Supplementary Methods

Data Analysis

To assess the robustness of findings with regards to potential restriction of the study population due to the matching, the inverse probability of treatment weighting (IPTW) approach, which uses all available patients, was used for sensitivity analyses.

Ethical approval

OPCRD has been reviewed and ethically approved by the NHS Health Research Authority to hold and process anonymised data (Research Ethics Committee reference: 15/EM/0150). Use of OPCRD data for this study was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) Committee (ADEPT Approval Reference 1417). Use of CPRD data was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Authority (ISAC reference number 17_175). The study was registered with the European Network Centre for Pharmacoepidemiology and Pharmacovigilance (registration number EUPAS-19323).

Substances used by the patients in the different inhalers.

Inhaler type	Substance(s)
Inhaled corticosteroids (ICS), single compound inhaler	beclometasone budesonide ciclesonide fluticasone propionate mometasone
Long-acting beta-adrenoceptor agonist (LABA), single compound inhaler	formoterol indacaterol olodaterol salmeterol
Long-acting muscarinic antagonists (LAMA), single compound inhaler	aclidinium glycopyrronium tiotropium umeclidinium
ICS+LABA fixed dose combination inhaler	beclometasone + formoterol

	budesonide + formoterol fluticasone propionate + salmeterol fluticasone furoate + vilanterol
LAMA+LABA fixed dose combination inhaler	umeclidinium + vilanterol aclidinium + formoterol glycopyrronium + indacaterol

Supplementary Results

Supplementary Table 1. Residual confounders adjusted for in the matched models

Covariate	1	2	3	4	5	6	7	8	9	10	11	12	13
Age	x	x	x	x	x	x	x	x	x	x	x	x	x
Gender	x	x	x	x	x	x	x	x	x	x	x	x	x
Exacerbations													
Antibiotics courses	x				x								
OCS courses						x					x		
OCS average daily dose						x	x						
OCS maintenance prescriptions						x							
Time since last exacerbation		x											
Time since last OCS course			x										
Time since last antibiotics course								x					
Time since last exacerbation									x				
SAMA prescriptions							x						x
SAMA cumulative dose		x					x						x
SABA prescriptions							x						
LAMA prescriptions						x							
Mucolytics prescriptions							x						
Nedocromil prescriptions													x
Sinusitis diagnosis													x
Glaucoma diagnosis								x					
CKD diagnosis								x					
Cataract diagnosis						x	x						
GERD status						x	x						
GOLD risk													x
Nasal polyps diagnosis							x						
Sleep disorder diagnosis							x						
Sleep apnoea diagnosis													x
Myocardial infarction history							x	x					
Anxiety/depression diagnosis							x						
Asthma ever							x	x					

1: First exacerbation; 2: First acute respiratory event; 3: Treatment failure; 4: First acute OCS course; 5: First antibiotics course; 6: Pneumonia diagnosis; 7: First HES hospitalisation; 8: First HES A&E attendance; 9: Exacerbation rate; 10: Acute OCS courses rate; 11: Antibiotics courses rate; 12: Acute respiratory events rate; 13: mMRC ≥2

Supplementary Table 2. Patient baseline characterisation, matched

Variable		LAMA/LABA (N=466)	Triple therapy (N=1,181)	P	SMD
BMI (kg/m2)	N (% non-missing)	463 (99.4)	1,167 (98.8)	0.095	6.8
	Mean (SD)	27.6 (6.2)	27.1 (6.6)		
	Median (IQR)	27.2 (23.1-30.6)	26.2 (22.7-30.5)		
Rhinitis diagnosis	Never, n (%)	394 (84.5)	1,004 (85.0)	0.964	1.0
	Active, n (%)	34 (7.3)	82 (6.9)		
	Ever, not active, n (%)	38 (8.2)	95 (8.0)		
Eczema diagnosis	Never, n (%)	342 (73.4)	845 (71.5)	0.503	3.0
	Active, n (%)	12 (2.6)	43 (3.6)		
	Ever, not active, n (%)	112 (24.0)	293 (24.8)		
Nasal polyps, ever	Yes, n (%)	7 (1.5)	12 (1.0)	0.405	4.4
Chronic sinusitis diagnosis, ever	Yes, n (%)	44 (9.4)	102 (8.6)	0.605	2.8
Pneumonia event, ever	Yes, n (%)	16 (3.4)	45 (3.8)	0.715	2.0
Bronchiectasis diagnosis, ever	Yes, n (%)	14 (3.0)	37 (3.1)	0.892	0.7
Gastroesophageal reflux disease diagnosis	Never, n (%)	365 (78.3)	954 (80.8)	0.525	6.0
	Active, n (%)	73 (15.7)	166 (14.1)		
	Ever, not active, n (%)	28 (6.0)	61 (5.2)		
Cardiovascular disease diagnosis, ever	Yes, n (%)	193 (41.4)	490 (41.5)	0.978	0.2
Ischaemic heart disease diagnosis, ever	Yes, n (%)	104 (22.3)	272 (23.0)	0.756	1.7
Heart failure diagnosis, ever	Yes, n (%)	32 (6.9)	80 (6.8)	0.946	0.4
Myocardial infarction diagnosis, ever	Yes, n (%)	52 (11.2)	133 (11.3)	0.953	0.3
Hypertension diagnosis, ever	Yes, n (%)	33 (7.1)	85 (7.2)	0.935	0.4
Diabetes diagnosis, ever	Yes, n (%)	65 (13.9)	154 (13.0)	0.625	2.7
Osteoporosis diagnosis, ever	Yes, n (%)	31 (6.7)	75 (6.4)	0.822	1.2
Sleep apnoea, ever	Yes, n (%)	3 (0.6)	15 (1.3)	0.271	6.4
Sleeping disorders, ever	Yes, n (%)	89 (19.1)	224 (19.0)	0.951	0.3
Glaucoma, ever	Yes, n (%)	14 (3.0)	48 (4.1)	0.309	5.7

Variable		LAMA/LABA (N=466)	Triple therapy (N=1,181)	P	SMD
Cataract, ever	Yes, n (%)	54 (11.6)	163 (13.8)	0.231	6.6
Chronic kidney disease diagnosis, ever	Yes, n (%)	69 (14.8)	169 (14.3)	0.796	1.4
Anxiety and/or depression diagnosis, ever	Yes, n (%)	212 (45.5)	527 (44.6)	0.749	1.7
Charlson Comorbidity Index	Mean (SD)	1.5 (0.9)	1.5 (0.9)	0.983	0.1
	Median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)		
Blood eosinophil count (10^9 cells/L)	N (% non-missing)	391 (83.9)	983 (83.2)	0.760	0.5
	Mean (SD)	0.3 (0.2)	0.3 (0.2)		
	Median (IQR)	0.2 (0.1-0.3)	0.2 (0.1-0.3)		
Time since blood eosinophil count reading	N (% non-missing)	391 (83.9)	983 (83.2)	0.478	5.9
	< 6 months, n (%)	191 (48.8)	437 (44.5)		
	6 <12 months, n (%)	76 (19.4)	206 (21.0)		
	2 years, n (%)	67 (17.1)	178 (18.1)		
	3 years, n (%)	26 (6.6)	87 (8.9)		
	4 years, n (%)	19 (4.9)	54 (5.5)		
	5 years, n (%)	12 (3.1)	21 (2.1)		
Neutrophil count (10^9 cells/L)	N (% non-missing)	370 (79.4)	883 (74.8)	0.270	10.3
	Mean (SD)	4.9 (1.8)	5.1 (2.1)		
	Median (IQR)	4.7 (3.6-5.8)	4.7 (3.7-6.0)		
Neutrophil count (categorised; 10^9 cells/L)	N (% non-missing)	370 (79.4)	883 (74.8)	0.344	4.3
	<2.0, n (%)	2 (0.5)	10 (1.1)		
	≥2.0 - <7.5, n (%)	337 (91.1)	782 (88.6)		
	≥7.5, n (%)	31 (8.4)	91 (10.3)		
Lymphocyte count (10^9 cells/L)	N (% non-missing)	367 (78.8)	880 (74.5)	0.097	9.4
	Mean (SD)	2.2 (0.9)	2.1 (0.9)		
	Median (IQR)	2.1 (1.6-2.6)	2.0 (1.5-2.6)		
Lymphocyte count (categorised; 10^9 cells/L)	N (% non-missing)	367 (78.8)	880 (74.5)	0.288	8.6
	<1.0, n (%)	9 (2.5)	38 (4.3)		

Variable		LAMA/LABA (N=466)	Triple therapy (N=1,181)	P	SMD
	≥1.0 - <4.5, n (%)	351 (95.6)	826 (93.9)		
	≥4.5, n (%)	7 (1.9)	16 (1.8)		
Leucocyte count (10^9 cells/L)	N (% non-missing)	427 (91.6)	1,073 (90.9)	0.010	15.8
	Mean (SD)	6.4 (2.8)	6.9 (3.1)		
	Median (IQR)	6.2 (4.3-8.4)	6.8 (4.6-8.9)		
Leucocyte count (categorised; 10^9 cells/L)	N (% non-missing)	427 (91.6)	1,073 (90.9)	0.305	8.6
	<4.0, n (%)	91 (21.3)	194 (18.1)		
	≥4 - <11, n (%)	307 (71.9)	794 (74.0)		
	≥11, n (%)	29 (6.8)	85 (7.9)		
PDE4 inhibitors prescriptions	0, n (%)	466 (100.0)	1,181 (100.0)		0.0
Macrolides prescriptions	≥1, n (%)	156 (33.5)	436 (36.9)	0.190	7.2
Mucolytics prescriptions	≥1, n (%)	53 (11.4)	169 (14.3)	0.116	8.8
Theophylline prescriptions	≥1, n (%)	12 (2.6)	41 (3.5)	0.353	5.2
LTRA prescriptions	≥1, n (%)	4 (0.9)	12 (1.0)	0.769	1.6
Nedocromil prescriptions	≥1, n (%)	1 (0.2)	2 (0.2)	0.846	1.0
SABA average daily dose (salbutamol equivalent µg)	Mean (SD)	382.9 (386.3)	385.2 (443.7)	0.164	0.6
	Median (IQR)	274.0 (109.6-602.7)	219.2 (54.8-602.7)		
SABA inhalers	0, n (%)	63 (13.5)	237 (20.1)	0.005	5.5
	1-2, n (%)	92 (19.7)	214 (18.1)		
	3-6, n (%)	120 (25.8)	243 (20.6)		
	7-10, n (%)	71 (15.2)	184 (15.6)		
	11-16, n (%)	86 (18.5)	185 (15.7)		
	≥17, n (%)	34 (7.3)	118 (10.0)		
SAMA average daily dose (mcg)	Mean (SD)	16.1 (55.4)	17.0 (64.9)	0.538	1.5
	Median (IQR)	7.2 (0.0-17.8)	5.9 (0.0-17.8)		
SAMA average daily dose (mcg; categorised))	0, n (%)	141 (30.3)	352 (29.8)	0.016	7.1
	1-20, n (%)	265 (56.9)	716 (60.6)		

Variable		LAMA/LABA (N=466)	Triple therapy (N=1,181)	P	SMD
	21-40, n (%)	34 (7.3)	79 (6.7)		
	41-60, n (%)	14 (3.0)	10 (0.8)		
	61-80, n (%)	2 (0.4)	1 (0.1)		
	>80, n (%)	10 (2.1)	23 (1.9)		
OCS average daily dose (mg)	Mean (SD)	1.6 (2.2)	1.6 (2.6)	0.182	0.5
	Median (IQR)	1.0 (0.4-2.1)	0.9 (0.0-1.9)		
Acute Respiratory Events, number in baseline year*	Mean (SD)	3.8 (2.5)	3.8 (2.5)	0.680	1.1
	Median (IQR)	3.0 (2.0-5.0)	3.0 (2.0-5.0)		
Number of exacerbations in baseline year*	Mean (SD)	2.7 (1.3)	2.8 (1.3)	0.383	4.1
	Median (IQR)	2.0 (2.0-3.0)	2.0 (2.0-3.0)		
Days since last exacerbation	Mean (SD)	64.7 (68.1)	61.7 (72.7)	0.043	4.3
	Median (IQR)	42.0 (14.0-99.0)	35.0 (8.0-85.0)		
Days since last exacerbation (categorised)	0, n (%)	58 (12.4)	202 (17.1)	0.002	9.6
	1-14, n (%)	60 (12.9)	174 (14.7)		
	15-30, n (%)	81 (17.4)	172 (14.6)		
	31-60, n (%)	95 (20.4)	227 (19.2)		
	61-90, n (%)	44 (9.4)	128 (10.8)		
	91-180, n (%)	97 (20.8)	164 (13.9)		
	181-270, n (%)	22 (4.7)	91 (7.7)		
	271-360, n (%)	9 (1.9)	23 (1.9)		
Number of acute OCS courses in baseline year*	Mean (SD)	1.7 (1.5)	1.7 (1.6)	0.791	0.4
	Median (IQR)	2.0 (1.0-2.0)	2.0 (1.0-2.0)		
Days since last OCS prescription	Mean (SD)	1447.0 (4932.7)	1390.2 (5864.0)	0.386	1.0
	Median (IQR)	70.0 (21.0-247.0)	67.0 (19.0-286.0)		
Days since last OCS prescription (categorised)	0, n (%)	46 (9.9)	138 (11.7)	0.112	3.0
	1-14, n (%)	37 (7.9)	124 (10.5)		
	15-30, n (%)	64 (13.7)	138 (11.7)		

Variable		LAMA/LABA (N=466)	Triple therapy (N=1,181)	P	SMD
	31-60, n (%)	73 (15.7)	163 (13.8)		
	61-90, n (%)	33 (7.1)	91 (7.7)		
	91-180, n (%)	72 (15.5)	143 (12.1)		
	181-270, n (%)	27 (5.8)	80 (6.8)		
	271-360, n (%)	19 (4.1)	67 (5.7)		
	361-730, n (%)	8 (1.7)	40 (3.4)		
	>730, n (%)	87 (18.7)	197 (16.7)		

Variable		LAMA/LABA (N=466)	Triple therapy (N=1,181)	P	SMD
Number of antibiotic courses in baseline year*	Mean (SD)	1.7 (1.2)	1.7 (1.2)	0.692	2.7
	Median (IQR)	2.0 (1.0-2.0)	2.0 (1.0-2.0)		
Days since last antibiotics prescription	Mean (SD)	1071.5 (3409.4)	945.3 (4258.5)	0.161	3.3
	Median (IQR)	89.5 (29.0-259.0)	78.0 (25.0-243.0)		
Days since last antibiotics prescription (categorised)	0, n (%)	27 (5.8)	130 (11.0)	<0.001	7.1
	1-14, n (%)	40 (8.6)	95 (8.0)		
	15-30, n (%)	54 (11.6)	110 (9.3)		
	31-60, n (%)	67 (14.4)	183 (15.5)		
	61-90, n (%)	46 (9.9)	120 (10.2)		
	91-180, n (%)	93 (20.0)	153 (13.0)		
	181-270, n (%)	28 (6.0)	133 (11.3)		
	271-360, n (%)	31 (6.7)	53 (4.5)		
	361-730, n (%)	11 (2.4)	43 (3.6)		
	>730, n (%)	69 (14.8)	161 (13.6)		
GP consultations for COPD, number in baseline year*	Mean (SD)	1.9 (2.5)	2.0 (2.5)	0.282	2.6
	Median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)		
GP consultations for COPD, number in baseline year* (categorised)	0, n (%)	101 (21.7)	240 (20.3)	0.177	6.1
	1, n (%)	178 (38.2)	414 (35.1)		
	2-4, n (%)	139 (29.8)	415 (35.1)		
	5-7, n (%)	39 (8.4)	79 (6.7)		
	≥8, n (%)	9 (1.9)	33 (2.8)		
GP consultations, number in baseline year*	Mean (SD)	16.7 (9.9)	16.0 (9.8)	0.124	6.4
	Median (IQR)	14.0 (10.0-20.0)	14.0 (9.0-20.0)		
GP consultations, number in baseline year* (categorised)	0-1, n (%)	3 (0.6)	2 (0.2)	0.093	8.2
	2-4, n (%)	6 (1.3)	39 (3.3)		
	5-8, n (%)	63 (13.5)	195 (16.5)		
	9-13, n (%)	140 (30.0)	340 (28.8)		

Variable		LAMA/LABA (N=466)	Triple therapy (N=1,181)	P	SMD
	14-17, n (%)	86 (18.5)	210 (17.8)		
	18-22, n (%)	78 (16.7)	170 (14.4)		
	≥23, n (%)	90 (19.3)	225 (19.1)		

P = P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SMD = Standardised mean difference;

*includes the index date

Supplementary Table 3. Number of drugs other than LAMA taken by patients in baseline year. Medication groups considered: PDE4 inhibitors, macrolides, mucolytics, nedocromil, leukotriene receptor antagonists, theophylline, maintenance OCS. No patients used ICS or LABA in baseline.

	Unmatched		Matched	
Number of other drugs	**LAMA/LABA (N=492)**	**Triple therapy (N=2,603)**	**LAMA/LABA (N=466)**	**Triple therapy (N=1,181)**
0	255 (51.8)	1,158 (44.5)	238 (51.1)	575 (48.7)
1	180 (36.6)	1,053 (40.5)	174 (37.3)	442 (37.4)
2	48 (9.8)	302 (11.6)	46 (9.9)	125 (10.6)
3	7 (1.4)	75 (2.9)	6 (1.3)	35 (3.0)
4	2 (0.4)	13 (0.5)	2 (0.4)	3 (0.3)
5	(0.0)	2 (0.1)	(0.0)	1 (0.1)
Standardised Mean Difference	16.1		8.0	
Pearson χ^2, P value	0.043		0.41	

Supplementary Table 4. Duration of index drug treatment and drugs switched to

	Duration of LAMA/LABA use					
Switched to	>1-3 months	>3-6 months	>6-12 months	>1-2 years	>2 years	Total
None	31 (39.2)	37 (34.9)	57 (46.0)	63 (64.3)	43 (72.9)	231 (49.6)
LAMA		17 (16.0)	15 (12.1)	11 (11.2)	6 (10.2)	49 (10.5)
LABA	4 (5.1)	11 (10.4)	9 (7.3)	2 (2.0)	3 (5.1)	29 (6.2)
ICS/LAMA		1 (0.9)				1 (0.2)
ICS/LABA		1 (0.9)	3 (2.4)			4 (0.9)
LAMA/LABA/ICS	44 (55.7)	39 (36.8)	40 (32.3)	22 (22.4)	7 (11.9)	152 (32.6)
Total	79	106	124	98	59	466
	Duration of Triple Therapy use					
Switched to	>1-3 months	>3-6 months	>6-12 months	>1-2 years	>2 years	Total
None	79 (100.0)	84 (32.7)	120 (46.0)	165 (61.6)	233 (73.7)	681 (57.7)
LAMA		122 (47.5)	82 (31.4)	58 (21.6)	27 (8.5)	289 (24.5)
ICS			1 (0.4)			1 (0.1)
LABA				1 (0.4)		1 (0.1)
ICS/LAMA			1 (0.4)	2 (0.7)	1 (0.3)	4 (0.3)
LAMA/LABA		11 (4.3)	5 (1.9)	4 (1.5)	6 (1.9)	26 (2.2)
ICS/LABA		40 (15.6)	52 (19.9)	38 (14.2)	49 (15.5)	179 (15.2)
Total	79	257	261	268	316	1,181

Supplementary Table 5. Baseline characteristics of unmatched cohort

Variable		LAMA/LABA (N=492)	Triple therapy (N=2,603)	P	SMD
Age (years)	Mean (SD)	69.0 (10.7)	69.5 (10.2)	0.325	4.8
	Median (IQR)	69.0 (14.5)	70.0 (14.0)		
Age (years; categorised)	≥40 <60, n (%)	97 (19.7)	438 (16.8)	0.247	7.8
	≥60 <80, n (%)	315 (64.0)	1,696 (65.2)		
	≥80, n (%)	80 (16.3)	469 (18.0)		
Gender	Male, n (%)	246 (50.0)	1,329 (51.1)	0.667	2.1
Index year	Mean (SD)	2013.4 (3.4)	2011.6 (2.9)	<0.001	57.7
	Median (IQR)	2015.0 (5.0)	2012.0 (4.0)		
BMI (kg/m2)	N (% non-missing)	489 (99.4)	2,553 (98.1)	0.010	10.5
	Mean (SD)	27.5 (6.2)	26.9 (6.5)		
	Median (IQR)	27.1 (23.3-30.5)	26.1 (22.5-30.3)		
BMI (kg/m2; categorised)	N (% non-missing)	489 (99.4)	2,553 (98.1)	0.113	11.3
	<18.5, n (%)	23 (4.7)	169 (6.6)		
	≥18.5-<25, n (%)	153 (31.3)	889 (34.8)		
	≥25-<30, n (%)	170 (34.8)	820 (32.1)		
	≥30, n (%)	143 (29.2)	675 (26.4)		
Current smoker	No, n (%)	266 (54.1)	1,468 (56.4)	0.339	4.7
	Yes, n (%)	226 (45.9)	1,135 (43.6)		
Asthma diagnosis, ever	Yes, n (%)	39 (7.9)	317 (12.2)	0.007	14.2
Rhinitis diagnosis	Never, n (%)	415 (84.3)	2,258 (86.7)	0.361	6.2
	Active, n (%)	35 (7.1)	154 (5.9)		
	Ever, not active, n (%)	42 (8.5)	191 (7.3)		
Eczema diagnosis	Never, n (%)	362 (73.6)	1,827 (70.2)	0.108	5.7
	Active, n (%)	14 (2.8)	124 (4.8)		
	Ever, not active, n (%)	116 (23.6)	652 (25.0)		

Variable		LAMA/LABA (N=492)	Triple therapy (N=2,603)	P	SMD
Nasal polyps	Yes, n (%)	7 (1.4)	37 (1.4)	0.998	0.0
Chronic sinusitis diagnosis	Yes, n (%)	47 (9.6)	193 (7.4)	0.104	7.7
Pneumonia event	Yes, n (%)	19 (3.9)	94 (3.6)	0.786	1.3
Bronchiectasis diagnosis	Yes, n (%)	15 (3.0)	91 (3.5)	0.617	2.5
Gastroesophageal reflux disease diagnosis	Never, n (%)	382 (77.6)	2,152 (82.7)	0.013	13.7
	Active, n (%)	79 (16.1)	348 (13.4)		
	Ever, not active, n (%)	31 (6.3)	103 (4.0)		
Cardiovascular disease diagnosis	Yes, n (%)	211 (42.9)	1,030 (39.6)	0.169	6.7
Ischaemic heart disease diagnosis	Yes, n (%)	109 (22.2)	560 (21.5)	0.751	1.6
Heart failure diagnosis	Yes, n (%)	33 (6.7)	174 (6.7)	0.985	0.1
Myocardial infarction diagnosis	Yes, n (%)	53 (10.8)	281 (10.8)	0.988	0.1
Hypertension diagnosis	Yes, n (%)	33 (6.7)	187 (7.2)	0.706	1.9
Diabetes diagnosis	Yes, n (%)	67 (13.6)	323 (12.4)	0.459	3.6
Osteoporosis diagnosis	Yes, n (%)	34 (6.9)	202 (7.8)	0.515	3.3
Sleep apnoea	Yes, n (%)	3 (0.6)	25 (1.0)	0.451	4.0
Sleeping disorders	Yes, n (%)	95 (19.3)	490 (18.8)	0.801	1.2
Glaucoma	Yes, n (%)	15 (3.0)	100 (3.8)	0.394	4.3
Cataract	Yes, n (%)	58 (11.8)	341 (13.1)	0.426	4.0
Chronic kidney disease diagnosis	Yes, n (%)	75 (15.2)	358 (13.8)	0.382	4.2
Anxiety and/or depression diagnosis	Yes, n (%)	227 (46.1)	1,075 (41.3)	0.046	9.8
Charlson Comorbidity Index	Mean (SD)	1.5 (0.9)	1.5 (0.9)	0.686	0.7
	Median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)		
Charlson Comorbidity Index (categorised)	≤ 1, n (%)	349 (70.9)	1,874 (72.0)	0.639	0.7
	2-4, n (%)	84 (17.1)	425 (16.3)		
	5-9, n (%)	26 (5.3)	109 (4.2)		
	≥10, n (%)	33 (6.7)	195 (7.5)		

Variable		LAMA/LABA (N=492)	Triple therapy (N=2,603)	P	SMD
Blood eosinophil count (10^9 cells/L)	N (% non-missing)	413 (83.9)	2,157 (82.9)	0.871	0.8
	Mean (SD)	0.3 (0.2)	0.3 (0.2)		
	Median (IQR)	0.2 (0.1-0.3)	0.2 (0.1-0.3)		
Blood eosinophil count (categorised; 10^9 cells/L)	N (% non-missing)	413 (83.9)	2,157 (82.9)	0.016	2.4
	<.05, n (%)	8 (1.9)	102 (4.7)		
	.05-.14, n (%)	117 (28.3)	528 (24.5)		
	.15-.24, n (%)	118 (28.6)	640 (29.7)		
	.25-.34, n (%)	83 (20.1)	389 (18.0)		
	.35-.44, n (%)	28 (6.8)	218 (10.1)		
	.45-.54, n (%)	23 (5.6)	114 (5.3)		
	.55-.64, n (%)	10 (2.4)	73 (3.4)		
	≥.65, n (%)	26 (6.3)	93 (4.3)		
Time since blood eosinophil count reading	N (% non-missing)	413 (83.9)	2,157 (82.9)	0.292	7.5
	< 6 months, n (%)	202 (48.9)	923 (42.8)		
	6 <12 months, n (%)	80 (19.4)	481 (22.3)		
	2 years, n (%)	70 (16.9)	407 (18.9)		
	3 years, n (%)	30 (7.3)	186 (8.6)		
	4 years, n (%)	19 (4.6)	107 (5.0)		
	5 years, n (%)	12 (2.9)	53 (2.5)		
Neutrophil count (10^9 cells/L)	N (% non-missing)	394 (80.1)	1,939 (74.5)	0.326	8.3
	Mean (SD)	4.9 (1.8)	5.1 (2.1)		
	Median (IQR)	4.7 (3.6-5.8)	4.7 (3.7-6.0)		
Neutrophil count (categorised; 10^9 cells/L)	N (% non-missing)	394 (80.1)	1,939 (74.5)	0.104	3.2
	<2.0, n (%)	2 (0.5)	31 (1.6)		
	≥2.0 - <7.5, n (%)	358 (90.9)	1,700 (87.7)		
	≥7.5, n (%)	34 (8.6)	208 (10.7)		
Lymphocyte count (10^9 cells/L)	N (% non-missing)	391 (79.5)	1,933 (74.3)	0.261	7.1

Variable		LAMA/LABA (N=492)	Triple therapy (N=2,603)	P	SMD
	Mean (SD)	2.2 (0.9)	2.2 (0.9)		
	Median (IQR)	2.1 (1.6-2.6)	2.1 (1.5-2.6)		
Lymphocyte count (categorised; 10^9 cells/L)	N (% non-missing)	391 (79.5)	1,933 (74.3)	0.131	9.5
	<1.0, n (%)	10 (2.6)	94 (4.9)		
	≥1.0 - <4.5, n (%)	374 (95.7)	1,803 (93.3)		
	≥4.5, n (%)	7 (1.8)	36 (1.9)		
Leucocyte count (10^9 cells/L)	N (% non-missing)	452 (91.9)	2,352 (90.4)	0.079	9.7
	Mean (SD)	6.4 (2.8)	6.7 (3.1)		
	Median (IQR)	6.1 (4.3-8.4)	6.6 (4.3-8.7)		
Leucocyte count (categorised; 10^9 cells/L)	N (% non-missing)	452 (91.9)	2,352 (90.4)	0.811	2.0
	<4.0, n (%)	93 (20.6)	480 (20.4)		
	≥4 - <11, n (%)	328 (72.6)	1,690 (71.9)		
	≥11, n (%)	31 (6.9)	182 (7.7)		
PDE4 inhibitors prescriptions	≥1, n (%)	0 (0.0)	1 (0.0)	0.664	2.8
Macrolides prescriptions	≥1, n (%)	162 (32.9)	1,073 (41.2)	0.001	17.2
Mucolytics prescriptions	≥1, n (%)	55 (11.2)	347 (13.3)	0.193	6.6
Theophylline prescriptions	≥1, n (%)	13 (2.6)	93 (3.6)	0.298	5.4
LTRA prescriptions	≥1, n (%)	4 (0.8)	39 (1.5)	0.234	6.4
Nedocromil prescriptions	≥1, n (%)	1 (0.2)	3 (0.1)	0.618	2.2
SABA prescriptions	0, n (%)	65 (13.2)	525 (20.2)	0.003	7.1
	1-2, n (%)	116 (23.6)	495 (19.0)		
	3-5, n (%)	102 (20.7)	511 (19.6)		
	6-9, n (%)	112 (22.8)	536 (20.6)		
	≥10, n (%)	97 (19.7)	536 (20.6)		
SABA inhalers	0, n (%)	65 (13.2)	525 (20.2)	0.001	4.0
	1-2, n (%)	105 (21.3)	449 (17.2)		
	3-6, n (%)	124 (25.2)	560 (21.5)		

Variable		LAMA/LABA (N=492)	Triple therapy (N=2,603)	P	SMD
	7-10, n (%)	73 (14.8)	404 (15.5)		
	11-16, n (%)	89 (18.1)	404 (15.5)		
	≥17, n (%)	36 (7.3)	261 (10.0)		
SABA average daily dose (salbutamol equivalent µg)	Mean (SD)	384.5 (415.8)	388.3 (465.1)	0.177	0.9
	Median (IQR)	274.0 (106.8-602.7)	219.2 (54.8-547.9)		
SABA average daily dose (salbutamol equivalent µg; categorised)	0, n (%)	65 (13.2)	525 (20.2)	0.007	7.5
	1-100, n (%)	57 (11.6)	244 (9.4)		
	101-200, n (%)	89 (18.1)	408 (15.7)		
	201-300, n (%)	58 (11.8)	252 (9.7)		
	301-400, n (%)	45 (9.1)	233 (9.0)		
	>400, n (%)	178 (36.2)	941 (36.2)		
SAMA prescriptions	0, n (%)	439 (89.2)	2,260 (86.8)	0.530	7.4
	1, n (%)	12 (2.4)	72 (2.8)		
	2, n (%)	7 (1.4)	46 (1.8)		
	≥3, n (%)	34 (6.9)	225 (8.6)		
SAMA average daily dose (mcg)	Mean (SD)	22.7 (86.9)	13.4 (48.4)	0.775	13.1
	Median (IQR)	5.9 (0.0-17.8)	5.9 (0.0-17.8)		
SAMA average daily dose (mcg; categorised)	0, n (%)	157 (31.9)	740 (28.4)	<0.001	11.9
	1-20, n (%)	268 (54.5)	1,642 (63.1)		
	21-40, n (%)	35 (7.1)	168 (6.5)		
	41-60, n (%)	14 (2.8)	21 (0.8)		
	61-80, n (%)	2 (0.4)	2 (0.1)		
	>80, n (%)	16 (3.3)	30 (1.2)		
LAMA prescriptions	0, n (%)	155 (31.5)	722 (27.7)	0.010	15.7
	1-3, n (%)	92 (18.7)	465 (17.9)		
	4-6, n (%)	81 (16.5)	338 (13.0)		

Variable		LAMA/LABA (N=492)	Triple therapy (N=2,603)	P	SMD
	7-9, n (%)	56 (11.4)	300 (11.5)		
	10-12, n (%)	64 (13.0)	469 (18.0)		
	≥13, n (%)	44 (8.9)	309 (11.9)		
OCS average daily dose (mg)	Mean (SD)	1.6 (2.3)	1.6 (2.4)	0.884	0.9
	Median (IQR)	1.0 (0.3-2.0)	1.0 (0.0-2.1)		
OCS average daily dose (mg; categorised)	<2.5, n (%)	397 (80.7)	2,144 (82.4)	0.703	4.1
	≥2.5 - <5, n (%)	56 (11.4)	282 (10.8)		
	≥5 - <7.5, n (%)	18 (3.7)	75 (2.9)		
	≥7.5, n (%)	21 (4.3)	102 (3.9)		
Acute Respiratory Events, number in baseline year*	Mean (SD)	3.8 (2.5)	3.9 (2.4)	0.151	4.3
	Median (IQR)	3.0 (2.0-5.0)	4.0 (2.0-5.0)		
Acute Respiratory Events, number in baseline year* (categorised)	0, n (%)	23 (4.7)	103 (4.0)	0.221	10.6
	1, n (%)	48 (9.8)	224 (8.6)		
	2, n (%)	94 (19.1)	416 (16.0)		
	3, n (%)	106 (21.5)	560 (21.5)		
	≥4, n (%)	221 (44.9)	1,300 (49.9)		
Number of exacerbations in baseline year*	Mean (SD)	2.7 (1.3)	2.8 (1.4)	0.021	10.3
	Median (IQR)	2.0 (2.0-3.0)	2.0 (2.0-3.0)		
Number of exacerbations in baseline year* (categorised)	2, n (%)	302 (61.4)	1,458 (56.0)	0.123	10.4
	3, n (%)	114 (23.2)	653 (25.1)		
	4, n (%)	36 (7.3)	253 (9.7)		
	≥5, n (%)	40 (8.1)	239 (9.2)		
Days since last exacerbation	Mean (SD)	64.0 (67.6)	60.0 (71.0)	0.008	5.8
	Median (IQR)	42.0 (14.0-98.5)	33.0 (7.0-85.0)		
Days since last exacerbation (categorised)	0, n (%)	62 (12.6)	465 (17.9)	0.001	11.6
	1-14, n (%)	64 (13.0)	397 (15.3)		
	15-30, n (%)	84 (17.1)	392 (15.1)		

Variable		LAMA/LABA (N=492)	Triple therapy (N=2,603)	P	SMD
	31-60, n (%)	99 (20.1)	465 (17.9)		
	61-90, n (%)	51 (10.4)	272 (10.4)		
	91-180, n (%)	100 (20.3)	370 (14.2)		
	181-270, n (%)	23 (4.7)	200 (7.7)		
	271-360, n (%)	9 (1.8)	42 (1.6)		
Acute OCS courses, number in baseline year*	Mean (SD)	1.7 (1.5)	1.8 (1.6)	0.201	7.4
	Median (IQR)	2.0 (1.0-2.0)	2.0 (1.0-2.0)		
Acute OCS courses, number in baseline year* (categorised)	0, n (%)	104 (21.1)	495 (19.0)	0.754	4.4
	1, n (%)	127 (25.8)	691 (26.5)		
	≥2, n (%)	258 (52.4)	1,401 (53.8)		
	4, n (%)	3 (0.6)	16 (0.6)		
Days since last OCS prescription	Mean (SD)	1484.1 (4888.5)	1192.8 (4773.6)	0.015	6.0
	Median (IQR)	78.0 (22.5-276.5)	62.0 (16.0-252.0)		
Days since last OCS prescription (categorised)	0, n (%)	47 (9.6)	321 (12.3)	0.007	10.1
	1-14, n (%)	37 (7.5)	304 (11.7)		
	15-30, n (%)	65 (13.2)	311 (11.9)		
	31-60, n (%)	76 (15.4)	351 (13.5)		
	61-90, n (%)	37 (7.5)	197 (7.6)		
	91-180, n (%)	76 (15.4)	309 (11.9)		
	181-270, n (%)	28 (5.7)	186 (7.1)		
	271-360, n (%)	22 (4.5)	124 (4.8)		
	361-730, n (%)	9 (1.8)	88 (3.4)		
	>730, n (%)	95 (19.3)	412 (15.8)		
Number of antibiotic courses in baseline year*	Mean (SD)	1.7 (1.2)	1.8 (1.3)	0.349	5.8
	Median (IQR)	2.0 (1.0-2.0)	2.0 (1.0-2.0)		
Number of antibiotic courses in baseline year* (categorised)	0, n (%)	83 (16.9)	433 (16.6)	0.278	6.0
	1, n (%)	123 (25.0)	643 (24.7)		

Variable		LAMA/LABA (N=492)	Triple therapy (N=2,603)	P	SMD
	2, n (%)	193 (39.2)	955 (36.7)		
	3, n (%)	68 (13.8)	366 (14.1)		
	4, n (%)	13 (2.6)	133 (5.1)		
	≥5, n (%)	12 (2.4)	73 (2.8)		
Days since last antibiotics prescription	Median (IQR)	86.0 (28.5-252.5)	80.0 (23.0-238.0)	0.171	3.2
Days since last antibiotics prescription (categorised)	0, n (%)	31 (6.3)	290 (11.1)	0.001	6.2
	1-14, n (%)	44 (8.9)	226 (8.7)		
	15-30, n (%)	56 (11.4)	255 (9.8)		
	31-60, n (%)	69 (14.0)	360 (13.8)		
	61-90, n (%)	51 (10.4)	250 (9.6)		
	91-180, n (%)	97 (19.7)	383 (14.7)		
	181-270, n (%)	30 (6.1)	279 (10.7)		
	271-360, n (%)	31 (6.3)	124 (4.8)		
	361-730, n (%)	12 (2.4)	86 (3.3)		
	>730, n (%)	71 (14.4)	350 (13.4)		
GOLD severity of airflow limitation	N (% non-missing)	392 (79.7)	2,166 (83.2)	0.002	17.4
	Mild (FEV1 % predicted >80), n (%)	45 (11.5)	204 (9.4)		
	Moderate (FEV1 % predicted [50,80)), n (%)	204 (52.0)	948 (43.8)		
	Severe (FEV1 % predicted [30,50)), n (%)	95 (24.2)	698 (32.2)		
	Very severe (FEV1 % predicted <30), n (%)	48 (12.2)	316 (14.6)		
GOLD risk groups (symptoms and risk based)	N (% non-missing)	407 (82.7)	2,109 (81.0)	0.001	18.0
	C, n (%)	251 (61.7)	1113 (52.8)		
	D, n (%)	156 (38.3)	996 (47.2)		
mMRC score	N (% non-missing)	407 (82.7)	2,109 (81.0)	0.010	16.5
	0: Not troubled by breathlessness, n (%)	38 (9.3)	191 (9.1)		

Variable		LAMA/LABA (N=492)	Triple therapy (N=2,603)	P	SMD
	1: Short of breath, n (%)	213 (52.3)	922 (43.7)		
	2: Slower in walking, n (%)	97 (23.8)	599 (28.4)		
	3: Stopping for breath, n (%)	51 (12.5)	314 (14.9)		
	4: Too breathless to leave the house, n (%)	8 (2.0)	83 (3.9)		
GP consultations for COPD, number in baseline year*	Mean (SD)	1.9 (2.5)	2.0 (2.4)	0.187	3.5
	Median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-3.0)		
GP consultations for COPD, number in baseline year* (categorised)	0, n (%)	104 (21.1)	523 (20.1)	0.332	6.8
	1, n (%)	192 (39.0)	935 (35.9)		
	2-4, n (%)	147 (29.9)	875 (33.6)		
	5-7, n (%)	39 (7.9)	192 (7.4)		
	≥8, n (%)	10 (2.0)	78 (3.0)		
GP consultations, number in baseline year*	Mean (SD)	16.8 (9.9)	16.2 (9.7)	0.102	6.1
	Median (IQR)	14.0 (11.0-20.0)	14.0 (10.0-20.0)		
GP consultations, number in baseline year* (categorised)	0-1, n (%)	3 (0.6)	8 (0.3)	0.319	8.1
	2-4, n (%)	6 (1.2)	66 (2.5)		
	5-8, n (%)	65 (13.2)	404 (15.5)		
	9-13, n (%)	145 (29.5)	766 (29.4)		
	14-17, n (%)	91 (18.5)	478 (18.4)		
	18-22, n (%)	86 (17.5)	400 (15.4)		
	≥23, n (%)	96 (19.5)	481 (18.5)		

P = P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SMD = Standardised difference; * includes the index date

Supplementary Table 6 - Sensitivity analysis excluding patients with history of asthma

N=1,470	Unadjusted		Adjusted		
Time until first	HR (95% CI)	P	HR (95% CI)	P	Adjusted for:
Exacerbation	0.84 (0.74-0.97)	0.014	0.81 (0.71-0.93)	**0.004**	Time since last exacerbation
Acute respiratory event	0.81 (0.72-0.92)	**0.001**	0.81 (0.72-0.92)	**0.001**	
Treatment failure	0.71 (0.62-0.80)	**<0.001**	0.68 (0.60-0.78)	**<0.001**	Time since last exacerbation
Acute OCS course	0.88 (0.76-1.01)	0.075	0.84 (0.72-0.98)	0.024	Time since last exacerbation
Antibiotics course	0.86 (0.73-1.00)	0.044	0.83 (0.71-0.98)	0.029	Number of antibiotics courses
Pneumonia	1.18 (0.72-1.94)	0.513	NC		
Hospitalisation	0.75 (0.46-1.20)	0.229	NC		
A&E	0.74 (0.44-1.25)	0.265	NC		

Supplementary Table 7. Results of model fit statistics comparing continuous and categorical effect modifiers

Presentation	Blood eosinophil count AIC	Blood eosinophil count BIC	Exacerbation rate AIC	Exacerbation rate BIC
First exacerbation				
Continuous	1322.2	1395.4	1811.9	1887.6
Categorical	1327.0	1421.0	1823.7	1921.0
First acute respiratory event				
Continuous	1567.4	1677.1	2162.0	2275.6
Categorical	1575.6	1706.2	2167.3	2302.5
Treatment failure				
Continuous	1445.2	1539.3	1968.8	2066.1
Categorical	1449.6	1564.5	1984.1	2103.1
First acute OCS course				
Continuous	1160.4	1207.4	1587.8	1636.4
Categorical	1168.0	1235.9	1598.5	1668.8
First antibiotics course				
Continuous	1050.0	1123.1	1462.0	1537.7
Categorical	1052.9	1146.9	1468.7	1566.0
Exacerbation rate				
Continuous	1251.1	1329.7	1707.7	1791.1
Categorical	1255.1	1352.2	1713.5	1816.5
Acute OCS courses rate				
Continuous	954.2	999.3	1299.0	1347.2
Categorical	959.9	1023.1	1313.4	1380.8
Antibiotics courses rate				
Continuous	929.6	1006.5	1273.9	1355.9
Categorical	931.0	1026.0	1284.4	1385.8
Acute respiratory events rate				
Continuous	1790.9	1837.8	2462.9	2512.4
Categorical	1796.0	1861.5	2467.1	2536.4
mMRC ≥2				
Continuous	176.3	244.6	243.5	322.4
Categorical	178.7	261.3	249.4	344.1

Categories used for blood eosinophil count: <0.15, 0.15-0.34, 0.35-0.44 and ≥0.45 10^9 cells/L. Categories used for exacerbation rate: 2, 3, 4 and ≥5 exacerbations/year.

AIC = Akaike's information criterion; BIC = Schwarz's Bayesian information criterion. Models for time until first pneumonia, hospital admission, and emergency room attendance could not be used to compare model fit

Supplementary Table 8. Adjusted marginal effects of TT compared to DB at different numbers of exacerbations in the baseline year from a model including an interaction term of treatment and the (continuous) number of exacerbations

	Interaction	2 exacerbations		3 exacerbations		4 exacerbations		5 exacerbations	
Time until …	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
First exacerbation	0.043	0.93 (0.70-1.22)	0.594	0.69 (0.49-0.99)	0.042	0.45 (0.20-0.99)	0.048	0.24 (0.05-1.15)	0.074
First acute respiratory event	0.003*	0.79 (0.66-0.95)	0.014	0.56 (0.38-0.81)	0.002	0.35 (0.15-0.80)	0.013	0.19 (0.04-0.87)	0.033
Treatment failure	0.058	0.88 (0.73-1.05)	0.159	0.71 (0.54-0.93)	0.014	0.52 (0.28-0.96)	0.036	0.33 (0.10-1.09)	0.068
First OCS course	0.018	1.06 (0.83-1.36)	0.640	0.83 (0.63-1.08)	0.166	0.55 (0.28-1.07)	0.077	0.29 (0.07-1.22)	0.092
First antibiotics course	0.469	0.82 (0.48-1.39)	0.454	0.67 (0.38-1.18)	0.168	0.53 (0.19-1.48)	0.225	0.39 (0.07-2.29)	0.298
Rate of …	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Exacerbations	0.072	0.95 (0.78-1.17)	0.648	0.84 (0.72-0.99)	0.036	0.74 (0.60-0.92)	0.007	0.66 (0.48-0.90)	0.010
OCS courses	0.205	0.87 (0.67-1.11)	0.262	0.78 (0.64-0.95)	0.013	0.70 (0.54-0.91)	0.008	0.63 (0.42-0.93)	0.021
Antibiotics courses	0.977	0.90 (0.70-1.16)	0.407	0.90 (0.74-1.10)	0.297	0.90 (0.67-1.22)	0.500	0.91 (0.57-1.44)	0.673
Acute respiratory events	0.801	0.80 (0.69-0.94)	0.005	0.79 (0.70-0.90)	0.000	0.78 (0.66-0.93)	0.004	0.77 (0.60-0.99)	0.043
Having …	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
mMRC ≥2	0.252	1.06 (0.94-1.20)	0.322	1.00 (0.90-1.11)	0.971	0.95 (0.82-1.10)	0.460	0.90 (0.73-1.10)	0.298

* P-value of interaction term <0.05 after adjustment for 10 statistical tests following Holm's method [22]

Supplementary Table 9. Adjusted marginal effects of TT compared to DB at different blood eosinophil counts from a model including an interaction term of treatment and the (continuous) blood eosinophil count

	Interaction	0.05 x10^9/L		0.15 x10^9/L		0.25 x 10^9/L		0.35 x 10^9/L		0.45 x 10^9/L		0.55 x10^9/L		0.65 x10^9/L	
Time until …	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
First exacerbation	0.015	1.11 (0.91-1.36)	0.320	1.01 (0.87-1.17)	0.867	0.92 (0.81-1.04)	0.196	0.84 (0.71-0.98)	0.031	0.75 (0.59-0.97)	0.025	0.68 (0.47-0.97)	0.032	0.60 (0.37-0.98)	0.041
First acute respiratory event	0.031	0.96 (0.82-1.12)	0.612	0.89 (0.79-1.01)	0.083	0.82 (0.72-0.93)	0.002	0.74 (0.62-0.89)	0.001	0.66 (0.50-0.87)	0.003	0.57 (0.38-0.86)	0.007	0.48 (0.27-0.87)	0.015
Treatment failure	0.016	1.04 (0.89-1.20)	0.641	0.97 (0.86-1.08)	0.553	0.90 (0.81-0.99)	0.030	0.83 (0.72-0.94)	0.005	0.75 (0.61-0.93)	0.008	0.68 (0.50-0.93)	0.015	0.61 (0.40-0.94)	0.024
First OCS course	<0.001*	1.24 (1.01-1.53)	0.038	1.10 (0.96-1.27)	0.177	0.97 (0.87-1.08)	0.595	0.84 (0.72-0.98)	0.027	0.72 (0.56-0.93)	0.013	0.61 (0.41-0.91)	0.016	0.50 (0.28-0.90)	0.022
First antibiotics course	0.417	0.94 (0.57-1.57)	0.818	0.87 (0.60-1.26)	0.452	0.80 (0.58-1.09)	0.160	0.73 (0.49-1.09)	0.121	0.67 (0.38-1.18)	0.165	0.61 (0.28-1.33)	0.218	0.56 (0.20-1.54)	0.263
Rate of …	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Exacerbations	0.389	0.94 (0.68-1.31)	0.724	0.89 (0.70-1.14)	0.365	0.85 (0.70-1.03)	0.102	0.80 (0.65-1.00)	0.052	0.76 (0.57-1.02)	0.071	0.72 (0.49-1.07)	0.105	0.69 (0.42-1.13)	0.140
OCS courses	0.396	0.90 (0.60-1.34)	0.594	0.84 (0.63-1.13)	0.256	0.79 (0.63-1.00)	0.053	0.74 (0.58-0.96)	0.024	0.70 (0.50-0.98)	0.040	0.66 (0.42-1.04)	0.072	0.62 (0.34-1.11)	0.106
Antibiotics courses	0.559	0.83 (0.55-1.25)	0.377	0.87 (0.65-1.17)	0.361	0.91 (0.72-1.16)	0.465	0.96 (0.72-1.27)	0.779	1.01 (0.68-1.50)	0.968	1.06 (0.62-1.80)	0.835	1.11 (0.56-2.20)	0.763
Acute respiratory events	0.261	0.91 (0.70-1.19)	0.503	0.86 (0.71-1.05)	0.136	0.82 (0.70-0.95)	0.010	0.77 (0.65-0.92)	0.003	0.73 (0.58-0.92)	0.008	0.69 (0.51-0.94)	0.020	0.65 (0.44-0.97)	0.037
Having …	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
mMRC ≥2	0.265	1.18 (0.94-1.49)	0.148	1.13 (0.96-1.33)	0.156	1.07 (0.94-1.21)	0.292	1.01 (0.88-1.17)	0.837	0.96 (0.79-1.18)	0.719	0.92 (0.70-1.20)	0.528	0.87 (0.61-1.23)	0.436

* P-value of interaction term <0.05 after adjustment for 10 statistical tests following Holm's method [22]