

SUPPLEMENTARY DATA

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Supplementary Table S1: Descriptive analysis: characteristics of patients categorised according to severity of COPD (GOLD stage), cases and controls

Characteristic	CASES					CONTROLS ^a				
	No. of subjects	GOLD stage				No. of subjects	GOLD stage			
		1 No. (%)	2 No. (%)	3 No. (%)	4 No. (%)		1 No. (%)	2 No. (%)	3 No. (%)	4 No. (%)
Exacerbators	3,051	448 (14.7)	1,584 (51.9)	853 (28.0)	166 (5.4)	9,440	1,542 (16.3)	4,690 (49.7)	2,547 (27.0)	661 (7.0)
Infrequent	2,124	331 (15.6)	1,115 (52.5)	575 (27.1)	103 (4.9)	6,715	1,148 (17.1)	3,376 (50.3)	1,748 (26.0)	443 (6.6)
Frequent	927	117 (12.6)	469 (50.6)	278 (30.0)	63 (6.8)	2,725	394 (14.5)	1,314 (48.2)	799 (29.3)	218 (7.0)
Gender	3,051	448 (14.7)	1,584 (51.9)	853 (28.0)	166 (5.4)	9,440	1,542 (16.3)	4,690 (49.7)	2,547 (27.0)	661 (7.0)
Men	1,623	202 (12.5)	846 (52.1)	454 (28.0)	121 (7.5)	4,974	686 (13.8)	2,424 (48.7)	1,440 (29.0)	424 (8.5)
Women	1,428	246 (17.2)	738 (51.7)	399 (27.9)	45 (3.2)	4,466	856 (19.2)	2,266 (50.7)	1,107 (24.8)	237 (5.3)
Index age (years)	3,051	448 (14.7)	1,584 (51.9)	853 (28.0)	166 (5.4)	9,440	1,542 (16.3)	4,690 (49.7)	2,547 (27.0)	661 (7.0)
Under 60	229	34 (14.9)	127 (55.5)	55 (24.0)	13 (5.9)	719	156 (21.7)	339 (47.2)	176 (24.5)	48 (6.7)
60–69	781	127 (16.3)	401 (51.3)	205 (26.3)	48 (6.2)	2,422	411 (17.0)	1,214 (50.2)	602 (24.9)	195 (8.1)
70–79	1,221	160 (13.1)	655 (53.6)	336 (27.5)	70 (5.7)	3,815	575 (15.1)	1,874 (49.1)	1,097 (28.8)	269 (7.1)
80 and over	820	127 (15.5)	401 (48.9)	257 (31.3)	35 (4.3)	2,484	400 (16.1)	1,263 (50.9)	672 (27.1)	149 (6.0)
Smoking status^b	3,051	448 (14.7)	1,584 (51.9)	853 (28.0)	166 (5.4)	9,440	1,542 (16.3)	4,690 (49.7)	2,547 (27.0)	661 (7.0)
Non-smoker	276	5 (19.6)	150 (54.4)	61 (22.1)	11 (4.0)	854	197 (23.1)	417 (48.8)	187 (21.9)	53 (6.2)
Ex-smoker	1,421	204 (14.4)	730 (51.4)	413 (29.1)	74 (5.2)	4,315	660 (15.3)	2,093 (48.5)	1,238 (28.7)	324 (7.5)
Current smoker	1,354	190 (14.0)	704 (52.0)	379 (28.0)	81 (6.0)	4,271	685 (16.0)	2,180 (51.0)	1,122 (26.3)	284 (6.7)
BMI^b	3,037	446 (14.7)	1,577 (51.9)	848 (27.9)	166 (5.5)	9,404	1,537 (16.3)	4,676 (49.7)	2,536 (27.0)	655 (7.0)
Underweight	164	12 (7.3)	73 (44.5)	60 (36.6)	19 (11.6)	717	59 (8.2)	278 (38.8)	269 (37.5)	111 (15.5)
Normal weight	955	107 (11.2)	463 (48.5)	313 (32.8)	72 (7.5)	3,445	484 (14.1)	1,650 (47.9)	1,016 (29.5)	295 (8.6)
Over weight	986	158 (16.2)	523 (53.0)	254 (25.8)	51 (5.2)	3,078	559 (18.2)	1,575 (51.2)	779 (25.3)	165 (5.4)
Obese	932	169 (18.3)	518 (55.6)	221 (23.7)	24 (2.6)	2,164	435 (20.1)	1,173 (54.2)	472 (21.8)	84 (3.9)
Family history	3,051	448 (14.7)	1,584 (51.9)	853 (28.0)	166 (5.4)	9,440	1,542 (16.3)	4,690 (49.7)	2,547 (27.0)	661 (7.0)
Yes	886	142 (16.0)	479 (54.1)	224 (25.3)	41 (4.6)	2,598	467 (18.0)	1,386 (53.4)	605 (23.3)	140 (5.4)
Hypertension	3,051	448 (14.7)	1,584 (51.9)	853 (28.0)	166 (5.4)	9,440	1,542 (16.3)	4,690 (49.7)	2,547 (27.0)	661 (7.0)
Yes	1,573	236 (15.0)	832 (52.9)	445 (28.3)	60 (3.8)	4,713	785 (16.7)	2,428 (51.5)	1,239 (26.3)	261 (5.5)
Dyslipidaemia	3,051	448 (14.7)	1,584 (51.9)	853 (28.0)	166 (5.4)	9,440	1,542 (16.3)	4,690 (49.7)	2,547 (27.0)	661 (7.0)
Yes	637	111 (17.4)	359 (56.4)	150 (23.6)	17 (2.7)	2,019	384 (19.0)	1,061 (52.6)	466 (23.1)	108 (5.4)
Diabetes	3,051	448 (14.7)	1,584 (51.9)	853 (28.0)	166 (5.4)	9,440	1,542 (16.3)	4,690 (49.7)	2,547 (27.0)	661 (7.0)
Yes	517	70 (13.5)	277 (53.6)	146 (28.2)	24 (4.6)	1,575	253 (16.1)	823 (52.3)	414 (26.3)	85 (5.4)
Atrial fibrillation^b	3,051	448 (14.7)	1,584 (51.9)	853 (28.0)	166 (5.4)	9,440	1,542 (16.3)	4,690 (49.7)	2,547 (27.0)	661 (7.0)
Yes	390	41 (10.5)	224 (57.4)	107 (27.4)	18 (4.6)	1,000	147 (14.7)	485 (48.5)	293 (29.3)	75 (7.5)
Heart failure^b	3,051	448 (14.7)	1,584 (51.9)	853 (28.0)	166 (5.4)	9,438	1,542 (16.3)	4,688 (49.7)	2,547 (27.0)	661 (7.0)
Yes	420	39 (9.3)	208 (49.5)	142 (33.8)	31 (7.4)	929	116 (12.5)	446 (48.0)	281 (30.3)	86 (9.3)
CVDs	3,051	448 (14.7)	1,584 (51.9)	853 (28.0)	166 (5.4)	9,440	1,542 (16.3)	4,690 (49.7)	2,547 (27.0)	661 (7.0)
no CVD	2,185	318 (14.6)	1,095 (50.1)	644 (29.5)	128 (5.9)	6,956	1,133 (16.3)	3,443 (49.5)	1,872 (26.9)	508 (7.3)
1 CVD	597	94 (15.8)	333 (55.8)	142 (23.8)	28 (4.7)	1,779	302 (17.0)	873 (49.1)	493 (27.7)	111 (6.2)
2 or more CVDs	269	36 (13.4)	156 (58.0)	67 (23.8)	10 (3.7)	705	107 (15.2)	374 (53.1)	182 (25.8)	42 (6.0)

a Including duplicates.

b Some missing data.

Abbreviations: BMI, Body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease

Supplementary Table S2: Descriptive analysis: characteristics of patients categorised according to severity of COPD (medication-based staging), cases and controls

Characteristic	CASES					CONTROLS ^a				
	No. of subjects	Disease severity				No. of subjects	Disease severity			
		1 No. (%)	2 No. (%)	3 No. (%)	4 No. (%)		1 No. (%)	2 No. (%)	3 No. (%)	4 No. (%)
Exacerbators	3,590	842 (23.5)	591 (16.5)	1,402 (39.1)	755 (21.0)	10,774	2,853 (26.5)	2,056 (19.1)	4,154 (38.6)	1,711(15.9)
Infrequent	2,545	642 (25.2)	411 (16.2)	1,013(39.8)	479 (18.8)	7,757	2,220 (28.6)	1,469 (18.9)	2,991 (38.6)	1,077(13.9)
Frequent	1,045	200 (19.1)	180 (17.2)	389 (37.2)	276 (26.4)	3,017	633 (21.0)	567 (19.5)	1,163 (38.5)	634 (21.0)
Gender	3,590	842 (23.5)	591 (16.5)	1,402(39.1)	755(21.0)	10,774	2,853 (26.5)	2,056 (19.1)	4,154 (38.6)	1,711(15.9)
Men	1,868	414 (22.2)	326 (17.5)	713 (38.2)	415 (22.2)	5,608	1,517 (27.1)	1,112 (19.8)	2,114 (37.0)	865 (15..5)
Women	1,722	428 (24.9)	265 (15.4)	689 (40.0)	340 (19.7)	5,166	1,336 (25.9)	944 (18.3)	2,040 (39.5)	846 (16..4)
Index age (years)	3,590	842 (23.5)	591 (16.5)	1,402 (39.1)	755 (21.0)	10,774	2,853 (26.5)	2,056 (19.1)	4,154 (38.6)	1,711(15.9)
Under 60	268	60 (22.4)	48 (17.9)	106 (39.6)	54 (20.2)	800	213 (26.7)	126 (15.8)	355 (44.5)	106 (13.3)
60–69	875	191 (21.8)	142 (16.2)	345 (39.4)	197 (22.5)	2,642	684 (19.0)	522 (19.2)	1,033 (39.1)	403 (15.1)
70–79	1,417	340 (24.0)	230 (16.2)	552 (39.0)	295 (20.8)	4,279	1,065 (24.9)	825(19.1)	1,617 (37.8)	722(18.1)
80 and over	1,030	251 (24.4)	171 (16.6)	399 (38.7)	209 (20.3)	3,053	891 (29.1)	583 (19.1)	1,149 (37.6)	430 (14.1)
Smoking status^b	3,589	842 (23.5)	591 (16.5)	1,401(39.0)	755 (21.0)	10,765	2,691 (26.6)	1,908 (18.8)	3,898 (38.6)	1,614(16.0)
Non-smoker	368	111(30.2)	39 (10.6)	154 (41.9)	64 (17.4)	1,089	320 (29.4)	164 (15.1)	442 (40.6)	163 (15.0)
Ex-smoker	1,632	349 (21.4)	296 (18.1)	614 (37.6)	373 (22.9)	4,828	1,214 (25.3)	966 (20.0)	1,820 (37.7)	828 (17.3)
Current smoker	1,589	382 (24.0)	256 (16.1)	633 (39.8)	318 (20.0)	4,848	1,314(26.0)	925 (19.1)	1,889 (36.3)	720 (14.8)
BMI^b	3,491	808 (23.2)	581 (16.6)	1,370 (39.2)	732 (21.0)	10,519	2,763 (26.3)	2,020 (19.7)	4,067 (38.0)	1,669(15.9)
Underweight	192	48 (25.0)	30 (15.6)	72 (37.5)	42 (21.9)	825	199 (24.1)	161 (18.8)	309 (37.5)	111 (18.9)
Normal weight	1,109	255 (23.0)	187 (16.9)	421(38.0)	246 (22.2)	3,908	1,052 (26.9)	726 (17.9)	1,416 (39.5)	645 (16.5)
Overweight	1,123	271 (24.1)	176 (15.7)	454 (40.4)	222 (19.8)	3,389	902 (28.2)	656 (19.4)	1,345 (25.3)	486 (5.4)
Obese	1,067	234 (21.9)	188 (17.6)	423 (39.6)	222 (20.8)	2,397	610 (25.1)	477 (19.2)	928 (38.7)	384 (15.9)
Family history	3,590	842 (23.5)	591 (16.5)	1,402(39.1)	755(21.0)	10,774	2,853 (26.5)	2,056 (19.1)	4,154 (38.6)	1,711(15.9)
Yes	995	225 (22.5)	168 (16.9)	388 (40.1)	214 (21.5)	2,911	766 (26.0)	563 (19.4)	1,106 (38.3)	476 (16.4)
Hypertension	3,590	842 (23.5)	591 (16.5)	1,402(39.1)	755(21.0)	10,774	2,853 (26.5)	2,056 (19.1)	4,154 (38.6)	1,711(15.9)
Yes	1,829	432 (23.6)	292 (16.0)	745 (40.7)	360 (19.7)	5,343	1,452 (27.2)	1,014 (19.0)	2,097 (39.3)	780 (14.5)
Dyslipidaemia	3,590	842 (23.5)	591 (16.5)	1,402(39.1)	755 (21.0)	10,774	2,853 (26.5)	2,056 (19.1)	4,154 (38.6)	1,711(15.9)
Yes	730	162 (22.5)	121 (16.8)	290 (40.3)	147 (20.4)	2,241	603 (27.0)	438(19.6)	874 (37.1)	353 (15.4)
Diabetes	3,590	842 (23.5)	591 (16.5)	1,402(39.1)	755 (21.0)	10,774	2,853 (26.5)	2,056 (19.1)	4,154 (38.6)	1,711(15.9)
Yes	596	135 (22.7)	105 (17.6)	221 (37.1)	135 (22.7)	1,785	476 (26.1)	323 (18.3)	673 (37.3)	313 (17.4)
Atrial fibrillation^b	3,590	842 (23.5)	591 (16.5)	1,402(39.1)	755 (21.0)	10,774	2,852 (26.5)	2,056 (19.1)	4,154 (38.6)	1,711(15.9)
Yes	464	101 (21.8)	75 (16.2)	177 (38.2)	111 (23.9)	1,187	331 (27.7)	236 (19.5)	426 (35.3)	194 (16.5)
Heart failure^b	3,590	842 (23.5)	591 (16.5)	1,402 (39.1)	755(21.0)	10,772	2,852 (26.6)	2,056 (19.1)	4,153 (38.6)	1,711(15.9)
Yes	535	126 (23.6)	81 (15.1)	197 (36.8)	131 (24.5)	1,130	274 (24.9)	234 (20.0)	395 (34.3)	227 (20.1)
CVDs	3,590	842 (23.5)	591 (16.5)	1,402(39.1)	755 (21.0)	10,774	2,853 (26.5)	2,056 (19.1)	4,154 (38.6)	1,711(15.9)
no CVD	2,555	602 (23.6)	421 (16.5)	1,018 (39.8)	514 (20.1)	7,925	2,084 (26.3)	1,482 (18.5)	3,156 (39.9)	1,203(15.3)
1 CVD	719	172 (23.9)	118 (16.4)	263 (36.6)	166 (23.1)	2,039	546 (26.0)	413 (20.3)	723 (35.7)	357 (17.5)
2 or more CVDs	316	68 (21.5)	52 (16.5)	121 (38.3)	75 (23.7)	810	223 (27.2)	161 (19.1)	275 (33.8)	151 (18.6)

a Including duplicates.

b Some missing data.

Abbreviations: BMI, Body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease

APPENDIX: Data management: using medication history to stage disease severity

Given the availability of detailed records of medication history for the patients in the study population, the possibility of using these data to derive an alternative measure of disease severity was explored.

Medication histories were available for all 13,512 patients who make up the study cohort. Individual records provided information on the class of medication prescribed (“Original therapy group” in Table A1) and the corresponding date of prescription. Using the NICE COPD management guidelines¹, the original therapy groupings were streamlined to reflect the broad classes of medications that would be prescribed to patients at a given stage of disease. For instance, short-acting medications (SABA and SAMA) are recommended for patients with mild COPD, and thus all medications of this type were assigned to therapy group 1 in the revised scheme. As patients progress to moderate disease, they will likely be prescribed long-acting medications (LABA and LAMA), which accordingly are assigned to therapy group 2 in the revised scheme (see Table A1).

Table A1: COPD medications

Class of medication	Original therapy group	Revised therapy group	Frequency	Percentage
SABA	1	1	12,738	22.3
SAMA	2	1	4,732	8.3
SABA + CROMO	3	1	13	0.02
SABA + SAMA	8	1	1,808	3.2
LABA	4	2	4,941	8.63
LAMA	9	2	7,061	12.3
LABA + ICS	5, 6	3	9,404	16.4
ICS	7	3	8,801	15.4
OCS	10	4	201	0.35
CORTICO	11	NA	0	0.0
OXYGEN	12	4	688	1.20
ROFLUMILAST	13	4	15	0.03
THEOPHILLINE	14	4	2,512	4.4
AZITHROMYCIN	15	4	863	1.5
MUCOLYTICS	16	4	3,456	6.0

SABA, Short-acting beta₂ agonist

SAMA, short-acting muscarinic antagonist

SABA + CROMO, Short-acting beta₂ agonist plus sodium chromoglycate

LABA, Long-acting beta₂ agonist

LAMA, Long-acting muscarinic antagonist

ICS, Inhaled corticosteroid

ORS, oral corticosteroid

Using this revised grouping, it is our intention to code patients who are only ever prescribed group 1 medications as having “mild” disease. If however they are prescribed a group 2 medication at some

¹ NICE. *COPD: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care* [update]. London, UK: National Institute for Health and Clinical Excellence; 2010.

point in their medication history, they should be coded as having “moderate” disease. Likewise, patients taking any combination of group 1, 2 and/or 3 medications (but not a group 4 medication) should be described as having “severe” disease, and patients recorded as having been prescribed a group 4 medication should be accorded a “very severe” disease status.

Initial staging of patients according to their medication history did not take into account any records which had a prescription date more than 6 months after the patient’s index date². The purpose of excluding subsequent prescriptions is to ensure that the staging of the patient’s disease status reflects their status as close to the time of their VTE event (or selection as a control) as possible. A “lag-time” of 6 months was factored in to take account of the fact that patients are likely to develop and experience worsening disease for a period of time before being prescribed a new medication to manage their symptoms. However, a sizeable proportion of patients were found to only have prescription records 6-months post their index date. In the interests of generating an as complete as possible medication-based staging dataset, the first record post the index date plus 6 months was used to stage patients who only had records 6-months post their index date.

Thus staging of patients according to their medication history followed the following order of preference of record selection:

1. For patients with one or more records within a given 18-month period (12 months prior to the index date plus 6 months post the index date), staging was based on the highest class of medication prescribed during that time interval;
2. For patients without relevant records within the above-mentioned time interval, staging was based on the class of medication prescribed at any point prior to the start of the 18-month interval (in the case of multiple pre-interval records, the record nearest to the start of the above-mentioned interval was selected);
3. For patients without relevant records neither within the above-mentioned time interval nor in the period prior to this interval, staging was based on the class of medication prescribed 6-months post their index date (in the case of multiple post-interval records, the first post-interval record was selected).

A total of 386 patients in the cohort were missing both a medication date and medication class. Since all patients in the cohort have a diagnosis of COPD, it was assumed that these patients had mild disease and were coded as such. A further 12 patients had only a single entry in the data set, with a medication date but no corresponding medication group. As no reasonable inference can be made regarding the disease status of this group of patients, they were coded as having missing data. Another 1046 patients had at least one medication record that was missing a medication class (but included a medication date): staging of these patients was based on their other medication records.

² For cases the index date is the date they experienced the outcome of interest; for controls the index date is the date of their selection.