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# Inhaled corticosteroids and risk of lower respiratory tract infection with *Moraxella catarrhalis* in patients with chronic obstructive pulmonary disease

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## ABSTRACT

**Background** Use of inhaled corticosteroids (ICS) is common in patients with chronic obstructive pulmonary disease (COPD) and has been associated with an increased risk of pneumonia. *Moraxella catarrhalis* is one of the most common bacterial causes of infectious exacerbation in COPD. Currently, to our knowledge, no studies have investigated if ICS increases the risk of lower respiratory tract infection with *M. catarrhalis* in patients with COPD.

**Objective** To investigate if accumulated ICS use in patients with COPD, is associated with a dose-dependent risk of infection with *M. catarrhalis*.

**Methods** This observational cohort study included 18 870 persons with COPD who were registered in The Danish Register of COPD. Linkage to several nationwide registries was performed.

Exposure to ICS was determined by identifying all prescriptions for ICS, redeemed within 365 days prior to study entry. Main outcome was a lower respiratory tract sample positive for *M. catarrhalis*. For the main analysis, a Cox multivariate regression model was used.

We defined clinical infection as admission to hospital and/or a redeemed prescription for a relevant antibiotic, within 7 days prior to 14 days after the sample was obtained.

**Results** We found an increased, dose-dependent, risk of a lower respiratory tract sample with *M. catarrhalis* among patients who used ICS, compared with non-users. For low and moderate doses of ICS HR was 1.65 (95% CI 1.19 to 2.30, p=0.003) and 1.82 (95% CI 1.32 to 2.51, p=0.0002), respectively. In the group of patients with highest ICS exposure, the HR of *M. catarrhalis* was 2.80 (95% CI 2.06 to 3.82, p<0.0001). Results remained stable in sensitivity analyses. 87% of patients fulfilled the criteria for clinical infection, and results remained unchanged in this population.

**Conclusion** Our study shows a dose-dependent increased risk of infection with *M. catarrhalis* associated to ICS exposure.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The use of inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD) is associated to an increased risk of pneumonia, seemingly in a dose-dependent manner. Moreover, ICS use has been linked to an increased risk of several specific bacterial pathogens.

### WHAT THIS STUDY ADDS

⇒ To our knowledge, the association between ICS and *Moraxella catarrhalis*, one of the most common causes of infectious exacerbation in patients with COPD, has not previously been examined. We found a strong and dose-dependent association between ICS and risk of lower respiratory tract infection with *M. catarrhalis*.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ More knowledge is needed regarding the increased risk of infections associated with ICS. This is necessary to best balance beneficial effect against risk of adverse events, and hence provide the best possible treatment for patients with COPD in the future.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) comprises a combination of bronchitis and emphysema and involves chronic inflammation of the lung. Inhaled corticosteroids (ICS) are anti-inflammatory drugs that are recommended in patients with COPD with frequent or severe exacerbations (≥2 or ≥1 leading to hospital admission within the last year) and increased blood eosinophil count.[1 2] In this group of patients, ICS in combination with bronchodilators have been shown to reduce the risk of recurrent exacerbations and may improve lung function.[3] However, studies have not been unequivocal in regard to effect on all-cause mortality,[4–6] and the use of ICS in patients with COPD has been associated with an increased risk of pneumonia.[7 8]

The immunosuppressive effects of ICS have been shown to affect the interplay between

microbiome and host and may augment the bacterial burden and alter the lower airway microbial composition.[9 10] Both bacterial colonisation and infection with pathogenic bacteria play an important role in COPD pathogenesis, contributing to inflammatory response, lung damage and exacerbations.[11]

*Moraxella catarrhalis*, a Gram-negative aerobic diplococcus, is an important cause of upper and lower respiratory tract infections. It is known to affect patients with COPD and is a common cause of bacterial exacerbation.[12 13] *M. catarrhalis* may also colonise the lower airways in stable COPD, which is associated to worsened COPD symptoms and increased risk of subsequent exacerbation.[14–16]

*M. catarrhalis* is often found as a copathogen with other bacterial species or viruses[13] and thus, risk of lower respiratory tract infection with *M. catarrhalis* could be especially susceptible to changes in lung microbiome and immunosuppression.

The aim of the study was to find out whether there is an association between ICS use and the rate of lower respiratory tract sample positive for *M. catarrhalis* in patients with COPD.

## METHODS

### Data sources

Data from regional and nationwide administrative registries was accessed. Linkage between registries was done by using unique personal identifications numbers, ensuring exact linkage on patient level allowing complete follow-up.

The following registries were used:

1. The Danish Register of COPD (DrCOPD) was used to identify patients with COPD. It is a nationwide register that holds individual patient data on demographics and all outpatient visits at all hospital-based pulmonary clinics and hospital admissions due to exacerbation of COPD since 2010.[17]
2. The Danish National Patient Registry holds data on all hospital admissions and all hospital outpatient visits including primary and secondary diagnoses, and was used to characterise comorbidities in the study population.[18]
3. The Danish National Database of Reimbursed Prescriptions (DNDRP) includes data on all reimbursed prescriptions redeemed at Danish community-based and hospital-based outpatient pharmacies.[19] DNDRP was used to identify prescribed and redeemed medication.
4. Information on deaths was obtained from The Danish register of Causes of Death.
5. Microbiological data from the Clinical Microbiology Departments in Eastern Denmark (Region Zealand and Capital Region) was used to identify samples positive for *M. catarrhalis* and copathogens.

### Study population

The study considered all patients registered in DrCOPD with an outpatient clinic visit between 1 January 2010 and 31 October 2017. Table 1 presents an overview of the study population. Study entry was defined as the first outpatient clinic visit. Patients with only in-hospital registrations were not included as these contacts do not hold information on patient characteristics for example, severity of airflow obstruction, degree of dyspnoea and smoking status. Likewise, patients with outpatient contacts but no registration of body mass index (BMI), forced expired volume in the 1 s (FEV1) or smoking status, in neither the first nor following contacts, were excluded allowing for complete case analysis. Patients from western Denmark were excluded as we could not gain access to microbiological data from western Denmark. *M. catarrhalis* was identified in a lower respiratory tract culture (ie, sputum, tracheal secretion, bronchial secretion or bronchial alveolar lavage) obtained after study entry. Patients with a lower respiratory tract culture positive for *M. catarrhalis* 30 days prior to study entry were excluded.

Patients with malignant neoplasm (International Classification of Disease (ICD-10 codes: C00–43 and C45–C97) or immunodeficiency (ICD-10 codes: D80–84, D85, D89) 5 years prior to study entry or prescription of disease-modifying antirheumatics drugs (Anatomical Therapeutic Chemical (ATC)-codes: L04A×03, L01AA01, A07EC01, L04AD01, L04AA13, L04A×01, L04AA06, P01BA02) 12 months prior to study entry were excluded, since these conditions and drugs are suspected to be associated with the study outcome. For the same reasons patients prescribed with azithromycin prophylaxis, defined as reimbursed prescriptions for accumulated ≥30 tablets (500 mg) of azithromycin 12 months prior to study entry, were excluded. Online supplemental table 1 lists the ICD-10 codes used to define exclusion criteria and comorbidities. Patients were followed for 365 days from study entry until first positive sample with *M. catarrhalis*, death or end of study 31 October 2017.

### Exposure to ICS

All prescriptions for ICS, alone or in a combination inhaler, redeemed within 365 days prior to study entry were identified. Doses of ICS were converted to budesonide-equivalent doses: Beclomethasone and mometasone were considered equivalent to budesonide. Fluticasone propionate and furoate were considered 2 and 10 times as potent as budenoside, respectively. Ciclesonide was considered 2.5 times as potent as budenoside.[20 21]

Dose response was assessed by categorising ICS exposure by tertiles based on the accumulated dose of ICS in the year prior to study entry (low, moderate or high dose). Non-use was used as a reference category.

### Clinical *M. catarrhalis* infection

Clinical *M. catarrhalis* infection was defined as admission to hospital within 7 days before or 14 days after a positive culture with *M. catarrhalis* and/or redemption of antibiotics from a Danish pharmacy for airway infection 7 days

Table 1 Baseline characteristics of the study population

| | Total | No ICS | Low ICS | Medium ICS | High ICS |
|---|---|---|---|---|---|
| No of subjects | 18867 (100.0) | 5687 (30.1) | 4361 (23.1) | 4457 (23.6) | 4362 (23.1) |
| Demographics | | | | | |
| Age | 69.6 (62.0–77.0) | 68.5 (60.3–76.0) | 69.3 (61–76.8) | 70.3 (63.4–77.5) | 70.6 (63.7–77.6) |
| Female | 10188 (54.0) | 2691 (47.3) | 2278 (52.2) | 2486 (55.8) | 2732 (62.6) |
| BMI, median (IQR) | 25 (21–29) | 25 (22–29) | 25 (22–29) | 25 (21–29) | 24 (21–28) |
| Pulmonary parameters | | | | | |
| FEV1 (%) median (IQR) | 49 (36–63) | 57 (44–70) | 53 (40–66) | 45 (34–58) | 40 (29–53) |
| FEV1 (%) | | | | | |
| ≥80 | 1262 (6.7) | 620 (10.9) | 337 (7.7) | 183 (4.1) | 122 (2.8) |
| 50–79 | 8101 (42.9) | 3048 (53.6) | 2177 (49.9) | 1664 (37.3) | 1212 (27.8) |
| 30–49 | 6578 (34.9) | 1609 (28.3) | 1399 (32.1) | 1760 (39.5) | 1810 (41.5) |
| <30 | 2926 (15.5) | 410 (7.2) | 448 (10.3) | 850 (19.1) | 1218 (27.9) |
| Smoking status | | | | | |
| Current | 7206 (38.2) | 2610 (45.9) | 1732 (39.7) | 1435 (32.2) | 1429 (32.8) |
| Former | 10990 (58.2) | 2879 (50.6) | 2442 (56.0) | 2871 (64.4) | 2798 (64.1) |
| Never | 671 (3.6) | 198 (3.5) | 187 (4.3) | 151 (3.4) | 135 (3.1) |
| Severe COPD exacerbations* | | | | | |
| 0 | 12944 (68.6) | 4626 (81.3) | 2974 (68.2) | 2863 (64.2) | 2481 (56.9) |
| 1 | 3822 (20.3) | 826 (14.5) | 952 (21.8) | 984 (22.1) | 1060 (24.3) |
| ≥2 | 2101 (11.1) | 235 (4.1) | 435 (10.0) | 610 (13.7) | 821 (18.8) |
| Comorbidity | | | | | |
| All-cause hospitalisation* | 11938 (63.3) | 3414 (60.0) | 2852 (65.4) | 2793 (62.7) | 2879 (66.0) |
| Hypertension | 5010 (26.6) | 1583 (27.8) | 1167 (26.8) | 1189 (26.7) | 1071 (24.6) |
| Atrial fibrillation | 2459 (13.0) | 773 (13.6) | 595 (13.6) | 589 (13.2) | 502 (11.5) |
| Myocardial infarction | 949 (5.0) | 290 (5.1) | 219 (5.0) | 206 (4.6) | 234 (5.4) |
| Heart failure | 2774 (14.7) | 865 (15.2) | 681 (15.6) | 617 (13.8) | 611 (14.0) |
| Peripheral vascular disease | 1533 (8.1) | 525 (9.2) | 350 (8.0) | 345 (7.7) | 313 (7.2) |
| Cerebrovascular disease | 1184 (6.3) | 384 (6.8) | 299 (6.9) | 251 (5.6) | 250 (5.7) |
| Diabetes mellitus | 2023 (10.7) | 662 (11.7) | 489 (11.2) | 418 (9.4) | 454 (10.4) |
| Renal disease | 756 (4.0) | 277 (4.9) | 185 (4.2) | 147 (3.3) | 147 (3.4) |
| Asthma | 2158 (11.4) | 296 (5.2) | 501 (11.5) | 676 (15.2) | 685 (15.7) |
| Bronchiectasi | 243 (1.3) | 76 (1.3) | 54 (1.2) | 53 (1.2) | 60 (1.4) |
| Use of medication* | | | | | |
| LABA or LAMA | 13341 (70.7) | 2941 (51.7) | 2990 (68.6) | 3619 (81.2) | 3791 (86.9) |
| Theofylline | 645 (3.4) | 43 (0.8) | 80 (1.8) | 177 (4.0) | 345 (7.9) |
| Oral corticosteroids | 7233 (38.3) | 1074 (18.9) | 1578 (36.2) | 2070 (46.4) | 2511 (57.5) |

Data are presented as n (%) unless otherwise specified. Further baseline characteristics are available in online supplemental file 2.
*12 months prior to study entry.
BMI, body mass index; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LABA, long-acting β2-agonis; LAMA, long-acting muscarinic antagonist; MRC, Medical Research Council.

before or 14 days after a positive culture with *M. catarrhalis*.

Following antibiotics were considered as given for airway infection: phenoxymethylpenicillin, amoxicillin, amoxicillin with clavulanic acid, azithromycin, roxithromycin, clarithromycin, moxifloxacin, ciprofloxacin and doxycycline (ATC codes: J01CE02, J01CA04, J01CR02, J01FA01, J01FA06, J01FA09, J01FA10, J01MA02, J01MA14, J01AA02). Not all of these are active towards *M. catarrhalis*. However, in the definition of the outcome, prescription of antibiotics was used as a proxy for clinical infection (not as 'adequate treatment'), and further,

many prescriptions could be done before the culture sample was reported to the physician.

### Copathogens

A copathogen was defined as a lower respiratory tract culture, obtained on the same date as a positive *M. catarrhalis* sample, positive for a different pathogen. We did not include samples for fungal or viral pathogens.

### Statistical analysis

The risk of lower respiratory tract sample with *M. catarrhalis* 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 *M. catarrhalis*. The model was adjusted for the following suspected confounders and markers of disease severity: age, sex, severity of airway obstruction (percentage of predicted FEV1), BMI, smoking status (never, former or current smoker), calendar year of entry in DrCOPD and accumulated dose of oral corticosteroids 365 days prior to study entry.

Two models were applied as sensitivity analysis—a propensity score matched model using the greedy-match method and a propensity score weighted model using multinominal propensity scores.

For the propensity matched model, patients exposed to high or moderate ICS doses were matched 1:1 with patients exposed to low or no ICS dose in a propensity matched population, based on the same variables used in the main analysis. An unadjusted Cox proportional hazard regression model was then used to estimate the risk of a positive sample with *M. catarrhalis* associated with ICS use.

The propensity score weighted model was applied using multinominal propensity score weighting[22] based on the same variables used in the adjusted main analysis. Covariate balance between treatment groups was assessed using absolute standardised mean differences (ASMD) with ASMD≤0.1 indicating sufficient balance. A weighted Cox proportional hazard regression model was then used to estimate the risk of a lower respiratory tract sample with *M. catarrhalis* associated with the use of ICS.

The regression models were tested for proportion of hazards and linearity of continuous variables and were found to be valid. A p<0.05 was considered statistically significant. All statistical analyses were performed by using SAS statistical software (V.3.71 Enterprise Edition, SAS Institute), except for the propensity weighted model, for which the Twang package[23] for R statistical software (V.2022.07.2, RStudio) was used.

## RESULTS

We included 18 867 patients (figure 1). Table 1 shows details on the study population, including comorbidities and prescriptions. A total of 521 (2.8%) patients were found to have a lower respiratory tract sample positive for *M. catarrhalis*. Mean follow-up time was 332 days (SD±84 days).

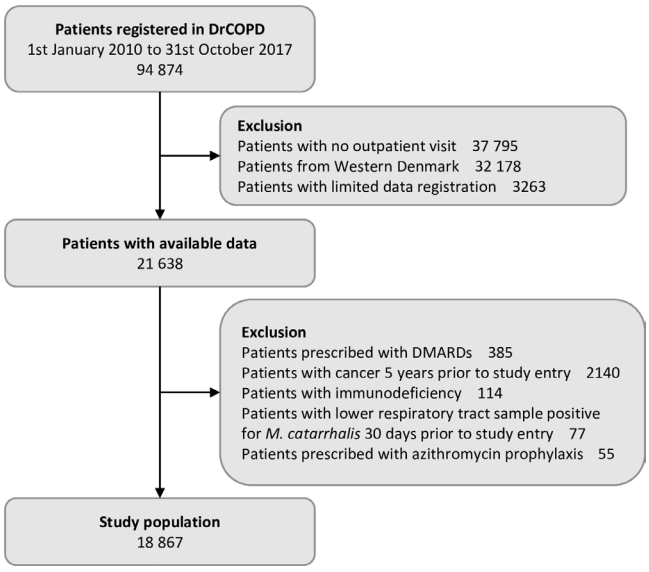


**Figure 1** Flow chart illustrating the selection of the study population. DrCOPD, Danish Register of Chronic Obstructive Pulmonary Disease; DMARDS, disease-modifying antirheumatics drugs.

The group of patients with low ICS exposure received <328 µg budesonide equivalents daily, moderate dose received 328–821 µg, and high dose received >821 µg. Details regarding ICS use are shown in table 2.

Crude incidence rate of a *M. catarrhalis* a positive sample the control group with no ICS use was 1.1% per person-year. Incidence rates were found to be higher with increasing ICS dose, reaching 6.1% in the high ICS group (table 3 and figure 2) corresponding to a crude number needed to harm of 20.0.

### Main analysis

Adjusted Cox regression showed significantly higher risk of lower respiratory tract sample with *M. catarrhalis* among patients with ICS use compared with non-users (table 3). For low and moderate doses of ICS HR was 1.65 (95% CI 1.19 to 2.30, p=0.003) and 1.82 (95% CI 1.32 to 2.51, p=0.0002), respectively. In the group of patients with highest ICS exposure, the HR of *M. catarrhalis* was 2.80 (95% CI 2.06 to 3.82, p<0.0001).

### Sensitivity analyses

The propensity score matched population comprised 13 536 patients, consisting of 6769 patients receiving no or low-dose ICS matched 1:1 to patients with moderate or high-dose ICS. Results remained stable compared with the main analysis, although with somewhat more marked increase in risk of lower respiratory tract sample with *M. catarrhalis* in the high ICS group (HR 3.61 (95% CI 2.57 to 5.07, p<0.0001)) relatively to the low and moderate

Table 2 Overview of ICS use in the study population

| | Total | Low ICS | Moderate ICS | High ICS |
|---|---|---|---|---|
| No of subjects, n (%) | 13 180 (69.9) | 4361 (23.1) | 4457 (23.6) | 4362 (23.1) |
| Accumulated daily budesonide equivalent dose (µg), median (IQR) | | | | |
| Total ICS | 579 (263–1041) | 164 (105–263) | 579 (473–658) | 1397 (1052–1894) |
| Budesonide | 421 (164–658) | 158 (105–263) | 526 (421–631) | 947 (631–1262) |
| Fluticasone proprionate | 904 (329–1644) | 164 (164–329) | 493 (329–658) | 1479 (986–1973) |
| Fluticasone furoate | 454 (227–832) | 189 (76–302) | 454 (227–548) | 907 (454–1097) |
| Beclometasone | 219 (110–460) | 110 (110–197) | 329 (197–526) | 395 (197–778) |
| Mometasone | 658 (247–1085) | 132 (66–263) | 461 (157–707) | 888 (625–1430) |
| Ciclesonide | 263 (132–395) | 132 (132–263) | 263 (197–395) | 461 (263–756) |
| No of individual users, n (%) | | | | |
| Budesonide | 9410 (49.9) | 3550 (81.4) | 3682 (82.6) | 2178 (49.9) |
| Fluticasone proprionate | 4901 (26.0) | 862 (19.8) | 1121 (25.2) | 2918 (66.9) |
| Fluticasone furoate | 118 (0.6) | 18 (0.4) | 48 (1.1) | 52 (1.2) |
| Beclometasone | 190 (1.0) | 58 (1.3) | 77 (1.7) | 55 (1.3) |
| Mometasone | 51 (0.3) | 9 (0.2) | 10 (0.2) | 32 (0.7) |
| Ciclesonide | 42 (0.2) | 15 (0.3) | 13 (0.3) | 14 (0.3) |

Please note that individuals may have received more than one type of ICS.
ICS, inhaled corticosteroids.

ICS group (HR 1.90 (95% CI 1.31 to 2.75, p=0,0008) and 2.15 (95% CI 1.50 to 3.05, p<0.0001), respectively).

The multinominal propensity score weighted analysis yielded results similar to those of the main analysis, with HR 2.65 (95% CI 2.30 to 3.05, p<0.0001) for risk of positive sample with *M. catarrhalis* among users of high-dose ICS compared with non-users (table 3).

A post hoc stratification for asthma was performed using the same Cox multivariate regression model as in the main analysis. Results remained stable when analysing the strata containing only patients with no registration of an asthma diagnosis 5 years prior to study entry (online supplemental table 3). In the strata containing only patients who did have an asthma diagnosis, results did not reach statistical significance.

### Clinical *M. catarrhalis* infection

Of the 521 patients with a positive culture for *M. catarrhalis* 455 (87%) patients were found to have clinical *M. catarrhalis* infection (defined in methods). A total of 309 patients were admitted to hospital within 7 days before or 14 days after the positive sample was obtained. A total of 258 patients redeemed a prescription for a relevant antibiotic within 7 days before or 14 days after a positive culture for *M. catarrhalis*.

In the Cox multivariate regression model using clinical *M. catarrhalis* infection as outcome, results remained similar compared with the main analysis with HR 1.57 (95% CI 1.09 to 2.224, p=0.014), HR 1.85 (95% CI 1.31 to 2.60, p=0.0004) and HR 2.88 (95% CI 2.07 to 4.02, p<0.0001) for low, medium and high ICS respectively compared with non-users (table 4).

### Copathogens

In 176 (34%) individual patients with a positive culture for *M. catarrhalis*, one or more different pathogens were present in samples obtained on the same day. In 29 patients, 2 or more copathogens were found. In total, there were 206 positive samples for copathogens. The most common bacteria were *Streptococcus pneumoniae* (34.5%), *Hemophilus influenzae* (25.8%), *Pseudomonas aeruginosa* (9.7%) and *Staphylococcus aureus* (5.8%). We found similar prevalence of copathogens regardless of ICS dose (online supplemental table 4).

## DISCUSSION

We found a strong and dose-dependent association between ICS use and risk of lower respiratory tract sample with *M. catarrhalis* in patients with COPD. High doses of ICS were associated to an almost threefold increased risk, but even low doses of ICS showed increased risk (HR 1.65). Results remained stable in sensitivity analyses.

To our knowledge, the relationship between ICS and risk of lower respiratory tract infection with *M. catarrhalis* has not previously been investigated. It is well described that ICS use, especially in high doses, is associated with increased risk of pneumonia in patients with COPD.[7 8 24 25] However, different risk/incidence rates have been reported due to differences in selected population

**Table 3** Results of main analysis and sensitivity analyses with sample positive for *Moraxella catarrhalis* as outcome

| | No of patients | No of events | Crude incidence rate | Cox multivariate regression model (n=18 867) | | Propensity matched analysis (n=13 536) | | Propensity weighted analysis (n=18 867) | |
|---|---|---|---|---|---|---|---|---|---|
| | n | n | Events per person-year | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| Total | 18 867 | 521 | 0.0303 | | | | | | |
| No ICS | 5687 | 59 | 0.0113 | Ref. | | Ref. | | Ref. | |
| Low ICS | 4361 | 92 | 0.0229 | 1.65 (1.19 to 2.30) | 0.003 | 1.90 (1.31 to 2.75) | 0.0008 | 1.57 (1.35 to 1.83) | <0.0001 |
| Moderate ICS | 4457 | 134 | 0.0329 | 1.82 (1.32 to 2.51) | 0.0002 | 2.15 (1.50 to 3.07) | <0.0001 | 1.76 (1.52 to 2.05) | <0.0001 |
| High ICS | 4362 | 236 | 0.0612 | 2.80 (2.06 to 3.82) | <0.0001 | 3.61 (2.57 to 5.07) | <0.0001 | 2.65 (2.30 to 3.05) | <0.0001 |

Patients with no ICS use 12 months prior to study entry are not included in the table. Low <328 µg, moderate 328–821 µg, high >821 µg daily budesonide equivalents. Non-use of ICS was used as reference in all analyses.
ICS, inhaled corticosteroids.




**Figure 2** Cumulative incidence of lower respiratory tract sample positive for *Moraxella catarrhalis* according to ICS exposure in 18 867 patients with COPD. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids.

(age, BMI, FEV1, etc) and exposures including ICS type and dose.

Long-term use of ICS in patients with COPD has been shown to affect the lung microbiome, and although much is yet to be learnt, current data suggest that ICS use may increase bacterial load and may promote the persistence of certain bacterial pathogens including *H. influenzae*.[10 26] *M. catarrhalis* has previously been described to often participate as a copathogen in respiratory tract infections with other bacteria including *H. influenzae* and *P. aeruginosa*.[13] This pattern was also present in the data presented here, in which we found copathogens to be present in 34% of cases. Previous work from our group has demonstrated dose-dependent increased is risk of both *P. aeruginosa* (HR 3.58 (95% CI 2.75 to 4.65) for >800 µg budesonide equivalents compared with ICS non-users)[27] and *H. influenzae* (HR 1.90 (95% CI 1.52 to 2.38) for >300 µg budesonide equivalents compared with non-users)[28] related to ICS use.

Although it is difficult to extrapolate and compare exact risks due to differences in design, as well as dose and type of ICS, the overall picture is that ICS is associated to an increased risk of infection with a variety of different pathogens, and that the risk is dose-dependent. Our results are well in line with this.

The Danish COPD registry in combination with the national registries, based on personal identification numbers, allow for uniquely detailed epidemiological data on a patient level. 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. In addition, our registry includes many important confounders such as smoking status, oral and ICS use, lung function by FEV1, MRC and BMI.

Limitations of this study include limited knowledge of the clinical situation in which the samples were obtained. This especially since the pathogenic potential of *M.*

Table 4 Sensitivity analysis using clinical *Moraxella catarrhalis* infection as outcome

| | No of patients | No of events | Cox multivariate regression model (n=18867) | |
|---|---|---|---|---|
| | n | n | HR (95% CI) | P value |
| Total | 18867 | 455 | | |
| No ICS | 5687 | 59 | Ref. | |
| Low ICS | 4361 | 92 | 1.57 (1.09 to 2.24) | 0.014 |
| Moderate ICS | 4457 | 134 | 1.85 (1.31 to 2.60) | 0.0004 |
| High ICS | 4362 | 236 | 2.88 (2.07 to 4.02) | <0.0001 |

Clinical *M. catarrhalis* infection was defined as a lower respiratory tract culture positive for *M. catarrhalis* combined with admission to hospital and/or redeemed prescription for an antibiotic related to airway infections, within 7 days before or 14 days after the positive sample was obtained.
ICS, inhaled corticosteroids.

*catarrhalis* has been cause for discussion both historically and in more recent years.[12 13] For example, Murphy *et al* found that a significant part of positive *M. catarrhalis* sputum samples were associated to asymptomatic colonisation.[16] Contradictory to this we found that the vast majority (87%) of patients with a sample positive for *M. catarrhalis* were either admitted to hospital or redeemed a prescription for an antibiotic, that is, had a clinically significant infection. This discrepancy likely arises from the difference in testing routines in the two studies. In the study by Murphy *et al*, sputum samples were collected when patients had signs of exacerbation but also routinely monthly. The data represented in this study, on the other hand, stem from the Danish clinical setting where samples are collected primarily on suspicion of infection and most often in the hospital setting.

Another limitation of the study is that we only know from the available data that the ICS prescriptions were redeemed, and not whether the patients adhered to treatment. This, however, could be considered an advantage as it makes the data more 'real life' where compliance is not given. Finally, we have defined ICS exposure in the year prior to study entry, and thus, there may be cases where ICS was discontinued in the study period.

The results presented here are in line with previous findings in other studies regarding ICS use and respiratory infections, but due to the observational design of the study, we cannot determine a causal relationship. Prospective studies examining ICS exposure in different doses, clinically confirming pneumonia, identifying microbiological agents and studying the imposed effect on mortality and quality of life are needed to confirm the correlation and clarify clinical significance.

In conclusion, our findings support that ICS, especially high doses must be prescribed with care in patients with COPD. We note that potency of the different ICS products should be kept in mind.

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**Supplemental table 1** International Classification of diseases 10th revision (ICD-10) codes used for definition of comorbidities.

| Diagnosis | ICD-10 |
|---|---|
| **Exclusion criteria** | |
| Cancer | C00-C43, C45-C99 |
| Immunodeficiency | D80-D84, D86-D89 |
| **Comorbidities** | |
| Hypertension | I10-I15 |
| Atrial fibrillation | I48 |
| Myocardial infarction | I121-I123 |
| Heart failure | I42, I50, J81, I110, I130, I132 |
| Peripheral vascular disease | I70-I74, I77, I79 |
| Cerebrovascular disease | I60–I64, G458, G459 |
| Systemic connective tissue disease | M30-M36 |
| Inflammatory polyarthropathy | M05-M14 |
| Depression | F32-34 |
| Diabetes mellitus | E10-E14 |
| Renal disease | N02-N08, N11, N14, N18, N19, N26, N158-165, N168, I120, I 131, I132, E102, E112, E122, E132, E142, Z992 |
| Asthma | J45 |
| Bronchiectasis | J47 |
| **Charlson comorbidity index** | |
| Connective tissue disease | M05, M06, M315, M32-M34, M351, M353, M360 |
| Myocardial infarction | I10-I22, I252 |
| Heart failure | I420, I425-I1429, I50, I099, I110, I130, I255, I132, I43, P290 |
| Peripheral vascular disease | I70-I71, I1731, I1738, I1739, I771, I790, I1792, K551, K558, K559, Z958, Z959, |
| Cancer | Na (excluded) |
| COPD | Na (all patients) |
| Diabetes mellitus, uncomplicated | E100, E101, E106, E108-E111, E 116, E118-121, E 126, E 128-E131, E136, E138-E141, E146, E148-E149 |
| Diabetes mellitus with end-organ damage | E102-E105, E107, E112-E115, E117, E122-E125, E127, E132-E135, E137, E142-E145, E147 |
| Cerebrovascular disease | G45, G46, H340, I160-I169 |
| Liver disease, mild | B128, K700-703, K709, K713-K715, K717, K73-K74, K760, K762-K764, K768-K769, Z944 |
| Liver disease, severe | K765-K767, I850, I859, I84, I982, K704, K711, K721, K729 |
| Renal disease | I120, I131, N032-N037, N052-N057, N18-N19. N250, Z490-Z492, Z940, Z992 |
| AIDS | B20-B22, B24 |
| Peptic ulcer disease | K25-K28 |
| Hemiplegia | G041, G114, G801-G802, G810-G834, G839 |
| Dementia | G30, G311, F00-F03, F051 |

**Supplemental table 2.** Supplementary baseline characteristics of the study population.

| | Total | No ICS | Low ICS | Medium ICS | High ICS |
|---|---|---|---|---|---|
| no. of subjects | 18867 (100.0) | 5687 (30.1) | 4361 (23.1) | 4457 (23.6) | 4362 (23.1) |
| **Pulmonary parameters** | | | | | |
| MRC, median (IQR) | 3 (2-4) | 2 (2-3) | 3 (2-3) | 3 (2-4) | 3 (3-4) |
| MRC group | | | | | |
| MRC 1 | 1904 (10.1) | 1062 (18.7) | 704 (16.1) | 533 (12.0) | 436 (10.0) |
| MRC 2 | 5669 (30.0) | 2320 (40.8) | 1682 (38.6) | 1415 (31.7) | 1083 (24.8) |
| MRC 3 | 6259 (33.2) | 1918 (33.7) | 1691 (38.8) | 1817 (40.8) | 1664 (38.1) |
| MRC 4 | 3956 (21.0) | 1058 (18.6) | 1030 (23.6) | 1266 (28.4) | 1433 (32.9) |
| MRC 5 | 2187 (11.6) | 590 (10.4) | 574 (13.2) | 758 (17.0) | 1096 (25.1) |
| Unknown MRC | 277 (1.5) | 124 (2.2) | 65 (1.5) | 53 (1.2) | 35 (0.8) |
| **Comorbidity** | | | | | |
| Charlson Comorbidity Index | 4 (3-5) | 4 (3-5) | 4 (3-5) | 4 (3-5) | 4 (3-5) |
| Systemic connective tissue disease | 356 (1.9) | 125 (2.2) | 88 (2.0) | 76 (1.7) | 67 (1.5) |
| Inflammatory polyarthropathy | 699 (3.7) | 212 (3.7) | 178 (4.1) | 166 (3.7) | 143 (3.3) |
| Depression | 676 (3.6) | 168 (3.0) | 165 (3.8) | 175 (3.9) | 168 (3.9) |
| **Use of medication 12 months prior to cohort entry** | | | | | |
| Antibiotics* | 13005 (68.9) | 3321 (58.4) | 2981 (68.4) | 3249 (72.9) | 3449 (79.1) |
| Oral corticosteroids (accumulated dose in 12 months) | | | | | |
| ≤500 mg | 3631 (19.2) | 686 (12.1) | 898 (20.6) | 984 (22.1) | 1063 (24.4) |
| >500 mg | 3602 (19.1) | 388 (6.8) | 680 (15.6) | 1086 (24.4) | 1448 (33.2) |

Data are presented as n (%) unless otherwise specified. MRC, Medical Research Council Dyspnoea Scale. *Redeemed prescription of any antibiotic drug 12 months prior to study entry.

**Supplemental table 3.** Stratification for asthma

| | **Patients without asthma (n=16,709)** | | **Patients with asthma (n=2158)** | |
|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| **No ICS** | Ref. | | Ref. | |
| **Low ICS** | 1.68 (1.20-2.36) | 0.0025 | 2.54 (0.30-21.82) | 0.40 |
| **Moderate ICS** | 1.72 (1.24-2.40) | 0.0014 | 5.88 (0.78-44.28) | 0.086 |
| **High ICS** | 2.73 (1.98-3.76) | <0.0001 | 7.30 (0.97-54.75) | 0.053 |

Results of a cox multivariate regression model, stratified for medical history of asthma and using the same covariates as in the main analysis. 16,709 patients with COPD had no registration of asthma diagnosis 5 years prior to study entry (no events = 459). 2158 patients did have an asthma diagnosis registered (no. events 62). ICS, inhaled corticosteroid.

**Supplemental table 4.** Prevalence of multi-pathogen infection

| | **Patients with *M. catarrhalis*** (n) | **Patients with co-pathogens** (n) | **Prevalence of multi-pathogen infection** (%) |
|---|---|---|---|
| **No ICS** | 59 | 23 | 38.98 |
| **Low ICS** | 92 | 30 | 32.61 |
| **Moderate ICS** | 134 | 34 | 25.37 |
| **High ICS** | 236 | 89 | 37.71 |
| **Total** | 521 | 176 | 33.78 |

Co-pathogens were defined as at least one other positive lower airway sample obtained on the same date as the positive *M.* catarrhalis sample.