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Original research

Use of inhaled corticosteroids and risk of acquiring *Pseudomonas aeruginosa* in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background Inhaled corticosteroids (ICS) are commonly used to treat COPD and are associated with increased risk of pneumonia. The aim of this study was to assess if accumulated use of ICS is associated with a dose-dependent risk of a positive airway culture with *Pseudomonas aeruginosa* in patients with COPD.

Methods We conducted a multiregional epidemiological cohort study including Danish COPD patients followed in outpatient clinics during 2010–2017. ICS use was categorised based on accumulated prescriptions redeemed 365 days prior to cohort entry. Cox proportional hazard regression model was used to estimate the risk of acquiring *P. aeruginosa*. Propensity score matched models were used as sensitivity analyses.

Results A total of 21 408 patients were included in the study, of which 763 (3.6%) acquired *P. aeruginosa* during follow-up. ICS use was associated with a dose-dependent risk of *P. aeruginosa* (low ICS dose: HR 1.38, 95% CI 1.03 to 1.84, p=0.03; moderate ICS dose: HR 2.16, 95% CI 1.63 to 2.85, p<0.0001; high ICS dose: HR 3.58, 95% CI 2.75 to 4.65, p<0.0001; reference: no ICS use). A propensity matched model confirmed the results (high ICS dose compared with no/low/moderate ICS dose: HR 2.05, 95% CI 1.76 to 2.39, p p<0.0001).

Conclusion Use of ICS in patients with COPD followed in Danish outpatient clinics was associated with a substantially increased and dose-dependent risk of acquiring *P. aeruginosa*. Caution should be taken when administering high doses of ICS in severely ill patients with COPD. These results should be confirmed in comparable cohorts and other settings.

Key messages

What is the key question?

► Do inhaled corticosteroids (ICS) increase the risk of acquiring *Pseudomonas aeruginosa* in patients with COPD?

What is the bottom line?

► Use of inhaled corticosteroids is associated with a significant and dose-related risk of acquiring *P. aeruginosa* in patients with COPD.

Why read on?

► This is the first study to assess the risk of acquiring a positive airway culture with *P. aeruginosa* after use of ICS in a large and well-characterised population of patients with COPD.

INTRODUCTION

Inhaled corticosteroids (ICS) are commonly used as pharmacological treatment in patients with COPD and are currently recommended to reduce the risk of recurrent exacerbations in patients with severe disease.[1–3] However, ICS appear to have minimal or no impact on lung function and may not be needed or effective in patients with mild to moderate COPD and in those without eosinophilic inflammation.[4 5] Furthermore, their usefulness is currently being debated due to potential side effects with increased risk of pneumonia and mycobacterial infections.[6–9] Concordantly, evidence suggests that the risk of infection is dose related[10 11] and highest among patients with more severe airflow obstruction.[12]

Previous observational studies have shown that presence of positive airway culture with *Pseudomonas aeruginosa* in patients with COPD is associated with severe disease, frequent hospitalisations and death.[13–16] Thus, this subgroup of patients with COPD might be extra susceptible to the possible harmful effects of pharmacotherapy with ICS.

Few data are available on ICS as a risk factor for *P. aeruginosa*. Smaller prospective studies investigating patients admitted to hospital with an exacerbation of COPD have found that *P. aeruginosa* was associated with prior systemic corticosteroid treatment and use of antibiotics.[17 18] So far, no studies have specifically investigated the potential association between use of ICS and risk of *P. aeruginosa* in patients with COPD. Thus, we conducted a large cohort study to explore the risk of *P. aeruginosa* in patients with COPD related to the accumulated dose of ICS given during the last twelve months prior to their first outpatient clinic visit.

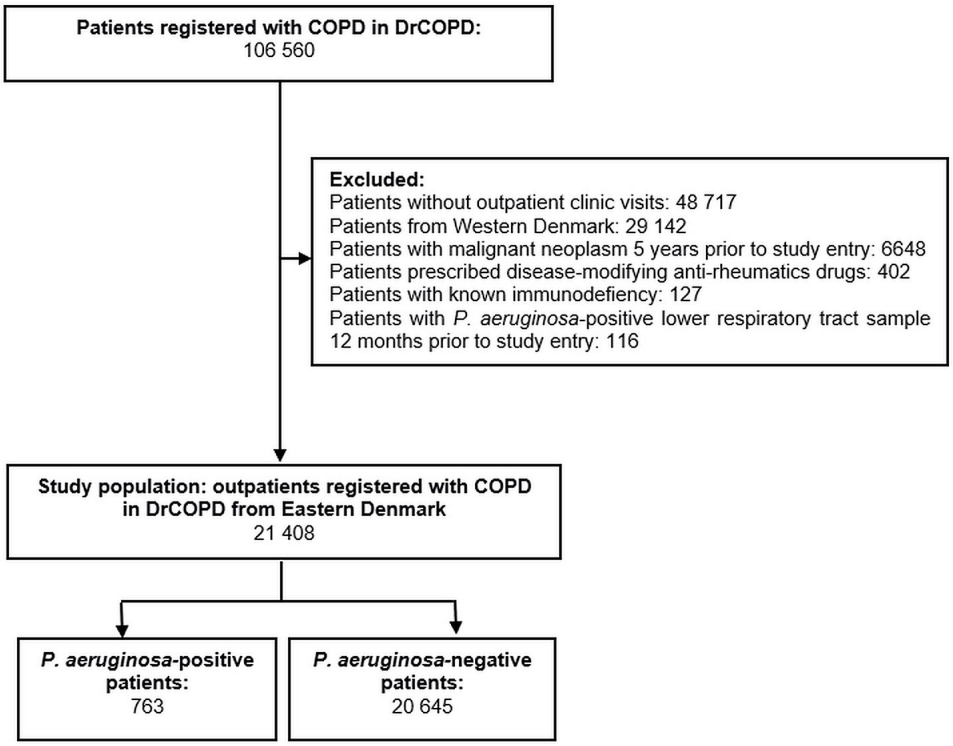

Figure 1 Study population: 21 408 patients registered with COPD in the Danish Register of COPD (DrCOPD) from 1 January 2010 to 31 October 2017.

Table 3 Cox regression hazard estimates for risk of *Pseudomonas aeruginosa* with use of inhaled corticosteroids in the study population (N=21 408)

P. aeruginosa event	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
ICS exposure, µg *				
No use	ref		ref	
Low <400	1.77 (1.33 to 2.36)	<0.0001	1.38 (1.03 to 1.84)	0.0296
Moderate 400–800	3.37 (2.58 to 4.42)	<0.0001	2.16 (1.63 to 2.85)	<0.0001
High >800	6.41 (5.00 to 8.20)	<0.0001	3.58 (2.75 to 4.65)	<0.0001
Accumulated OCS dose 365 days prior to cohort entry, mg				
No use	ref		ref	
Low <1825	2.18 (1.86 to 2.55)	<0.0001	1.28 (1.09 to 1.52)	0.0035
High ≥1825	3.23 (2.65 to 3.94)	<0.0001	1.48 (1.20 to 1.83)	0.0003
Active smoking †	0.91 (0.77 to 1.06)	0.217	1.11 (0.95 to 1.31)	0.200
Age (per year increased)	1.03 (1.03 to 1.04)	<0.0001	1.03 (1.02 to 1.04)	<0.0001
Male	1.08 (0.93 to 1.24)	0.309	1.31 (1.14 to 1.52)	0.0002
BMI (per class increase; 1–5) ‡	0.73 (0.67 to 0.79)	<0.0001	0.80 (0.74 to 0.87)	<0.0001
GOLD stage (per increase to next stage; 1–4)§	1.95 (1.76 to 2.16)	<0.0001	1.47 (1.32 to 1.63)	<0.0001
Prescription of any antibiotics 365 days prior to cohort entry	2.88 (2.42 to 3.42)	<0.0001	2.09 (1.74 to 2.50)	<0.0001

The model is adjusted for calendar year for study entry and all variables displayed in the table.
*Daily budesonide equivalent doses based on the accumulated ICS dose 365 days prior to cohort entry.
†Reference: never or former smoking.
‡BMI class (kg/m^2); 1: <18.5, 2: 18.5–24.9, 3: 25–29.9, 4: 30–34.9, 5: ≥35.
§Increase in predicted FEV_1% severity stage defined by the GOLD: 1: ≥80, 2: 50–79; 3: 30–49, 4:<30.
¶.
BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroids; OCS, Oral Corticosteroids.

Table 1 Patient characteristics at cohort entry and by *Pseudomonas aeruginosa* event in 21 408 patients with COPD

All patients		*P. aeruginosa*-positive patients	*P. aeruginosa*-negative patients	P value*	Adjusted OR (95% CI)†
No of subjects	21 408 (100)	763 (3.6)	20 645 (96.4)		
Demographics					
Age (year), median (IQR)	69 (62–76)	70 (64–76)	69 (62–76)	0.0007	1.08 (1.08 to 1.09)
Male	9619 (44.9)	346 (45.4)	9273 (44.9)	0.8241	1.25 (1.17 to 1.34)
BMI, median (IQR)	25 (21–29)	23(20-27)	25 (21–29)	<0.0001	
Unknown BMI	4527 (21.1)	130 (17.0)	4397 (21.3)		
BMI class:					
<18.5 kg/m^2	1681 (7.9)	95 (12.5)	1586 (7.7)	<0.0001	0.81 (0.78 to 0.84)
18.5–24.9 kg/m^2	6398 (29.9)	268 (35.1)	6130 (29.7)		
25–29.9 kg/m^2	5018 (23.4)	180 (23.6)	4838 (23.4)		
30–34.9 kg/m^2	2457 (11.5)	61 (8.0)	2396 (11.6)		
≥35 kg/m^2	5854 (27.3)	159 (20.8)	5695 (27.6)		
Pulmonary parameters					
MRC, median (IQR)	3 (2–4)	3 (3–4)	3 (2–4)		
Unknown MRC	4823 (21.9)	173 (19.1)	4650 (22.0)	<0.0001	
FEV_1% predicted, median (IQR)	49 (36–63)	39 (30–50)	49 (36–63)		
Unknown FEV_1%	4293 (20.1)	126 (16.5)	4167 (20.2)	<0.0001	
FEV_1% predicted, severity of spirometric obstruction:					
≥80	1108 (5.2)	15 (2.0)	1093 (5.3)	<0.0001	1.77 (1.69 to 1.86)
50–79	7227 (33.8)	152 (19.9)	7075 (34.3)		
30–49	6416 (30.0)	314 (41.1)	6102 (29.6)		
<30	6657 (31.1)	282 (37.0)	6375 (30.9)		
Smoking status					
Active	6590 (30.8)	217 (28.4)	6373 (30.8)	<0.0001	1.39 (1.28 to 1.49)
Former ≤6 months	591 (2.8)	10 (1.3)	581 (2.8)		
Former >6 months	9386 (43.8)	395 (51.8)	8991 (43.6)		
Never	576 (2.7)	17 (2.2)	559 (2.7)		
Unknown	4265 (19.9)	124 (16.3)	4141 (20.1)		
Hospital-requiring COPD exacerbation 12 months prior to cohort entry					
0	10 301 (48.1)	281 (36.8)	10 020 (48.5)	<0.0001	
1	4082 (19.1)	134 (17.6)	3948 (19.1)		
≥2	7025 (32.8)	348 (45.6)	6677 (32.3)		
All-cause hospitalisation 12 months prior to cohort entry	11 840 (55.3)	459 (60.2)	11 381 (55.1)	0.0061	
Comorbidity					
Inflammatory polyarthropathy	477 (2.2)	6 (0.79)	471 (2.3)	0.0037	
Systemic connective tissue disorder	497 (2.3)	23 (3.0)	474 (2.3)	0.2186	
Myocardial infarction	1661 (7.8)	60 (7.9)	1601 (7.8)	0.8904	
Atrial fibrillation	3106 (14.5)	104 (13.6)	3002 (14.5)	0.5298	
Heart failure	3511 (16.4)	119 (15.6)	3392 (16.4)	0.5839	
Hypertension	6670 (31.1)	228 (29.9)	6442 (31.2)	0.4498	
Renal failure	936 (4.4)	34 (4.5)	902 (4.4)	0.8571	
Peripheral vascular disease	1706 (8.0)	58 (7.6)	1648 (8.0)	0.7853	
Cerebrovascular disease	2041 (9.5)	63 (8.3)	1978 (9.6)	0.2334	
Diabetes mellitus, type 2	2654 (12.1)	106 (11.7)	2548 (12.0)	0.2334	

Continued

Table 1 Continued

All patients		*P. aeruginosa*-positive patients	*P. aeruginosa*-negative patients	P value*	Adjusted OR (95% CI)†
Asthma	3097 (14.5)	145 (19.0)	2952 (14.3)	0.0004	
Bronchiectasis	209 (0.98)	14 (1.8)	195 (0.94)	0.0223	
Use of medication 12 months prior to cohort entry					
Oral corticosteroids‡					
No use	13 159 (61.5)	315 (41.3)	12 844 (62.2)	<0.0001	
Low dose	6119 (28.6)	306 (40.1)	5813 (28.2)		
High dose	2130 (10.0)	142 (18.6)	1988 (9.6)		
Accumulated dose (mg), median (IQR)	625 (250–000)	1000 (500–2500)	500 (250–2000)	<0.0001	
Respiratory inhalation medicine					
Long-acting beta2-agonist or long-acting muscarin-antagonist	13 869 (64.8)	662 (86.8)	13 207 (64.0)	<0.0001	
Antibiotics §	12 324 (57.6)	598 (78.4)	11 726 (56.8)	<0.0001	1.14 (1.07 to 1.23)
Theophylline	691 (3.2)	55 (7.2)	636 (3.1)	<0.0001	

Data are presented as n (%) or median (IQR), unless otherwise specified.
*Group comparison was performed using non-parametric test (Wilcoxon two-sample test) and Fisher's exact test.
†The model is adjusted for all variables displayed in this column, calendar year and the accumulated ICS dose 365 days prior to cohort entry.
‡Low dose: accumulated dose <1825 mg; high dose: accumulated dose ≥1825 mg.
§Any antibiotic drug.
BMI, body mass index; ICS, inhaled corticosteroids; MRC, Medical Research Council Dyspnoea Scale.

METHODS

Data sources

For this study, the authors were granted access to data in nationwide and regional administrative registries in accordance with current Danish laws (Data Protection Agency: 2012-58-0004; The Danish National Committee on Health Research Ethics: H-15010949). According to these laws, informed consent is not required for registry-based studies. The linkage between registries was done by using unique personal identification numbers, which allows an exact linkage on patient level and ensures complete follow-up.[19]

The following registries was used:

1. The Danish Register of COPD (DrCOPD) was used to identify patients with COPD. DrCOPD is a nationwide register that holds individual patient data on demographics and all outpatient visits and hospital admissions due to exacerbation of COPD, in patients aged 30 years or above, at all hospital-based pulmonary clinics since 2010.[20]
2. The Danish National Patient Registry holds data on all hospital admissions since 1977 and all hospital outpatient visits since 1995 and was used to characterise comorbidities in the study population.[21]
3. The Danish National Database of Reimbursed Prescriptions (DNDRP) was used to identify prescribed and redeemed

Table 2 Use of ICS 365 days prior to cohort entry in 21 408 patients with COPD

	All patients	*Pseudomonas aeruginosa*-positive patients	*P. aeruginosa*-negative patients
Patients with ICS use	14 785 (69.1)	688 (90.2)	14 097 (68.3)
ICS exposure in ICS users, n (%)*			
Low	5030 (37.4)	126 (18.3)	5405 (38.3)
Moderate	4180 (28.3)	179 (26.0)	4001 (28.4)
High	5075 (34.3)	383 (55.7)	4692 (33.3)
Daily dose of ICS (µg), median (IQR)	559 (263–1026)	924 (493–1644)	530 (247–986)
Number of prescriptions by ICS type†			
Budesonide	51 445 (61.0)	2681 (50.5)	48 764 (61.7)
Fluticasone	31 678 (37.5)	2582 (48.6)	29 096 (36.7)
Beclomethasone	756 (0.90)	16 (0.30)	740 (0.94)
Momethasone	328 (0.39)	17 (0.32)	311 (0.39)
Ciclesonide	156 (0.18)	12 (0.23)	144 (0.18)

Data are presented as n (%) or median (IQR), unless otherwise specified.
Patients with no ICS use (n=6623) 365 days prior to cohort entry are not included in the table.
*Daily budesonide equivalent doses based on the accumulated ICS dose 365 days prior to cohort entry, µg : low <400; moderate 400–800; high >800.
†Last prescription redeemed prior to cohort entry.
ICS, inhaled corticosteroids.

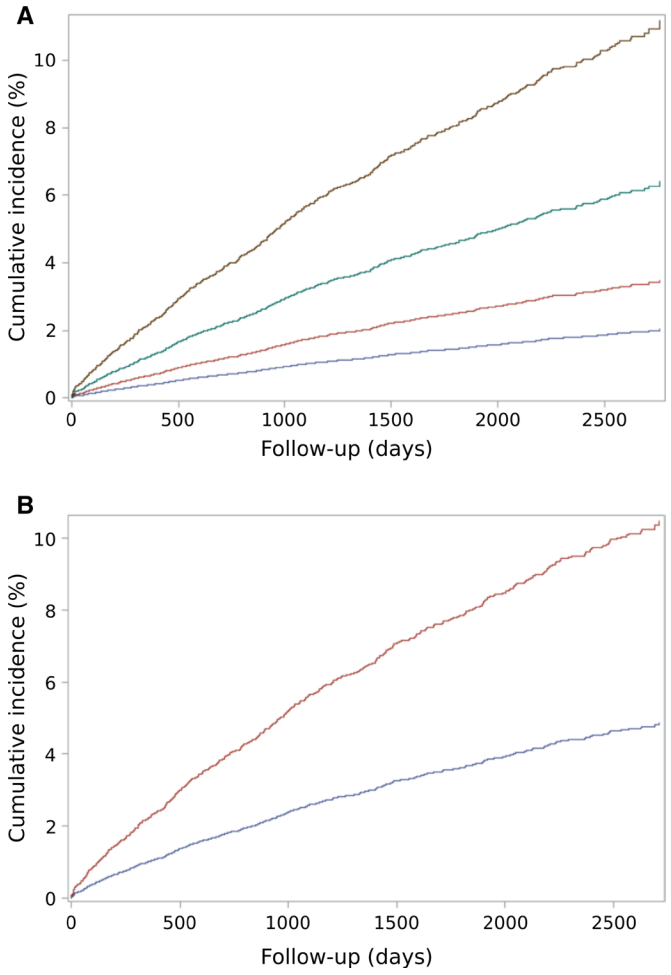

Figure 2 Cumulative incidence of *Pseudomonas aeruginosa* event according to exposure to inhaled corticosteroids in (A) 21 408 patients with COPD (brown line: high exposure, green line: moderate exposure, red line: low exposure, blue line: no exposure) and (B) 13 332 propensity matched patients with COPD (red line: high exposure, blue line: no/low/moderate exposure).

medication, including the exposure to ICS. The DNDRP is nationwide and includes data on all reimbursed prescriptions redeemed at Danish community and hospital-based outpatient pharmacies since 2004.[22]

4. Microbiological data from the Clinical Microbiology Departments in Eastern Denmark (Region Zealand and Capital Region), consisting of approximately 2.6 million inhabitants, were used to identify patients with *P. aeruginosa*.

Study population

The study considered all patients registered with an outpatient clinic visit from 1 January 2010 to 31 October 2017 in DrCOPD. Figure 1 illustrates an overview of the study. Cohort entry was defined as the date for the patients first outpatient clinic visit in DrCOPD. Patients with only in-hospital-registrations were not included since these registrations do not hold information on essential patient characteristics (severity of airflow obstruction, degree of dyspnoea, body mass index (BMI) and smoking status). Patients from the western part of Denmark were not included, since we could not gain access to microbiological data from these patients. *P. aeruginosa* was defined as any positive lower respiratory tract culture (*ie*, sputum, tracheal secretion, bronchial secretion and bronchial alveolar lavage) after cohort entry. Patients with *P. aeruginosa*-positive lower respiratory tract sample 12 months prior to cohort entry were excluded.

Patients with malignant neoplasm (International Classification of Disease (ICD)−10 codes: C00–C97) or immunodefiency (ICD-10 codes: D80-84, D85, D89) 5 years prior to cohort entry or prescription of disease-modifying antirheumatics drugs (Anatomical Therapeutic Chemical-codes: L04AX03, L01AA01, A07EC01, L04AD01, L04AA13, L04AX01, L04AA06, P01BA02) 12 months prior to cohort entry were excluded since these conditions and drugs were suspected to be associated with the study outcome and may affect the ability to interpret the results of the study exposure. Online supplemental table 1, lists the ICD-10 codes used to define comorbidities. All patients were followed from cohort entry until the first *P. aeruginosa*-positive sample, death or 31 October 2017.

Exposure to ICS

All prescriptions for ICS, alone or in combination inhaler, redeemed 365 days prior to cohort entry were identified. These included: beclomethasone, budesonide, fluticasone, ciclesonide and mometasone.

All doses of ICS were converted to budesonide-equivalent doses: beclomethasone and mometasone were considered equivalent to budesonide. Fluticasone proprionate and ciclesonide were converted to budesonide doses using a ratio of 2:1 respectively 2.5:1. Categorisation of ICS doses was assessed by dividing ICS exposure into low (<400 μg), moderate (400–800 μg) and high (>800 μg) daily dose according to international Global Initiative for Asthma guidelines[23] based on the accumulated dose in the year prior to the cohort entry. Non-use during the entire period was used as reference category.

Statistical analysis

Continuous variables are presented as median values and IQRs. Group comparisons were performed using a non-parametric test (Wilcoxon two-sample test) and t-test when appropriate. Categorical variables are reported as frequencies and proportions and compared between groups using Fisher's exact test. A p value less or equal to 0.05 was considered statistically significant. Statistical analyses were performed using SAS statistical software (V.3.71 Enterprise Edition, SAS Institute).

The risk *of P. aeruginosa* associated with use of ICS was estimated using a Cox proportional hazard regression model. Death was handled as a competing risk in the model since it impedes the occurrence of *P. aeruginosa*. The model was adjusted for suspected confounders and markers of disease severity based on previous literature in the field: age (continuous, year), sex (male vs female), severity of airway obstruction (percentage of predicted FEV_1; stage 1–4), 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. We report both unadjusted results of univariate analyses for each covariate above and results from the adjusted multivariate analyses with all covariates included in the same model

In patients with unknown FEV_1 and BMI, measurements from the first following outpatient clinic visit were used. Patients with unknown smoking status were classified as non-active smokers (most common among the patients with known status). We conducted a sensitivity analysis where missing BMI was categorised as ≥35 and missing FEV_1 was classified as <30 (online supplemental table 2). Exposure to oral corticosteroids was divided into low-dose and high-dose categories based on

the dose corresponding to a daily intake of <5 mg, respectively, ≥5 mg (low dose: <1825 mg; high dose ≥1825 mg). Non-use of oral corticosteroids in the entire prior year was used as reference group.

We did not model ICS as a time-dependent variable, as glucocorticoid use is associated with increased risk of long-term adverse effects,[24 25] including infection with other microbial agents than *P. aeruginosa*, that can occur even months after discontinuation.[26] The models were tested for linearity of continuous variables and proportion of hazards, using cumulative score residuals, and were found to be valid. Interactions between accumulated exposure of oral corticosteroids 365 days prior to cohort entry (p=0.93) as well as type of ICS (p=0.48) were tested and not found to be present. We reported data for all degrees of oral corticosteroid exposure and all types of ICS together. We conducted a supplemental analysis in a subgroup of patients with no use of OCS in the study population (online supplemental table 3) and also performed an analysis on ICS type (online supplemental table 4).

A propensity score matched model was applied as a sensitivity analysis using the greedy-match algorithm, created and maintained by biomedical statisticians at the Mayo Clinic.[27] Patients exposed to high ICS dose were matched 1:2 with patients who were exposed to no, low or moderate ICS dose based on the same variables used in the adjusted main analysis. An unadjusted Cox proportional hazard regression model, treating death as competing event, was then used to estimate the risk of *P. aeruginosa* associated with high ICS dose versus no/low/moderate ICS dose. The estimate was retested using a robust variance estimator, accounting for the lack of independence in outcome induced by the matching.[28]

RESULTS

The study cohort included 21 408 patients with COPD (figure 1). The median follow-up time was 1026 days (IQR: 417–1846), during which 763 (3.6%) patients were identified with a *P. aeruginosa*-positive respiratory tract sample. Patients with *P. aeruginosa* were more likely to have lower BMI (p<0.0001) and FEV1 (p<0.0001) and a higher rate of previous hospital-demanding exacerbations (p<0.0001) at cohort entry compared with *P. aeruginosa* negative patients (table 1). Prescriptions of respiratory drugs, oral corticosteroids and antibiotics were also more frequently filled in the group of *P. aeruginosa*-positive patients (table 1). As shown in table 2, the prevalence of use of ICS was markedly higher in patients with *P. aeruginosa* (90.2%) compared with *P. aeruginosa*-negative patients (68.3%). Budesonide and fluticasone were the most frequently used types of ICS in both groups.

Outcome

Use of ICS was associated with an increased risk of *P. aeruginosa* compared with non-use in unadjusted analyses (HR 3.74, 95% CI 2.95 to 4.75, p<0.0001) and the risk remained significantly increased after adjusting for covariates (HR 2.26, 95% CI 1.76 to 2.89, p<0.0001). There was a strong relationship between ICS dose and outcome, with stepwise increase of the *P. aeruginosa*-risk with the exposure to ICS (table 3). The risk was 3.6-fold increased (HR 3.58, 95% CI 2.75 to 4.65, p<0.0001) in patients with the highest ICS exposure. Figure 2A illustrates the cumulative incidence. The results remained stable after conducting a modified data imputation (online supplemental table 2) and after excluding patients (n=8249) with use of OCS 365 days prior to cohort entry (online supplemental table 3). Data on associations between ICS type and outcome are presented in online supplemental table 4.

Sensitivity analyses

A subgroup of 13 332 patients with COPD in the cohort population was formed using a propensity matched model, consisting of 4931 (37%) patients with high ICS exposure matched 1:2 with 8401 (63%) patients with no/low/moderate ICS exposure. Patient characteristics of the two groups are presented in online supplemental table 5. High exposure to ICS (reference: no, low or moderate ICS exposure) was associated with a twofold increased risk of *P. aeruginosa* (HR 2.05, 95% CI 1.76 to 2.39, p<0.0001). The difference remained significant when assessed by a stratified long-rank test (p<0.0001). The cumulative incidence is illustrated in figure 2B.

DISCUSSION

In our multiregional cohort study of over 20 000 outpatients with COPD, we found that ICS use was associated with a substantially and independent increased risk of acquiring a *P. aeruginosa*-positive lower respiratory airway culture. There was a strong dose-dependent 3.5-fold increased risk of *P. aeruginosa* in patients with the highest ICS exposure (no use of ICS as reference).

Few data are available on risk factors for *P. aeruginosa* in the setting of COPD. To our knowledge, this is the first study reporting ICS as a potential risk factor of *P. aeruginosa* in a large and unselected population of patients with COPD. Previous studies on risk factors for *P. aeruginosa* have primarily been conducted in smaller cohorts of hospitalised patients with exacerbation of COPD[17 18] and who might have been *P. aeruginosa*-positive prior to admission.

Despite lack of high-level evidence of an effect, ICS is widely used in cystic fibrosis, where *P. aeruginosa* is a well-known determinant of a subsequent worsening of prognosis.[29] Interestingly, an earlier double-blind placebo-controlled study investigating the effect of fluticasone in children 6–17 years was terminated prematurely due to an increase of first-time isolation of *P. aeruginosa* in the group treated with ICS compared with the placebo group.[29] However, data from a recent and similar trial found no increase in isolation of the bacteria in patients treated with ICS.[30]

Along the line with infectious lung complications to ICS, multiple larger population-based studies have demonstrated increased risk of pneumonia and mycobacterial infections with ICS use in patients with COPD.[7–11] Results from these studies cannot be directly compared with ours due to differences in methodologies, but several similarities are apparent. First, the high proportion of ICS-users in our cohort is comparable to the previous studies.[8–10] Second, like ours, these studies also report a robust dose-related risk[8 10] using similar dose categories.[10] Nevertheless, our risk estimates for acquiring *P. aeruginosa* seem to be substantially higher compared with the observed pneumonia risk increase associated with ICS use (not segregated in accumulated doses). Several COPD trials have also reported increased risk of pneumonia with ICS use,[12 31] and the risk of pneumonia is also seen when lower daily doses of ICS are used.[32 33] Like in other studies, fluticasone and budesonide were the most commonly prescribed types of ICS. However, in comparison to previous observational studies[10 11] that reported an increased risk of pneumonia in fluticasone-users compared with budesonide-users, we did not find any association between risk of *P. aeruginosa* and ICS type when testing for interaction. A sensitivity analysis revealed

that users of fluticasone were characterised by using a much higher (approximately double) dose of ICS in comparison to other ICS users. Thus, testing for fluticasone use actually tested whether high doses increased the risk of outcome (ie, not testing purely whether this specific chemical formulation increases the risk). Thus, based on our data, it seems that fluticasone is not associated with an excess risk.

Strengths of the study include observations based on a large and well-characterised population of patients diagnosed with COPD. Thus, we were able to adjust for several clinically important and potential cofounders. Moreover, the results were tested in several sensitivity analyses and the signal remained strong.

As in any database study, we cannot report actual intake of the ICS and some patients may have been non-adherent. However, repetitive collection of the prescribed medicine suggests that adherence is sufficient. Additionally, the proportion of patients with COPD on ICS correlates well with previous population studies.[8 10] Furthermore, in case of frequent non-adherence, a lower intake of ICS than registered would tend to underestimate the actual observed risk of *P. aeruginosa* infection among the ICS-users.

Although the results suggest a biological plausibility, no causal relationship can be determined due to the observational design of the study. However, taking into account that we have access to and controlled for some of the most important confounders, it is unlikely that confounding could explain an observed risk ratio of this magnitude. Possible biological mechanisms include ICS-induced alternations of the innate and adaptive immune system,[34 35] which has been reported to increase the bacterial load and change the microbial composition in the airways.[36] The possible causal association between ICS and *P. aeruginosa* is illustrated in a directed acyclic graph (DAG) in online supplemental figure 1.

To conclude, use of ICS in patients with COPD followed in Danish outpatient clinics was associated with a high and dose-related risk of acquiring *P. aeruginosa*. Caution should be taken when administering high dose of ICS in severely ill patients with COPD. These results should be confirmed in comparable cohorts and other settings.

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