Support statement: This study was supported by the Swiss National Science Foundation grant 320030_163311 to U. Frey and P. Latzin. Funding information for this article has been deposited with the Open Funder Registry.

Conflict of interest: None declared.

Acknowledgments: The authors would like to thank all study participants for participating in the study, along with our lung function technicians Gisela Wirz and Sharon Schmid, and our study nurses Christine Becher, Monika Graf, Barbara Hofer, Sandra Lüscher and Linda Beul-Béguin (all Division of Respiratory Medicine, Dept of Paediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland) for their support. We thank Karine Landgren Hugentobler (UKBB, Basel, Switzerland) for helping with English style.

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Eur Respir J 2016; 48: 925–928 | DOI: 10.1183/13993003.00439-2016 | Copyright ©ERS 2016

# Risk of nontuberculous mycobacterial pulmonary disease with obstructive lung disease

*To the Editor:*

Nontuberculous mycobacterial pulmonary disease (NTM-PD) is increasingly prevalent [1] and especially common in the elderly [2]. It is usually chronic, requiring complex therapy with suboptimal outcomes [3]. Risk factors for NTM-PD may be covert, presumably disordered mucociliary defences, or overt structural

lung abnormalities. In one study, 56% of NTM-PD patients had unexplained nontuberculous mycobacteria (NTM) and among the rest with structural lung disease, chronic obstructive pulmonary disease (COPD) was the most common predisposing condition [4].

Obstructive lung disease (OLD) is very common. In Ontario, Canada, during 1996–2007, COPD prevalence increased 23% [5] with a 25% lifetime risk [6], while asthma prevalence increased 55% [7] with a 34% lifetime risk [8]. Increasing OLD, especially COPD, which disproportionately affects older adults, has major implications for NTM-PD. In a review of cohorts of NTM-PD patients, 30% had underlying COPD [2]. Asthma is also associated with NTM-PD, being identified in 1.7% of patients with difficult-to-control asthma [9]. In the absence of population-based studies, accurate risk estimates of NTM-PD among patients with OLD remain elusive. We sought to ascertain the incidence of NTM-PD among OLD patients and the risk of NTM-PD conferred by OLD.

We conducted a longitudinal retrospective cohort study using linked health administrative and laboratory mycobacterial culture data, as described previously [10]. We included all registered Ontarians aged ⩾35 years on January 1, 2001, who did not have previous NTM infection and followed them for incident NTM-PD. We censored observations at the earliest of emigration, death or December 31, 2013. We considered people aged ⩾35 years exclusively because both NTM-PD and COPD rarely occur in younger people [2]. This study was approved by the responsible institutional review committees.

COPD was identified using the more specific previously validated algorithm (one or more hospitalisations for COPD, or three or more outpatient claims within 2 years (sensitivity 57.5%, specificity 95.4%)) [11]. Asthma was identified using a validated algorithm (one or more hospitalisations for asthma or two or more outpatient claims within 2 years (sensitivity 83.8%, specificity 76.5%)) [12]. Because some patients had both COPD and asthma, the groups were not mutually exclusive. Incident NTM-PD was defined by the isolation of the same NTM species from two or more sputum, or one or more bronchoscopy or lung biopsy samples during the study period [10]. We identified comorbidities known to be associated with NTM-PD (diabetes mellitus, chronic kidney disease (CKD), gastro-oesophageal reflux disease (GORD), HIV infection and rheumatoid arthritis) using validated algorithms [10]. We identified solid-organ transplants and lung malignancies from provincial registries, bronchiectasis and haematopoietic stem cell transplants using diagnostic and procedure information from inpatient and outpatient records, and prior culture-confirmed tuberculosis infection.

Characteristics of Ontarians with and without OLD were compared using one-way ANOVA for continuous variables and Chi-squared tests for categorical variables. Non-OLD patients were followed from January 2001 until the earliest of OLD diagnosis, emigration, death or December 2013. OLD patients were followed from January 2001 (prevalent OLD cases) or the date of OLD diagnosis (incident OLD cases), until the earliest of emigration, death or December 2013. We attributed NTM-PD to OLD if the patient was in the OLD cohort before the occurrence of NTM-PD. To assess for the possibility that manifestations of NTM-PD led to a new and invalid designation of OLD, we performed a sensitivity analysis wherein follow-up for the outcome (NTM-PD) began 1 year after OLD diagnosis. Using the earliest available data, we looked back to 1991 to identify OLD and comorbidities, and to 1998 to identify NTM isolation.

NTM-PD incidence was calculated per 100 000 person-years with Poisson 95% confidence intervals. Hazard ratios comparing OLD and non-OLD groups were calculated using Cox proportional hazards regression, adjusted for age, sex, income, rurality and comorbidities associated with NTM-PD [10]; OLD and comorbidities associated with NTM-PD were modelled in a time-varying fashion. Analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC, USA), and STATA, version 9.2 (StataCorp, College Station, TX, USA). All tests were two-tailed with the Type I error ($\alpha$) rate set at 5%.

During the study period, among 6 290 603 Ontarians aged ⩾35 years, 853 830 (13.6%) had OLD. At the start of the study, people with COPD/asthma were older (65.5/54.2 *versus* 52.7 years) and more likely to have GORD (14.1%/10.5% *versus* 6.4%), CKD (4.0%/1.9% *versus* 1.2%), rheumatoid arthritis (2.0%/1.3% *versus* 0.7%), lung cancer (1.5%/0.4% *versus* 0.1%) and bronchiectasis (2.0%/1.0% *versus* 0.3%) ($p<0.001$ for all comparisons). Compared with people without OLD, COPD patients were more often male (52.0% *versus* 48.3%, $p<0.001$), while asthma patients were less often male (40.0% *versus* 48.3%, $p<0.001$). The incidence of NTM-PD was higher in the OLD groups than in the non-OLD group (table 1). Fully adjusted hazard ratios for incident NTM-PD demonstrated substantial and statistically significant increased risks among people with COPD (8.7, 95% CI 8.3–9.2) and asthma (5.1, 95% CI 4.8–5.5) relative to the non-OLD group. The incidence of NTM-PD was particularly high in the ⩾65-year age groups (COPD 161.9, 95% CI 155.7–168.3; asthma 123.7, 95% CI 115.8–132.0; non-OLD 17.4, 95% CI 16.6–18.2 per 100 000 person-years). In the sensitivity analysis, delaying the start of follow-up for NTM-PD to 1 year after OLD diagnosis, some NTM-PD cases shifted from the OLD group to the non-OLD group, leading to

TABLE 1 Nontuberculous mycobacterial pulmonary disease (NTM-PD) among adults ⩾35 years of age, with and without obstructive lung disease in Ontario, Canada, 2001–2013

| NTM-PD | Total Ontario population | No obstructive lung disease | COPD | Asthma |
|---|---|---|---|---|
| **Subjects** | 6 290 603 | 5 436 773 | 543 119 | 406 712 |
| **Primary analysis** | | | | |
| Cases | 9658 | 4398 | 4538 | 1850 |
| Incidence (95% CI)[#] | 13.33 (13.07–13.60) | 6.63 (6.44–6.83) | 143.26 (139.12–147.49) | 52.83 (50.45–55.30) |
| Unadjusted HR (95% CI) | Not applicable | 1.00 (ref.) | 20.03 (19.19–20.91) | 8.47 (7.99–8.98) |
| Age- and sex-adjusted HR (95% CI) | Not applicable | 1.00 (ref.) | 12.51 (11.94–13.10) | 7.74 (7.30–8.21) |
| Fully adjusted HR (95% CI)[¶] | Not applicable | 1.00 (ref.) | 8.73 (8.29–9.18) | 5.14 (4.83–5.47) |
| **Sensitivity analysis** | | | | |
| Cases | Not applicable | 5350 | 3650 | 1564 |
| Incidence (95% CI)[#] | Not applicable | 8.01 (7.80–8.23) | 128.54 (124.40–132.77) | 48.12 (45.77–50.57) |
| Unadjusted HR (95% CI) | Not applicable | 1.00 (ref.) | 15.45 (14.79–16.13) | 7.27 (6.84–7.72) |
| Age- and sex-adjusted HR (95% CI) | Not applicable | 1.00 (ref.) | 9.15 (8.73–9.59) | 6.58 (6.19–6.99) |
| Fully adjusted HR (95% CI)[¶] | Not applicable | 1.00 (ref.) | 6.01 (5.71–6.33) | 4.26 (3.99–4.55) |

Because some patients with chronic obstructive pulmonary disease (COPD) also had asthma and some patients with asthma also had COPD, these two groups were not mutually exclusive. Primary analysis: NTM-PD was assigned to COPD or asthma if NTM-PD was diagnosed at any time after the diagnosis of COPD or asthma. Sensitivity analysis: NTM-PD was assigned to COPD or asthma if NTM-PD diagnosed ⩾1 year after the diagnosis of COPD or asthma. Asthma was defined as fulfilling the diagnostic definition of asthma, regardless of co-existing COPD. COPD was defined as fulfilling the diagnostic definition of COPD, regardless of co-existing asthma. Hazard ratios (HRs) were calculated by Cox proportional hazards regression. [#]: calculated per 100 000 person-years with Poisson 95% confidence intervals; [¶]: controlling for age, sex, income, rurality and comorbidities that may be associated with NTM-PD (bronchiectasis, chronic kidney disease, diabetes mellitus, gastro-oesophageal reflux disease, HIV infection, lung cancer, rheumatoid arthritis, transplantation (haematopoietic stem cell or solid organ) and prior culture-proven tuberculosis) modelled in a time-varying fashion.

a small increase in incidence among non-OLD patients, and small reductions in incidence and hazard ratios among OLD patients, but the hazard ratios remained strongly significant.

In this population-based study of >6 million people, COPD and asthma were associated with approximately nine-fold and five-fold higher adjusted incidences of NTM-PD. An association between OLD and NTM-PD has been previously identified but incompletely studied. In a prior Danish study, all NTM-PD cases were matched with population-based controls, and odds ratios for COPD and asthma were 15.7 (95% CI 11.4–21.5) and 7.8 (95% CI 5.2–11.6) [13]. Despite differing methods and a different study population, our work confirms this association and also provides incidence rates of NTM-PD among patients with OLD. The present study is consistent with a prior estimate of NTM-PD among patients with difficult-to-control asthma, wherein 1.7% had NTM-PD [9], compared with 0.5% of all people with asthma in the present study (1850 of 406 712 asthmatics). Causes for increased NTM-PD risk among OLD patients may vary between OLD subtypes. Parenchymal destruction in COPD may represent a structural factor that impairs clearance of inhaled pathogens, while bronchial hyperresponsiveness may impair mucociliary clearance in asthma. Medications may also be important. Associations with NTM-PD have been demonstrated with both systemic [14] and inhaled [13] corticosteroids.

Our study has limitations. First, the COPD diagnostic algorithm has high specificity (95.4%) but low sensitivity (57.5%). The high positive predictive value (81.3%) reduces biased attribution of NTM-PD symptoms to invalid COPD designations. However, the algorithm fails to detect a large proportion of people with COPD, including COPD-associated NTM-PD, likely underestimating the association between COPD and NTM-PD. Alternatively, if the algorithm preferentially identifies severe COPD cases, there may be an overestimation of the association. Secondly, the lack of data on medications prevented their assessment as NTM-PD risk factors. However, based on the large hazard ratios, it is unlikely that adjusting for medications would nullify the risk estimates for NTM-PD among OLD patients. Thirdly, the absence of clinical data compels defining NTM-PD exclusively microbiologically, misclassifying some patients with NTM colonisation as having disease, and overestimating disease rates. This misclassification rate is likely small, however, as microbiologically based definitions of NTM-PD exhibit high accuracy [15].

Clinicians should be mindful of the strong association between NTM-PD and OLD, and maintain a high index of suspicion for the former, especially with the increasing prevalence of both diseases.

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**High incidence of NTM pulmonary disease in people with COPD and asthma (142 and 53 per 100 000 person-years)** http://ow.ly/2laN300kLOV

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Received: Jan 06 2016 | Accepted after revision: April 23 2016 | First published online: June 10 2016

Support statement: The authors acknowledge and thank The Physicians' Services Inc. Foundation for funding support provided for this research study. This research was also supported by the Institute for Clinical Evaluative Sciences (ICES) and Public Health Ontario (PHO), which both receive funding from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES, PHO, or MOHLTC is intended or should be inferred. Funding information for this article has been deposited with the Open Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

Acknowledgements: Datasets used in this study were linked using unique encoded identifiers and analysed at ICES. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statement expressed herein are those of the author, and not necessarily those of CIHI.

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