ORIGINAL ARTICLE

# Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis

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► An additional appendix is published online only. To view this file please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2012-201772).

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Received 15 February 2012
Accepted 14 June 2012
Published Online First 10 July 2012

**To cite:** Andréjak C, Nielsen R, Thomsen Vibeke Ø, *et al*. *Thorax* 2013;**68**:256–262.

## ABSTRACT

**Background** Chronic respiratory disease and inhaled corticosteroid (ICS) therapy for chronic obstructive pulmonary disease (COPD) increase the risk of pneumonia. Few data are available on the association of these risk factors with non-tuberculous mycobacterial (NTM) pulmonary disease.

**Methods** This study examined chronic respiratory diseases and ICS use as risk factors in a population-based case-control study encompassing all adults in Denmark with microbiologically confirmed NTM pulmonary disease between 1997 and 2008. The study included 10 matched population controls per case. Conditional logistic regression was used to compute adjusted ORs for NTM pulmonary disease with regard to chronic respiratory disease history.

**Results** Overall, chronic respiratory disease was associated with a 16.5-fold (95% CI 12.2 to 22.2) increased risk of NTM pulmonary disease. The adjusted OR for NTM disease was 15.7 (95% CI 11.4 to 21.5) for COPD, 7.8 (95% CI 5.2 to 11.6) for asthma, 9.8 (95% CI 2.03 to 52.8) for pneumoconiosis, 187.5 (95% CI 24.8 to 1417.4) for bronchiectasis, and 178.3 (95% CI 55.4 to 574.3) for tuberculosis history. ORs were 29.1 (95% CI 13.3 to 63.8) for patients with COPD on current ICS therapy and 7.6 (95% CI 3.4 to 16.8) for patients with COPD who had never received ICS therapy. Among patients with COPD, ORs increased according to ICS dose, from 28.1 for low-dose intake to 47.5 for high-dose intake (more than 800 µg/day). The OR was higher for fluticasone than for budesonide.

**Conclusion** Chronic respiratory disease, particularly COPD treated with ICS therapy, is a strong risk factor for NTM pulmonary disease.

### Key messages

**What is the key question?**

► Chronic respiratory disease, including chronic obstructive pulmonary disease (COPD), and inhaled corticosteroids increase the risk of pneumonia. There are virtually no data on the association of these risk factors with non-tuberculous mycobacterial (NTM) pulmonary disease.

**What is the bottom line?**

► This population-based case–control study provides strong evidence that the risk of NTM pulmonary disease is substantially increased in adults with asthma, COPD, bronchiectasis and previous tuberculosis.

**Why read on?**

► Among patients with COPD, the risk of NTM pulmonary disease is clearly associated with use, dose and type of inhaled corticosteroid.

## INTRODUCTION

The global incidence of non-tuberculous mycobacterial (NTM) pulmonary disease averages one case per 100 000 person-years, is probably underestimated, and is increasing.[1–3] Prognosis is poor: overall 3-year cumulative death rate is 34% and the death rate for certain strains is even higher (69% for *Mycobacteria xenopi*).[1 4] However, few data are available on risk factors for NTM. A case–control study of 206 patients with NTM pulmonary disease, 381 patients with tuberculosis and 180 controls conducted among gold miners in South Africa[5] found that severe silicosis (adjusted OR 5.0, 95% CI 2.0 to 12.3) and previous tuberculosis treatment (adjusted OR 9.6, 95% CI 4.2 to 22.1) increased NTM risk. Another case–control study suggested that pulmonary NTM disease often affects a distinct risk group of patients who are morphologically characterised as tall and lean, with a high prevalence of scoliosis, pectus excavatum, mitral valve prolapse, and cystic fibrosis transmembrane conductance regulator mutations.[6]

The prevalence of chronic respiratory disease, particularly chronic obstructive pulmonary disease (COPD), is increasing worldwide. COPD now affects 8% of adults in the USA[7] and more than 10% of adults in Denmark.[8 9] In NTM case series worldwide, a high prevalence of comorbid chronic respiratory diseases (particularly COPD but also pneumoconiosis and bronchiectasis) has been observed affecting between 10% and 50% of all patients with NTM.[1 5 10–12] In a Danish population-based cohort of 1282 patients who had NTM isolated from respiratory tract samples, the most prevalent comorbidity by far was any chronic respiratory disease, present in 27% of patients colonised with NTM and 46% of patients who fulfilled criteria for definite pulmonary NTM disease.[1]

Chronic respiratory disease including COPD, bronchiectasis, pneumoconiosis and asthma may increase the propensity for NTM disease by causing mucosal damage and compromising local immunity, with impaired clearance of secretions,

abnormal composition of airway surface liquid, abnormal composition of sputum, and airway damage caused by persistent inflammation associated particularly with COPD.[7 13] Moreover, up to 50% of patients with COPD and most patients with asthma receive long-term therapy with inhaled corticosteroids (ICSs).[14] COPD per se and ICS therapy for COPD have been shown to increase pneumonia risk,[15 16] but data are lacking on the association between these risk factors and pulmonary NTM disease.

Using a case–control study design, this study took advantage of Denmark's population-based databases to examine different types of chronic respiratory diseases and ICS therapy as risk factors for NTM pulmonary disease.

## METHODS

### Identification of patients with NTM disease (cases)

The Danish healthcare system provides tax-supported healthcare to all residents and guarantees free access to hospitals and primary medical care. A unique identifier (the Central Population Registry number) assigned to every Danish citizen allowed for exact linkage among all databases used in this study.

The Statens Serum Institut in Copenhagen receives pulmonary specimens from all patients throughout Denmark for mycobacterial culture.[17] Its nationwide registry contains microbiological data from all adults in Denmark with any NTM-positive specimen. As explained in detail previously,[1 18] patients aged 15 or over with definite NTM pulmonary disease between 1 January 1997 and 31 December 2008 were identified based on the number and type of positive specimens. Patients with definite pulmonary NTM disease were defined as those with more than three NTM-positive pulmonary specimens, or three positive specimens including one or more obtained by bronchoscopy in follow-up to lesions seen on chest x-ray, or three positive specimens including one or more positive bronchial wash, bronchial biopsy or pleural effusion, or at least one positive specimen from a lung biopsy. A previous medical chart review for a sample of 30 out of 335 patients with definite pulmonary NTM disease according to our definition showed that 100% of these patients meet the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) 2007 criteria for definite NTM pulmonary disease.[1 18]

### Identification of population control subjects

The Danish Central Population Registry, which is updated daily, contains electronic records of dates of birth, changes in marital status, changes of address, dates of emigration, and dates of death for the entire Danish population since 1968. On the diagnosis date of each patient with NTM (the index date, or the date of the NTM-positive sample that confirmed definite NTM disease), 10 control subjects were randomly selected from the Central Population Registry, matched by age (same year of birth), sex and place of residence (same county) using the risk set sampling technique.[19]

### Data on chronic respiratory diseases

The Danish National Registry of Patients,[20] which covers all Danish hospitals, contains data on inpatient admissions from non-psychiatric hospitals since 1977 and on emergency room and hospital outpatient clinic visits since 1995. The Danish National Registry of Patients was used to identify all cases and controls with a diagnosis of chronic respiratory disease recorded before or on the NTM infection index date (see online data supplement for codes). An exception was new tuberculosis diagnoses made for the first time on the NTM infection index date because of the likelihood of misclassification.

### Data on inhaled corticosteroids

Prescription databases track individual-level prescription records from all pharmacies in northern Denmark. This region has a population of approximately 1.8 million people (one-third of Denmark's population).[21] For NTM cases and controls living in northern Denmark, information was obtained on current ICS use (beclometasone, mometasone, fluticasone and budesonide) or combinations of ICSs and long acting β agonists (see online data supplement for codes). The primary exposure in our analysis was any prescription filled in the 180-day period before the index date. For current ICS type, we use the most recent prescription filled.

### Data on confounding factors

Data on potential confounding factors were collected from the Danish National Registry of Patients, the prescription database and the Danish Central Population Registry. For each person, data were retrieved on 19 major comorbid disease categories included in the Charlson comorbidity index and diagnosed before or on the NTM infection index date.[22] Three comorbidity levels were defined as low (score of 0), medium (score of 1–2) and high (score ≥3). Adjustments were made separately for presence of alcoholism-related disorders not included in the Charlson comorbidity index. For the dataset of patients from northern Denmark, data were obtained on current use of systemic corticosteroids and other immunosuppressants within the year prior to the NTM infection date. The Central Population Registry in northern Denmark also provided data on markers of socioeconomic status (eg, marital status (married, never married, divorced, widowed or marital status unknown), and degree of urbanisation (residence in a rural area with a population of 0–10 000; in a provincial town with a population of 10 000–100 000 or in a city with >100 000 inhabitants)).

### Statistical analysis

Conditional logistic regression analysis was used to compute crude and adjusted ORs with associated 95% CIs as a measure of RR for NTM disease among subjects with and without chronic respiratory disease. Respiratory diseases were further categorised by type (COPD, asthma, pneumoconiosis, bronchiectasis, cystic fibrosis, previous tuberculosis and chronic respiratory failure) and, for major respiratory diseases in the northern Denmark dataset, by use or non-use of ICSs. For the overall analysis in Denmark, adjustments were made for the level of comorbidity and for alcoholism-related conditions. For the analysis using the northern Denmark dataset, additional adjustments were made for use of oral corticosteroids and other immunosuppressants, marital status, and urbanisation of residence. All analyses were performed using SAS V.9.2 software. The study was approved by the Danish Data Protection Agency, records 1-16-02-1-08 and 2009-41-3866. Data were obtained from Danish registries, which are generally available to researchers and their use does not require informed consent.

## RESULTS

### Data describing the nationwide dataset

We identified 332 patients with pulmonary NTM disease in Denmark, and 3320 population controls (table 1). The study population was 58.1% men and 41.9% women, with a median age of 64 years. A total of 167 cases (50.3%) and 205 controls (6.2%) had a diagnosis for a chronic respiratory disease on the

**Table 1** Characteristics of cases with non-tuberculous mycobacterial pulmonary disease and matched population controls from Denmark as a whole and from northern Denmark

| | Cases | Population controls |
|---|---|---|
| Overall Danish population | 332 | 3320 |
| Men, n (%) | 193 (58.1) | 1930 (58.1) |
| Median age, years (IQR) | 64 (54–73) | 64 (54–73) |
| Charlson comorbidity index | | |
| Low (score=0), n (%) | 87 (26.2) | 2224 (67.0) |
| Medium (score=1–2), n (%) | 178 (53.6) | 784 (23.6) |
| High (score=3+), n (%) | 67 (20.2) | 312 (9.4) |
| Charlson comorbidity index excluding the chronic pulmonary disease category | | |
| Low (score=0), n (%) | 177 (53.3) | 2315 (69.7) |
| Medium (score=1–2), n (%) | 113 (34.0) | 722 (21.7) |
| High (score=3+), n (%) | 42 (12.6) | 283 (8.5) |
| Alcoholism-related conditions, n (%) | 30 (9.0) | 106 (3.2) |
| Population in northern Denmark | 112 | 1120 |
| Men, n (%) | 66 (59.0) | 660 (59.0) |
| Median age, years (IQR) | 64 (54–73) | 64 (54–73) |
| Charlson comorbidity index | | |
| Low (score=0), n (%) | 23 (20.5) | 770 (68.7) |
| Medium (score=1–2), n (%) | 65 (58.0) | 278 (24.8) |
| High (score=3+), n (%) | 24 (21.4) | 72 (6.4) |
| Charlson comorbidity index excluding the chronic pulmonary disease category | | |
| Low (score=0), n (%) | 54 (48.2) | 804 (71.8) |
| Medium (score=1–2), n (%) | 46 (41.1) | 259 (23.1) |
| High (score=3+), n (%) | 12 (10.7) | 57 (5.1) |
| Alcoholism-related conditions, n (%) | 10 (8.9) | 30 (2.7) |
| Any inhaled corticoids before diagnosis, n (%) | 63 (56.2) | 109 (9.7) |
| Any inhaled corticoids 180 days before diagnosis, n (%) | 51 (45.5) | 59 (5.3) |
| Any immunosuppressant 1 year before diagnosis, n (%) | 32 (28.6) | 69 (60.7) |
| Degree of urbanisation | | |
| ≤10 000 inhabitants, n (%) | 25 (22.3) | 203 (18.1) |
| 10 000–100 000 inhabitants, n (%) | 55 (49.1) | 604 (55.9) |
| >100 000 inhabitants, n (%) | 32 (28.6) | 313 (28.0) |
| Marital status | | |
| Married, n (%) | 72 (64.3) | 680 (60.7) |
| Never married, n (%) | 12 (10.7) | 148 (13.2) |
| Divorced, n (%) | 14 (12.5) | 116 (10.4) |
| Widowed, n (%) | 14 (12.5) | 176 (15.7) |

index date for NTM infection. Among these, 140 cases (42.2%) and 159 controls (4.8%) had a history of COPD, 50 cases (15.1%) and 71 controls (2.1%) had a history of asthma, 55 cases (16.6%) and 7 controls (0.2%) had a history of tuberculosis, 3 cases (0.9%) and 3 controls (0.1%) had a history of pneumoconiosis, 18 cases (5.4%) and 2 controls (0.1%) had a history of bronchiectasis, and 18 cases (5.1%) and no controls (0%) had a history of cystic fibrosis (tables 1 and 2). Among the patients with COPD, diagnosis occurred within the 2 years prior to the NTM diagnosis in 29.2%, 2–5 years in 27.8%, and more than 5 years in 42.8% of patients. More than half (53%) of the patients with COPD experienced an exacerbation requiring hospitalisation in the year prior to the NTM diagnosis.

### OR estimates in the nationwide dataset

Overall, chronic respiratory disease was associated with a highly increased risk of NTM pulmonary disease. The unadjusted OR for NTM disease among patients with any chronic respiratory disease was 18.0 (95% CI 13.4 to 24.2) and the adjusted OR was 16.5 (95% CI 12.2 to 22.2 (table 2). Compared with individuals without the respective chronic respiratory disease, the adjusted OR for NTM was 15.7 (95% CI 11.4 to 21.5) for patients with COPD, 7.8 (95% CI 5.2 to 11.6) for patients with asthma, 9.8 (95% CI 2.03 to 52.8) for patients with pneumoconiosis, 187.5 (95% CI 24.8 to 1417.4) for patients with bronchiectasis and 178.3 (95% CI 55.4 to 574.3) for patients with a history of tuberculosis. For patients with COPD, those with recently diagnosed COPD (within the previous 2 years) had a higher NTM risk increase (OR 22.5) than those with COPD diagnosed more than 5 years previously (OR 12.9), possibly due to COPD survivor bias.

### Descriptive data for the northern Denmark cohort

A total of 112 patients with NTM and 1120 population controls were identified in northern Denmark (table 3). Similar to nationwide findings, 58.9% were men and 41.1% were women, with a median age of 64 years. More than half of all patients with NTM (64 cases, 57.1%) and 84 controls (7.5%) were previously diagnosed with chronic respiratory disease, and the vast majority of these (48.2% of all NTM cases and 6.0% of controls) had COPD. Among patients with NTM and chronic respiratory disease, 64% were current ICS users, including 70% of patients with COPD and 80% of patients with asthma. The main types of ICS used by NTM cases were fluticasone (54%) and budesonide (44%).

### OR estimates for the northern Denmark cohort

The unadjusted OR for NTM disease among patients with chronic respiratory diseases in northern Denmark was 19.3 (95% CI 11.6 to 31.9) and the adjusted OR was 15.6 (95% CI 8.9 to 27.5) (table 3). The adjusted OR for COPD was 13.1 (95% CI 7.4 to 23.3). When respiratory disease exposure by ICS treatment was subdivided, the adjusted OR was 7.6 (95% CI 3.4 to 16.8) for patients with COPD with no ICS use compared with 19.6 (95% CI 9.7 to 39.6) for those who had ever used ICSs and 29.1 (95% CI 13.3 to 63.8) for those with current ICS use. The adjusted OR for asthma was 1.6 (95% CI 0.6 to 3.9), with no substantial difference according to the particular ICS treatment. When ICSs was further subdivided by ICS dose and type, the adjusted OR for patients with COPD increased from 28.1 (95% CI 10.7 to 73.4) for doses lower than 800 µg/day (low dose) to 47.5 (95% CI 9.5 to 236.7) for doses higher than 800 µg/day (high dose). The adjusted OR for patients with COPD was higher for fluticasone (40.8; 95% CI 14.0 to 119.5) than for budesonide (19.8; 95% CI 7.2 to 54.4). The adjusted OR for NTM pulmonary disease among patients with COPD also increased with the number of exacerbations recorded during the previous year, from 9.5 (95% CI 5.0 to 18.1) for no exacerbations to 39.0 (95% CI 9.1 to 167.5) for more than three exacerbations.

## DISCUSSION

As Winthrop stated in 2010,[23] it is surprising that, for an important infection such as NTM for which three major ATS statements on diagnosis,[18 24 25] treatment and prevention have been issued, there have been virtually no population-based studies addressing the most basic epidemiological questions: who, what, where and how much? This population-based case–control study provides evidence that chronic respiratory disease is a strong risk factor for NTM pulmonary disease in adults. In addition, ICS treatment of chronic lung disease including

**Table 2** ORs for non-tuberculous mycobacterial pulmonary disease in Denmark according to the presence of chronic respiratory disease

| Exposure | Cases (n=332), n (%) | Population controls (n=3320), n (%) | Unadjusted OR (95% CI) | Adjusted OR* (95% CI) |
|---|---|---|---|---|
| Any chronic respiratory disease | | | | |
| Absent | 165 (49.7) | 3115 (93.8) | 1.0 (ref.) | 1.0 (ref.) |
| Present | 167 (50.3) | 205 (6.2) | 18.0 (13.4 to 24.2) | 16.5 (12.2 to 22.2) |
| COPD | | | | |
| Absent | 192 (57.8) | 3161 (95.2) | 1.0 (ref.) | 1.0 (ref.) |
| Present | 140 (42.2) | 159 (4.8) | 17.4 (12.8 to 23.8) | 15.7 (11.4 to 21.5) |
| Present, first COPD diagnosis | | | | |
| Within 2 years | 41 (29.3) | 42 (26.4) | 23.4 (13.8 to 39.7) | 22.5 (13.1 to 38.5) |
| 2–5 years earlier | 39 (27.8) | 30 (18.9) | 18.4 (11.2 to 30.1) | 16.2 (9.8 to 26.7) |
| >5 years earlier | 60 (42.8) | 87 (54.7) | 14.4 (9.6 to 21.5) | 12.9 (8.58 to 19.4) |
| Present, with hospitalised COPD exacerbation | | | | |
| 0 within last year | 66 (47.1) | 134 (84.2) | 7.6 (5.1 to 11.1) | 6.3 (4.2 to 9.4) |
| 1 within last year | 28 (20.0) | 12 (7.5) | 43.9 (21.9 to 87.7) | 44.0 (21.8 to 88.9) |
| 2 within last year | 12 (8.6) | 6 (3.7) | 18.3 (5.9 to 57.0) | 17.5 (5.6 to 54.7) |
| ≥3 within last year | 34 (24.2) | 7 (4.4) | 65.2 (29.1 to 146.0) | 64.5 (28.5 to 146.2) |
| Asthma | | | | |
| Absent | 282 (84.9) | 3249 (97.9) | 1.0 (ref.) | 1.0 (ref.) |
| Present | 50 (15.1) | 71 (2.1) | 8.3 (5.6 to 12.3) | 7.8 (5.2 to 11.6) |
| Pneumoconiosis | | | | |
| Absent | 329 (99.1) | 3318 (99.9) | 1.0 (ref.) | 1.0 (ref.) |
| Present | 3 (0.9) | 3 (0.1) | 10.0 (2.0 to 49.6) | 9.8 (1.9 to 50.5) |
| Bronchiectasis | | | | |
| Absent | 314 (94.6) | 3318 (99.9) | 1.0 (ref.) | 1.0 (ref.) |
| Present | 18 (5.4) | 2 (0.06) | 174.3 (23 to 1304) | 187.5 (25 to 1417) |
| Previous tuberculosis | | | | |
| Absent | 277 (83.4) | 3313 (99.8) | 1.0 (ref.) | 1.0 (ref.) |
| Present | 55 (16.6) | 7 (0.2) | 176.2 (55.1 to 563.5) | 178.3 (55.4 to 574.3) |
| Chronic respiratory failure | | | | |
| Absent | 317 (95.5) | 3316 (99.9) | 1.0 (ref.) | 1.0 (ref.) |
| Present | 15 (4.5) | 4 (0.1) | 37.5 (12.4 to 112.9) | 28.1 (9.2 to 85.8) |

*OR adjusted for level of comorbidity and alcoholism-related conditions.
COPD, chronic obstructive pulmonary disease.

COPD is associated with substantially increased risk of NTM pulmonary disease.

In this nationwide study, all patients with definite pulmonary NTM disease according to our definition in Denmark over a 12-year period were included, eliminating some of the selection problems found in other studies. We chose to include only 'definite' pulmonary NTM cases from our previous cohort,[1] although some of the 'possible' NTM cases likely had pulmonary NTM disease as well according to the less stringent ATS/IDSA 2007 criteria. Thus, our findings should be generalised with caution. The association with chronic lung disease may be different and possibly weaker for NTM disease with less stringent microbiological criteria, as we previously observed a lower prevalence of chronic lung disease in possible than definite NTM cases.[1] We were able to make adjustments for a wide range of important underlying diseases by using modified Charlson comorbidity index scores at the individual patient level in the risk analysis. An important potential limitation stems from more frequent hospitalisations and probable closer surveillance for infections in patients with COPD and other respiratory diseases. This could lead to overestimation of their risk of NTM pulmonary disease. However, an earlier observation was made of a much higher death rate among pulmonary NTM-colonised and NTM-infected cases with comorbidities, including respiratory disease, than among patients with NTM without such comorbidities,[1] arguing against coincidental findings due to close surveillance. Some misclassification of chronic respiratory diseases may have occurred in the registries, but the positive predictive value of COPD diagnoses is reportedly high (ie, 92%[26]). It is also unlikely that unmeasured or unknown confounders could explain the ORs of the magnitude observed. Here, adjustments were made for several important risk factors that only modestly decreased the NTM RR from chronic respiratory disease. Smoking is the predominant risk factor for COPD in Denmark, and active smoking may increase the risk of NTM pulmonary disease through bronchial inflammation, although data on this association are sparse. Unfortunately, we lacked the data necessary to examine the role of smoking and other lifestyle factors in our study. Misclassification of data on confounders might also have led to some residual confounding. However, registration of previous diagnoses should be at least as complete for patients with chronic respiratory disease as it is for other individuals, leading to conservative risk estimates.

Persons with pulmonary NTM disease in our study were predominantly older men, similar to findings in the USA 20–30 years ago,[27] whereas a recent report from Oregon found that pulmonary NTM was most common among older women.[28] Chronic respiratory diseases were very prevalent in our study population and the rate of ICS use was surprisingly high. Indeed, almost half of our patients with NTM pulmonary

**Table 3** ORs for non-tuberculous mycobacterial pulmonary disease in northern Denmark according to the presence of chronic respiratory disease and inhaled corticosteroid use

| Exposure | Case patients (n=112) | Population controls (n=1120) | Unadjusted OR (95% CI) | Adjusted OR* (95% CI) | Adjusted OR (95% CI) for Denmark as a whole |
|---|---|---|---|---|---|
| Any chronic respiratory disease | | | | | 16.5 (12.2 to 22.2) |
| Absent | 48 (42.9) | 1036 (92.5) | 1.0 (ref.) | 1.0 (ref.) | |
| Present | 64 (57.1) | 84 (7.5) | 19.3 (11.6 to 31.9) | 15.6 (8.9 to 27.5) | |
| Present with no history of ICS use | 17/64 (26.5) | 33/84 (39.3) | 12.2 (6.0 to 24.8) | 11.5 (5.4 to 24.5) | |
| Present with ever use of ICS | 47/64 (73.5) | 51/84 (60.7) | 24.7 (13.8 to 44.2) | 19.1 (9.9 to 36.9) | |
| Ever use of ICS | | | | | |
| Current ICS use (within 6 months) | 41/47 (87.2) | 37/51 (72.5) | 28.5 (15.4 to 52.9) | 24.3 (11.9 to 49.7) | |
| Former ICS use (>6 months ago) | 6/47 (12.8) | 14/51 (27.4) | 13.3 (4.6 to 37.9) | 8.8 (2.9 to 26.8) | |
| Current use, mean daily dose of ICS | | | | | |
| Low (0–799 µg/day over 365 days) | 15/41 (36.5) | 24/37 (64.9) | 14.2 (6.6 to 30.8) | 15.5 (6.6 to 36.1) | |
| High (800+ µg/day over 365 days) | 7/41 (17.1) | 4/37 (10.8) | 63.3 (14.1 to 284.3) | 64.9 (12.2 to 344.6) | |
| Missing data on dose | 19/41 (46.4) | 9/37 (24.3) | 67.4 (24.2 to 187.3) | 44.6 (14.2 to 140.1) | |
| Current use, type of ICS | | | | | |
| Beclometasone | 1/41 (2.4) | 1/37 (2.7) | 26.0 (1.2 to 581.2) | 36.9 (1.6 to 862.1) | |
| Budenoside | 18/41 (43.9) | 20/37 (54.1) | 23.1 (10.6 to 50.1) | 19.8 (8.4 to 46.6) | |
| Fluticasone | 22/41 (53.7) | 15/37 (40.5) | 36.5 (16.0 to 83.2) | 31.0 (11.9 to 81.2) | |
| Combination | 0 | 1/37 (2.7) | – | – | |
| COPD | | | | | 15.6 (11.4 to 21.5) |
| Absent | 58 (51.8) | 1053 (94.0) | 1.0 (ref.) | 1.0 (ref.) | |
| Present | 54 (48.2) | 67 (6.0) | 16.2 (9.8 to 26.6) | 13.1 (7.4 to 23.3) | |
| Present, first COPD diagnosis | | | | | |
| Within 2 years | 17/54 (31.5) | 16/67 (23.9) | 20.1 (9.0 to 44.8) | 14.7 (6.1 to 35.6) | 22.5 (13.1 to 38.5) |
| 2–5 years earlier | 15/54 (27.8) | 21/67 (31.3) | 7.9 (3.3 to 18.9) | 4.7 (1.8 to 12.4) | 16.2 (9.8 to 26.7) |
| >5 years earlier | 22/54 (40.7) | 30/67 (44.8) | 13.6 (7.2 to 25.7) | 11.6 (5.5 to 24.6) | 12.9 (8.58 to 19.4) |
| Present, with hospitalised COPD exacerbation | | | | | |
| 0 within last year | 29/54 (53.7) | 51/67 (76.1) | 11.1 (6.2 to 19.9) | 9.5 (5.0 to 18.1) | 6.3 (4.2 to 9.4) |
| 1 within last year | 7/54 (13.0) | 6/67 (8.9) | 25.8 (7.5 to 89.5) | 23.5 (6.9 to 80.0) | 44.0 (21.8 to 88.9) |
| 2 within last year | 5/54 (9.3) | 4/67 (6.0) | 21.8 (4.9 to 97.5) | 20.3 (4.1 to 101.4) | 17.5 (5.6 to 54.7) |
| ≥3 within last year | 13/54 (24.1) | 6/67 (8.9) | 53.6 (16.5 to 174.2) | 39.0 (9.1 to 167.5) | 64.5 (28.5 to 146.2) |
| Present with no history of ICS use | 13/54 (24.1) | 31/67 (46.3) | 7.9 (3.8 to 16.6) | 7.6 (3.4 to 16.8) | |
| Present with ever use of ICS | 41/54 (75.9) | 36/67 (53.7) | 24.6 (163.5 to 45.1) | 19.6 (9.7 to 39.6) | |
| Ever use of ICS | | | | | |
| Current ICS use (within 6 months) | 38/41 (92.7) | 26/36 (72.2) | 30.4 (15.9 to 58.0) | 29.1 (13.3 to 63.8) | |
| Former ICS use (>6 months ago) | 3/41 (7.3) | 10/36 (27.8) | 7.3 (1.9 to 28.6) | 3.8 (0.9 to 16.8) | |
| Current use, mean daily dose of ICS | | | | | |
| Low (0–799 µg/day over 365 days) | 15/38 (39.4) | 15/26 (57.7) | 21.9 (9.4 to 50.7) | 28.1 (10.7 to 73.4) | |
| High (800+ µg/day over 365 days) | 7/38 (18.4) | 3/26 (11.5) | 52.7 (12.1 to 230.0) | 47.5 (9.5 to 236.7) | |
| Missing dose | 16/38 (42.1) | 8/26 (30.8) | 37.5 (14.5 to 97.0) | 26.3 (8.7 to 79.0) | |
| Current use, type of ICS | | | | | |
| Beclometasone | 1/38 (2.6) | 0 | | | |
| Budenoside | 16/38 (42.1) | 15/26 (57.7) | 22.2 (9.5 to 51.8) | 19.8 (7.2 to 54.4) | |
| Fluticasone | 21/38 (55.3) | 10/26 (38.5) | 42.3 (16.6 to 107.9) | 40.8 (14.0 to 119.5) | |
| Asthma | | | | | 7.8 (5.2 to 11.6) |
| Absent | 102 (91.1) | 1097 (98) | 1.0 (ref.) | 1.0 (ref.) | |
| Present | 10 (8.9) | 23 (2.1) | 4.4 (2.1 to 9.4) | 1.6 (0.6 to 3.9) | |
| Present with no history of ICS use | 1/10 (10.0) | 2/23 (8.7) | 5.0 (0.5 to 55.2) | 4.3 (0.4 to 51.2) | |
| Present with ever use of ICS | 9/10 (90.0) | 21/23 (91.3) | 4.4 (2.0 to 9.6) | 1.4 (0.5 to 3.7) | |
| Ever use of ICS | | | | | |
| Current ICS use (within 6 months) | 8/9 (88.9) | 16/21 (76.2) | 5.0 (2.1 to 11.7.) | 1.5 (0.5 to 4.1) | |
| Former ICS use (>6 months ago) | 1/9 (11.1) | 5/21 (23.8) | 2.1 (6.2 to 18.1) | 1.6 (0.5 to 9.7) | |
| Current use, mean daily dose of ICS | | | | | |
| Low (0–799 µg/day over 365 days) | 5/8 (62.5) | 11/16 (68.7) | 4.5 (1.6 to 13.1) | | |
| High (800+ µg/day over 365 days) | 0 | 2/16 (12.5) | | | |
| Missing dose | 3/8 (37.5) | 3/16 (18.8) | 10.2 (2.1 to 50.6) | 1.8 (0.3 to 11.9) | |
| Current use, type of ICS | | | | | |
| Beclometasone | 1/8 (12.5) | 1/16 (6.2) | 10.0 (0.6 to 159.9) | 20.4 (1.2 to 341.0) | |
| Budenoside | 2/8 (25.0) | 7/16 (43.8) | 2.9 (0.6 to 13.8) | 0.6 (0.1 to 4.2) | |
| Fluticasone | 5/8 (62.5) | 8/16 (50.0) | 6.3 (2.1 to 19.3) | 1.5 (0.4 to 5.8) | |

Continued

**Table 3** Continued

| Exposure | Case patients (n=112) | Population controls (n=1120) | Unadjusted OR (95% CI) | Adjusted OR* (95% CI) | Adjusted OR (95% CI) for Denmark as a whole |
|---|---|---|---|---|---|
| Pneumoconiosis | | | | | |
| Absent | 109 (97.3) | 1118 (99.8) | 1.0 (ref.) | 1.0 (ref.) | |
| Present | 3 (2.7) | 2 (0.2) | 15.0 (2.5 to 89.7) | 6.9 (0.9 to 53.3) | 9.8 (1.9 to 50.5) |
| Chronic respiratory failure | | | | | |
| Absent | 104 (92.9) | 1119 (99.9) | 1.0 (ref.) | | |
| Present | 8 (7.1) | 1 (0.1) | 80.0 (10 to 639.3) | 46.4 (5.2 to 418.0) | 28.1 (9.2 to 85.8) |

*OR adjusted for level of comorbidity, alcoholism-related conditions, use of oral corticosteroids and other immunosuppressive therapy the year before non-tuberculous mycobacterial disease diagnosis, marital status and urbanisation of place of residence.
COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid.

disease received ICSs within 180 days prior to their NTM diagnosis date compared with 5% of our age-matched control patients. Adjusted ORs increased significantly for patients with chronic respiratory disease according to the extent of ICS use, particularly in patients with COPD. The key question is whether ICS therapy is causally associated with increased NTM disease in patients with COPD or mainly reflects increased COPD severity. Nonetheless, the fact that ORs were highest for high-dose ICS users even after adjustment for use of oral steroids and comorbidities is consistent with the hypothesis that ICS therapy is a true risk factor for NTM disease. Furthermore, even though guidelines suggest that only patients with Global Initiative for Chronic Obstructive Lung Disease stage III and IV COPD with frequent COPD exacerbations are candidates for ICSs, in our study almost two-thirds (47 of 73) of the patients with COPD who were treated with ICSs had no COPD exacerbation during the prior year (data not shown), suggesting that not only patients with the most severe COPD received ICS therapy in clinical practice. For patients with asthma, we found no difference in the level of risk of NTM disease among those with and without ICS treatment. Most asthma management guidelines including GINA (Global Initiative Against Asthma) recommend use of ICSs as first-line therapy for all patients except those with mild intermittent asthma. For this reason the vast majority of study patients with asthma received ICSs. This probably explains the similar risk level among patients with asthma with and without this treatment.

The mechanism behind any association between ICS therapy and increased pulmonary NTM risk remains unclear. ICS therapy may compromise local immunity and ICSs may exert systemic effects through partial but consistent systemic absorption (eg, skin bruising and subcapsular cataracts have been described with ICS use).[29] However, chronic respiratory disease is likely to increase pulmonary NTM risk through persistent inflammation and impaired clearance of secretions. Locally applied anti-inflammatory drugs, such as ICSs, theoretically could lead to patients' improvement locally and thus decrease their risk of NTM disease. Unfortunately, our data did not allow us to assess these hypotheses in detail. The type and daily dose of ICSs seemed to affect the risk of NTM pulmonary disease in our patients, although the statistical precision of our findings was limited. Corroborating findings on the association between ICS use and pneumonia risk,[13 30] high doses of ICSs (higher than 800 µg per day) and use of fluticasone showed the strongest associations with NTM pulmonary disease. Pharmacokinetic properties including clearance of ICSs from the airways could contribute to these differences (eg, the half life of the budesonide glucocorticoid receptor complex (4.6 h) is 60% shorter than the half life of the fluticasone propionate–receptor complex (7.7 h)).[31]

Based on this study, it can be concluded that patients with chronic respiratory disease, particularly COPD treated with ICSs, are at highly increased risk of pulmonary NTM disease. These results could partly explain the parallel trends of increased incidence of NTM disease and of COPD. Clinicians should be aware of this association and use all available diagnostic tools to confirm or rule out definitive NTM pulmonary disease, including at least three sputum samples and a chest x-ray or chest CT in patients with COPD and other chronic respiratory diseases.

**Contributors** Claire Andréjak did the conception and design of the study, interpreted the data, drafted the article and gave final approval of the version to be published. Rikke B Nielsen did the analysis and contributed to the interpretation of data, and revisited critically the article for important intellectual content. She gave final approval of the version to be published. Vibeke Ø Thomsen contributed to the interpretation of data and revisited critically the article for important intellectual content. She gave final approval of the version to be published. Pierre Duhaut contributed to the conception of the study, revisited critically the article for important intellectual content, and gave final approval of the version to be published. Henrik Toft Sørensen contributed to the conception of the study, revisited critically the article for important intellectual content and gave final approval of the version to be published. Reimar W Thomsen did the conception and design, revisited critically the article for important intellectual content and gave final approval of the version to be published.

**Funding** This study was supported by the Karen Elise Jensen Foundation, Denmark.

**Competing interests** None.

**Patient consent** This is a retrospective study. Data were obtained by Danish registries. This was approved by the Danish Data Protection Agency.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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