SUPPLEMENTAL MATERIAL

Table S1. Datasets used for the study, provided by Alberta Health (Government of Alberta Ministry of Health)

Database	Description
NACRS	Includes data from all emergency department visits and some outpatient-based ambulatory care, including information on services, diagnostic and procedure codes
DAD	Includes data from inpatient stays, including information on services, diagnostic and procedure intervention codes as well as length of stay
PIN	Includes information on medication dispenses and associated information at the pharmacy level (all private and public plans)
Population Registry	Includes basic demographic information, including age, gender, and zone
Practitioner Claims	Includes provider claims data for physicians and other providers for insured health services, and reports on provider and service data
Vital statistics – deaths	Includes death information

Abbreviations: DAD: Discharge Abstract Database; NACRS: National Ambulatory Care Reporting System; PIN: Pharmaceutical Information Network

Table S2. Algorithms for the identification of COPD patients

ICD-9-CM / ICD-10-CA	Code	Code description	Definition algorithm during the cohort year
ICD-9-CM	491	Chronic bronchitis	≥ 2 outpatient visits (physician claims) in the primary position on separate days and within two years (2nd visit as index date)
	492	Emphysema	
	496	Chronic airways obstruction, not elsewhere classified	
ICD-10-CA	J41	Chronic bronchitis	1 inpatient (DAD) admission in any position (discharge date as index date)
	J42	Unspecified chronic bronchitis	
	J43	Emphysema	
	J44	Other chronic obstructive pulmonary disease	

Abbreviations: DAD: Discharge abstract database; ICD-9-CM: International statistical classification of diseases and related health problems, 9th revision, Canadian modification; ICD-10-CA: International statistical classification of diseases and related health problems, 10th revision, Canadian modification.

* Government of Alberta: Alberta Health, Analytics and Performance Reporting Branch. Interactive Health Data Application: COPD. 2022. http://www.ahw.gov.ab.ca/IHDA_Retrieval/ShowMetaDataNotesServlet?3702

Table S3. Medications of interest and corresponding ATC codes

Treatment Class	ATC code	Medication	Category
Antibiotics	J01	Antibiotics	
SABA	R03AC02	salbutamol	short-acting inhaler
	R03AC03	terbutaline	short-acting inhaler
SAMA	R03BB01	ipratropium	short-acting inhaler
LAMA	R03BB04	tiotropium	long-acting single inhaler
	R03BB05	aclidinium	long-acting single inhaler
	R03BB06	glycopyrronium	long-acting single inhaler
	R03BB07	umeclidinium	long-acting single inhaler
LABA	R03AC12	salmeterol	long-acting single inhaler
	R03AC13	formoterol	long-acting single inhaler
	R03AC18	indacaterol	long-acting single inhaler
	R03AC19	olodaterol	long-acting single inhaler
ICS	R03BA01	beclometasone	long-acting single inhaler
	R03BA02	budesonide	long-acting single inhaler
	R03BA05	fluticasone	long-acting single inhaler
	R03BA07	mometasone	long-acting single inhaler
	R03BA08	ciclesonide	long-acting single inhaler
	R03BA09	fluticasone furoate	long-acting single inhaler
OCS	H02AB06	prednisolone	
	H02AB07	prednisone	
SABA + SAMA	R03AL02	salbutamol and ipratropium	short-acting inhaler
LAMA + LABA	R03AL03	umeclidinium and vilanterol	long-acting inhaler in combination
	R03AL04	glycopyrronium and indacaterol	long-acting inhaler in combination
	R03AL05	aclidinium and formoterol	long-acting inhaler in combination
	R03AL06	tiotropium and olodaterol	long-acting inhaler in combination
	R03AL	tiotropium and olodaterol	long-acting inhaler in combination
ICS + LABA	R03AK06	salmeterol and fluticasone	long-acting inhaler in combination
	R03AK07	formoterol and budesonide	long-acting inhaler in combination
	R03AK09	formoterol and mometasone	long-acting inhaler in combination
	R03AK10	vilanterol and fluticasone	long-acting inhaler in combination
ICS + LABA + LAMA	R03AL08	fluticasone furoate and vilanterol and umeclidinium bromide	long-acting inhaler in combination

Treatment Class	ATC code	Medication	Category
	R03AL11	formoterol and budesonide and glycopyrronium bromide	long-acting inhaler in combination
	R03AL12	indacaterol, glycopyrronium bromide and mometasone	long-acting inhaler in combination
Roflumilast	R03DX07	roflumilast	
Theophylline	R03DA04	theophylline	
Cardiac drugs	B01	antithrombotic agents	
	C01B	antiarrhythmics, class I and II	
	C01AA	digitalis glycosides	
	C02	antihypertensives	
	C03	diuretics	
	C07	beta-blocking agents	
	C08	calcium channel blockers	
	C09	agents acting on the renin-angiotensin system	
Metabolic drugs	C10	lipid-modifying agents	
	A10	antidiabetic agents (insulin and blood glucose-lowering drugs)	

Abbreviations: ATC: anatomical therapeutic chemical; OCS: oral corticosteroid; ICS: inhaled corticosteroid; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting beta agonist; SAMA: short-acting muscarinic antagonist

Table S4. ICD-10-CA codes to identify severe CV events

Categories of non-fatal severe CV event	ICD-10-CA codes
Acute coronary syndrome[1]: acute myocardial infarction and unstable angina	• I21 acute myocardial infarction or • I20.0 unstable angina
Heart failure decompensation[2]	• I50 (congestive) heart failure (only codes in the "most responsible diagnosis") • J81 acute pulmonary oedema
Cerebral ischemia[3,4]: cerebral infarction and TIA	• I63 cerebral infarction or • G45 TIA ("transient cerebral ischemic attacks and related syndromes")
Arrhythmias[5]: newly diagnosed AF and other serious cardiac arrhythmia including cardiac arrest	• I48 atrial fibrillation and flutter (new diagnosis defined as the absence of codes I48 prior to index) • I49 other cardiac arrhythmias (only new diagnosis defined as the absence of codes I49 prior to index) • I46 cardiac arrest

Abbreviations: AF: arial fibrillation; CV: cardiovascular; ICD-10-CA: International Statistical Classification of Diseases and Related Health Problems, 10th revision, Canadian modification; TIA: transient ischemic attack

Primary discharge ICD-10-CA codes (namely the "most responsible diagnosis code" i.e., reason for admission and the "post-admission diagnosis code" i.e., complication occurring during the hospital stay) were used to identify hospitalisations for acute coronary syndrome (I21 and I20.0) or ischemic stroke (I63 and G45) because these codes pertained to the diagnosis of acute outcomes.

For heart failure (I50 and J81), only the "most responsible diagnosis" codes were used to approximate the reason of hospitalisation. For arrhythmias (I48, I49 and I46), only new occurrences were considered, to exclude codes and hospitalisations for existing condition

References:

[1] Metcalfe A, Neudam A, Forde S, et al. Case definitions for acute myocardial infarction in administrative databases and their impact on in-hospital mortality rates. *Health Serv Res* 2013; **48**(1): 290-318.

[2] Davidson J, Banerjee A, Muzambi R, Smeeth L, Warren-Gash C. Validity of Acute Cardiovascular Outcome Diagnoses Recorded in European Electronic Health Records: A Systematic Review. *Clin Epidemiol* 2020; **12**: 1095-111.

[3]McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of Diagnostic Codes for Acute Stroke in Administrative Databases: A Systematic Review. *PLoS One* 2015; **10**(8): e0135834.

[4]Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10. *Stroke* 2005; **36**(8): 1776-81.

[5] Yao RJR, Andrade JG, Deyell MW, Jackson H, McAlister FA, Hawkins NM. Sensitivity, specificity, positive and negative predictive values of identifying atrial fibrillation using administrative data: a systematic review and meta-analysis. *Clin Epidemiol* 2019; **11**: 753-67.

Table S5. List of time-invariant and time-varying confounders selected *a priori*

	Categorisation	Period of measurement
Patient-related confounders		
Age at cohort entry	Continuous	CED
Sex	Male / Female	CED
Comorbidities (ICD-10-CA code)		
Diabetes mellitus type 2 (E11)	Yes / No	Entire available history
Disorders of lipoprotein metabolism and other lipidaemias (i.e., including hyperlipidaemia, hypercholesterolemia, dyslipidaemia) E78	Yes / No	Entire available history
Ischemic heart diseases (I20-I25)	Yes / No	Entire available history
Hypertensive diseases (I10-I15)	Yes / No	Entire available history
Heart failure (I50)	Yes / No	Entire available history
Cardiomyopathy (I25.5, I42.0, I42.6–I42.9, I43)	Yes / No	Entire available history
Pulmonary oedema (J81)	Yes / No	Entire available history
Pulmonary hypertension (I27.0, I27.2)	Yes / No	Entire available history
Venous thromboembolism (I26, I80, I81, I82, O08.2, O22.3, O87.1, O88.2)	Yes / No	Entire available history
Cerebrovascular disease (I60-69)	Yes / No	Entire available history
Atrial fibrillation (I48) and other arrythmias (I49)	Yes / No	Entire available history
Current (adult) asthma (J45/J46)	Yes / No	24-month lookback period
Chronic kidney disease, renal failure (N17-N19, I12.0, I13.1, I13.2)	Yes / No	Entire available history
Severe mental illness including recurrent and persistent depressive disorders (F33, F34), bipolar disorder (F30-31) and schizophrenia (F20-29)	Yes / No	Entire available history
Anxiety disorder (F40-48)	Yes / No	24-month lookback period
Medication (time-varying)		
Any use of cardiac / metabolic agents (see medications table below)	At least one dispensation of Cardiac or metabolic agent of each therapeutic subgroup (ATC level 2) in the prior 12 months	Time updated using a rolling 12-month time window. The baseline value was “yes” if a drug was recorded in the 12-month period preceding CED.
Long-term inhaled COPD drug use as single therapy (see medications table below): - LABA - LAMA - ICS	Yes (at least one dispensation in the prior 12 months) / No for each category	Time updated using a rolling 12-month time window. The baseline value was “yes” if a drug was recorded in the 12-month period preceding CED.
Long-term inhaled COPD drug use as combined therapy (see medications	Yes (at least one dispensation in the prior 12 months) / No for each	Time updated using a rolling 12-month time window. The baseline value was “yes” if a drug was

	Categorisation	Period of measurement
table below)	category	recorded in the 12-month period preceding CED.
Short-term inhaler: - SABA - SAMA	Yes (at least one dispensation in the prior 12 months) / No for each category	Time updated using a rolling 12-month time window. The baseline value was "yes" if a drug was recorded in the 12-month period preceding CED.
Roflumilast and/or theophylline	Yes (at least one dispensation in the prior 12 months) / No for each category	Time updated using a rolling 12-month time window. The baseline value was "yes" if a drug was recorded in the 12-month period preceding CED.
Other confounders		
Number of GP visits in the last 12 months		Time updated using a rolling 12-month time window. The baseline value was the number of GP visits in the 12-month period preceding CED
Number of exacerbations in the last 12 months	Count variable	Time updated using a rolling 12-month time window. For prevalent patients, the baseline value was the number of exacerbations in the 12-month period preceding CED.
Year at cohort entry	YYYY	CED
Incident COPD (vs. prevalent)	Yes / No	CED
Season (winter vs. not winter)	Winter / Not winter	Time updated at a change in value; baseline value denoted winter or not winter at cohort entry date. Winter was defined as December, January, February & March.

Abbreviations: ATC: Anatomical therapeutic chemical; CED: cohort entry date; COPD: chronic obstructive pulmonary disease; CV: cardiovascular; GP: general practitioner physician; ICD-10-CA: International Statistical Classification of Diseases and Related Health problems, 10th revision, Canadian modification; ICS: inhaled corticosteroid; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting beta agonist; SAMA: short-acting muscarinic antagonist

Table S6. Incidence rate and risk of a first cardiovascular event or all-cause death (composite and individual endpoints) following an exacerbation of any severity

Exposure time period	Crude incidence rate (95% CI) *	Unadjusted HR (95% CI)	Fully adjusted † HR (95% CI)
First severe CV event (any category, including all-cause death)			
Prior to the first exacerbation (reference) ‡	5.43 (5.36 - 5.50)	1	1
1-7 days	95.61 (92.59 - 98.71)	17.56 (16.95 - 18.20)	15.86 (15.17 - 16.58)
8-14 days	35.10 (33.14 - 37.15)	6.76 (6.38 - 7.17)	6.09 (5.71 - 6.50)
15-30 days	23.60 (22.49 - 24.75)	4.53 (4.31 - 4.76)	4.07 (3.84 - 4.30)
31-180 days	10.91 (10.61 - 11.22)	2.08 (2.02 - 2.15)	1.85 (1.78 - 1.92)
181-365 days	8.27 (7.97 - 8.58)	1.51 (1.45 - 1.57)	1.29 (1.23 - 1.34)
>365 days	7.35 (7.16 - 7.55)	1.24 (1.20 - 1.28)	1.08 (1.05 - 1.12)
Acute coronary syndrome			
Prior to the first exacerbation (reference)	0.80 (0.77 - 0.83)	1	1
1-7 days	14.11 (12.99 - 15.29)	18.79 (17.12 - 20.62)	24.57 (21.70 - 27.83)
8-14 days	2.14 (1.69 - 2.67)	3.08 (2.46 - 3.87)	4.10 (3.22 - 5.23)
15-30 days	1.39 (1.13 - 1.68)	1.97 (1.62 - 2.39)	2.57 (2.08 - 3.18)
31-180 days	0.79 (0.71 - 0.87)	1.14 (1.03 - 1.27)	1.40 (1.24 - 1.60)
181-365 days	0.83 (0.73 - 0.92)	1.21 (1.08 - 1.37)	1.39 (1.22 - 1.59)
>365 days	0.77 (0.71 - 0.83)	1.17 (1.07 - 1.28)	1.12 (1.02 - 1.23)
Heart failure decompensation			
Prior to the first exacerbation (reference)	0.56 (0.53 - 0.58)	1	1
1-7 days	21.45 (20.07 - 22.90)	43.06 (39.63 - 46.79)	72.34 (64.43 - 81.22)
8-14 days	2.52 (2.03 - 3.09)	5.53 (4.48 - 6.84)	9.55 (7.59 - 12.02)
15-30 days	1.16 (0.93 - 1.43)	2.50 (2.02 - 3.10)	4.13 (3.28 - 5.21)
31-180 days	0.68 (0.61 - 0.76)	1.54 (1.37 - 1.73)	2.25 (1.96 - 2.59)
181-365 days	0.49 (0.42 - 0.57)	1.14 (0.98 - 1.33)	1.44 (1.22 - 1.70)
>365 days	0.50 (0.45 - 0.55)	1.14 (1.02 - 1.28)	0.96 (0.86 - 1.08)
Cerebral ischemia			
Prior to the first exacerbation (reference)	0.51 (0.49 - 0.53)	1	1
1-7 days	5.14 (4.48 - 5.86)	10.52 (9.12 - 12.13)	16.12 (13.39 - 19.41)
8-14 days	1.14 (0.82 - 1.55)	2.37 (1.74 - 3.22)	3.72 (2.67 - 5.19)
15-30 days	0.74 (0.56 - 0.96)	1.55 (1.19 - 2.02)	2.39 (1.79 - 3.20)
31-180 days	0.54 (0.48 - 0.61)	1.12 (0.99 - 1.28)	1.58 (1.34 - 1.87)
181-365 days	0.55 (0.48 - 0.63)	1.15 (1.00 - 1.33)	1.47 (1.24 - 1.74)
>365 days	0.51 (0.46 - 0.57)	1.09 (0.98 - 1.22)	1.03 (0.92 - 1.15)
Arrhythmias (new diagnosis)			
Prior to the first exacerbation (reference)	0.44 (0.42 - 0.46)	1	1

Exposure time period	Crude incidence rate (95% CI) *	Unadjusted HR (95% CI)	Fully adjusted † HR (95% CI)
1-7 days	10.41 (9.46 - 11.43)	24.96 (22.34 - 27.88)	31.18 (26.84 - 36.21)
8-14 days	1.37 (1.02 - 1.80)	3.50 (2.63 - 4.64)	4.43 (3.27 - 5.99)
15-30 days	0.76 (0.57 - 0.98)	1.97 (1.52 - 2.56)	2.46 (1.85 - 3.25)
31-180 days	0.52 (0.45 - 0.58)	1.40 (1.22 - 1.59)	1.64 (1.40 - 1.92)
181-365 days	0.44 (0.37 - 0.51)	1.19 (1.01 - 1.40)	1.30 (1.09 - 1.55)
>365 days	0.40 (0.35 - 0.44)	1.10 (0.97 - 1.24)	0.99 (0.87 - 1.12)
All-cause death			
Prior to the first exacerbation (reference)	3.65 (3.59 - 3.71)	1	1
1-7 days	51.01 (48.89 - 53.18)	13.72 (13.12 - 14.35)	10.05 (9.52 - 10.60)
8-14 days	31.61 (29.83 - 33.46)	8.45 (7.96 - 8.96)	6.12 (5.72 - 6.54)
15-30 days	22.08 (21.05 - 23.15)	5.90 (5.62 - 6.20)	4.31 (4.06 - 4.56)
31-180 days	9.72 (9.45 - 10.00)	2.56 (2.48 - 2.64)	1.91 (1.84 - 1.99)
181-365 days	6.93 (6.67 - 7.21)	1.71 (1.64 - 1.78)	1.26 (1.20 - 1.31)
>365 days	6.13 (5.96 - 6.31)	1.33 (1.29 - 1.38)	1.11 (1.07 - 1.15)

Abbreviations: CI: confidence interval; CV: cardiovascular; HR: hazard ratio

* Crude rate (95% CI) was calculated as the number of first severe CV events or deaths per 100 person-years.

† Fully adjusted Cox model provided HR and 95% Confidence Intervals and included sex, comorbidities, year of cohort entry, residence at cohort entry, neighbourhood income quintile and time varying covariates (cardiac/metabolic agents, COPD medication use, general practitioner visits, number of exacerbations in last 12 months, season and time-varying age).

‡ Reference time was the earliest of: 1) a first exacerbation or 2) end of follow-up due to experiencing the event or right censoring.

Table S7. Risk of a first cardiovascular event or all-cause death following a severe, or a moderate exacerbation of COPD; covariate-adjusted hazard ratios from fitted Cox model with 95% confidence intervals

Exposure time period	Unadjusted HR (95% CI)	Fully adjusted * HR (95% CI)
Prior to the first exacerbation (reference) †	1	1
Moderate exacerbation		
1-7 days	2.74 (2.42 - 3.09)	2.47 (2.17 - 2.80)
8-14 days	2.28 (1.98 - 2.63)	2.06 (1.77 - 2.38)
15-30 days	1.85 (1.66 - 2.06)	1.71 (1.52 - 1.91)
31-180 days	1.17 (1.11 - 1.23)	1.13 (1.06 - 1.20)
181-365 days	0.95 (0.89 - 1.02)	0.94 (0.87 - 1.00)
>365 days	0.86 (0.82 - 0.90)	0.92 (0.87 - 0.96)
Severe exacerbation		
1-7 days	30.78 (29.67 - 31.93)	24.88 (23.75 - 26.07)
8-14 days	10.81 (10.14 - 11.51)	8.66 (8.08 - 9.29)
15-30 days	7.04 (6.66 - 7.44)	5.54 (5.21 - 5.89)
31-180 days	2.99 (2.89 - 3.10)	2.25 (2.16 - 2.35)
181-365 days	2.08 (1.99 - 2.18)	1.47 (1.40 - 1.55)
>365 days	1.62 (1.56 - 1.68)	1.20 (1.16 - 1.25)

Abbreviations: CI: confidence interval; HR: hazard ratio

* Fully adjusted model included sex, comorbidities, year of cohort entry, residence at cohort entry, neighbourhood income quintile and time-varying covariates (cardiac/metabolic agents, COPD medication use, general practitioner visits, number of exacerbations in last 12 months, season and time-varying age).

† Reference period was the time prior to the earliest of 1) a first exacerbation or 2) end of follow-up due to experiencing the event or right censoring.

Table S8. Risk of a first cardiovascular event or all-cause death following a first, or a second, or a third exacerbation of any severity in the incident cohort (N = 52917); covariate-adjusted hazard ratios from fitted Cox model with 95% confidence intervals

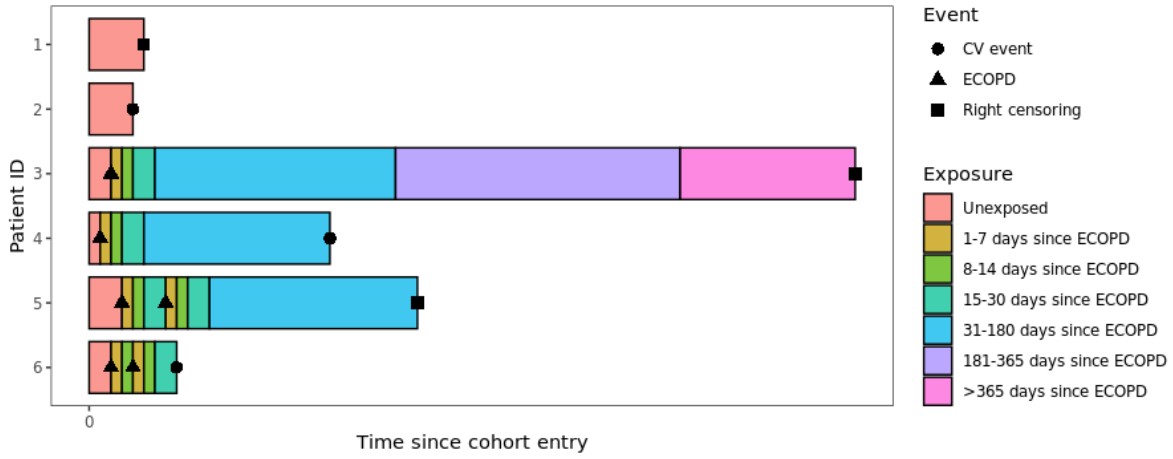
Exposure time period	Unadjusted HR (95% CI)	Fully adjusted * HR (95% CI)
Prior to the first exacerbation (reference) †	1	1
First exacerbation		
1-7 days	14.52 (12.69 - 16.61)	13.87 (12.07 - 15.94)
8-14 days	4.05 (3.18 - 5.16)	3.88 (3.03 - 4.95)
15-30 days	2.85 (2.36 - 3.44)	2.73 (2.25 - 3.31)
31-180 days	1.52 (1.38 - 1.66)	1.46 (1.32 - 1.61)
181-365 days	1.28 (1.16 - 1.41)	1.23 (1.11 - 1.36)
>365 days	1.13 (1.06 - 1.21)	1.04 (0.98 - 1.11)
Second exacerbation		
1-7 days	16.69 (14.45 - 19.28)	16.07 (13.77 - 18.75)
8-14 days	4.84 (3.64 - 6.43)	4.69 (3.51 - 6.27)
15-30 days	4.14 (3.35 - 5.10)	3.99 (3.21 - 4.96)
31-180 days	1.75 (1.55 - 1.98)	1.65 (1.44 - 1.89)
181-365 days	1.35 (1.17 - 1.57)	1.24 (1.06 - 1.46)
>365 days	1.20 (1.06 - 1.36)	1.05 (0.93 - 1.20)
Third+ exacerbation		
1-7 days	13.02 (11.44 - 14.82)	12.76 (10.77 - 15.13)
8-14 days	6.02 (4.92 - 7.37)	5.93 (4.71 - 7.48)
15-30 days	3.78 (3.16 - 4.52)	3.70 (3.00 - 4.56)
31-180 days	1.83 (1.64 - 2.05)	1.76 (1.53 - 2.03)
181-365 days	1.38 (1.17 - 1.63)	1.23 (1.03 - 1.47)
>365 days	1.56 (1.34 - 1.82)	1.31 (1.12 - 1.53)

Abbreviations: CI: confidence interval; COPD: chronic obstructive pulmonary disease; HR: hazard ratio

* Fully adjusted model included sex, comorbidities, year of cohort entry, residence at cohort entry, neighbourhood income quintile and time-varying covariates (cardiac/metabolic agents, COPD medication use, general practitioner visits, number of exacerbations in last 12 months, season and time-varying age).

† Reference period was the time prior to the earliest of 1) a first exacerbation or 2) end of follow-up due to experiencing the event or right censoring.

Figure S1. Patient follow-up during exposed, and unexposed periods of time



Abbreviations: CV: cardiovascular event or all-cause death; ECOPD: exacerbation from chronic obstructive pulmonary disease; Exposed: evidence of a patient exacerbation from chronic obstructive pulmonary disease; ID: patient identification number; Unexposed: no evidence of patient exacerbation from chronic obstructive pulmonary disease