Supplementary file for "Association between COPD exacerbations and early lung function decline under maintenance therapy"

METHODS

Study design and data sources

CPRD comprises de-identified, longitudinal medical records for over 11 million patients from 674 UK practices and is frequently used for medical and health research.[1] OPCRD consists of anonymized, longitudinal medical record data for over seven million patients from 650 primary care practices. It is a high-quality data source used regularly in clinical, epidemiological, and pharmaceutical research.[2-3]

Ethical approval

The study protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC approval number 17_117) and registered with the European Union electronic Register of Post-Authorization Studies (EU PAS Register number 19879). See online data supplement for further details. OPCRD has received a favorable opinion for clinical research use from the Health Research Authority (REC reference: 15/EM/0150). Governance is provided by the Anonymous Data Ethics Protocols and Transparency (ADEPT; ADEPT protocol 0818) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG, http://www.effectivenessevaluation.org/) to govern the standard of research conducted on internationally recognized databases.

Table S1. Demographic and clinical characteristics of patients treated with or without ICS as the highest level of therapy during follow-up

Variable		No ICS (N= 4,867)	ICS (N= 14,572)	Total (N= 19,439)	P	SMD
Year of index date	Mean (SD)	2008.7 (3.0)	2007.6 (3.1)	2007.8 (3.1)	<0.001	36.5
	Median (IQR)	2009.0 (2007.0;2011.0)	2007.0 (2005.0;2010.0)	2008.0 (2006.0;2010.0)		
Follow-up after initiation highest maintenance therapy, years	Mean (SD)	3.9 (2.0)	4.6 (2.5)	4.4 (2.4)	<0.001	32.9
	Median (IQR)	3.5 (2.4;4.9)	4.2 (2.7;6.0)	4.0 (2.6;5.8)		
Age group	35-59, n (%)	1,197 (24.6)	4,116 (28.2)	5,313 (27.3)	<0.001	7.9
	60-79, n (%)	3,270 (67.2)	9,362 (64.2)	12,632 (65.0)		
	80+, n (%)	400 (8.2)	1,094 (7.5)	1,494 (7.7)		
BMI	Mean (SD)	27.5 (5.6)	27.4 (5.7)	27.4 (5.7)	0.07	2.4
	Median (IQR)	26.9 (23.7;30.7)	26.8 (23.5;30.5)	26.8 (23.5;30.5)		
Rhinitis diagnosis	Never, n (%)	3,969 (81.5)	11,447 (78.6)	15,416 (79.3)	<0.001	6.1
	Active, n (%)	614 (12.6)	2,214 (15.2)	2,828 (14.5)		
	Ever, not active, n (%)	284 (5.8)	911 (6.3)	1,195 (6.1)		
Eczema diagnosis	Never, n (%)	3,946 (81.1)	11,865 (81.4)	15,811 (81.3)	0.62	1.2
	Active, n (%)	139 (2.9)	439 (3.0)	578 (3.0)		
	Ever, not active, n (%)	782 (16.1)	2,268 (15.6)	3,050 (15.7)		
Nasal polyps diagnosis	Ever, n (%)	36 (0.7)	191 (1.3)	227 (1.2)	0.001	5.7
Chronic sinusitis diagnosis	Ever, n (%)	238 (4.9)	859 (5.9)	1,097 (5.6)	0.01	4.4
GERD diagnosis	Ever, n (%)	721 (14.8)	1,881 (12.9)	2,602 (13.4)	<0.001	5.5
Diabetes Mellitus diagnosis	Ever, n (%)	475 (9.8)	1,256 (8.6)	1,731 (8.9)	0.02	3.9
Osteoporosis diagnosis	Ever, n (%)	200 (4.1)	601 (4.1)	801 (4.1)	0.96	0.1
Hypertension diagnosis	Ever, n (%)	1,808 (37.1)	5,172 (35.5)	6,980 (35.9)	0.04	3.4
Ischemic heart disease diagnosis	Ever, n (%)	854 (17.5)	2,389 (16.4)	3,243 (16.7)	0.06	3.1
Heart failure diagnosis	Ever, n (%)	148 (3.0)	425 (2.9)	573 (2.9)	0.66	0.7
Chronic kidney disease diagnosis	Ever, n (%)	352 (7.2)	716 (4.9)	1,068 (5.5)	<0.001	9.7
Depression diagnosis	Ever, n (%)	1,062 (21.8)	3,202 (22.0)	4,264 (21.9)	0.82	0.4
Anxiety diagnosis	Ever, n (%)	1,011 (20.8)	3,047 (20.9)	4,058 (20.9)	0.84	0.3
Sleep apnoea diagnosis	Ever, n (%)	40 (0.8)	82 (0.6)	122 (0.6)	0.05	3.1
Sleep disorder diagnosis	Ever, n (%)	571 (11.7)	1,716 (11.8)	2,287 (11.8)	0.93	0.1
GOLD stage of airflow limitation at index date	GOLD 2 (moderate):50-79, n (%)	4,240 (87.1)	12,959 (88.9)	17,199 (88.5)	<0.001	5.6
FEV_1/FVC ratio <0.7 at index date	N (% non-missing)	4,398 (90.4)	13,052 (89.6)	17,450 (89.8)	<0.001	7.8
	Yes, n (%)	3,790 (86.2)	10,884 (83.4)	14,674 (84.1)		
Blood eosinophil count, cells/µL, closest within 2 years of highest maintenance therapy initiation	N (% non-missing)	3,197 (65.7)	8,981 (61.6)	12,178 (62.6)	<0.001	13.0
	<50, n (%)	110 (3.4)	304 (3.4)	414 (3.4)		
	50-149, n (%)	955 (29.9)	2,411 (26.8)	3,366 (27.6)		
	150-249, n (%)	1,039 (32.5)	2,747 (30.6)	3,786 (31.1)		
	250-349, n (%)	550 (17.2)	1,670 (18.6)	2,220 (18.2)		
	350-449, n (%)	300 (9.4)	856 (9.5)	1,156 (9.5)		
	450-549, n (%)	128 (4.0)	437 (4.9)	565 (4.6)		

Variable		No ICS (N= 4,867)	ICS (N= 14,572)	Total (N= 19,439)	P	SMD
	550-649, n (%)	52 (1.6)	217 (2.4)	269 (2.2)		
	≥650, n (%)	63 (2.0)	339 (3.8)	402 (3.3)		
Blood eosinophil count, cells/µL	N (% non-missing)	3,197 (65.7)	8,981 (61.6)	12,178 (62.6)	<0.001	8.2
	<50, n (%)	110 (3.4)	304 (3.4)	414 (3.4)		
	50-349, n (%)	2,544 (79.6)	6,828 (76.0)	9,372 (77.0)		
	≥350, n (%)	543 (17.0)	1,849 (20.6)	2,392 (19.6)		
OCS courses, number in year prior to index date	0, n (%)	4,241 (87.1)	11,780 (80.8)	16,021 (82.4)	<0.001	17.5
	1, n (%)	474 (9.7)	1,913 (13.1)	2,387 (12.3)		
	2, n (%)	113 (2.3)	568 (3.9)	681 (3.5)		
	3, n (%)	18 (0.4)	177 (1.2)	195 (1.0)		
	≥4, n (%)	21 (0.4)	134 (0.9)	155 (0.8)		
Antibiotics courses with lower respiratory consultation, number in year prior to index date	None, n (%)	2,920 (60.0)	8,106 (55.6)	11,026 (56.7)	<0.001	12.4
	1, n (%)	1,146 (23.5)	3,419 (23.5)	4,565 (23.5)		
	2, n (%)	488 (10.0)	1,701 (11.7)	2,189 (11.3)		
	3, n (%)	179 (3.7)	759 (5.2)	938 (4.8)		
	≥4, n (%)	134 (2.8)	587 (4.0)	721 (3.7)		
Cumulative daily dose of oral steroids in year prior to index date (mg /day)	N (% non-missing)	857 (17.6)	3,911 (26.8)	4,768 (24.5)	0.001	1.5
	No OCS, n (%)	155 (18.1)	640 (16.4)	795 (16.7)		
	<2.5, n (%)	628 (73.3)	2,914 (74.5)	3,542 (74.3)		
	2.5 to <5, n (%)	33 (3.9)	234 (6.0)	267 (5.6)		
	5 to <7.5, n (%)	14 (1.6)	65 (1.7)	79 (1.7)		
	≥7.5, n (%)	27 (3.2)	58 (1.5)	85 (1.8)		
Daily SABA dose (µg/day)	No SABA, n (%)	2,751 (56.5)	5,881 (40.4)	8,632 (44.4)	<0.001	46.6
	1-100, n (%)	1,171 (24.1)	3,174 (21.8)	4,345 (22.4)		
	101-200, n (%)	562 (11.5)	2,315 (15.9)	2,877 (14.8)		
	201-300, n (%)	165 (3.4)	1,057 (7.3)	1,222 (6.3)		
	301-400, n (%)	77 (1.6)	608 (4.2)	685 (3.5)		
	>400, n (%)	141 (2.9)	1,537 (10.5)	1,678 (8.6)		
Any SAMA prescriptions	Yes, n (%)	516 (10.6)	2,269 (15.6)	2,785 (14.3)	<0.001	14.8
Type of therapy preceding FEV_1	Minimal therapy, n (%)	4,220 (86.7)	8,904 (61.1)	13,124 (67.5)	<0.001	73.4
	LAMA or LABA, n (%)	400 (8.2)	635 (4.4)	1,035 (5.3)		
	ICS, n (%)	163 (3.3)	2,216 (15.2)	2,379 (12.2)		
	ICSLABA or ICSLAMA, n (%)	65 (1.3)	2,263 (15.5)	2,328 (12.0)		
	LABALAMA, n (%)	13 (0.3)	21 (0.1)	34 (0.2)		
	Triple therapy, n (%)	6 (0.1)	533 (3.7)	539 (2.8)		
GP consultations, COPD-related, number in year prior to index date	None, n (%)	1,030 (21.2)	2,806 (19.3)	3,836 (19.7)	<0.001	8.1
	1, n (%)	3,523 (72.4)	10,500 (72.1)	14,023 (72.1)		
	2-4, n (%)	299 (6.1)	1,205 (8.3)	1,504 (7.7)		
	5-7, n (%)	14 (0.3)	56 (0.4)	70 (0.4)		
	≥8, n (%)	1 (0.0)	5 (0.0)	6 (0.0)		
	0-1, n (%)	30 (0.6)	129 (0.9)	159 (0.8)	0.63	0.7

Variable		No ICS (N= 4,867)	ICS (N= 14,572)	Total (N= 19,439)	P	SMD
GP consultations, all-cause, number in year prior to index date	2-4, n (%)	521 (10.7)	1,549 (10.6)	2,070 (10.6)		
	5-8, n (%)	1,213 (24.9)	3,563 (24.5)	4,776 (24.6)		
	9-13, n (%)	1,311 (26.9)	3,917 (26.9)	5,228 (26.9)		
	14-17, n (%)	694 (14.3)	2,059 (14.1)	2,753 (14.2)		
	18-22, n (%)	520 (10.7)	1,554 (10.7)	2,074 (10.7)		
	≥23, n (%)	578 (11.9)	1,801 (12.4)	2,379 (12.2)		

BMI = Body mass index; COPD = Chronic obstructive pulmonary disease; FEV_1 = Forced expiratory volume in one second; FVC = Forced vital capacity; GERD = Gastroesophageal reflux disease; GP = General practitioner; ICS = Inhaled corticosteroid; IQR = Interquartile range; OCS = Oral corticosteroid; P = P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SABA = Short-acting beta agonist; SAMA = Short-acting muscarinic antagonist; SD = Standard deviation; SMD = Standardised mean difference

Table S2. Demographic and clinical characteristics of patients by blood eosinophil count recorded closest to initiation of the highest level of maintenance therapy

Variable		<50 (N= 414)	50-349 (N= 9,372)	≥350 (N= 2,392)	Total (N= 12,178)	P	SMD <50*	SMD ≥350†
Year of index date	Mean (SD)	2008.1 (3.0)	2008.2 (2.9)	2008.1 (2.9)	2008.1 (2.9)	0.73	3.3	1.4
	Median (IQR)	2008.0 (2006.0;2010.0)	2008.0 (2006.0;2010.0)	2008.0 (2006.0;2010.0)	2008.0 (2006.0;2010.0)			
Follow-up after initiation highest therapy, years	Mean (SD)	3.9 (2.1)	4.2 (2.3)	4.3 (2.3)	4.2 (2.3)	0.02	15.5	2.7
	Median (IQR)	3.7 (2.3;5.0)	3.8 (2.6;5.5)	3.8 (2.6;5.6)	3.8 (2.6;5.5)			
Age group	35-59, n (%)	102 (24.6)	2,439 (26.0)	591 (24.7)	3,132 (25.7)	0.04	5.5	0.2
	60-79, n (%)	270 (65.2)	6,143 (65.5)	1,633 (68.3)	8,046 (66.1)			
	80+, n (%)	42 (10.1)	790 (8.4)	168 (7.0)	1,000 (8.2)			
Highest maintenance therapy	LABA or LAMA mono, n (%)	94 (22.7)	2,222 (23.7)	471 (19.7)	2,787 (22.9)	<0.001	9.0	5.6
	ICS monotherapy, n (%)	32 (7.7)	764 (8.2)	201 (8.4)	997 (8.2)			
	ICS + (LABA or LAMA), n (%)	95 (22.9)	2,599 (27.7)	747 (31.2)	3,441 (28.3)			
	LAMA + LABA dual, n (%)	16 (3.9)	322 (3.4)	72 (3.0)	410 (3.4)			
	Triple therapy, n (%)	177 (42.8)	3,465 (37.0)	901 (37.7)	4,543 (37.3)			
BMI	Mean (SD)	26.2 (5.8)	27.6 (5.7)	27.5 (5.3)	27.5 (5.6)	<0.001	23.6	1.4
	Median (IQR)	25.4 (22.2;29.3)	27.0 (23.6;30.8)	27.1 (23.8;30.5)	26.9 (23.6;30.7)			
Asthma diagnosis	Ever, n (%)	74 (17.9)	1,433 (15.3)	403 (16.8)	1,910 (15.7)	0.08	6.9	4.2
Rhinitis diagnosis	Never, n (%)	322 (77.8)	7,525 (80.3)	1,796 (75.1)	9,643 (79.2)	<0.001	4.9	9.1
	Active, n (%)	62 (15.0)	1,203 (12.8)	429 (17.9)	1,694 (13.9)			
	Ever, not active, n (%)	30 (7.2)	644 (6.9)	167 (7.0)	841 (6.9)			
Eczema diagnosis	Never, n (%)	330 (79.7)	7,505 (80.1)	1,863 (77.9)	9,698 (79.6)	0.05	0.5	4.3
	Active, n (%)	14 (3.4)	281 (3.0)	98 (4.1)	393 (3.2)			
	Ever, not active, n (%)	70 (16.9)	1,586 (16.9)	431 (18.0)	2,087 (17.1)			
Chronic sinusitis diagnosis	Ever, n (%)	27 (6.5)	561 (6.0)	179 (7.5)	767 (6.3)	0.03	2.2	6.0
GERD diagnosis	Ever, n (%)	65 (15.7)	1,450 (15.5)	325 (13.6)	1,840 (15.1)	0.07	0.6	5.3
Diabetes Mellitus diagnosis	Ever, n (%)	32 (7.7)	906 (9.7)	227 (9.5)	1,165 (9.6)	0.42	6.9	0.6
Hypertension diagnosis	Ever, n (%)	159 (38.4)	3,680 (39.3)	988 (41.3)	4,827 (39.6)	0.17	1.8	4.2
Ischemic heart disease diagnosis	Ever, n (%)	70 (16.9)	1,704 (18.2)	480 (20.1)	2,254 (18.5)	0.07	3.3	4.8
Heart failure diagnosis	Ever, n (%)	12 (2.9)	318 (3.4)	61 (2.6)	391 (3.2)	0.11	2.8	5.0
Chronic kidney disease diagnosis	Ever, n (%)	26 (6.3)	633 (6.8)	198 (8.3)	857 (7.0)	0.03	1.9	5.8
Depression diagnosis	Ever, n (%)	111 (26.8)	2,349 (25.1)	557 (23.3)	3,017 (24.8)	0.12	4.0	4.2
Anxiety diagnosis	Ever, n (%)	113 (27.3)	2,177 (23.2)	479 (20.0)	2,769 (22.7)	<0.001	9.4	7.8
Sleep apnoea diagnosis	Ever, n (%)	3 (0.7)	50 (0.5)	20 (0.8)	73 (0.6)	0.22	2.4	3.7
Sleep disorder diagnosis	Ever, n (%)	52 (12.6)	1,252 (13.4)	324 (13.5)	1,628 (13.4)	0.86	2.4	0.5
GOLD stage of airflow limitation at index date	GOLD 2 (moderate):50-79, n (%)	365 (88.2)	8,292 (88.5)	2,127 (88.9)	10,784 (88.6)	0.80	1.0	1.4
FEV_1/FVC ratio <0.7 at index date	N (% non-missing)	369 (89.1)	8,517 (90.9)	2,165 (90.5)	11,051 (90.7)	0.55	4.1	1.6
	Yes, n (%)	314 (85.1)	7,368 (86.5)	1,885 (87.1)	9,567 (86.6)			

Variable		<50 (N= 414)	50-349 (N= 9,372)	≥350 (N= 2,392)	Total (N= 12,178)	P	SMD <50*	SMD ≥350†
COPD exacerbations, number in year prior to index date	0, n (%)	234 (56.5)	5,309 (56.6)	1,257 (52.6)	6,800 (55.8)	0.01	5.2	9.5
	1, n (%)	97 (23.4)	2,385 (25.4)	628 (26.3)	3,110 (25.5)			
	2, n (%)	44 (10.6)	1,017 (10.9)	295 (12.3)	1,356 (11.1)			
	3, n (%)	24 (5.8)	401 (4.3)	130 (5.4)	555 (4.6)			
	≥4, n (%)	15 (3.6)	260 (2.8)	82 (3.4)	357 (2.9)			
COPD exacerbations, average annual rate after initiation of highest therapy, rounded	0, n (%)	293 (70.8)	6,402 (68.3)	1,547 (64.7)	8,242 (67.7)	0.02	0.8	7.9
	1, n (%)	82 (19.8)	2,189 (23.4)	609 (25.5)	2,880 (23.6)			
	2, n (%)	26 (6.3)	494 (5.3)	145 (6.1)	665 (5.5)			
	3, n (%)	5 (1.2)	167 (1.8)	49 (2.0)	221 (1.8)			
	≥4, n (%)	8 (1.9)	120 (1.3)	42 (1.8)	170 (1.4)			
COPD exacerbations, number in year prior to index date	Mean (SD)	0.8 (1.3)	0.7 (1.1)	0.8 (1.2)	0.7 (1.1)	<0.001	7.5	9.9
	Median (IQR)	0.0 (0.0;1.0)	0.0 (0.0;1.0)	0.0 (0.0;1.0)	0.0 (0.0;1.0)			
COPD exacerbations, annual rate after initiation of highest therapy	Mean (SD)	0.5 (1.0)	0.5 (0.8)	0.6 (0.9)	0.5 (0.8)	0.003	2.0	6.8
	Median (IQR)	0.2 (0.0;0.6)	0.2 (0.0;0.7)	0.2 (0.0;0.7)	0.2 (0.0;0.7)			
Antibiotics courses with lower respiratory consultation, number in year prior to index date	None, n (%)	202 (48.8)	5,046 (53.8)	1,243 (52.0)	6,491 (53.3)	0.05	9.4	5.7
	1, n (%)	107 (25.8)	2,340 (25.0)	593 (24.8)	3,040 (25.0)			
	2, n (%)	61 (14.7)	1,117 (11.9)	288 (12.0)	1,466 (12.0)			
	3, n (%)	27 (6.5)	471 (5.0)	155 (6.5)	653 (5.4)			
	≥4, n (%)	17 (4.1)	398 (4.2)	113 (4.7)	528 (4.3)			
Daily SABA dose (µg /day)	No SABA, n (%)	195 (47.1)	4,484 (47.8)	1,074 (44.9)	5,753 (47.2)	0.01	9.4	9.0
	1-100, n (%)	74 (17.9)	2,020 (21.6)	490 (20.5)	2,584 (21.2)			
	101-200, n (%)	63 (15.2)	1,325 (14.1)	361 (15.1)	1,749 (14.4)			
	201-300, n (%)	24 (5.8)	539 (5.8)	152 (6.4)	715 (5.9)			
	301-400, n (%)	14 (3.4)	300 (3.2)	97 (4.1)	411 (3.4)			
	>400, n (%)	44 (10.6)	704 (7.5)	218 (9.1)	966 (7.9)			
Any SAMA prescriptions	Yes, n (%)	46 (11.1)	1,289 (13.8)	320 (13.4)	1,655 (13.6)	0.29	8.0	1.1
Type of therapy preceding FEV_1	Minimal therapy, n (%)	273 (65.9)	6,474 (69.1)	1,610 (67.3)	8,357 (68.6)	0.16	7.9	3.5
	LAMA or LABA, n (%)	26 (6.3)	500 (5.3)	136 (5.7)	662 (5.4)			
	ICS, n (%)	51 (12.3)	1,038 (11.1)	271 (11.3)	1,360 (11.2)			
	ICSLABA or ICSLAMA, n (%)	43 (10.4)	1,078 (11.5)	301 (12.6)	1,422 (11.7)			
	LABALAMA, n (%)	0 (0.0)	23 (0.2)	4 (0.2)	27 (0.2)			
	Triple therapy, n (%)	21 (5.1)	259 (2.8)	70 (2.9)	350 (2.9)			
GP consultations, COPD-related, number in year prior to ID	None, n (%)	79 (19.1)	1,851 (19.8)	481 (20.1)	2,411 (19.8)	0.76	5.1	0.3
	1, n (%)	299 (72.2)	6,907 (73.7)	1,749 (73.1)	8,955 (73.5)			
	2-4, n (%)	36 (8.7)	596 (6.4)	157 (6.6)	789 (6.5)			
	5-7, n (%)	0 (0.0)	17 (0.2)	5 (0.2)	22 (0.2)			
	8+, n (%)	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)			

*As compared to 50-349 cells/µL category

† As compared to 50-349 cells/µL category

BMI = Body mass index; COPD = Chronic obstructive pulmonary disease; FEV_1 = Forced expiratory volume in one second; FVC = Forced vital capacity; GERD = Gastroesophageal reflux disease; GP = General practitioner; IQR = Interquartile range; P = P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SABA = Short-acting beta agonist; SAMA = Short-acting muscarinic antagonist; SD = Standard deviation; SMD = Standardized mean difference

Table S3. Regression coefficients from a multilevel mixed-effects linear regression model with the FEV_1 (ml) as the outcome variable in the subpopulation of patients who received ICS containing inhalers as the highest maintenance therapy with high blood eosinophil counts defined as ≥350 cells /µL

Number of observations=60,069	Fixed effect (95% CI)	P-value
Effects on intercept (spirometry around diagnosis)		
Intercept	1553.8 (1538.3;1569.3)	<0.001
BEC <50, yes=1	7.6 (-29.5;44.7)	0.69
BEC ≥350, yes=1	17.8 (0.7;34.9)	0.04
Exacerbation rate (after maintenance therapy initiation)	-16.1 (-23.6;-8.5)	<0.001
BEC <50 # Exacerbation rate	11.1 (-23.8;45.9)	0.53
BEC≥350 # Exacerbation rate	7.3 (-8.3;22.9)	0.36
Period of highest maintenance therapy, yes=1	49.5 (42.4;56.5)	<0.001
Gender, male=1	261.3 (244.5;278.0)	<0.001
Intermittent quitter, yes=1	-6.6 (-21.1;8.0)	0.37
Continuous smoker, yes=1	-0.5 (-16.8;15.7)	0.95
No smoking information, yes=1	28.1 (3.2;53.0)	0.03
Age, centered to 66 years	-19.1 (-19.8;-18.5)	<0.001
Weight, centered to 77 kg	0.7 (0.3;1.1)	<0.001
Height, centered to 1.67 m	2526.8 (2433.8;2619.8)	<0.001
Height squared, centered to 1.67 m	890.3 (372.4;1408.3)	<0.001
Effects on decline (slope)		
Time, in years	-28.7 (-31.6;-25.8)	<0.001
Time squared	0.4 (0.2;0.6)	0.001
BEC <50, yes=1	-7.1 (-13.8;-0.3)	0.04
BEC ≥350, yes=1	0.6 (-2.5;3.6)	0.72
Exacerbation rate	-6.7 (-8.0;-5.3)	<0.001
BEC<50 # Exacerbation rate	2.1 (-4.6;8.8)	0.53
BEC ≥350 # Exacerbation rate	2.3 (-0.4;5.1)	0.10
Period of highest maintenance therapy, yes=1	4.7 (2.6;6.8)	<0.001
Gender, male=1	-12.8 (-15.9;-9.8)	<0.001
Intermittent quitter, yes=1	-10.1 (-12.7;-7.5)	<0.001
Continuous smoker quitter, yes=1	-18.5 (-21.4;-15.6)	<0.001
No smoking information, yes=1	2.6 (-2.1;7.2)	0.28
Age, centered to 66 years	0.2 (0.1;0.3)	<0.001
Weight, centered to 77 kg	0.4 (0.3;0.4)	<0.001
Height, centered to 1.67 m	-47.3 (-63.9;-30.7)	<0.001

interaction term of variables; BEC=blood eosinophil count; CI = Confidence interval

Table S4. Regression coefficients from a multilevel mixed-effects linear regression model with the FEV_1 (ml) as the outcome variable in the subpopulation of patients who did not receive ICS containing inhalers as the highest maintenance therapy with high blood eosinophil counts defined as ≥350 cells /µL

Number of observations=18,959	Fixed effect (95% CI)	P-value
Effects on intercept (spirometry around diagnosis)		
Intercept	1589.4 (1564.4;1614.5)	<0.001
BEC <50, yes=1	-20.5 (-76.7;35.7)	0.47
BEC ≥350, yes=1	4.9 (-24.4;34.1)	0.75
Exacerbation rate (after maintenance therapy initiation)	-12.8 (-29.5;3.9)	0.13
BEC <50 # Exacerbation rate	25.3 (-26.4;77.1)	0.34
BEC≥350 # Exacerbation rate	17.8 (-20.5;56.1)	0.36
Period of highest maintenance therapy, yes=1	31.5 (19.7;43.3)	<0.001
Gender, male=1	296.7 (269.0;324.4)	<0.001
Intermittent quitter, yes=1	-5.8 (-30.4;18.9)	0.65
Continuous smoker, yes=1	-0.6 (-26.2;24.9)	0.96
No smoking information, yes=1	20.1 (-22.1;62.3)	0.35
Age, centered to 66 years	-20.7 (-21.8;-19.7)	<0.001
Weight, centered to 77 kg	0.3 (-0.4;0.9)	0.41
Height, centered to 1.67 m	2545.8 (2392.1;2699.6)	<0.001
Height squared, centered to 1.67 m	1476.7 (653.8;2299.6)	<0.001
Effects on decline (slope)		
Time, in years	-30.7 (-35.7;-25.6)	<0.001
Time squared	0.0 (-0.4;0.5)	0.87
BEC <50, yes=1	-0.8 (-11.3;9.8)	0.88
BEC ≥350, yes=1	8.7 (3.0;14.3)	0.003
Exacerbation rate	-2.3 (-5.4;0.7)	0.14
BEC<50 # Exacerbation rate	1.1 (-7.6;9.7)	0.81
BEC ≥350 # Exacerbation rate	-17.1 (-25.0;-9.1)	<0.001
Period of highest maintenance therapy, yes=1	7.6 (3.6;11.7)	<0.001
Gender, male=1	-11.5 (-16.8;-6.2)	<0.001
Intermittent quitter, yes=1	-9.2 (-13.9;-4.5)	<0.001
Continuous smoker quitter, yes=1	-20.4 (-25.4;-15.5)	<0.001
No smoking information, yes=1	-2.6 (-11.0;5.7)	0.54
Age, centered to 66 years	0.1 (-0.1;0.3)	0.31
Weight, centered to 77 kg	0.3 (0.2;0.4)	<0.001
Height, centered to 1.67 m	-63.6 (-92.9;-34.4)	<0.001

interaction term of variables; BEC=blood eosinophil count; CI = Confidence interval

Table S5. Regression coefficients from a multilevel mixed-effects linear regression model with the FEV_1 (ml) as the outcome variable in the subpopulation of patients who received ICS containing inhalers as the highest maintenance therapy with high blood eosinophil counts defined as ≥450 cells /µL

Number of observations=60,069	Fixed effect (95% CI)	P-value
Effects on intercept (spirometry around diagnosis)		
Intercept	1554.0 (1538.7;1569.3)	<0.001
BEC <50, yes=1	7.4 (-29.6;44.4)	0.69
BEC ≥450, yes=1	30.8 (8.3;53.3)	0.01
Exacerbation rate (after maintenance therapy initiation)	-14.0 (-21.0;-7.0)	<0.001
BEC <50 # Exacerbation rate	9.0 (-25.7;43.8)	0.61
BEC≥450 # Exacerbation rate	-3.3 (-24.4;17.8)	0.76
Period of highest maintenance therapy, yes=1	49.5 (42.5;56.5)	<0.001
Gender, male=1	261.4 (244.6;278.1)	<0.001
Intermittent quitter, yes=1	-6.5 (-21.1;8.0)	0.38
Continuous smoker, yes=1	-0.7 (-17.0;15.5)	0.93
No smoking information, yes=1	27.9 (3.0;52.9)	0.03
Age, centered to 66 years	-19.2 (-19.8;-18.5)	<0.001
Weight, centered to 77 kg	0.7 (0.3;1.1)	<0.001
Height, centered to 1.67 m	2526.4 (2433.4;2619.4)	<0.001
Height squared, centered to 1.67 m	893.7 (375.7;1411.7)	<0.001
Effects on decline (slope)		
Time, in years	-28.7 (-31.5;-25.8)	<0.001
Time squared	0.4 (0.2;0.6)	<0.001
BEC <50, yes=1	-7.0 (-13.7;-0.3)	0.04
BEC ≥450, yes=1	1.0 (-3.0;5.1)	0.62
Exacerbation rate	-6.8 (-8.0;-5.5)	<0.001
BEC<50 # Exacerbation rate	2.2 (-4.4;8.9)	0.51
BEC ≥450 # Exacerbation rate	5.8 (2.1;9.5)	0.002
Period of highest maintenance therapy, yes=1	4.7 (2.6;6.8)	<0.001
Gender, male=1	-12.9 (-15.9;-9.9)	<0.001
Intermittent quitter, yes=1	-10.0 (-12.6;-7.4)	<0.001
Continuous smoker quitter, yes=1	-18.5 (-21.4;-15.6)	<0.001
No smoking information, yes=1	2.6 (-2.1;7.2)	0.28
Age, centered to 66 years	0.2 (0.1;0.3)	<0.001
Weight, centered to 77 kg	0.4 (0.3;0.4)	<0.001
Height, centered to 1.67 m	-47.5 (-64.0;-30.9)	<0.001

interaction term of variables; BEC=blood eosinophil count; CI = Confidence interval

Table S6. Regression coefficients from a multilevel mixed-effects linear regression model with the FEV_1 (ml) as the outcome variable in the subpopulation of patients who did not receive ICS containing inhalers as the highest maintenance therapy with high blood eosinophil counts defined as ≥450 cells /µL

Number of observations=18,959	Fixed effect (95% CI)	P-value
Effects on intercept (spirometry around diagnosis)		
Intercept	1589.4 (1564.5;1614.2)	<0.001
BEC <50, yes=1	-19.7 (-75.8;36.3)	0.49
BEC ≥450, yes=1	26.4 (-16.1;69.0)	0.22
Exacerbation rate (after maintenance therapy initiation)	-11.8 (-27.6;4.1)	0.15
BEC <50 # Exacerbation rate	24.3 (-27.1;75.8)	0.35
BEC≥450 # Exacerbation rate	9.5 (-40.1;59.1)	0.71
Period of highest maintenance therapy, yes=1	30.9 (19.1;42.7)	<0.001
Gender, male=1	296.4 (268.7;324.1)	<0.001
Intermittent quitter, yes=1	-6.3 (-30.9;18.3)	0.62
Continuous smoker, yes=1	-0.9 (-26.5;24.6)	0.94
No smoking information, yes=1	20.9 (-21.3;63.0)	0.33
Age, centered to 66 years	-20.8 (-21.8;-19.7)	<0.001
Weight, centered to 77 kg	0.3 (-0.4;0.9)	0.41
Height, centered to 1.67 m	2547.6 (2393.9;2701.2)	<0.001
Height squared, centered to 1.67 m	1460.1 (637.5;2282.6)	<0.001
Effects on decline (slope)		
Time, in years	-30.0 (-35.0;-24.9)	<0.001
Time squared	0.0 (-0.4;0.5)	0.93
BEC <50, yes=1	-1.4 (-12.0;9.1)	0.79
BEC ≥450, yes=1	8.7 (0.3;17.1)	0.04
Exacerbation rate	-4.1 (-7.1;-1.2)	0.01
BEC<50 # Exacerbation rate	2.9 (-5.8;11.5)	0.52
BEC ≥450 # Exacerbation rate	-9.6 (-19.8;0.7)	0.07
Period of highest maintenance therapy, yes=1	7.7 (3.7;11.8)	<0.001
Gender, male=1	-11.5 (-16.8;-6.2)	<0.001
Intermittent quitter, yes=1	-9.0 (-13.7;-4.3)	<0.001
Continuous smoker quitter, yes=1	-20.4 (-25.4;-15.5)	<0.001
No smoking information, yes=1	-2.5 (-10.9;5.8)	0.55
Age, centered to 66 years	0.1 (-0.1;0.3)	0.33
Weight, centered to 77 kg	0.3 (0.2;0.4)	<0.001
Height, centered to 1.67 m	-65.0 (-94.3;-35.7)	<0.001

interaction term of variables; BEC=blood eosinophil count; CI = Confidence interval

Figure S1. Impact of annual exacerbation rate on annual FEV_1 decline in patients with ≥5 FEV_1 measurements available receiving ICS (N=7,024) and patients not receiving ICS (N=2,252) by blood eosinophil count. Error bars represent the 95% confidence interval of the mean FEV_1 decline. A) Blood eosinophil count <50 cells/µl; B) Blood eosinophil count 50-349 cells/µl; C) Blood eosinophil count ≥350 cells/µL

Figure S2. Impact of annual exacerbation rate on annual FEV_1 decline in patients receiving ICS and patients not receiving ICS by blood eosinophil count. Error bars represent the 95% confidence interval of the mean FEV_1 decline. A) Blood eosinophil count <50 cells/µl; B) Blood eosinophil count 50-449 cells/µl; C) Blood eosinophil count ≥450 cells/µl

Figure S3. Impact of annual exacerbation rate on FEV_1 decline in COPD patients without asthma ever recorded receiving ICS N=7,259) and similar patients not receiving ICS (N=3,009) by blood eosinophil count. Error bars represent the 95% confidence interval of the mean FEV_1 decline. A) Blood eosinophil count <50 cells/µl; B) Blood eosinophil count 50-349 cells/µl; C) Blood eosinophil count ≥350 cells/µl

Figure S4. Mean FEV_1 decline in patients receiving ICS and patients not receiving ICS by level of adherence to maintenance therapy

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