

SUPPLEMENTARY DATA

Table 1 of the supplementary data. ICD-9 and ICD-10 codes used to define COPD and COPD exacerbation

Code	Defines	Details
ICD-9		
492.8	COPD	Other emphysema
493.20	COPD	Chronic obstructive asthma
493.21	COPD exacerbation	Chronic obstructive asthma with exacerbation
496	COPD	Chronic airway obstruction, not elsewhere classified
491.20	COPD	Chronic obstructive bronchitis without acute exacerbation
491.22	COPD	Chronic obstructive bronchitis with bronchitis (acute)
491.21	COPD exacerbation	Chronic obstructive bronchitis with acute exacerbation
ICD-10		
J44	COPD	Other COPD
J44.0	COPD	COPD with acute lower respiratory infection
J44.1	COPD	COPD with (acute) exacerbation
J44.9	COPD	COPD, unspecified
J44.0	COPD exacerbation	COPD with acute lower respiratory infection
J44.1	COPD exacerbation	COPD with (acute) exacerbation

COPD, chronic obstructive pulmonary disease; ICD-9, International Classification of Disease, Ninth Revision; ICD-10, International Classification of Disease, Tenth Revision.

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Table 2 of the supplementary data. ICD-9 and ICD-10 codes used to define nonfatal cardiovascular outcomes

Code	Defines	Details
ICD-9		
410	Acute MI	Acute MI
411.1	Unstable angina	Intermediate coronary syndrome
411.8	Unstable angina	Other acute and subacute forms of ischemic heart disease
413	Angina	Angina pectoris
428.21	HF decompensation	Acute systolic HF
428.23	HF decompensation	Acute on chronic systolic HF
428.31	HF decompensation	Acute diastolic HF
428.33	HF decompensation	Acute on chronic diastolic HF
428.41	HF decompensation	Acute combined systolic and diastolic HF
428.43	HF decompensation	Acute on chronic combined systolic and diastolic HF
518.4	HF decompensation	Acute edema of lung, unspecified
514	HF decompensation	Pulmonary congestion and hypostasis
427.3	Acute AF	AF
427.4	Other ventricular dysrhythmia	Ventricular fibrillation and flutter
427.5	Resuscitated cardiac arrest	Cardiac arrest
434	Ischemic stroke and TIA	Occlusion and stenosis of precerebral arteries
435	Ischemic stroke and TIA	Occlusion of cerebral arteries
ICD-10		
I21	Acute MI and unstable angina	Acute MI
I21.0	Acute MI	STEMI
I21.1	Acute MI	STEMI
I21.2	Acute MI	STEMI
I21.3	Acute MI	Non-STEMI
I21.4	Acute MI	Non-STEMI
I21.9	Acute MI	Non-STEMI
I20.0	Acute MI and unstable angina	Unstable angina pectoris
I50.21	HF decompensation	Acute systolic (congestive) HF
I50.23	HF decompensation	Acute on chronic systolic (congestive) HF
I50.31	HF decompensation	Acute diastolic (congestive) HF
I50.33	HF decompensation	Acute on chronic diastolic (congestive) HF
I50.41	HF decompensation	Acute combined systolic (congestive) and diastolic (congestive) HF
I50.43	HF decompensation	Acute on chronic combined systolic (congestive) and diastolic (congestive) HF
J81	HF decompensation	Pulmonary edema
I48	Acute AF	AF and flutter

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I49	Other cardiac arrhythmias	Other cardiac arrhythmias
I46	Resuscitated cardiac arrest	Cardiac arrest
I63	Ischemic stroke and TIA	Cerebral infarction, unspecified
G45	Ischemic stroke and TIA	Transient cerebral ischemic attack, unspecified

AF, atrial fibrillation; HF, heart failure; ICD-9, International Classification of Disease, Ninth Revision; ICD-10, International Classification of Disease, 10th Revision; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

Table 3 of the supplementary data. Incident cohort - demographics and baseline characteristics

	All patients	No exacerbation during follow-up ^a	≥ 1 exacerbation during total follow-up
	N = 12 713	n = 3488	n = 9225
Sociodemographic characteristics			
<i>Age, y</i>			
Mean	62.9 ± 10.7	61.5 ± 4.6	63.3 ± 12.2
Median	62.2 [54.3–70.9]	62.3 [58.3–65.4]	61.9 [52.3–73.9]
<i>Sex (female)</i>	2740 (21.6)	768 (22)	1972 (21.6)
Behavioural risk factors			
<i>Tobacco use</i>			
Smoker	4545 (35.8)	2210 (63.4)	2335 (25.6)
Exsmoker	5943 (46.7)	646 (18.5)	5297 (58)
Never smoker	2225 (17.5)	632 (18.1)	1593 (17.4)
<i>Alcohol use disorder</i>	586 (4.6)	227 (6.5)	359 (3.9)
Associated comorbidities			
<i>Obesity</i>	2249 (17.7)	838 (24.0)	1411 (15.4)
<i>Diabetes mellitus type 2</i>	1990 (15.7)	399 (11.4)	1591 (17.4)
<i>Disorders of lipoprotein metabolism</i>	6802 (53.5)	2440 (70.0)	4362 (47.8)
<i>Ischemic heart disease</i>	2086 (16.4)	446 (12.8)	1640 (18.0)
<i>Hypertensive diseases</i>	7344 (57.8)	1840 (52.8)	5504 (60.3)
<i>HF and pulmonary oedema</i>	2564 (20.2)	539 (15.5)	2025 (22.2)
<i>Pulmonary hypertension</i>	402 (3.2)	69 (2.0)	333 (3.6)
<i>Venous thromboembolism</i>	901 (7.1)	165 (4.7)	736 (8.1)
<i>Cerebrovascular disease</i>	1146 (9.0)	212 (6.1)	934 (10.2)
<i>Arrhythmia</i>	1320 (10.4)	266 (7.6)	1054 (11.5)
<i>Current asthma</i>	1197 (9.4)	249 (7.1)	948 (10.4)
<i>Chronic kidney disease, renal failure</i>	1255 (9.9)	225 (6.5)	1030 (11.3)
<i>Severe mental illness</i>	1770 (13.9)	330 (9.5)	1440 (15.8)
<i>Anxiety disorder</i>	4604 (36.2)	1127 (32.3)	3477 (38.1)
Number of primary care physician visits in the 12 months preceding cohort entry			
<i>Mean</i>	6 ± 3	3.8 ± 2.2	6.9 ± 2.9
<i>Median</i>	6 [4–8]	4 [2–5]	7 [5–9]
Medication use^b			
<i>Long-acting inhaled COPD drug use</i>			
ICS	7421 (58.4)	1937 (55.5)	5484 (60.0)
LABA	8252 (64.9)	2193 (62.9)	6059 (66.3)
LAMA	5411 (42.6)	1408 (40.4)	4003 (43.8)
<i>Short-acting inhaler</i>			
SABA	12 012 (94.5)	3151 (90.3)	8861 (97.0)
SAMA	1328 (10.4)	343 (9.8)	985 (10.8)
<i>Roflumilast</i>	228 (1.8)	49 (1.4)	179 (2.0)

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<i>Any cardiac drug</i>	11 546 (90.8)	3104 (89)	8442 (92.4)
<i>Any metabolic drug</i>	7886 (62.0)	2060 (59.1)	5826 (63.8)

COPD, chronic obstructive pulmonary disease; HF, heart failure; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β_2 -agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

Data are expressed as No. (%), mean \pm standard deviation or median [interquartile range].

^aTotal follow-up was defined as time from cohort entry to earliest of 31 December 2019, loss to follow-up or onset of the first severe acute cardiovascular event of interest of any type, including all-cause death.

^bMedication use was defined as the dispensation of a medication of each class (which could be part of a fixed combination), at least once in the 12 months before the cohort entry date.

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Table 4 of the supplementary data. Crude IR of a first severe cardiovascular event (nonfatal event or all-cause death) within unexposed time and exposed time following moderate/severe exacerbation onset

Exposure to a moderate/severe exacerbation	Patients*	First events	PY of follow-up	Crude IR (95%CI) per 100 PY	
Nonfatal cardiovascular event					
<i>Prior to first exacerbation (reference)</i>	21 900	2922	55 204	5.29 (5.11-5.48)	
1-7 d	} Time since exacerbation onset	14 997	392	1046	37.47 (34.59-40.44)
8-14 d		14 725	189	1039	19.73 (17.42-22.26)
15-30 d		14 417	296	2346	11.94 (10.69-13.31)
31-180 d		13 718	1146	14 124	8.11 (7.67-8.58)
181-365 d		9780	521	8143	6.40 (5.89-6.95)
> 365 d		7917	444	6753	6.57 (6.01-7.19)
ACS					
<i>Prior to first exacerbation (reference)</i>	21 900	585	58 111	1.01 (0.93-1.09)	
1-7 d	} Time since exacerbation onset	17 952	83	1567	5.30 (4.29-6.52)
8-14 d		17 879	41	1550	2.65 (1.96-3.57)
15-30 d		17 823	69	3495	1.97 (1.56-2.49)
31-180 d		17 648	265	21 449	1.24 (1.10-1.39)
181-365 d		13 806	155	12 600	1.23 (1.05-1.44)
> 365 d		12 961	98	9301	1.05 (0.87-1.28)
HF decompensation					
<i>Prior to first exacerbation (reference)</i>	21 900	1479	57 927	2.55 (2.43-2.68)	
1-7 d	} Time since exacerbation onset	17 050	181	1416	12.78 (11.14-14.62)
8-14 d		16 938	101	1402	7.21 (5.97-8.68)
15-30 d		16 863	158	3161	5.00 (4.29-5.81)
31-180 d		16 461	582	19 313	3.01 (2.78-3.26)
181-365 d		12 673	291	11 310	2.57 (2.30-2.88)
> 365 d		11 920	180	8369	2.15 (1.86-2.48)
Cerebral ischemia					
<i>Prior to first exacerbation (reference)</i>	21 900	311	58 170	0.53 (0.48-0.60)	
1-7 d	} Time since exacerbation onset	18 206	57	1618	3.52 (2.73-4.54)
8-14 d		18 171	22	1600	1.38 (0.91-2.07)
15-30 d		18 145	27	3608	0.75 (0.51-1.09)
31-180 d		18 055	120	22 191	0.54 (0.45-0.65)
181-365 d		14 248	76	13 051	0.58 (0.47-0.73)
> 365 d		13 372	40	9616	0.42 (0.31-0.57)
Arrhythmia					
<i>Prior to first exacerbation (reference)</i>	21 900	898	58 045	1.55 (1.45-1.65)	
1-7 d		17 626	112	1511	7.41 (6.20-8.84)
8-14 d		17 538	40	1495	2.68 (1.97-3.62)
15-30 d		17 495	66	3372	1.96 (1.54-2.48)
31-180 d		17 152	375	20 642	1.82 (1.64-2.01)

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181-365 d	} Time since exacerbation onset	13 414	211	12 102	1.74 (1.53-1.99)
> 365 d		12 652	145	8827	1.64 (1.40-1.93)
All-cause death					
<i>Prior to first exacerbation (reference)</i>		21 900	876	57 129	1.53 (1.44-1.64)
1-7 d	} Time since exacerbation onset	18 241	757	1625	46.57 (44.16-49.00)
8-14 d		18 208	366	1634	22.40 (20.44-24.48)
15-30 d		18 191	396	3667	10.80 (9.83-11.84)
31-180 d		18 116	1108	22 506	4.92 (4.65-5.21)
181-365 d		14 296	306	13 188	2.32 (2.08-2.59)
> 365 d		11 847	225	10 693	2.10 (1.85-2.39)

95%CI, 95% confidence interval; ACS, acute coronary syndrome; HF, heart failure; IR, incidence rate;

PY, patient-years.

Shaded time periods (including time prior to first exacerbation and all follow-up time of never exacerbating patients) were considered unexposed to exacerbations.

* Number of patients contributing at least 1 day of data in this period from the overall population of 24 393 patients.

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Table 5 of the supplementary data. Unadjusted HR (95%CI) for time to a first severe cardiovascular event (any event [nonfatal event or all-cause death] and by event type) within exposed time periods following a moderate/severe exacerbation vs unexposed time (univariable model)

Exposure to a moderate/severe exacerbation		Unadjusted HR (95%CI) for time to first severe cardiovascular event
Cardiovascular event of any type (including all-cause death)		
<i>Prior to first exacerbation (reference)</i>		1
1-7 d	} Time since exacerbation onset	10.27 (9.46-11.16)
8-14 d		8.39 (7.67-9.18)
15-30 d		4.45 (4.10-4.84)
31-180 d		2.43 (2.30-2.58)
181-365 d		1.80 (1.65-1.97)
> 365 d		1.61 (1.45-1.78)
Nonfatal cardiovascular event (death as a censoring event)		
<i>Prior to first exacerbation (reference)</i>		1
1-7 d	} Time since exacerbation onset	8.70 (7.82-9.68)
8-14 d		4.62 (4.01-5.33)
15-30 d		2.82 (2.49-3.19)
31-180 d		2.33 (2.17-2.50)
181-365 d		2.66 (2.42-2.93)
> 365 d		2.60 (2.35-2.89)
ACS		
<i>Prior to first exacerbation (reference)</i>		1
1-7 d	} Time since exacerbation onset	6.27 (4.96-7.93)
8-14 d		3.10 (2.25-4.27)
15-30 d		2.33 (1.81-3.01)
31-180 d		1.69 (1.44-1.97)
181-365 d		2.19 (1.81-2.66)
> 365 d		2.09 (1.73-2.53)
HF decompensation		
<i>Prior to first exacerbation (reference)</i>		1
1-7 d	} Time since exacerbation onset	6.57 (5.62-7.69)
8-14 d		3.62 (2.95-4.43)
15-30 d		2.61 (2.21-3.08)
31-180 d		1.83 (1.65-2.02)
181-365 d		2.14 (1.87-2.44)
> 365 d		1.95 (1.71-2.23)
Cerebral ischemia		
<i>Prior to first exacerbation (reference)</i>		1
1-7 d		7.53 (5.64-10.06)
8-14 d		2.91 (1.88-4.50)
15-30 d		1.60 (1.08-2.39)
31-180 d		1.34 (1.07-1.67)

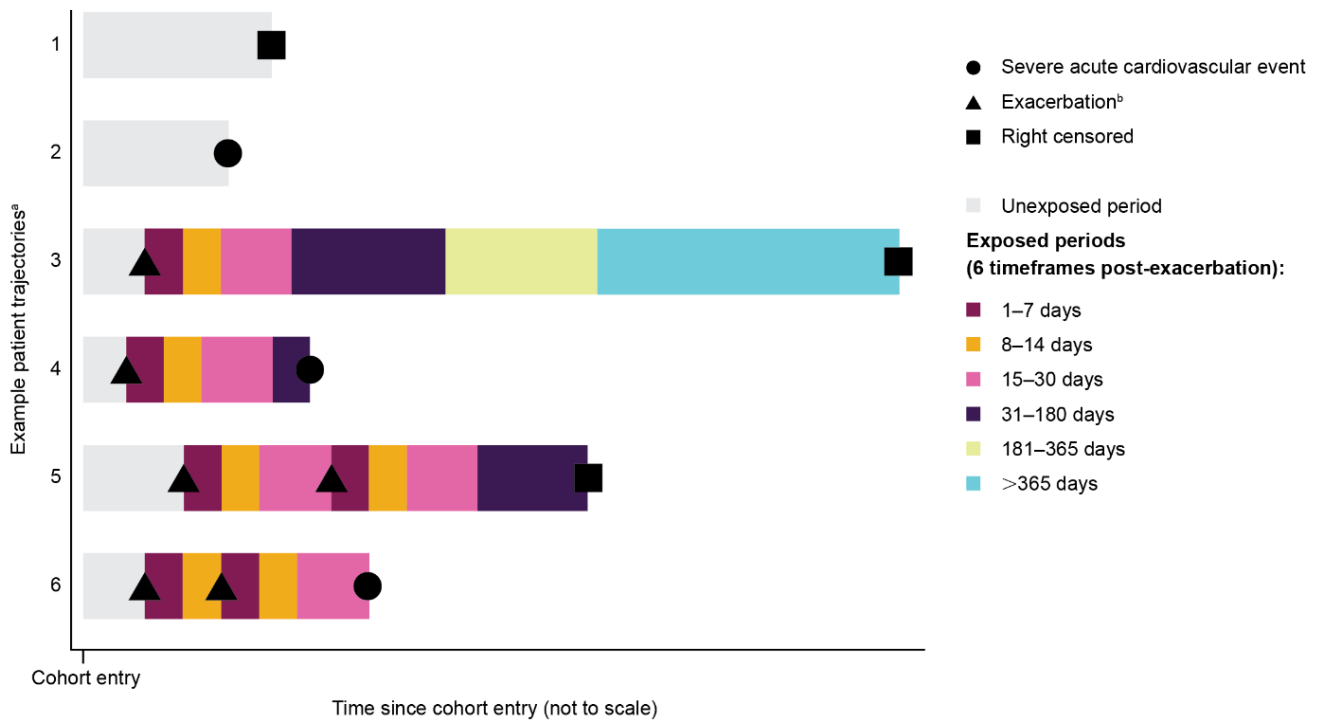
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181-365 d	} Time since exacerbation onset	1.88 (1.43-2.46)
> 365 d		1.44 (1.10-1.89)
Arrhythmia		
<i>Prior to first exacerbation (reference)</i>		1
1-7 d	} Time since exacerbation onset	5.57 (4.56-6.80)
8-14 d		1.95 (1.60-2.39)
15-30 d		1.42 (1.17-1.74)
31-180 d		1.63 (1.34-2.00)
181-365 d		2.03 (1.73-2.39)
> 365 d		2.07 (1.76-2.43)
All-cause death		
<i>Prior to first exacerbation (reference)</i>		1
1-7 d	} Time since exacerbation onset	21.58 (19.50-23.88)
8-14 d		10.31 (9.09-11.68)
15-30 d		4.94 (4.38-5.59)
31-180 d		2.14 (1.95-2.35)
181-365 d		0.96 (0.83-1.09)
> 365 d		0.96 (0.82-1.12)

95%CI, 95% confidence interval; ACS, acute coronary syndrome; HF, heart failure; HR, hazard ratio.

Shaded time periods (including time prior to first exacerbation and all follow-up time of never exacerbating patients) were considered unexposed to exacerbations.

Figure 1 of the supplementary data. Definition of exposure and nonexposure

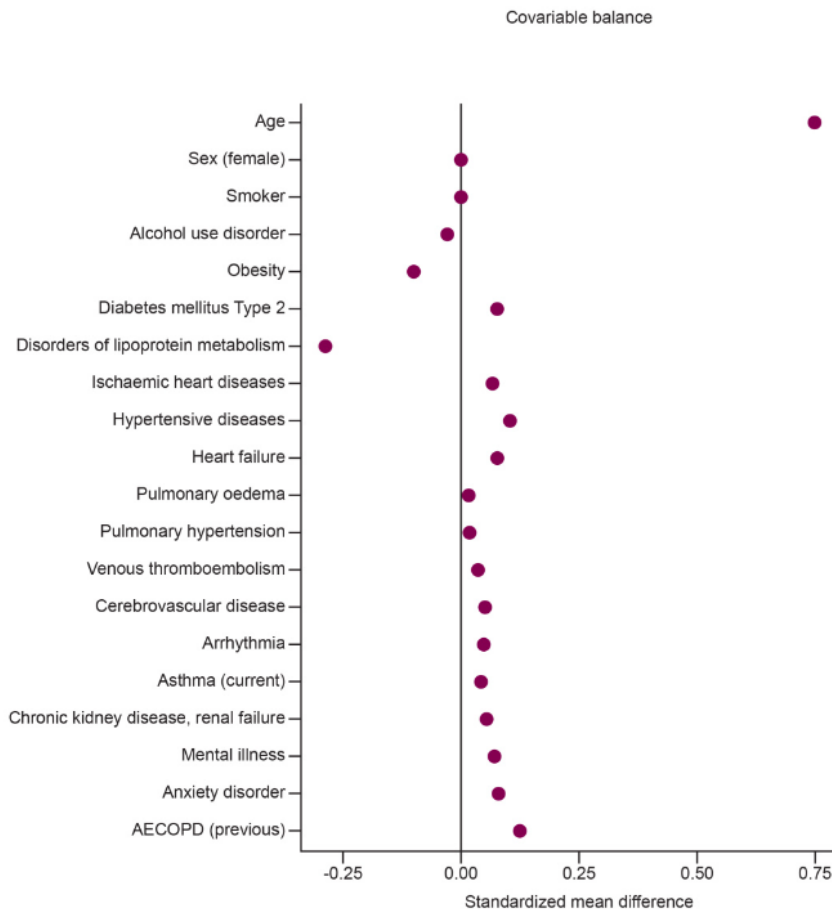


^a Multiple exacerbations can occur within trajectory profiles 5 and 6; on the examples shown, there are two exacerbations.

^b A moderate or severe exacerbation indicates the beginning of the exposure window.

Figure 2 of the supplementary data. Baseline covariate balance plot (Love plot) comparison of patients who ever and never exacerbated during follow-up

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The x-axis (standardized mean differences) expresses the extent to which each of the items analyzed is more represented in one cohort or the other. The further to the right of the central axis (0.00), the greater the presence of each of the items analyzed.

AECOPD, acute exacerbation of chronic obstructive pulmonary disease (includes moderate and severe exacerbations: moderate exacerbations were defined as those requiring an outpatient visit with a diagnosis code for COPD [see table 1 of the supplementary data] and dispensation of oral corticosteroids and/or antibiotics within 5 days following the visit and for a maximum of 15 days; severe exacerbations were defined as those requiring an emergency department visit or a hospitalization of ≥ 1 night with a discharge diagnosis code for COPD exacerbation [see table 1 of the supplementary data]).