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Inhaled corticosteroids and *Stenotrophomonas maltophilia* in outpatients with chronic obstructive pulmonary disease: a retrospective cohort study

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ABSTRACT

Objectives Inhaled corticosteroids (ICS) are widely used in patients with chronic obstructive pulmonary disease (COPD). However, ICS are associated with an increased risk of adverse effects.

We aimed to determine whether an association between a lower respiratory tract culture with *Stenotrophomonas maltophilia* and increasing ICS dosing in patients with COPD exists.

Design An observational cohort study of outpatients with COPD in Denmark between 2010 and 2018.

ICS exposure was categorised into four groups based on average daily consumption 1 year prior to inclusion: no use, low ICS dose (≤400 µg), moderate ICS dose (400–800 µg) and high ICS dose (>800 µg). Dose–response relationship was investigated by a multivariable Cox proportional hazards regression.

Results Of the total 22 689 patients, 459 had lower respiratory tract cultures positive for *S. maltophilia*. The HR of *S. maltophilia* increased with increasing daily ICS dose: low ICS dose HR 2.6 (95% CI 1.6 to 4.0), moderate ICS dose HR 3.0 (95% CI 1.9 to 4.6) and high ICS dose HR 5.7 (95% CI 3.8 to 8.5).

Conclusions We found that ICS was associated with a high, dose-dependent increased hazard of *S. maltophilia* in outpatients with COPD. High dose users had a nearly six times increased hazard compared with non-users of ICS. When appropriate, attempts at de-escalating ICS treatment should be made.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Treatment with inhaled corticosteroids has been linked to a higher prevalence of pneumonia in patients with chronic obstructive pulmonary disease (COPD) in both clinical trials and cohort studies but has never been investigated in relation to colonisation of the lower respiratory tract by *Stenotrophomonas maltophilia*.

WHAT THIS STUDY ADDS

⇒ This study finds a dose–response relationship between increasing doses of inhaled corticosteroid and hazard for *S. maltophilia* in the lower respiratory tract. The clear dose–response relationship supports a causal relation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study underlines the importance of continuous monitoring treatment and treatment response in patients with COPD, and when possible, step down or stop inhaled corticosteroid treatment.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) affects approximately 400 million people worldwide and is a leading cause of death.[1] COPD is associated with airway inflammation,[2] and oral and inhaled corticosteroids (ICS) are often used in stable state disease as well as during acute exacerbation as a mean to reduce mucosal swelling and inflammation.[3]

ICS are associated with an increased risk of adverse effects such as pneumonia,[4 5] osteoporosis and diabetes.[6 7] Additionally, infections with other Gram-negative opportunistic bacteria, such as *Pseudomonas aeruginosa* and mycobacterial infections, have been associated with ICS use in patients with COPD, both associated with worsened outcome.[8–14] However, no knowledge on ICS in relation to *Stenotrophomonas maltophilia* exists.

S. maltophilia, an ubiquitous, aerobic, non-fermentative, Gram-negative bacillus is a global opportunistic pathogen.[15] Further, *S.*

maltophilia is an important nosocomial pathogen associated with a crude mortality in hospitalised ranging between 14% and 69% with an attributable mortality rate of up to 37.5%.[16 17]

The role of *S. maltophilia* in patients with COPD is poorly understood, and it is debated whether it should be considered a marker of disease progression or regarded as a pathogen in chronic lung diseases such as cystic fibrosis.[18] In a Canadian population of outpatients with COPD, *S. maltophilia* was detected in 10% of patients and associated with a twofold increase in mortality.[19] In a recent study from our group, *S. maltophilia* in the lower respiratory tract was associated with a threefold increased risk of both hospitalisation-requiring exacerbation of COPD and death.[20]

The aim of this study was to determine, among all outpatients with COPD from the Eastern part of Denmark, and with 100% follow-up on microbiological sampling and vital status, whether the risk of acquiring a lower respiratory tract culture with *S. maltophilia* was associated with increasing daily ICS doses. Specifically, we aimed to investigate if there was a dose–response relationship between ICS dose and *S. maltophilia* in the lower respiratory tract, as our hypothesis was that ICS use was associated with a dose-dependent risk of isolation of *S. maltophilia* in the lower respiratory tract.

METHODS

Data sources

Data were collected from the following databases, which were accessible through the Danish Health Data Authority:

1. The Danish Register of COPD (DrCOPD) was used to identify patients with specialist-verified COPD. DrCOPD is a nationwide register that comprises individual patient data, for example, severity of airflow obstruction, body mass index (BMI), Medical Research Council (MRC) Dyspnoea Scale and smoking status, at all respiratory outpatient clinic visits since 2010.[21]
2. The Danish National Patient Registry contains data on all hospital contacts since 1995, including diagnoses and length of contact.[22]
3. The Danish National Database of Reimbursed Prescriptions is nationwide and includes data on all redeemed prescriptions. The register includes information on the strength, dose, product name and Anatomical Therapeutic Chemical classification of each prescription.[23]
4. Microbiological data from the Clinical Microbiology Departments in Eastern Denmark (Region Zealand and Capital Region) consist of approximately 2.6 million inhabitants. The register contains information on all microbiological samples including lower respiratory tract cultures, and by that used to identify patients with *S. maltophilia*. Samples containing sputum, tracheal secretion and bronchoalveolar wash were considered representative for the lower respiratory tract.

Study design

This was a retrospective, registry-based cohort study of Danish outpatients with COPD.

The study cohort comprised all patients registered with an outpatient clinic visit from 1 January 2010 to 31 October 2017 in DrCOPD. The majority of patients with COPD in Denmark attend their general practitioner for management of COPD, but those with most severe disease are referred to hospital-based outpatient clinics and included in DrCOPD. We had only access to microbiological data on patients residing in Eastern Denmark; hence, patients residing in Western Denmark were excluded as we had no access to microbiological data on these patients. However, we judged that the power of the study was sufficient despite only using the Eastern Danish data, due to the large number of cases in the cohort.

We excluded patients with a history of immunodeficiency and cancer, except for non-melanoma malignancies of the skin, within the last 5 years prior to cohort entry. Also, patients with a lower respiratory tract sample positive for *S. maltophilia* within 365 days of cohort entry were excluded.

Cohort entry was defined as the date for the patient's first outpatient clinic visit in DrCOPD. We only included patients with outpatient registrations, as in-hospital registrations do not contain information on essential patient characteristics: severity of airflow obstruction (forced expired volume in the first second (FEV_1)), degree of dyspnoea (MRC Dyspnoea Scale), BMI and smoking status.

Patients were followed for 5 years or until the first of either (1) end of microbiological sample follow-up on 1 July 2018, (2) event of *S. maltophilia* or (3) death.

Exposure to ICS

All prescriptions for ICS, alone or in fixed combination with long-acting bronchodilators, redeemed 365 days prior to cohort entry and during the study period were identified.

ICS was handled as a time-dependant variable; cumulated dose was based on prescriptions redeemed within 365 days prior to cohort entry to assess an average daily dose and updated for every 365 days of follow-up.

All doses of ICS were converted to budesonide-equivalent doses, as shown in table 1, as the potency varies as much as a factor 10 regarding local treatment effect.[24] Patients with no ICS use during the study period were used as the reference category, while ICS users were separated into three subgroups: low ICS dose (≤400 µg), moderate ICS dose (400–800 µg) and high ICS dose (>800 µg) daily dose according to international guidelines.[25]

Statistical analyses

The risk of acquiring a lower respiratory tract culture positive for *S. maltophilia* associated with use of ICS was estimated using a Cox proportional hazards

Table 1 Equipotent doses of the different ICS drugs analysed[24]

Drug	Budesonide	Momethasone	Beclomethasone	Beclomethasone HFA	Fluticasone propionate	Fluticasone furoate	Ciclesonide
Dose (µg)	100	100	100	50	50	10	40

ICS, inhaled corticosteroids.

regression, censoring for death. Both unadjusted and adjusted results are presented. The multivariable model was adjusted for known and suspected confounders as well as markers of disease: age (continuous (year)), sex (male vs female), FEV_1 (continuous (%)), BMI (continuous (kg/m^2)), smoking status (active vs not active) and cumulated dose of oral corticosteroids (none, low: ≤250 mg prednisolone, high: >250 mg prednisolone) and calendar year for entry in DrCOPD. Cumulated oral corticosteroids were calculated by redeemed prescriptions 365 days prior to cohort entry, with ≤250 mg prednisolone corresponding to treatment for one exacerbation of COPD and >250 mg prednisolone corresponding to treatment for two or more exacerbation episodes. Prior exacerbation, FEV_1, BMI and smoking status have earlier been showed to be strong predictors of exacerbation of COPD.[26] Results are shown as HRs with 95% CIs.

For sensitivity analysis, we performed a multinomial propensity score (PS)-weighted Cox proportional hazards regression, as we had four levels of exposure.[27]

Model validation

Proportional hazards assumption was tested as an interaction with time, in addition to testing for linearity of the continuous covariates. Continuous covariates failing test for linearity were handled using penalised splines, which did not alter the results.

Missing data were handled by the substantive model for multiple imputation, with 100 imputations with each 20 iterations.[28]

Data management and statistical analyses were performed using Statistical Analysis Software V.9.4 (SAS Institute). Multiple imputation, Cox proportional hazards regression and inverse probability of treatment weighting were completed in R Studio V.4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) with the SMCFCS V.1.6.1, MITOOLS V.2.4, SURVIVAL V.3.3.1 and TWANG V.2.5 packages respectively.

Patient and public involvement

In the Steering Committee of our organisation (COP:TRIN), we have patient representation to ensure

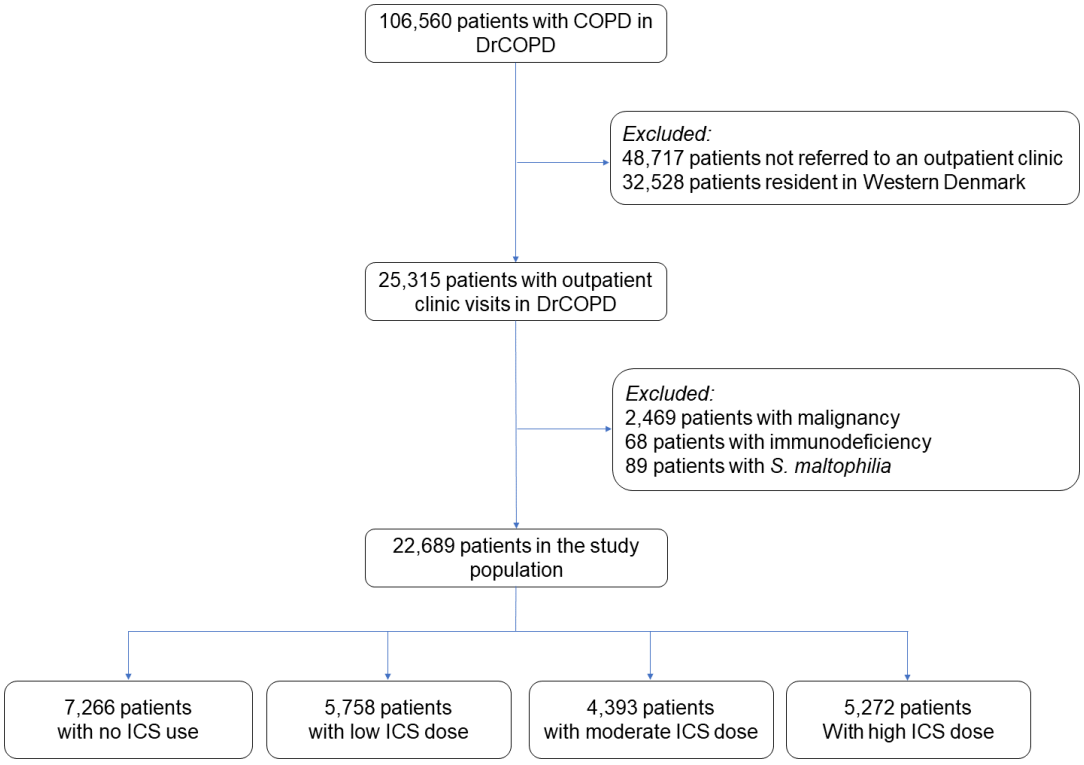

Figure 1 Study flowchart. DrCOPD: Danish Register of COPD, ICS: Inhaled corticosteroid.

that patients' opinions and interpretations are taken seriously. This allows them to influence the design and conduct of trials and observational studies. For example, studies like this one.

Further, we have recently, as chairs and initiators, conducted a global Delphi survey on outcomes in COPD trials, in which patients, relatives and patient organisations were invited and participated.

We seek to inform patients, whenever we conduct nationwide observational studies, by making press releases and by discussing results with the Danish lung patient organisation.

RESULTS

A total of 106 560 patients with COPD were identified in DrCOPD. Of these, 57 843 had at least one outpatient visit during the study period. Patients from Western Denmark (n=32 528) were excluded

Table 2 Baseline characteristics at study entry of outpatients with COPD according to use of inhaled corticosteroid

	Inhaled corticosteroid group			
	None (n=7266)	Low (n=5758)	Moderate (n=4393)	High (n=5272)
Daily budesonide equivalents (µg), median (IQR)	0	184 (110–316)	579 (473–658)	1315 (986–1808)
Sex female, n (%)	3543 (48.8)	3049 (53.0)	2511 (57.2)	3276 (62.1)
Age (years), median (IQR)	68.5 (60.0–76.3)	69.3 (61.1–76.9)	70.5 (63.5–77.6)	71.0 (63.9–78.0)
FEV_1 (%), median (IQR), missing (%)	57.0 (44.0–70.0) (16.4)	52.0 (40.0–65.0) (10.7)	45.0 (33.0–58.0) (8.5)	40.0 (29.0–53.0) (8.0)
BMI (kg/m^2), median (IQR), missing (%)	25.0 (22.0–29.0) (17.7)	25.0 (22.0–29.0) (11.5)	25.0 (21.0–29.0) (8.8)	24.0 (21.0–28.0) (7.8)
MRC Dyspnoea Scale, median (IQR)	2 (2–3)	3 (2–3)	3 (2–4)	3 (3–4)
Smoking status				
Not active smoker, n (%)	3292 (45.3)	3167 (55.0)	2764 (62.9)	3309 (62.8)
Active smoker, n (%)	2773 (38.2)	1981 (34.4)	1281 (29.3)	1568 (29.7)
Smoking status missing, n (%)	1201 (16.5)	610 (10.6)	342 (7.8)	395 (7.5)
Oral corticosteroid*				
None, n (%)	5992 (82.5)	3685 (64.0)	2409 (54.8)	2327 (44.1)
Low dose, n (%)	444 (6.1)	631 (11.0)	489 (11.1)	657 (12.5)
High dose, n (%)	830 (11.4)	1442 (25.0)	1495 (34.0)	2288 (43.4)
Comorbidities†				
Cerebrovascular disease, n (%)	695 (9.6)	529 (9.2)	353 (8.0)	419 (7.9)
Asthma, n (%)	479 (6.6)	894 (15.5)	834 (19.0)	1124 (21.3)
Atrial fibrillation, n (%)	1086 (14.9)	836 (14.5)	648 (14.8)	691 (13.1)
Depression, n (%)	327 (4.5)	270 (4.7)	211 (4.8)	272 (5.2)
Diabetes mellitus, n (%)	945 (13.0)	685 (11.9)	446 (10.2)	599 (11.4)
Congestive heart failure, n (%)	1265 (17.4)	947 (16.4)	712 (16.2)	847 (16.1)
Ischaemic heart disease, n (%)	534 (7.3)	463 (8.1)	285 (6.5)	374 (7.1)
Renal disease, n (%)	398 (5.5)	275 (4.8)	161 (3.7)	203 (3.9)
Peripheral vascular disease, n (%)	828 (11.4)	595 (10.3)	406 (9.2)	438 (8.3)

*Oral corticosteroids accumulated dose 365 days prior to study entry: none: no use, low dose: ≤250 mg prednisolone, high dose: >250 mg prednisolone.
†Comorbidities registered in the Danish National Patient Registry prior to study entry (online supplemental appendix 1).
BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in the first second; MRC, Medical Research Council; n, number.

Table 3 Hazard for acquisition of *Stenotrophomonas maltophilia* with use of inhaled corticosteroid

	Unadjusted		Adjusted	
	HR	CI	HR	CI
Inhaled corticosteroid group*				
None	Ref	–	Ref	–
Low dose	3.0	1.9 to 4.7	2.6	1.6 to 4.0
Moderate dose	4.4	2.9 to 6.6	3.0	1.9 to 4.6
High dose	9.9	6.8 to 14.5	5.7	3.8 to 8.5

The analysis was adjusted for: age, sex, forced expired volume in the first second, body mass index, smoking status and oral corticosteroid use.
*Inhaled corticosteroid cumulated daily dose in budesonide equivalents: none: no use, low dose: ≤400 µg, moderate dose: 400–800 µg, high dose: >800 µg.

due to no accessible microbiological data. Additionally, patients with a diagnosis of malignant disease (n=2469) or immunodeficiency (n=68) within 5 years before study entry were excluded, as well as those with a lower respiratory tract sample positive for *S. maltophilia* (n=89) within 365 days prior to potential cohort entry.

In total, 22 689 patients were included and contributed 70 896 person-years of risk-time for the analysis (figure 1). A lower respiratory tract sample positive for *S. maltophilia* was found in 459 (2.0%) patients (no ICS use: 35, low ICS dose: 67, moderate ICS dose: 114 and high ICS dose: 243). Baseline characteristics are listed in table 2, and definitions of comorbidities are in online supplemental appendix 1. In general, with increasing daily ICS dose, a decrease in FEV_1 and increase in high-dose oral corticosteroids as well as an increase in prevalence of asthma were observed.

The adjusted Cox proportional hazards regression showed an increased HR of acquiring a lower respiratory tract sample positive for *S. maltophilia* with a dose–response relationship in the low, moderate and high ICS dose group compared with the no use of ICS group: low dose: HR 2.6 (CI 1.6 to 4.0), moderate dose: HR 3.0 (CI 1.9 to 4.6) and high dose: HR 5.7 (CI 3.8 to 8.5), which was an attenuation of the unadjusted results (table 3 and figure 2; for full adjusted analysis, see online supplemental appendix 2).

The PS sensitivity analysis confirmed the main finding: low dose: HR 2.4 (CI 1.5 to 3.8), moderate dose: HR 2.6 (CI 1.6 to 4.1) and high dose: HR 5.2 (CI 3.4 to 8.0), respectively.

Of the included patients, 2932 (13%) had one or more clinical values missing from the outpatient clinic visit. In most cases, when missing data were seen, FEV_1, BMI, MRC Dyspnoea Scale and smoking status were missing together, telling us that somehow the values were not correctly reported from the outpatient clinic. This indicates that data were missing at

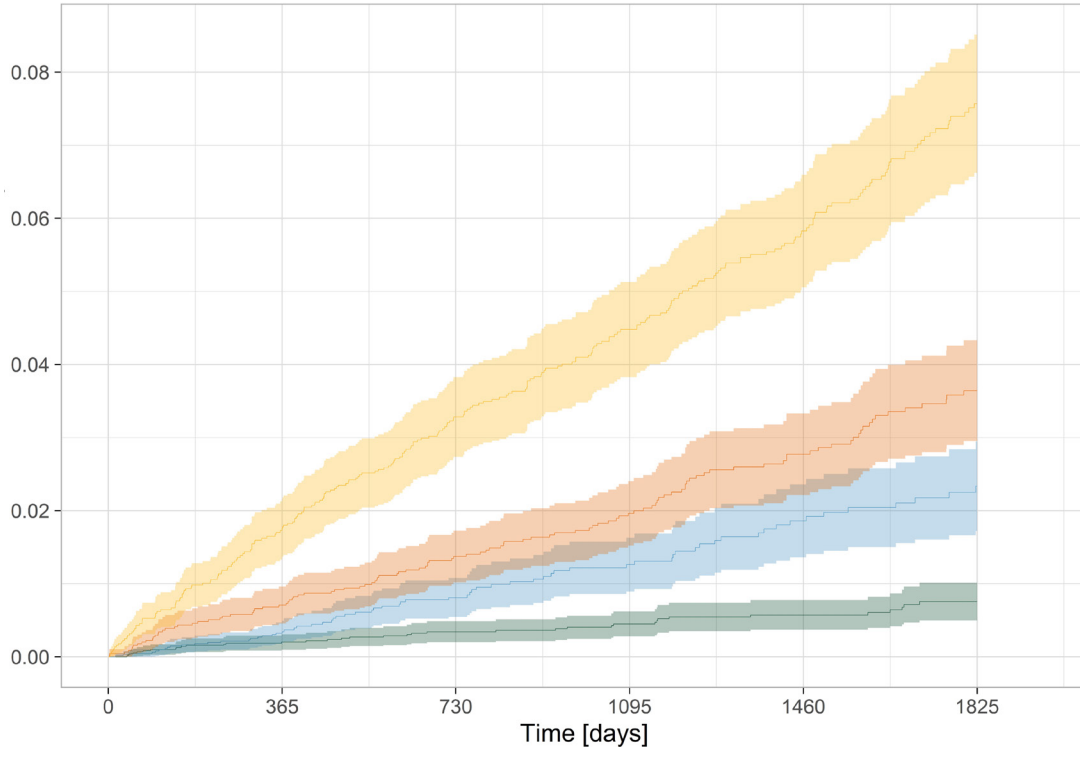

Figure 2 Cumulative incidence of *positive lower respiratory tract sample for S. maltophilia within 5 years of first outpatient clinic visit* according to exposure to inhaled corticosteroid use (green: no use, blue: low dose, red: moderate dose, and yellow: high dose. Mean in solid, 95% confidence interval in transparent).

random, and thus allowed for handling by multiple imputation.

DISCUSSION

In this regional registry-based cohort of outpatients with COPD, we found that ICS treatment was associated with a marked, dose–response-related, increased hazard of a lower respiratory tract sample positive for *S. maltophilia*. The result was robust for adjustment and by an inverse probability of treatment-weighted sensitivity analysis.

The evidence on COPD and the role of *S. maltophilia* is sparse, and even slimmer when considering ICS use in patients with COPD. A single study has found an association between ICS and infection with *S. maltophilia*, but not differentiated by ICS doses.[19] A meta-analysis covering eight studies on *S. maltophilia* in intensive care units shows an association between COPD and *S. maltophilia* pneumonia.[29]

Other larger population-based studies have demonstrated increased risk of pneumonia, infection with *P. aeruginosa* and mycobacterial infections with ICS use in patients with COPD.[8–12] Results from these studies cannot be directly compared, but several similarities are apparent. First, the high proportion of ICS users in our cohort is comparable with the previous studies, and like ours, these studies also report a robust dose-related risk. Several COPD trials have also reported increased risk of pneumonia with ICS use[30 31] and the risk of pneumonia was also seen when lower daily doses of ICS are used.[32 33]

It is debated whether *S. maltophilia* in the lower respiratory tract represents a pathogen-causing infection or is merely a benign colonising bacterium found in those with the most advanced degree of COPD. A recent study from our group has demonstrated that *S. maltophilia* certainly is associated with a steep increase in disease burden following infection.

Also, in patients with cystic fibrosis, *S. maltophilia* is a well-established contributor to irreversible decline in lung function and increase in exacerbation, and the pathogenesis is closely linked to well-studied and complex virulence mechanisms, cross-infection and multiresistance.[18]

Strengths of the current study include observations based on a large and well-characterised population of patients with a respiratory specialist-verified and spirometry-confirmed diagnosis of COPD. The patients have one or more outpatient clinic visits but are in all other aspects unselected. Also, we have data giving us information on actual ICS doses redeemed at the pharmacy and not only prescriptions. Last, there is a 100% follow-up for lower respiratory tract sample positive for *S. maltophilia*, as all patients, we argue, with *S. maltophilia* would have relevant symptoms and, thus have a lower respiratory tract sample analysed.

Despite the noted strengths, our study has some important limitations. First, we cannot report actual intake of the ICS, since the data did not contain information on adherence. Some patients may fail to administer the inhalation correctly. However, repetitive collection of the prescribed medicine suggests some degree of adherence and we have no reason to suspect different degrees of adherence in the three strata of ICS users. Additionally, the proportion of patients with COPD on ICS correlates well with previous population studies.[9 10] Second, ICS seems to correlate with more severe COPD and confounding by indication may be a concern; however, our registries contain many important confounders such as smoking status, oral corticosteroid use, lung function by FEV_1 and nutrition status, allowing us to account for these. We cannot rule out residual confounding, but the paramount effect of ICS after adjusting indicates that confounding by no mean can be the only explanation of the found association between ICS and *S. maltophilia*. Third, we do not have lower respiratory tract sample from all patients, but we argue that patients followed in an outpatient clinic with relevant symptoms (phlegm, coughing, elevated markers of infection, fever) would have a sample taken.

To conclude, use of ICS in patients with COPD who were followed in outpatient clinics was associated with a substantial dose–response-related hazard of getting a lower respiratory tract culture positive for *S. maltophilia*. The large and seemingly strong dose–response relationship of this hazard suggests a causal relationship. Hence, we argue that ICS should only be administered specifically to patients with COPD who have a documented need as per guideline recommendations, and caution should be taken when prescribing higher doses of ICS, especially since it is unclear whether high doses are more effective in patients with COPD than low and moderate doses.[5 34]

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval In Denmark, retrospective use of registry data does not require patient consent nor approval from the Danish National Committee on Health Research Ethics.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data supporting the findings of this study are available from the Danish Health Data Authority following application and approval from the Danish Health Authority. Restrictions apply to the availability of these data, which were used under the licence for this study.

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