

SUPPLEMENTARY MATERIAL

SUPPLEMENTAL TABLE 1 International Classification of Disease 10th revision (ICD-10) used for the definition of comorbidities

Comorbidity	ICD-10 codes
Immunodeficiency with predominantly antibody defects	D80
Combined immunodeficiencies	D81
Immunodeficiency associated with other major defects	D82
Common variable immunodeficiency	D83
Other immunodeficiencies	D84
Sarcoidosis	D86
Other disorders involving the immune mechanism, not elsewhere classified	D89
Seropositive rheumatoid arthritis	M05
Other rheumatoid arthritis	M06
Polyarteritis nodosa and related conditions	M30
Systemic lupus erythematosus	M32
Dermatopolymyositis	M33
Systemic sclerosis	M34
Other systemic involvement of connective tissue	M35
Systemic disorders of connective tissue in diseases classified elsewhere	M36
Myositis	M60
Myocardial infarction	I21-I22
Atrial fibrillation	I48
Heart failure	I110, I42, I50, J81
Hypertension	I10-I15
Peripheral vascular disease	I700, I702, I709, I739
Cerebrovascular disease	I60-I64, G458, G459
Diabetes mellitus	E10-14
Renal failure	I120, I131, I132, E102, E112, E132, E142, N02-N08, N11, N14, N158, N159, N160, N162-N164, N168, N18, N19, N26
Asthma	J45
Bronchiectasis	J47

SUPPLEMENTAL TABLE 2 Cox-regression hazard estimates for risk of *Pseudomonas aeruginosa* with use of inhaled corticosteroids in the study population (N=21 408) after data imputation categorising missing BMI as ≥ 35 and missing FEV₁ as < 30 .

<i>Pseudomonas aeruginosa</i> event	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
ICS exposure, μg^a				
No use	ref		ref	
Low < 400	1.77 (1.33-2.36)	<0.0001	1.38 (1.03-1.84)	0.031
Moderate 400-800	3.37 (2.58-4.42)	<0.0001	2.15 (1.63-2.84)	<0.0001
High > 800	6.41 (5.00-8.20)	<0.0001	3.56 (2.74-4.63)	<0.0001
Accumulated OCS dose 365 days prior to cohort entry, mg				
No use	ref		ref	
Low < 1825	2.18 (1.86-2.55)	<0.0001	1.28 (1.09-1.52)	0.003
High ≥ 1825	3.23 (2.65-3.94)	<0.0001	1.48 (1.20-1.83)	0.0003
Active smoking^b	0.91 (0.77-1.06)	0.217	1.11 (0.94-1.31)	0.231
Age (per year increased)	1.03 (1.03-1.04)	<0.0001	1.03 (1.02-1.04)	<0.0001
Male	1.08 (0.93-1.24)	0.309	1.31 (1.14-1.52)	0.0002
BMI (per class increase)^c	0.80 (0.76-0.85)	<0.0001	0.81 (0.77-0.86)	<0.0001
GOLD stage (per increase to next stage)^d	1.44 (1.33-1.56)	<0.0001	1.45 (1.32-1.59)	<0.0001
Prescription of any antibiotics 365 days prior to cohort entry^e	2.88 (2.42-3.42)	<0.0001	2.08 (1.74-2.50)	<0.0001
Abbreviations: ICS; Inhaled Corticosteroids, BMI; Body Mass Index (kg/m^2), OCS; Oral Corticosteroids, FEV ₁ ; Forced expiratory volume in the first second. The model is adjusted for calendar year for study entry and all variables displayed in the table.				
^a Daily budesonide equivalent doses based on the accumulated ICS dose 365 days prior to cohort entry.				
^b Reference: never or former smoking.				
^c BMI class (kg/m^2); 1: <18.5 , 2: 18.5-24.9, 3: 25-29.9, 4: 30-34.9, 5: ≥ 35 .				
^d Increase in predicted FEV ₁ % severity stage defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).				
^e Reference: no prescription.				

SUPPLEMENTAL TABLE 3 Cox-regression hazard estimates for risk of *Pseudomonas aeruginosa* with use of inhaled corticosteroids in patients (N= 13 159) with no use of oral corticosteroids 365 days prior to cohort entry.

<i>Pseudomonas aeruginosa</i> event	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
ICS exposure, µg^a				
No use	ref		ref	
Low < 400	1.51 (1.06-2.16)	0.023	1.31 (0.92-1.88)	0.137
Moderate 400-800	2.48 (1.75-3.53)	<0.0001	1.90 (1.33-2.72)	0.0005
High > 800	5.13 (3.75-7.02)	<0.0001	3.65 (2.63-5.04)	<0.0001
Active smoking^b	0.93 (0.73-1.19)	0.565	1.15 (0.89-1.48)	0.282
Age (per year increased)	1.03 (1.02-1.05)	<0.0001	1.03 (1.02-1.04)	<0.0001
Male	1.21 (0.97-1.51)	0.087	1.49 (1.19-1.87)	0.0005
BMI (per class increase)^c	0.75 (0.66-0.85)	<0.0001	0.79 (0.69-0.90)	0.0003
GOLD stage (per increase to next stage)^d	1.87 (1.59-2.20)	<0.0001	1.55 (1.32-1.83)	<0.0001
Prescription of any antibiotics 365 days prior to cohort entry^e	2.21 (1.76-2.77)	<0.0001	2.04 (1.62-2.57)	<0.0001

Abbreviations: ICS; Inhaled Corticosteroids, BMI; Body Mass Index (kg/m²), FEV₁; Forced expiratory volume in the first second. The model is adjusted for calendar year for study entry and all variables displayed in the table.

^a Daily budesonide equivalent doses based on the accumulated ICS dose 365 days prior to cohort entry.

^b Reference: never or former smoking.

^c BMI class (kg/m²); 1: <18.5, 2: 18.5-24.9, 3: 25-29.9, 4: 30-34.9, 5: ≥35.

^d Increase in predicted FEV₁% severity stage defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

^e Reference: no prescription.

SUPPLEMENTAL TABLE 4 Cox-regression hazard estimates for risk of *Pseudomonas aeruginosa* with type of inhaled corticosteroids in patients (N= 14 785) exposed to ICS 365 days prior to cohort entry: user of Fluticasone (N=4326) versus user of other type of ICS (N=10 459).

<i>Pseudomonas aeruginosa</i> event	Adjusted HR (95% CI)	P-value
ICS type		
Fluticasone	1.60 (1.37-1.86)	<0.0001
Other type of ICS ^a	ref	
Daily dose of ICS, µg (median, IQR) ^b		
ICS type		
Fluticasone	986 (493-1808)	
Other type of ICS	473 (210-789)	

Abbreviations: ICS; Inhaled Corticosteroids.

^a Beclomethasone, budesonide, ciclesonide and mometasone.

^b Budesonide equivalent doses.

The model is adjusted for age (continuous, year), sex (male vs. female), severity of airway obstruction (percentage of predicted forced expiratory volume in the first second; FEV₁; stage 1-4), body mass index (BMI; class 1-5), smoking status (active vs. not active), antibiotic use (yes vs. no) and accumulated dose of oral corticosteroids (high vs. low) 365 days prior to cohort entry and calendar year for entry in DrCOPD.

SUPPLEMENTAL TABLE 5 Patient characteristics at cohort entry and according to ICS exposure in 13 332 propensity matched patients with COPD.

	All patients	Patients with high ICS exposure	Patients with no, low or moderate ICS exposure
Number of patients	13 332 (100)	4 931 (37)	8 401 (63)
Demographics			
Age (year), median (IQR)	69 (64-76)	69 (64-76)	69 (64-76)
Male	5 179 (38.9)	1 875 (38.0)	3 304 (39.3)
BMI, median (IQR)	25 (22-27)	25 (21-27)	25 (22-27)
BMI-class			
<18.5	1 255 (9.4)	548 (11.1)	707 (8.4)
18.5-24,9	4 198 (31.5)	1 643 (33.3)	2 555 (30.4)
25-29,9	5 764 (43.2)	1 917 (38.9)	3 847 (45.8)
30-34,9	1 362 (10.2)	540(11.1)	822 (9.8)
≥35	753(5.7)	283 (5.7)	470 (4.7)
Pulmonary parameters			
MRC, median (IQR)	3 (2-4)	3 (3-4)	3 (2-4)
FEV ₁ % predicted, median (IQR)	48 (35-51)	46 (33-50)	49 (36-52)
FEV₁% predicted, severity of spirometric obstruction			
≥ 80	280 (2.1)	120 (2.4)	160 (1.9)
50-79	3 464 (26.0)	1 215 (24.6)	2 249 (26.8)
30-49	7 516 (56.4)	2 666 (54.1)	4 850 (57.7)
<30	2 079 (15.5)	930 (18.9)	1 142 (13.6)
Active smoking status at study entry	3 816 (28.6)	1 388 (28.2)	2 428 (28.9)
Hospital-requiring COPD exacerbation 12 months prior to study entry			
0	5 684 (42.6)	1 942 (39.4)	3 742 (44.5)
1	2 605 (19.5)	911 (18.5)	1 694 (20.2)
≥ 2	5 043 (37.8)	2 078 (42.1)	2 965 (35.3)
All-cause hospitalisation 12 months prior to study entry	7 645 (57.3)	2 758 (55.9)	4 887(58.2)
Comorbidity			

Inflammatory polyarthropathy	325 (2.4)	101 (2.1)	224 (2.7)
Systemic connective tissue disorder	353 (2.7)	99 (2.0)	254 (3.0)
Myocardial infarction	1 050 (7.9)	379 (7.7)	671 (8.0)
Atrial fibrillation	1 941 (14.6)	642(13.0)	1 299 (15.5)
Heart failure	2 252 (16.9)	804 (16.3)	1 448 (17.2)
Hypertension	4 128 (31.0)	1 445 (29.3)	2 683 (31.9)
Renal failure	540 (4.1)	182 (3.7)	358 (4.3)
Peripheral vascular disease	1 063 (8.0)	347 (7.0)	716 (8.5)
Cerebrovascular disease	1 289 (9.7)	449 (9.1)	840 (10.0)
Diabetes mellitus, type 2	1 584 (11.9)	579 (11.7)	1 005 (12.0)
Asthma	2 219 (16.6)	1 128 (22.9)	1 091 (13.0)
Bronchiectasis	140 (1.1)	57 (1.2)	83 (1.0)
Oral corticosteroids ^a			
No use	6 420 (48.2)	2 146 (43.5)	4 274 (50.9)
Low dose	3 993 (37.5)	1 966 (39.9)	3 027 (37.5)
High dose	1 919 (14.4)	819 (16.6)	1 100 (13.1)
Theophylline	606 (4.6)	356 (7.2)	250 (3.0)
Respiratory inhalation medicine			
Long-acting beta2-agonist or long-acting muscarin-antagonist	9 778 (73.3)	4 198 (85.1)	5 580 (66.4)
Antibiotics ^b	9 061 (68.0)	3 445 (69.9)	5 616 (66.9)

Data are presented as n (%) or median (IQR), unless otherwise specified.

Abbreviations: ICS; inhaled corticosteroids, COPD; Chronic Obstructive Pulmonary Disease, IQR; Interquartile range, MRC; Medical Research Council Dyspnoea Scale, BMI; Body Mass Index (kg/m²), FEV₁; Forced Expiratory Volume in the first second

^a Low dose < 1825; high dose ≥1825 mg.

^b Any antibiotic drug.
