9%	1,301	4.0%
SAMA	85	0.3%	69	0.2%
SABA/SAMA combination (fixed or loose)	719	2.2%	680	2.1%
LAMA	2,200	6.7%	1,733	5.3%
LABA/LAMA combination (fixed or loose)	287	0.9%	236	0.7%
LABA/ICS combination (fixed or loose)	2,814	8.6%	2,307	7.0%
LABA/LAMA/ICS combination (fixed or loose)	9	0.0%	8	0.0%
Methylxanthines	188	0.6%	129	0.4%
PDE4 Inhibitors	89	0.3%	59	0.2%

Single treatment/fixed combination: Patients who have at least one period of ≥60 days consecutive treatment or two separate periods of ≥30 days consecutive treatment with a maximum 7 days permitted between these two ≥30 day periods, or at least 180 days of cumulative treatment for each year within the corresponding follow-up period.

Loose combination: at least one ≥60 days consecutive overlap or two ≥30 days consecutive overlap considering 7 days as allowed gap for each year within the corresponding follow-up year

COPD, Chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, Long-acting beta-agonist; LAMA, Long-acting muscarinic antagonist; PDE4, phosphodiesterase-4; SABA, Short-acting beta-agonist; SAMA, Short-acting muscarinic antagonist standard deviation

Table S10. Sensitivity analysis on the definition of severe exacerbations during five-year follow-up period across cohorts

	COPD with GERD (N=71,150)	**COPD without GERD (N=71,150)**	**COPD with diabetes (N=55,182)**	**COPD without diabetes (N=55,182)**	**COPD with osteoporosis/ osteopenia (N=32,895)**	**COPD without osteoporosis/ osteopenia (N=32,895)**
N patients (%)	20,966 (29.5)	13,193 (18.5)	13,803 (25.0)	12,084 (21.9)	9,772 (29.7)	7,661 (23.3)
Mean number (SD)	0.64 (1.47)	0.30 (0.83)	0.51 (1.31)	0.38 (0.99)	0.63 (1.42)	0.43 (1.12)

Severe COPD exacerbations in the original analysis were defined as a hospitalization or emergency room (ER) admission with a primary diagnosis for COPD. In the sensitivity analysis, severe COPD exacerbations were defined as a hospitalization admission with a primary diagnosis for COPD.

COPD, Chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; SD, standard deviation

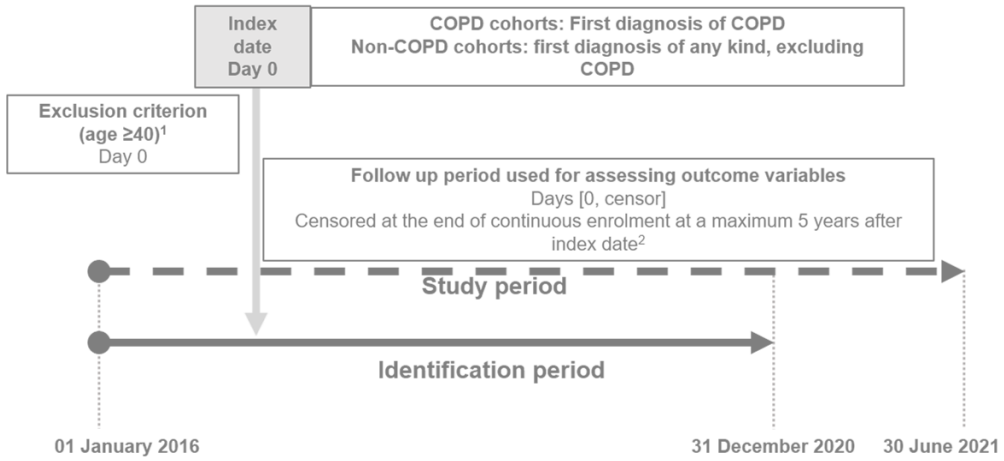

Figure S1. Study design

[1]Floating window from 01 Jan 2016 to 31 Dec 2020.

[2]Follow-up is defined as up to five years after index date (inclusive), until end of follow-up. Patients were followed up until the end of the study period. If a patient died, or the period of continuous enrollment ends, the earliest of these was considered as the end of follow-up.

Age and sex were assessed at diagnosis. Exclusion criteria: throughout identification period patients were assessed to ensure that their presence in a cohort reflected their medical diagnoses, i.e. patients diagnosed with diabetes after index date were excluded from the non-diabetes cohort. Patients had to have 365 days of continuous enrollment after index date. COPD, Chronic obstructive pulmonary disease