

**MAJOR ADVERSE CARDIOVASCULAR EVENTS AND CAUSE-SPECIFIC
MORTALITY AFTER HOSPITALISATION IN COPD**

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ONLINE DATA SUPPLEMENT

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CPRD: ADDITIONAL LINKAGE, DATA AVAILING, CONSENT FOR PUBLICATION AND ETHICS STATEMENTS, AND RESEARCH DATA QUALITY INFORMATION

Ethics approval and consent to participate:

CPRD has NHS Health Research Authority (HRA) Research Ethics Committee (REC) approval to allow the collection and release of anonymised primary care data for observational research [NHS HRA REC reference number: 05/MRE04/87]. Each year CPRD obtains Section 251 regulatory support through the HRA Confidentiality Advisory Group (CAG), to enable patient identifiers, without accompanying clinical data, to flow from CPRD contributing GP practices in England to NHS Digital, for the purposes of data linkage [CAG reference number: 21/CAG/0008]. The protocol for this research was approved by CPRD's Research Data Governance (RDG) Process (protocol number: 22_002514) and the approved protocol is available upon request. Linked pseudonymised data was provided for this study by CPRD. Data is linked by NHS Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select general practices consent to this process at a practice level with individual patients having the right to opt-out.

Consent for publication, and availability of data and materials:

Datasets generated and/or analysed in this study are not publicly available, however, data are available on request from the CPRD. Their provision requires the purchase of a license, and this license does not permit the authors to make them publicly available to all. This work used data from the version collected in February 2022 and has clearly specified the data selected in the Methods section. To allow identical data to be obtained by others, via the purchase of a license, the code lists will be provided upon request. Licenses are available from the CPRD (<http://www.cprd.com>): The Clinical Practice Research Datalink Group, The Medicines and Healthcare products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU.

Additional linkage information:

Linked pseudonymised socioeconomic data from the Index of Multiple Deprivation (IMD), and secondary care data from Hospital Episode Statistics (HES) were provided for this study by CPRD for patients in England. Data is linked by NHS Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select general practices consent to this process at a practice level, with individual patients having the right to opt-out. Use of HES and ONS data is Copyright © (2023), re-used with the permission of The Health & Social Care Information Centre

Data research quality information:

CPRD checks several elements of data quality prior to making these data available for research (such as the volume of the data, data elements, and checks at different levels). Details on the data quality and the strategies undertaken by CPRD to ensure data quality are available at

<https://www.cprd.com/data-quality>. Moreover, Wolf et. al. (2019, doi: <https://doi.org/10.1093/ije/dyz034>) offers a data profile on CPRD data, including demographic information and population representation, linkage to other datasets, and data strengths and weaknesses.

VARIABLE DEFINITIONS LIST

Variable	Dataset location	Definition
EXPOSURE: HOSPITALISATION		
Hospitalisation (any)	HES APC (first position ICD10 codes only)	ICD10 code not considered
Elective	HES APC	Defined as elective according to HES dictionary, where admission record ('admimeth' is 11, 12m or 13).
Emergency	HES APC	Defined as emergency according to the HES dictionary, where admission record ('admimeth' is 21, 22, 23, 24, 25, 2A, 2B, 2C, 2D, or 28).
Hospitalisation (cardiovascular)	HES APC (first position ICD10 codes only)	Any ICD10 code from ICD chapter 9 (starting with "I-")
Elective	HES APC	Defined as elective according to HES dictionary, where admission record ('admimeth' is 11, 12m or 13).
Emergency	HES APC	Defined as emergency according to the HES dictionary, where admission record ('admimeth' is 21, 22, 23, 24, 25, 2A, 2B, 2C, 2D, or 28).
Hospitalisation (respiratory)	HES APC (first position ICD10 codes only)	Any ICD10 code from ICD chapter 10 (starting with "J-")
Elective	HES APC	Defined as elective according to HES dictionary, where admission record ('admimeth' is 11, 12m or 13).
Emergency	HES APC	Defined as emergency according to the HES dictionary, where admission record ('admimeth' is 21, 22, 23, 24, 25, 2A, 2B, 2C, 2D, or 28).
OUTCOME: MACE		
Acute coronary syndrome	HES APC (first position ICD10 codes only)	Unstable angina ST elevated myocardial infarction (STEMI) Non-ST elevated myocardial infarction (non-STEMI)
Arrhythmia	HES APC (first position ICD10 codes only)	Atrial fibrillation / flutter Cardiac arrest Other arrhythmias
Heart failure	HES APC (first position ICD10 codes only)	HFpEF HFrEF Decompensated HF Acute pulmonary oedema Dilated cardiomyopathy Takotsubo cardiomyopathy
Ischaemic stroke	HES APC (first position ICD10 codes only)	Ischaemic stroke
OUTCOME: MORTALITY	ONS record	Binary

Cardiovascular-specific	ONS record (first position ICD10 code only)	Binary
COPD-specific	ONS record (first position ICD10 code only)	Binary
COVARIATES		
Age	CPRD Aurum measured as the difference between index date and year of birth	Continuous variable
Sex	CPRD Aurum	Male or female
Socioeconomic status	Linked data – Index of Multiple Deprivation (IMD)	Index of Multiple Deprivation: Quintiled measurement of deprivation, ranging from 1 (most deprived) to 5 (least deprived)
Smoking status	CPRD Aurum	Ex-smoker or current smoker (most recent patient record)
Body Mass Index*	CPRD Aurum	BMI = weight (kg) / height ² (m), most recent within the five years before start of follow-up - Healthy weight (18.5 to 24.9 kg.m ⁻²) - Underweight (<18.5 kg.m ⁻²) - Overweight (25.0 to 29.9 kg.m ⁻²) - Obese (>30.0 kg.m ⁻²)
Depression	CPRD Aurum	Binary; Any record prior to index date
Anxiety	CPRD Aurum	Binary; Any record prior to index date
Gastro-oesophageal reflux disease	CPRD Aurum	Binary; Any record prior to index date
Lung cancer	CPRD Aurum	Binary; Any record prior to index date
Hypertension	CPRD Aurum	Binary; Any record prior to index date
Type 2 diabetes mellitus	CPRD Aurum	Binary; Any record prior to index date
Cardiovascular history	CPRD Aurum HES APC	Binary Record of: - Acute coronary syndrome - Arrhythmias - Heart failure - Ischaemic stroke Any record prior to index date
Asthma	CPRD Aurum	Binary Any record prior to index date
COPD exacerbation group	CPRD Aurum HES APC	Defined as one of the following categories based on the year preceding index date: - None - 1 moderate, 0 severe - 2 moderate, 0 severe

		<ul style="list-style-type: none"> - 3+ moderate, 0 severe - Any moderate, 1 severe - Any moderate, 2+ severe <p>Moderate exacerbation is a record in primary care only; severe exacerbation required secondary care. Methodology has been previously validated**</p>
MRC dyspnoea score*	CPRD Aurum	<p>Categorical variable based on the two years prior to index date or three months after index date:</p> <ul style="list-style-type: none"> - Grade 1: no dyspnoea except on strenuous exercise - Grade 2: dyspnoea when walking up a short hill - Grade 3: dyspnoea limits walking pace and participant stops to catch breath - Grade 4: stops to catch breath after walking 100m on level ground - Grade 5: dyspnoea limits leaving home and performing daily activities
GOLD disease severity*	CPRD Aurum	<p>Categorical variable on lung function (degree of airflow limitation) based on the two years prior to index date or three months after index date:</p> <ul style="list-style-type: none"> - GOLD1: FEV₁ predicted ≥80% - GOLD2: FEV₁ predicted 50% to 80% - GOLD3: FEV₁ predicted 30 to 50% - GOLD4: FEV₁ predicted <30%
Medication		
Long-acting medication	CPRD Aurum	<p>Any record of short-acting inhalers in the year prior to index date:</p> <ul style="list-style-type: none"> - Long-acting beta agonists (LABA) - Long-acting muscarinic antagonists (LAMA) - Combination LABA-LAMA - Inhaled corticosteroids (ICS) - Combination ICS-LABA - Combination ICS-LAMA - Combination ICS-LABA-LAMA (triple therapy) <p>Combination therapies are fixed and/or open</p>
Short-acting medication	CPRD Aurum	<p>Any record of short-acting inhalers in the year prior to index date:</p> <ul style="list-style-type: none"> - Short-acting beta agonists (SABA) - Short-acting muscarinic antagonists (SAMA) - Combination SABA-SAMA <p>Combination therapies are fixed and/or open</p>

Codelists available at: <https://github.com/NHLI-Respiratory-Epi/Hospitalisations-MACE-in-COPD>

Abbreviations: HES: Hospital Episode Statistics | APC – Admitted Patient Care | CPRD – Clinical Practice Research Datalink | MACE – major adverse cardiovascular events | BMI – body mass index | IMD – Index of Multiple Deprivation | HFpEF – heart failure with preserved ejection fraction | HFrfEF – heart failure with reduced ejection fraction | COPD – chronic obstructive pulmonary disease | MRC – Medical Research Council | GOLD – Global Initiative for Obstructive Lung Disease

Table E1: Cohort baseline characteristics

	Whole	No hospitalisation	Hospitalisations			Cardiovascular hospitalisations			Respiratory hospitalisations			Non-cardiorespiratory hospitalisations		
			All	Emergency	Elective	All	Emergency	Elective	All	Emergency	Elective	All	Emergency	Elective
N (%)	312,121 {100}	73,290 {23.5}	238,831 {76.5}	116,469 {37.3}	122,362 {39.2}	24,560 {7.9}	15,869 {5.1}	8,691 {2.9}	45,827 {14.7}	41,807 {13.4}	4,020 {1.3}	168,444 {54.0}	58,793 {18.9}	109,651 {35.1}
Mean age^{1,2} (SD)	69.0 (11.3)	64.1 (11.3)	70.5 (10.9)	71.7 (11.5)	69.4 (10.2)	71.9 (10.1)	73.3 (10.3)	69.5 (9.3)	71.1 (11.3)	71.5 (11.3)	66.6 (10.4)	70.2 (10.9)	71.5 (11.8)	69.5 (10.3)
Sex^{1,2}														
<i>Male</i>	167,178 (53.6)	39,356 (53.7)	127,822 (53.5)	61,318 (52.7)	66,504 (54.4)	15,408 (62.7)	9,588 (60.4)	5,820 (67.0)	22,243 (50.7)	20,958 (50.1)	2,285 (56.8)	89,171 (52.9)	30,772 (52.3)	58,399 (53.3)
<i>Female</i>	144,943 (46.4)	33,934 (46.3)	111,009 (46.5)	55,151 (47.4)	55,858 (45.7)	9,152 (37.3)	6,281 (39.6)	2,871 (33.0)	22,584 (49.3)	20,849 (49.9)	1,735 (43.2)	79,273 (47.1)	28,021 (47.7)	51,252 (46.7)
Smoking status^{1,2}														
<i>Ex</i>	150,024 (48.1)	31,449 (42.9)	118,575 (49.7)	56,489 (48.5)	42,086 (50.7)	12,868 (52.4)	8,181 (51.6)	4,687 (53.9)	21,707 (47.4)	19,707 (47.1)	2,000 (49.8)	84,000 (49.9)	28,601 (48.7)	55,399 (50.5)
<i>Current</i>	162,097 (51.9)	41,841 (57.1)	120,256 (50.4)	59,980 (51.5)	60,276 (49.3)	11,692 (47.6)	7,688 (48.5)	4,004 (46.1)	24,120 (52.6)	22,100 (52.9)	2,020 (50.3)	84,444 (50.1)	30,192 (51.4)	54,252 (49.5)
BMI²														
<i>Healthy weight</i>	93,213 (29.9)	20,619 (28.1)	72,594 (30.4)	36,352 (31.2)	36,242 (29.6)	6,529 (26.6)	4,329 (27.3)	2,200 (25.3)	15,018 (32.8)	13,760 (32.9)	1,258 (31.3)	51,047 (30.3)	18,263 (31.1)	32,784 (29.9)
<i>Underweight</i>	14,322 (4.5)	2,685 (3.7)	11,637 (4.9)	7,319 (6.3)	4,318 (3.5)	786 (3.2)	576 (3.6)	210 (2.4)	3,809 (8.3)	3,608 (8.6)	201 (5.0)	7,042 (4.2)	3,135 (5.3)	3,907 (3.6)
<i>Overweight</i>	93,076 (29.8)	20,493 (28.0)	72,583 (30.4)	32,498 (27.9)	40,085 (32.8)	7,979 (32.5)	4,948 (31.2)	3,031 (34.9)	11,656 (25.4)	10,418 (24.9)	1,238 (30.8)	52,948 (31.4)	17,132 (29.1)	35,816 (32.7)
<i>Obese</i>	84,831 (27.2)	17,935 (24.5)	66,896 (28.0)	31,396 (27.0)	35,500 (29.0)	7,812 (31.8)	5,003 (31.5)	2,809 (32.2)	11,105 (24.2)	10,096 (24.2)	1,009 (25.1)	47,979 (28.5)	16,297 (27.7)	31,682 (28.9)
<i>Missing</i>	26,679 (8.6)	11,558 (15.8)	15,121 (6.3)	8,904 (7.6)	6,217 (5.1)	1,454 (5.9)	1,013 (6.4)	441 (5.1)	4,239 (9.3)	3,925 (9.4)	314 (7.8)	9,428 (5.6)	3,966 (6.8)	5,462 (5.0)
SES (IMD)^{1,2}														
1	43,460 (13.9)	10,165 (13.8)	33,295 (13.9)	15,068 (12.9)	18,277 (14.9)	3,525 (14.4)	2,220 (14.0)	1,305 (15.0)	5,772 (12.6)	5,168 (12.4)	604 (15.0)	23,998 (14.3)	7,680 (13.1)	16,318 (14.9)
2	53,989 (17.3)	12,591 (17.2)	41,398 (17.3)	19,269 (16.5)	22,129 (18.1)	4,395 (17.9)	2,838 (17.9)	1,557 (17.9)	7,426 (16.2)	6,695 (16.0)	731 (18.2)	29,577 (17.6)	9,736 (16.6)	19,841 (18.1)
3	57,437 (18.4)	13,615 (18.6)	43,822 (18.4)	21,087 (18.1)	22,735 (18.6)	4,568 (18.6)	2,924 (18.4)	1,644 (18.9)	8,274 (18.1)	7,577 (18.1)	697 (17.3)	30,980 (18.4)	10,586 (18.0)	20,394 (18.6)
4	68,815 (22.1)	16,352 (22.3)	52,463 (22.0)	25,878 (22.2)	26,585 (21.7)	5,412 (22.0)	3,536 (22.3)	1,876 (21.6)	10,316 (22.5)	9,422 (22.5)	894 (22.2)	36,735 (21.8)	12,920 (22.0)	23,815 (21.7)
5	88,211 (28.3)	20,512 (28.0)	67,699 (28.4)	35,082 (30.1)	32,617 (26.7)	6,637 (27.0)	4,335 (27.3)	2,302 (26.5)	14,014 (30.6)	12,920 (30.9)	1,094 (27.2)	47,048 (27.9)	17,827 (30.3)	29,221 (26.7)
<i>Missing</i>	209 (0.1)	55 (0.1)	154 (0.1)	85 (0.1)	69 (0.1)	23 (0.1)	16 (0.1)	7 (0.1)	25 (0.1)	25 (0.1)	0 (0.0)	106 (0.1)	44 (0.1)	62 (0.1)
Depression^{1,2}	84,481 (27.1)	19,679 (26.9)	64,802 (27.1)	31,859 (27.4)	32,943 (26.9)	5,718 (23.3)	3,643 (23.0)	2,075 (23.9)	12,335 (26.9)	17,006 (28.9)	29,743 (27.1)	46,749 (27.8)	11,210 (26.8)	1,125 (28.0)

Anxiety^{1,2}	73,937 (23.7)	16,886 (23.0)	57,051 (23.9)	28,416 (24.4)	28,635 (23.4)	5,075 (20.7)	3,320 (20.9)	1,755 (20.2)	10,920 (23.8)	9,992 (23.9)	928 (23.1)	41,056 (24.4)	15,104 (25.7)	25,952 (23.7)
GORD^{1,2}	55,993 (17.0)	9,547 (13.0)	43,446 (18.2)	19,263 (16.5)	24,183 (19.8)	4,282 (17.4)	2,662 (16.8)	1,620 (18.6)	6,807 (14.9)	6,057 (14.5)	750 (18.7)	32,357 (19.2)	10,544 (17.9)	21,813 (19.9)
Lung cancer^{1,2}	4,750 (1.5)	457 (0.6)	4,293 (1.8)	2,091 (1.8)	2,202 (1.8)	222 (0.9)	170 (1.1)	52 (0.6)	824 (1.8)	721 (1.7)	103 (2.6)	3,247 (1.9)	1,200 (2.0)	2,047 (1.9)
Hypertension^{1,2}	151,111 (48.4)	27,887 (38.1)	123,224 (51.6)	61,591 (52.9)	61,633 (50.4)	14,629 (59.6)	9,541 (60.1)	5,088 (58.4)	22,375 (48.8)	20,669 (49.4)	1,706 (42.4)	86,220 (51.2)	31,381 (53.4)	54,839 (50.0)
Diabetes (type 2)^{1,2}	56,175 (18.0)	9,203 (12.6)	46,972 (19.7)	24,177 (20.8)	22,795 (18.6)	5,931 (24.2)	3,912 (24.7)	2,019 (23.2)	8,463 (18.5)	7,875 (18.8)	588 (14.6)	32,578 (19.3)	12,390 (21.1)	20,188 (18.4)
CV history^{1,2}	74,995 (24.0)	7,629 (10.4)	67,366 (28.2)	45,117 (38.7)	22,249 (18.2)	15,307 (62.3)	12,182 (76.8)	3,125 (36.0)	14,246 (31.1)	13,568 (32.5)	678 (16.9)	37,813 (22.5)	19,367 (32.9)	18,446 (16.8)
Asthma^{1,2}	85,711 (27.5)	16,880 (23.0)	68,831 (28.8)	33,504 (28.8)	35,327 (28.9)	6,139 (25.0)	4,005 (25.2)	2,134 (24.6)	14,112 (30.8)	12,875 (30.8)	1,237 (30.8)	48,580 (28.8)	16,624 (28.3)	31,956 (29.1)
Exacerbation group^{1,2}														
None	191,495 (61.4)	52,740 (72.0)	138,755 (58.1)	52,094 (44.7)	86,661 (70.8)	15,584 (63.5)	9,356 (59.0)	6,228 (71.7)	8,113 (17.7)	5,747 (13.8)	2,366 (58.9)	115,058 (68.3)	36,991 (62.9)	78,067 (71.2)
1 moderate, 0 severe	48,243 (15.5)	12,062 (16.5)	36,181 (15.2)	14,524 (12.5)	21,657 (17.7)	3,940 (16.0)	2,494 (15.7)	1,446 (16.6)	3,132 (6.8)	2,349 (5.6)	783 (19.5)	29,109 (17.3)	9,681 (16.5)	19,428 (17.7)
2 moderate, 0 severe	14,464 (4.6)	3,369 (4.6)	11,095 (4.7)	4,549 (3.9)	6,546 (5.4)	1,205 (4.9)	786 (5.0)	419 (4.8)	1,086 (2.4)	819 (2.0)	267 (6.6)	8,804 (5.2)	2,944 (5.0)	5,860 (5.3)
3+ moderate, 0 severe	7,540 (2.4)	1,449 (2.0)	6,091 (2.6)	2,651 (2.3)	3,440 (2.8)	640 (2.6)	436 (2.8)	204 (2.4)	707 (1.5)	541 (1.3)	166 (4.1)	4,744 (2.8)	1,674 (2.9)	3,070 (2.8)
Any moderate, 1 severe	44,980 (14.4)	3,337 (4.6)	41,645 (17.4)	38,061 (32.7)	3,584 (2.9)	2,898 (11.8)	2,546 (16.0)	352 (4.1)	29,239 (63.8)	28,868 (69.1)	371 (9.2)	9,508 (5.6)	6,647 (11.3)	2,861 (2.6)
Any moderate, 2+ severe	5,397 (1.7)	333 (0.5)	5,064 (2.1)	4,590 (3.9)	474 (0.4)	293 (1.2)	251 (1.6)	42 (0.5)	3,550 (7.8)	3,483 (8.3)	67 (1.7)	1,221 (0.7)	856 (1.5)	365 (0.3)
MRC dyspnoea score²														
1	38,518 (12.3)	4,524 (6.2)	33,994 (14.2)	12,551 (10.8)	21,443 (17.5)	3,243 (13.2)	1,928 (12.2)	1,315 (15.1)	3,504 (7.7)	2,933 (7.0)	571 (14.2)	27,247 (16.2)	7,690 (13.1)	19,557 (17.8)
2	82,877 (26.6)	7,094 (9.7)	75,783 (31.7)	31,691 (27.2)	44,092 (36.0)	7,724 (31.5)	4,764 (30.0)	2,960 (34.1)	10,345 (22.6)	9,115 (21.8)	1,230 (30.6)	57,714 (34.3)	17,812 (30.3)	39,902 (36.4)
3	57,717 (18.5)	3,535 (4.8)	54,182 (22.7)	27,602 (23.7)	26,580 (21.7)	5,829 (23.7)	3,872 (24.4)	1,957 (22.5)	10,397 (22.7)	9,568 (22.9)	829 (20.6)	37,956 (22.5)	14,162 (24.1)	23,794 (21.7)
4	30,395 (9.7)	1,569 (2.1)	28,826 (12.1)	17,813 (15.3)	11,013 (9.0)	3,076 (12.5)	2,216 (14.0)	860 (9.9)	8,190 (17.9)	7,717 (18.5)	473 (11.8)	17,560 (10.4)	7,880 (13.4)	9,680 (8.8)
5	6,593 (2.1)	323 (0.4)	6,270 (2.6)	4,579 (3.9)	1,691 (1.4)	549 (2.2)	448 (2.8)	101 (1.2)	2,520 (5.5)	2,420 (5.8)	100 (2.5)	3,201 (1.9)	1,711 (2.9)	1,490 (1.4)
Missing	96,021 (30.8)	56,245 (76.7)	39,776 (16.7)	22,233 (19.1)	17,543 (14.3)	4,139 (16.9)	2,641 (16.6)	1,498 (17.2)	10,871 (23.7)	10,054 (24.1)	817 (20.3)	24,766 (14.7)	9,538 (16.2)	15,228 (13.9)
GOLD²														
Mild	71,438 (22.9)	18,624 (25.4)	52,814 (22.1)	20,577 (17.7)	32,237 (26.4)	5,202 (21.2)	3,093 (19.5)	2,109 (24.3)	5,785 (12.6)	4,969 (11.9)	816 (20.3)	41,827 (24.8)	12,515 (21.3)	29,312 (26.7)
Moderate	127,674 (40.9)	31,706 (43.3)	95,968 (40.2)	41,810 (35.9)	54,158 (44.3)	10,413 (42.4)	6,458 (40.7)	3,955 (45.5)	13,636 (29.8)	11,991 (28.7)	1,645 (40.9)	71,919 (42.7)	23,361 (39.7)	48,558 (44.3)
Severe	49,287	9,384	39,903	22,607	17,296	3,896	2,730	1,166	11,035	10,315	720	24,972	9,562	15,410

	(15.8)	(12.8)	(16.7)	(19.4)	(14.1)	(15.9)	(17.2)	(13.4)	(24.1)	(24.7)	(17.9)	(14.8)	(16.3)	(14.1)
Very severe	10,497	1,462	9,035	6,431	2,604	673	488	185	4,327	4,146	181	4,035	1,797	2,238
	(3.4)	(2.0)	(3.8)	(5.5)	(2.1)	(2.7)	(3.1)	(2.1)	(9.4)	(9.9)	(4.5)	(2.4)	(3.1)	(2.0)
Missing	53,225	12,114	41,111	25,044	16,067	4,376	3,100	1,276	11,044	10,386	658	25,691	11,558	14,133
	(17.1)	(16.5)	(17.2)	(21.5)	(13.1)	(17.8)	(19.5)	(14.7)	(24.1)	(24.8)	(16.4)	(15.3)	(19.7)	(12.9)
Short-acting medication^{1,2}														
None	69,945	20,974	48,971	21,981	26,990	5,468	3,340	2,128	7,307	6,481	826	36,196	12,160	24,036
	(22.4)	(28.6)	(20.5)	(18.9)	(22.1)	(22.3)	(21.1)	(24.5)	(15.9)	(15.5)	(20.6)	(21.5)	(20.7)	(21.9)
SAMA	3,938	775	3,163	1,405	1,758	358	231	127	423	377	46	2,382	797	1,585
	(1.3)	(1.1)	(1.3)	(1.2)	(1.4)	(1.5)	(1.5)	(1.5)	(0.9)	(0.9)	(1.1)	(1.4)	(1.4)	(1.5)
SABA	220,044	49,024	171,020	84,673	86,347	17,197	11,279	5,918	34,424	31,531	2,893	119,399	41,863	77,536
	(70.5)	(66.9)	(71.6)	(72.7)	(70.6)	(70.0)	(71.1)	(68.1)	(75.1)	(75.4)	(72.0)	(70.9)	(71.2)	(70.7)
SABA-SAMA	18,194	2,517	15,677	8,410	7,267	1,537	1,019	518	1,537	3,418	255	10,467	3,973	6,494
	(5.8)	(3.4)	(6.6)	(7.2)	(5.9)	(6.3)	(6.4)	(6.0)	(6.3)	(8.2)	(6.3)	(6.2)	(6.8)	(5.9)
Medication^{1,2}														
None	136,369	42,167	94,202	44,146	50,056	9,972	6,343	3,629	15,696	14,268	1,428	68,534	23,535	44,999
	(43.7)	(57.5)	(39.4)	(37.9)	(40.9)	(40.6)	(40.0)	(41.8)	(34.3)	(34.1)	(35.5)	(40.7)	(40.0)	(41.0)
ICS	27,342	8,518	18,824	8,595	10,229	1,983	1,273	710	2,883	2,591	292	13,958	4,731	9,227
monotherapy	(8.8)	(11.6)	(7.9)	(7.4)	(8.4)	(8.1)	(8.0)	(8.2)	(6.3)	(6.2)	(7.3)	(8.3)	(8.1)	(8.4)
LAMA	38,307	9,288	29,019	12,981	16,038	3,321	2,078	1,243	4,083	3,636	447	21,615	7,267	14,348
monotherapy	(12.3)	(12.7)	(12.2)	(11.2)	(13.1)	(13.5)	(13.1)	(14.3)	(8.9)	(8.7)	(11.1)	(12.8)	(12.4)	(13.1)
LABA	6,988	1,367	5,621	2,457	3,164	661	398	263	756	701	55	4,204	1,358	2,846
monotherapy	(2.2)	(1.9)	(2.4)	(2.1)	(2.6)	(2.7)	(2.5)	(3.0)	(1.7)	(1.7)	(1.4)	(2.5)	(2.3)	(2.6)
LABA-LAMA	12,330	2,629	9,701	4,677	5,024	1,095	700	395	1,715	1,557	158	6,891	2,420	4,471
	(4.0)	(3.6)	(4.1)	(4.0)	(4.1)	(4.5)	(4.4)	(4.5)	(3.7)	(3.7)	(3.9)	(4.1)	(4.1)	(4.1)
ICS-LABA	4,906	924	3,982	1,889	2,093	373	248	125	708	651	57	2,901	990	1,911
	(1.6)	(1.3)	(1.7)	(1.6)	(1.7)	(1.5)	(1.6)	(1.4)	(1.5)	(1.6)	(1.4)	(1.7)	(1.7)	(1.7)
ICS-LAMA	6,019	1,021	4,998	2,372	2,626	536	353	183	821	737	84	3,641	1,282	2,359
	(1.9)	(1.4)	(2.1)	(2.0)	(2.2)	(2.2)	(2.2)	(2.1)	(1.8)	(1.8)	(2.1)	(2.2)	(2.2)	(2.2)
Triple therapy	79,860	7,376	72,484	39,352	33,132	6,619	4,476	2,143	19,165	17,666	1,499	46,700	17,210	29,490
	(25.6)	(10.1)	(30.4)	(33.8)	(27.1)	(27.0)	(28.1)	(24.7)	(41.8)	(42.3)	(37.3)	(27.7)	(29.3)	(26.9)

{%} indicates percentage of the study group from the total sample size (N=312,121); (%) indicates percentage of people with the characteristic out of people the study group (N at top of column)

ABBREVIATIONS:

BMI = body mass index | Socioeconomic IMD = index of multiple deprivation | GORD = gastro-oesophageal reflux disease | CV = cardiovascular | MRC = Medical Research Council | GOLD = Global Initiative for Obstructive Lung Disease | SABA = short-acting beta agonist | SAMA = short-acting muscarinic antagonist | ICS = inhaled corticosteroids | LABA = long-acting beta agonist | LAMA = long-acting muscarinic antagonist

Covariate definitions: ¹ Adjusted for in main statistical models (reported in main manuscript) | ² Adjusted for in sensitivity analyses (reported in supplementary material)

COVARIATE DEFINITIONS (more granular detail available in the supplementary material):

Age, sex, and IMD = provided in CPRD Aurum data or linked data

BMI: most recent record within the last five years, underweight: <18.5kg.m⁻²; healthy weight: 18.5 to 24.9kg.m⁻²; overweight: 25.0 to 29.9kg.m⁻²; obese: >30kg.m⁻²

Covariates defined by any lifetime record prior to start of follow-up: smoking history, depression, anxiety, GORD, lung cancer, hypertension, diabetes, asthma, cardiovascular history

Cardiovascular history: any lifetime record of acute coronary syndrome, heart failure, arrhythmia, or ischaemic stroke; either in primary care or secondary care prior to start of follow-up

COPD exacerbation groups defined in the year preceding follow-up. Severity determined by care level: moderate = primary care record only | severe = secondary care record

MRC dyspnoea score: most recent value between two years before and three months after start of follow-up

GOLD group: determined by spirometry values; the most recent value between two years before and three months after start of follow-up

Medications determined in the year prior to the start of follow-up

Table E2: Risk of study outcomes amongst people with COPD who were hospitalised (study exposure group) compared with people who were not hospitalised (study control group) using different models to assess degree of confounding of indication through sensitivity models

Outcome	Exposure and control groups	N	N (%)-outcome	Models					
				Crude	Fully adjusted ¹	Doubly robust propensity score adjusted; all variables ¹	Fully adjusted ¹ without BMI, GOLD & MRC (Primary model in manuscript)	Doubly robust propensity score adjusted ¹ ; without BMI, GOLD & MRC	Fully adjusted ¹ without BMI, GOLD & MRC; excluding those with a hospitalisation in the year preceding follow-up
MACE	<i>Hospitalised</i>	238,811	11,811 (5.0)	14.97	12.23	12.08	7.89	7.88	10.15
	<i>Not hospitalised</i>	73,290	248 (0.3)	(13.20, 16.98)	(8.54, 17.52)	(8.43, 17.30)	(6.95, 8.96)	(6.93, 8.95)	(8.46, 12.17)
Mortality: all-cause	<i>Hospitalised</i>	238,811	22,183 (9.3)	3.23	1.70	1.66	1.80	1.71	2.39
	<i>Not hospitalised</i>	73,290	2,181 (3.0)	(3.09, 3.37)	(1.54, 1.87)	(1.51, 1.83)	(1.72, 1.89)	(1.64, 1.79)	(2.25, 2.55)
Mortality: COPD	<i>Hospitalised</i>	238,811	5,388 (2.3)	2.77	0.83	0.80	1.06	0.94	1.10
	<i>Not hospitalised</i>	73,290	601 (0.8)	(2.55, 3.01)	(0.70, 0.99)	(0.67, 0.95)	(0.97, 1.16)	(0.86, 1.02)	(0.97, 1.25)
Mortality: Cardiovascular	<i>Hospitalised</i>	238,811	4,349 (1.8)	1.68	0.71	0.70	0.80	0.77	0.89
	<i>Not hospitalised</i>	73,290	799 (1.1)	(1.56, 1.81)	(0.61, 0.83)	(0.60, 0.82)	(0.74, 0.87)	(0.71, 0.84)	(0.79, 0.99)
Mortality: Non-cardiorespiratory	<i>Hospitalised</i>	238,811	12,446 (5.2)	5.00	4.10	4.01	3.52	3.38	5.75
	<i>Not hospitalised</i>	73,290	781 (1.07)	(4.65, 5.37)	(3.43, 4.91)	(3.35, 4.80)	(3.27, 3.79)	(3.14, 3.64)	(5.15, 6.42)

¹ **Fully adjusted:** age, sex, smoking status, BMI category (underweight: <18.5kg.m⁻²; healthy weight: 18.5 to 24.9kg.m⁻²; overweight: 25.0 to 29.9kg.m⁻²; obese: >30kg.m⁻²), IMD quintile, COPD exacerbation group (frequency and severity-defined), MRC dyspnoea scale, GOLD airflow obstruction group, short-acting bronchodilators (SABA, SAMA, or SABA-SAMA), COPD medications (ICS, LABA, LAMA, and all combinations thereof), asthma, depression, anxiety, GORD, lung cancer, hypertension, diabetes, and cardiovascular history (lifetime record in either primary or secondary care of acute coronary syndrome, heart failure, arrhythmia, or ischaemic stroke)

ABBREVIATIONS:

COPD = chronic obstructive pulmonary disease | BMI = body mass index | Socioeconomic IMD = index of multiple deprivation | GORD = gastro-oesophageal reflux disease | CV = cardiovascular | MRC = Medical Research Council | GOLD = Global Initiative for Obstructive Lung Disease | SABA = short-acting beta agonist | SAMA = short-acting muscarinic antagonist | ICS = inhaled corticosteroids | LABA = long-acting beta agonist | LAMA = long-acting muscarinic antagonist
Bonferroni corrected at P < 0.0125

Table E3: Risk of MACE* amongst people with COPD who were had an elective or emergency hospitalisation (study exposure groups) compared with people who were not hospitalised (study control group)

		N	N (%) -outcome	Primary model¹	Crude	Fully adjusted²	Without hospitalisation³
Any hospitalisation cause	<i>No hospitalisation</i>	73,290	248 (0.3)				
	<i>Elective hospitalisation</i>	122,362	4,005 (3.3)	7.04 (6.19, 8.07)	9.80 (8.62, 11.15)	10.95 (7.64, 15.70)	8.94 (9.69, 14.01)
	<i>Emergency hospitalisation</i>	116,469	7,806 (6.7)	8.85 (7.78, 10.06)	20.52 (18.09, 23.29)	13.85 (9.67, 19.86)	11.65 (9.69, 14.01)
Cardiovascular hospitalisation	<i>No hospitalisation</i>	73,290	248 (0.3)				
	<i>Elective hospitalisation</i>	8,691	824 (9.5)	17.90 (15.45, 20.74)	29.26 (25.39, 33.73)	29.32 (20.25, 42.46)	24.53 (19.91, 30.23)
	<i>Emergency hospitalisation</i>	15,869	2,493 (15.7)	19.83 (16.76, 22.40)	50.75 (44.54, 57.83)	31.70 (21.90, 45.89)	26.63 (21.66, 32.75)
Respiratory hospitalisation	<i>No hospitalisation</i>	73,290	248 (0.3)				
	<i>Elective hospitalisation</i>	4,020	123 (3.1)	6.61 (5.31, 8.22)	9.15 (7.37, 11.36)	9.47 (6.19, 14.48)	8.02 (5.86, 11.52)
	<i>Emergency hospitalisation</i>	41,807	2,332 (5.6)	7.22 (6.19, 8.43)	16.96 (14.88, 19.33)	11.19 (7.66, 16.33)	9.19 (7.33, 11.52)
Non-cardiorespiratory hospitalisation	<i>No hospitalisation</i>	73,290	248 (0.3)				
	<i>Elective hospitalisation</i>	109,651	3,058 (2.8)	6.17 (5.42, 7.03)	8.34 (7.33, 9.49)	9.63 (6.72, 13.82)	7.59 (6.30, 9.15)
	<i>Emergency hospitalisation</i>	58,793	2,981 (5.1)	7.44 (6.52, 8.49)	15.39 (13.52, 17.52)	11.35 (7.91, 16.31)	9.50 (7.86, 11.48)

MACE: Major adverse cardiovascular event = acute coronary syndrome, arrhythmia, ischaemic stroke, or heart failure (defined by ICD10 codes)

¹ **This model is presented in the manuscript; Adjusted for:** age, sex, smoking status, IMD quintile, COPD exacerbation group (frequency and severity-defined), short-acting bronchodilators (SABA, SAMA, or SABA-SAMA), COPD medications (ICS, LABA, LAMA, and all combinations thereof), asthma, depression, anxiety, GORD, lung cancer, hypertension, diabetes, and cardiovascular history (lifetime record in either primary or secondary care of acute coronary syndrome, heart failure, arrhythmia, or ischaemic stroke)

² **Adjusted for:** all covariates of primary model with the addition of MRC dyspnoea scale, GOLD airflow obstruction group, and BMI category (underweight: <18.5kg.m⁻²; healthy weight: 18.5 to 24.9kg.m⁻²; overweight: 25.0 to 29.9kg.m⁻²; obese: >30kg.m⁻²)

³ **Adjusted for: all covariates for primary model; excludes all people who had had a record of hospitalisation in the year preceding follow-up**

Bonferroni corrected at P<0.00625

Table E4: Risk of all-cause mortality amongst people with COPD who were had an elective or emergency hospitalisation (study exposure groups) compared with people who were not hospitalised (study control group)

		N	N (%) -outcome	Primary model¹	Crude	Fully adjusted²	Without hospitalisation³
Any hospitalisation cause	<i>No hospitalisation</i>	73,290	2,181 (3.0)				
	<i>Elective hospitalisation</i>	122,362	6,511 (5.3)	1.32 (1.25, 1.38)	1.80 (1.72, 1.89)	1.29 (1.17, 1.42)	1.79 (1.67, 1.91)
	<i>Emergency hospitalisation</i>	116,469	15,672 (13.5)	2.49 (2.37, 2.61)	4.81 (4.60, 5.03)	2.34 (2.12, 2.58)	3.45 (1.67, 1.91)
Cardiovascular hospitalisation	<i>No hospitalisation</i>	73,290	2,181 (3.0)				
	<i>Elective hospitalisation</i>	8,691	385 (4.4)	1.00 (0.89, 1.12)	1.50 (1.34, 1.67)	1.06 (0.91, 1.25)	1.17 (1.00, 1.37)
	<i>Emergency hospitalisation</i>	15,869	1,980 (12.5)	1.62 (1.50, 1.76)	4.43 (4.17, 4.70)	1.84 (1.61, 2.10)	2.24 (1.99, 2.51)
Respiratory hospitalisation	<i>No hospitalisation</i>	73,290	2,181 (3.0)				
	<i>Elective hospitalisation</i>	4,020	320 (8.0)	1.99 (1.77, 2.24)	2.73 (2.43, 3.07)	1.95 (1.65, 2.30)	2.77 (2.36, 3.25)
	<i>Emergency hospitalisation</i>	41,807	6,141 (14.7)	1.99 (1.85, 2.14)	5.27 (5.02, 5.53)	2.03 (1.80, 2.30)	3.15 (2.85, 3.49)
Non-cardiorespiratory hospitalisation	<i>No hospitalisation</i>	73,290	2,181 (3.0)				
	<i>Elective hospitalisation</i>	109,651	5,806 (5.3)	1.31 (1.25, 1.38)	1.79 (1.71, 1.88)	1.30 (1.17, 1.43)	1.78 (1.66, 1.91)
	<i>Emergency hospitalisation</i>	58,793	7,551 (12.8)	2.60 (2.47, 2.73)	4.58 (4.37, 4.81)	2.51 (2.27, 2.78)	3.56 (3.31, 3.82)

¹ **This model is presented in the manuscript; Adjusted for:** age, sex, smoking status, IMD quintile, COPD exacerbation group (frequency and severity-defined), short-acting bronchodilators (SABA, SAMA, or SABA-SAMA), COPD medications (ICS, LABA, LAMA, and all combinations thereof), asthma, depression, anxiety, GORD, lung cancer, hypertension, diabetes, and cardiovascular history (lifetime record in either primary or secondary care of acute coronary syndrome, heart failure, arrhythmia, or ischaemic stroke)

² **Adjusted for:** all covariates of primary model with the addition of MRC dyspnoea scale, GOLD airflow obstruction group, and BMI category (underweight: <18.5kg.m⁻²; healthy weight: 18.5 to 24.9kg.m⁻²; overweight: 25.0 to 29.9kg.m⁻²; obese: >30kg.m⁻²)

³ **Adjusted for:** all covariates for primary model; excludes all people who had had a record of hospitalisation in the year preceding follow-up
Bonferroni corrected at P < 0.00625

Table E5: Risk of cardiovascular-specific mortality amongst people with COPD who were had an elective or emergency hospitalisation (study exposure groups) compared with people who were not hospitalised (study control group)

		N	N (%) -outcome	Primary model¹	Crude	Fully adjusted²	Without hospitalisation³
Any hospitalisation cause	<i>No hospitalisation</i>	73,290	799 (1.1)				
	<i>Elective hospitalisation</i>	122,362	1,084 (0.9)	0.56 (0.51, 0.61)	0.81 (0.74, 0.89)	0.52 (0.44, 0.61)	0.61 (0.54, 0.69)
	<i>Emergency hospitalisation</i>	116,469	3,265 (2.8)	1.08 (0.99, 1.18)	2.60 (2.40, 2.81)	0.96 (0.82, 1.13)	1.26 (1.12, 1.41)
Cardiovascular hospitalisation	<i>No hospitalisation</i>	73,290	799 (1.09)				
	<i>Elective hospitalisation</i>	8,691	170 (2.0)	1.07 (0.90, 1.27)	1.80 (1.53, 2.13)	1.04 (0.82, 1.33)	1.15 (0.90, 1.46)
	<i>Emergency hospitalisation</i>	15,869	876 (5.5)	1.64 (1.45, 1.85)	5.20 (4.72, 5.72)	1.63 (1.32, 2.01)	2.01 (1.69, 2.39)
Respiratory hospitalisation	<i>No hospitalisation</i>	73,290	799 (1.1)				
	<i>Elective hospitalisation</i>	4,020	46 (1.1)	0.79 (0.59, 1.07)	1.05 (0.78, 1.41)	0.82 (0.56, 1.20)	0.99 (0.67, 1.47)
	<i>Emergency hospitalisation</i>	41,807	1,000 (2.4)	0.78 (0.67, 0.89)	2.21 (2.01, 2.43)	0.85 (0.67, 1.08)	0.96 (0.77, 1.21)
Non-cardiorespiratory hospitalisation	<i>No hospitalisation</i>	73,290	799 (1.1)				
	<i>Elective hospitalisation</i>	109,651	868 (0.8)	0.50 (0.45, 0.55)	0.72 (0.66, 0.80)	0.48 (0.40, 0.57)	0.54 (0.47, 0.61)
	<i>Emergency hospitalisation</i>	58,793	1,389 (2.4)	0.97 (89, 1.07)	2.18 (2.00, 2.38)	0.88 (0.75, 1.05)	1.07 (0.94, 1.22)

¹ **This model is presented in the manuscript; Adjusted for:** age, sex, smoking status, IMD quintile, COPD exacerbation group (frequency and severity-defined), short-acting bronchodilators (SABA, SAMA, or SABA-SAMA), COPD medications (ICS, LABA, LAMA, and all combinations thereof), asthma, depression, anxiety, GORD, lung cancer, hypertension, diabetes, and cardiovascular history (lifetime record in either primary or secondary care of acute coronary syndrome, heart failure, arrhythmia, or ischaemic stroke)

² **Adjusted for:** all covariates of primary model with the addition of MRC dyspnoea scale, GOLD airflow obstruction group, and BMI category (underweight: <18.5kg.m⁻²; healthy weight: 18.5 to 24.9kg.m⁻²; overweight: 25.0 to 29.9kg.m⁻²; obese: >30kg.m⁻²)

³ **Adjusted for: all covariates for primary model; excludes all people who had had a record of hospitalisation in the year preceding follow-up**
Bonferroni corrected at P < 0.00625

Table E6: Risk of COPD-specific mortality amongst people with COPD who were had an elective or emergency hospitalisation (study exposure groups) compared with people who were not hospitalised (study control group)

		N	N (%) -outcome	Primary model¹	Crude	Fully adjusted²	Without hospitalisation³
Any hospitalisation cause	<i>No hospitalisation</i>	73,290	601 (0.8)				
	<i>Elective hospitalisation</i>	122,362	843 (0.7)	0.58 (0.53, 0.65)	0.84 (0.76, 0.93)	0.54 (0.45, 0.65)	0.64 (0.55, 0.74)
	<i>Emergency hospitalisation</i>	116,469	4,545 (3.9)	1.53 (1.39, 1.67)	4.84 (4.44, 5.27)	1.13 (0.95, 1.35)	1.79 (1.56, 2.05)
Cardiovascular hospitalisation	<i>No hospitalisation</i>	73,290	601 (0.8)				
	<i>Elective hospitalisation</i>	8,691	391 (2.5)	0.53 (0.40, 0.70)	0.80 (0.61, 1.05)	0.57 (0.40, 0.82)	0.51 (0.34, 0.76)
	<i>Emergency hospitalisation</i>	15,869	57 (0.7)	0.94 (0.80, 1.11)	3.03 (2.67, 3.44)	0.99 (0.76, 1.30)	1.08 (0.84, 1.39)
Respiratory hospitalisation	<i>No hospitalisation</i>	73,290	601 (0.8)				
	<i>Elective hospitalisation</i>	4,020	58 (1.4)	1.11 (0.85, 1.46)	1.76 (1.35, 2.31)	0.95 (0.67, 1.36)	1.27 (0.85, 1.89)
	<i>Emergency hospitalisation</i>	41,807	2,756 (6.6)	2.01 (1.77, 2.27)	8.29 (7.59, 9.05)	1.62 (1.32, 2.00)	3.25 (2.71, 3.91)
Non-cardiorespiratory hospitalisation	<i>No hospitalisation</i>	73,290	601 (0.8)				
	<i>Elective hospitalisation</i>	109,651	728 (0.7)	0.53 (0.45, 0.59)	0.81 (0.73, 0.90)	0.52 (0.43, 0.62)	0.56 (0.48, 0.66)
	<i>Emergency hospitalisation</i>	58,793	1,398 (2.4)	1.17 (1.05, 1.29)	2.92 (2.66, 3.22)	0.95 (0.79, 1.14)	1.34 (1.15, 1.56)

¹ **This model is presented in the manuscript; Adjusted for:** age, sex, smoking status, IMD quintile, COPD exacerbation group (frequency and severity-defined), short-acting bronchodilators (SABA, SAMA, or SABA-SAMA), COPD medications (ICS, LABA, LAMA, and all combinations thereof), asthma, depression, anxiety, GORD, lung cancer, hypertension, diabetes, and cardiovascular history (lifetime record in either primary or secondary care of acute coronary syndrome, heart failure, arrhythmia, or ischaemic stroke)

² **Adjusted for:** all covariates of primary model with the addition of MRC dyspnoea scale, GOLD airflow obstruction group, and BMI category (underweight: <18.5kg.m⁻²; healthy weight: 18.5 to 24.9kg.m⁻²; overweight: 25.0 to 29.9kg.m⁻²; obese: >30kg.m⁻²)

³ **Adjusted for:** all covariates for primary model; excludes all people who had had a record of hospitalisation in the year preceding follow-up Bonferroni corrected at P < 0.00625

Table E7: Descriptive statistics and rates of major adverse cardiovascular events (MACE) in people with COPD by hospitalisation group (not hospitalised; and hospitalised, stratified by hospitalisation type [emergency or elective] and cause [respiratory, cardiovascular, and non-cardiorespiratory])

	N	Median (IQR) follow up time (years)	Absolute events per year N (%)*	Person- years	Incidence rate (95%CI) (events per 1000 person- years)
WHOLE COHORT	312,121	1 (1 to 1)	12,059 (3.9)	304,888.9	39.6 (38.9, 40.3)
Not hospitalised	73,290	1 (1 to 1)	248 (0.3)	73,183.3	3.4 (3.0, 3.8)
Hospitalisation (any)	238,831	1 (1 to 1)	11,881 (5.0)	213,705.7	51.0 (50.1, 51.9)
<i>Hospitalisation (elective)</i>	122,362	1 (1 to 1)	4,005 (3.3)	120190.0	33.3 (32.3, 34.4)
<i>Hospitalisation (emergency)</i>	116,469	1 (1 to 1)	7,806 (6.7)	111,515.6	70.0 (68.4, 71.6)
Cardiovascular hospitalisation (any)	24,560	1 (1 to 1)	3,317 (13.5)	22,328.0	148.6 (143.6, 153.7)
<i>Cardiovascular hospitalisation (elective)</i>	8,691	1 (1 to 1)	824 (9.5)	8,185.1	100.7 (94.0, 107.8)
<i>Cardiovascular hospitalisation (emergency)</i>	15,869	1 (1 to 1)	2,493 (15.7)	14,142.9	176.3 (169.5, 183.3)
Respiratory hospitalisation (any)	45,827	1 (1 to 1)	2,455 (5.4)	44,330.0	55.4 (53.2, 57.6)
<i>Respiratory hospitalisation (elective)</i>	4,020	1 (1 to 1)	123 (3.1)	3,957.3	31.1 (26.0, 37.1)
<i>Respiratory hospitalisation (emergency)</i>	41,807	1 (1 to 1)	2,332 (5.6)	40,372.7	57.8 (55.5, 60.1)
Non-cardiorespiratory hospitalisation (any)	168,444	1 (1 to 1)	6,039 (3.6)	165,047.7	36.6 (35.7, 37.5)
<i>Non-cardiorespiratory hospitalisation (elective)</i>	109,651	1 (1 to 1)	3,058 (2.8)	108,047.7	28.3 (27.3, 29.3)
<i>Non-cardiorespiratory hospitalisation (emergency)</i>	58,793	1 (1 to 1)	2,981 (5.1)	57,000.0	52.3 (50.5, 54.2)

* The denominator for the absolute event percentages is the study group (N-column)

Table E8: Descriptive statistics and rates of all-cause mortality in people with COPD by hospitalisation group (not hospitalised; and hospitalised, stratified by hospitalisation type [emergency or elective] and cause [respiratory, cardiovascular, and non-cardiorespiratory])

	N	Median (IQR) follow up time (years)	Absolute events per year N (%)*	Person-time (person-years)	Incidence rate (95%CI) (events per 1000 person-years)
WHOLE COHORT	312,121	1 (1 to 1)	24,364 (7.8)	298,233.9	81.7 (80.7, 82.7)
Not hospitalised	73,290	1 (1 to 1)	2,181 (3.0)	72,087.8	30.3 (29.0, 31.6)
Hospitalisation (any)	238,831	1 (1 to 1)	22,183 (9.3)	226,146.1	98.1 (96.8, 99.4)
<i>Hospitalisation (elective)</i>	122,362	1 (1 to 1)	6,511 (5.3)	119,187.9	54.6 (53.3, 56.0)
<i>Hospitalisation (emergency)</i>	116,469	1 (1 to 1)	15,672 (13.5)	106,958.2	146.5 (144.2, 148.8)
Cardiovascular hospitalisation (any)	24,560	1 (1 to 1)	2,365 (9.6)	23,183.8	102.0 (98.0, 106.2)
<i>Cardiovascular hospitalisation (elective)</i>	8,691	1 (1 to 1)	385 (4.4)	8,497.9	45.3 (41.0, 50.1)
<i>Cardiovascular hospitalisation (emergency)</i>	15,869	1 (1 to 1)	1,980 (12.5)	14,686.0	134.8 (129.0, 140.9)
Respiratory hospitalisation (any)	45,827	1 (1 to 1)	6,461 (14.1)	41,997.0	153.8 (150.1, 157.6)
<i>Respiratory hospitalisation (elective)</i>	4,020	1 (1 to 1)	320 (8.0)	3,852.9	83.1 (74.4, 92.7)
<i>Respiratory hospitalisation (emergency)</i>	41,807	1 (1 to 1)	6,141 (14.7)	38,144.2	161.0 (157.0, 165.1)
Non-cardiorespiratory hospitalisation (any)	168,444	1 (1 to 1)	13,357 (7.9)	160,965.3	83.0 (81.6, 84.4)
<i>Non-cardiorespiratory hospitalisation (elective)</i>	109,651	1 (1 to 1)	5,806 (5.3)	106,837.1	54.3 (53.0, 55.8)
<i>Non-cardiorespiratory hospitalisation (emergency)</i>	58,793	1 (1 to 1)	7,551 (12.8)	54,128.1	139.5 (136.4, 142.7)

* The denominator for the absolute event percentages is the study group (N-column)

Table E9: Descriptive statistics and rates of COPD-specific mortality in people with COPD by hospitalisation group (not hospitalised; and hospitalised, stratified by hospitalisation type [emergency or elective] and cause [respiratory, cardiovascular, and non-cardiorespiratory])

	N	Median (IQR) follow up time (years)	Absolute events per year amongst those who died (n = 24,364) N (%)*	Person-time (person-years)	Incidence rate (95%CI) (events per 1000 person-years)**
WHOLE COHORT	312,121	1 (1 to 1)	5,989 (24.6)	308,772.7	19.4 (18.9, 19.9)
Not hospitalised	73,290	1 (1 to 1)	601 (2.5)	72,951.6	8.2 (7.6, 8.9)
Hospitalisation (any)	238,831	1 (1 to 1)	5,388 (22.1)	235,821.1	22.8 (22.2, 23.5)
<i>Hospitalisation (elective)</i>	122,362	1 (1 to 1)	843 (3.5)	121,983.9	6.9 (6.5, 7.4)
<i>Hospitalisation (emergency)</i>	116,469	1 (1 to 1)	4,545 (18.7)	113,837.2	39.9 (38.8, 41.1)
Cardiovascular hospitalisation (any)	24,560	1 (1 to 1)	448 (1.8)	24,319.4	18.4 (16.8, 20.2)
<i>Cardiovascular hospitalisation (elective)</i>	8,691	1 (1 to 1)	57 (0.2)	8,664.4	6.6 (5.1, 8.5)
<i>Cardiovascular hospitalisation (emergency)</i>	15,869	1 (1 to 1)	391 (1.6)	15,654.9	25.0 (22.6, 27.6)
Respiratory hospitalisation (any)	45,827	1 (1 to 1)	2,814 (11.5)	44,165.8	63.7 (61.4, 66.1)
<i>Respiratory hospitalisation (elective)</i>	4,020	1 (1 to 1)	58 (0.2)	3,991.2	14.5 (11.2, 18.8)
<i>Respiratory hospitalisation (emergency)</i>	41,807	1 (1 to 1)	2,756 (11.3)	40,174.6	68.6 (66.1, 71.2)
Non-cardiorespiratory hospitalisation (any)	168,444	1 (1 to 1)	2,126 (8.7)	167,335.9	12.7 (12.2, 13.3)
<i>Non-cardiorespiratory hospitalisation (elective)</i>	109,651	1 (1 to 1)	728 (3.0)	109,328.3	6.7 (6.2, 7.2)
<i>Non-cardiorespiratory hospitalisation (emergency)</i>	58,793	1 (1 to 1)	1,398 (5.7)	58,007.7	24.1 (22.9, 25.4)

*The denominator for the absolute event percentages is the people who died of any cause (N = 24,364) across all study groups

** Rates are calculated relative to the whole cohort (to align with the Cox models)

Table E10: Descriptive statistics and rates of cardiovascular disease-specific mortality in people with COPD by hospitalisation group (not hospitalised; and hospitalised, stratified by hospitalisation type [emergency or elective] and cause [respiratory, cardiovascular, and non-cardiorespiratory])

	N	Median (IQR) follow up time (years)	Absolute events per year amongst those who died (n = 24,364) N (%)*	Person-time (person-years)	Incidence rate (95%CI) (events per 1000 person-years)**
WHOLE COHORT	312,121	1 (1 to 1)	5,148 (21.1)	309,215.9	16.6 (16.2, 17.1)
Not hospitalised	73,290	1 (1 to 1)	799 (3.3)	72,859.5	11.0 (10.2, 11.8)
Hospitalisation (any)	238,831	1 (1 to 1)	4,349 (17.9)	236,356.4	18.4 (17.9, 19.0)
<i>Hospitalisation (elective)</i>	122,362	1 (1 to 1)	1,084 (4.4)	121,836.8	8.9 (8.4, 9.4)
<i>Hospitalisation (emergency)</i>	116,469	1 (1 to 1)	3,265 (13.4)	114,519.6	28.5 (27.5, 29.5)
Cardiovascular hospitalisation (any)	24,560	1 (1 to 1)	1,046 (4.3)	23,910.3	43.7 (41.2, 46.5)
<i>Cardiovascular hospitalisation (elective)</i>	8,691	1 (1 to 1)	170 (0.7)	8,598.1	19.8 (17.0, 23.0)
<i>Cardiovascular hospitalisation (emergency)</i>	15,869	1 (1 to 1)	876 (3.6)	15,312.2	57.2 (53.5, 61.1)
Respiratory hospitalisation (any)	45,827	1 (1 to 1)	1,046 (4.3)	45,214.7	23.1 (21.8, 24.6)
<i>Respiratory hospitalisation (elective)</i>	4,020	1 (1 to 1)	46 (0.2)	3,998.3	11.5 (8.6, 15.4)
<i>Respiratory hospitalisation (emergency)</i>	41,807	1 (1 to 1)	1,000 (4.1)	41,216.5	24.3 (22.8, 25.8)
Non-cardiorespiratory hospitalisation (any)	168,444	1 (1 to 1)	2,257 (9.3)	167,231.4	13.5 (13.0, 14.1)
<i>Non-cardiorespiratory hospitalisation (elective)</i>	109,651	1 (1 to 1)	868 (3.6)	109,240.5	7.9 (7.4, 8.5)
<i>Non-cardiorespiratory hospitalisation (emergency)</i>	58,793	1 (1 to 1)	1,389 (5.7)	57,990.9	24.0 (22.7, 25.2)

*The denominator for the absolute event percentages is the people who died of any cause (N = 24,364) across all study groups

** Rates are calculated relative to the whole cohort (to align with the Cox models)

Table E11: Cause-specific mortality across people with COPD, stratified by hospitalisation cause (any, cardiovascular, respiratory, or non-cardiorespiratory), and sub-stratified by hospitalisation type (all, elective, or emergency), where number (percentages) by ICD10 chapter represent the proportion of people who died in each stratum and/or sub-stratum

ICD10 chapter	Whole population N (%)	No hospitalisation N (%)	Hospitalisations N (%)			Cardiovascular hospitalisations N (%)			Respiratory hospitalisations N (%)			Non-cardiorespiratory hospitalisations N (%)		
			All	Emergency	Elective	All	Emergency	Elective	All	Emergency	Elective	All	Emergency	Elective
Whole cohort	312,121 {100}	73,290 {23.5}	238,831 {76.5}	116,469 {37.3}	122,362 {39.2}	24,560 {7.9}	15,869 {5.1}	8,691 {2.9}	45,827 {14.7}	41,807 {13.4}	4,020 {1.3}	168,444 {54.0}	58,793 {18.9}	109,651 {35.1}
Any death	24,364 [7.8]	2,181 [3.0]	22,183 [9.3]	15,672 [13.5]	6,511 [5.3]	2,365 [9.6]	1,980 [12.5]	385 [4.4]	6,461 [14.1]	6,141 [14.7]	320 [8.0]	13,357 [7.9]	7,551 [12.8]	5,806 [5.3]
Cause specific death¹														
<i>I: Infectious and parasitic diseases</i>	191 (0.8)	7 (0.3)	184 (0.8)	132 (0.8)	52 (0.8)	25 (1.1)	22 (1.1)	3 (0.8)	51 (0.8)	45 (0.7)	6 (1.9)	108 (0.8)	65 (0.9)	43 (0.7)
<i>II: Neoplasms</i>	8,582 (35.3)	373 (17.3)	8,209 (37.1)	4,578 (29.3)	3,631 (55.9)	394 (16.7)	327 (16.6)	67 (17.5)	1,362 (21.1)	1,205 (19.7)	157 (49.1)	6,453 (48.4)	3,046 (40.4)	3,407 (58.8)
<i>III: Blood, blood-forming organs, immune mechanisms</i>	29 (0.1)	1 (0.1)	28 (0.1)	16 (0.1)	12 (0.2)	2 (0.1)	2 (0.1)	0 (0.0)	6 (0.1)	6 (0.1)	0 (0.0)	20 (0.2)	8 (0.1)	12 (0.2)
<i>IV: Endocrine, nutritional, metabolic</i>	179 (0.7)	14 (0.7)	165 (0.8)	125 (0.8)	40 (0.6)	28 (1.2)	24 (1.2)	4 (1.0)	39 (0.6)	38 (0.6)	1 (0.3)	98 (0.7)	63 (0.8)	35 (0.6)
<i>V: Mental and behavioural</i>	415 (1.7)	27 (1.3)	388 (1.8)	357 (2.3)	31 (0.5)	33 (1.4)	32 (1.6)	1 (0.3)	105 (1.6)	103 (1.7)	2 (0.6)	250 (1.9)	222 (3.0)	28 (0.5)
<i>VI: Nervous system</i>	323 (1.3)	25 (1.2)	298 (1.4)	247 (1.6)	51 (0.8)	18 (0.8)	17 (0.9)	1 (0.3)	87 (1.4)	83 (1.4)	4 (1.3)	193 (1.5)	147 (2.0)	46 (0.8)
<i>VII: Eye and adnexa</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<i>VIII: Ear and mastoid process</i>	1 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

<i>IX: Circulatory system</i>	5,149 (21.2)	799 (37.0)	4,350 (19.7)	3,266 (20.9)	1,084 (16.7)	1,047 (44.5)	877 (44.5)	170 (44.4)	1,046 (16.2)	1,000 (16.3)	46 (14.4)	2,257 (16.9)	1,389 (18.4)	868 (15.0)
<i>X: Respiratory system</i>	7,435 (30.6)	735 (34.0)	6,700 (30.3)	5,568 (35.6)	1,132 (17.4)	599 (25.4)	517 (26.2)	82 (21.4)	3,330 (51.7)	3,241 (52.9)	89 (27.8)	2,771 (20.8)	1,810 (24.0)	961 (16.6)
<i>XI: Digestive system</i>	955 (3.9)	61 (2.8)	894 (4.0)	650 (4.2)	244 (3.8)	98 (4.2)	68 (3.5)	30 (7.8)	192 (3.0)	185 (3.0)	7 (2.2)	604 (4.5)	397 (5.3)	207 (3.6)
<i>XII: Skin and subcutaneous tissue</i>	64 (0.3)	5 (0.2)	59 (0.3)	47 (0.3)	12 (0.2)	11 (0.5)	9 (0.5)	2 (0.5)	15 (0.2)	15 (0.2)	0 (0.0)	33 (0.3)	23 (0.3)	10 (0.2)
<i>XIII: Musculoskeletal and connective tissue</i>	104 (0.4)	11 (0.5)	93 (0.4)	69 (0.4)	24 (0.4)	9 (0.4)	7 (0.4)	2 (0.5)	26 (0.4)	25 (0.4)	1 (0.3)	58 (0.4)	37 (0.5)	21 (0.4)
<i>XIV: Genitourinary</i>	300 (1.2)	14 (0.7)	286 (1.3)	224 (1.4)	62 (1.0)	37 (1.6)	28 (1.4)	9 (2.4)	63 (1.0)	62 (1.0)	1 (0.3)	186 (1.4)	134 (1.8)	52 (0.9)
<i>XV: Pregnancy, childbirth, puerperium</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<i>XVI: Perinatal conditions</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<i>XVII: Congenital, deformations, chromosomal</i>	12 (0.1)	1 (0.1)	11 (0.1)	7 (0.0)	4 (0.1)	2 (0.1)	1 (0.1)	1 (0.3)	5 (0.4)	5 (0.1)	0 (0.0)	4 (0.0)	1 (0.0)	3 (0.1)
<i>XVIII: Symptoms, signs</i>	116 (0.5)	23 (1.1)	93 (0.4)	78 (0.5)	15 (0.2)	8 (0.3)	7 (0.4)	1 (0.3)	23 (0.4)	23 (0.4)	0 (0.0)	62 (0.5)	48 (0.6)	14 (0.2)
<i>XIX: Injury, poisoning, other external</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<i>XX: External</i>	432 (1.8)	65 (3.0)	367 (1.7)	268 (1.7)	99 (1.5)	43 (1.8)	33 (1.7)	10 (2.6)	97 (1.5)	91 (1.5)	6 (1.9)	227 (1.7)	144 (1.9)	83 (1.4)

¹Defined as the primary cause of death according to Office of National Statistics (ONS) death certification

{%} indicate study group percentage of the total cohort (N=312,121) | [%] are percentages of study group who died | (%) are percentages of those who died by cause of death