Paradoxical results in the study of risk factors of chronic obstructive pulmonary disease (COPD) re-admission

Judith Garcia-Aymericha,*, Ramon M Marradesb, Eduard Monsóc, Esther Barreirod, Eva Farreroe, Josep M Antóaf, on behalf of the EFRAM Investigators1

aRespiratory and Environmental Health Research Unit, IMIM, Doctor Aiguader 80, 08003 Barcelona, Catalonia, Spain
bDepartment of Pneumology, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain
cDepartment of Pneumology, Hospital Germans Trias i Pujol, Badalona, Spain
dDepartment of Pneumology, Hospital del Mar, Barcelona, Spain
eDepartment of Pneumology, Ciutat Sanitària i Universitària de Bellvitge, L'Hospitalet de Llobregat, Spain
fDepartment of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain

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Summary We have previously reported an apparently paradoxical association between medical care related factors and an increased risk of chronic obstructive pulmonary disease (COPD) re-hospitalisation, in a cohort of 346 COPD subjects from Barcelona, Spain. Confounding by severity or by indication is a plausible explanation. We tested the confounding effect of severity-related variables on these paradoxical associations. Forced expiratory volume in one second (FEV₁), arterial oxygen pressure (PO₂) and previous COPD admissions were associated with: (1) the presence of medical care related factors, and (2) re-admission during follow-up. Risks of re-admission associated with most of the medical care related factors were reduced after adjustment for the severity variables. The risk associated with long-term oxygen therapy use changed from a crude OR of 2.36 (95% CI: 1.79–3.11) to an adjusted OR of 1.38 (0.95–2.00), while that associated with anticholinergics use varied from 3.52 (2.37–5.21) to 2.10 (1.32–3.36). We concluded that the excess risk of COPD re-admission associated with medical care related factors might be partially due to confounding by indication. Residual confounding may still account for part of the remaining excess risk. True adverse effects of some pharmacological treatments cannot be excluded.

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Introduction

Several studies on the course of chronic obstructive pulmonary disease (COPD) and its determinants have found paradoxical or unexpected results. Smoking cessation has been independently related to an increased risk of COPD re-admission,\(^1\) a lack of reduction in overall mortality\(^2\) and even to an increase of respiratory mortality\(^3\) in COPD patients. Schols et al.\(^4\) found that in severe COPD, maintenance treatment with systemic glucocorticoids was related to an increased mortality in a dose-dependent manner, independently of sex, age, body mass index, forced expiratory volume in 1 s (FEV\(\text{subscript}1\)), arterial oxygen pressure (PO\(\text{subscript}2\)), and use of inhaled corticosteroids. Some medical care related factors, such as being controlled by a pulmonologist, taking anticholinergics, taking oral corticosteroids, influenza vaccination, respiratory rehabilitation and long-term oxygen therapy, were related to an increased risk of COPD re-admission, contrary to the authors’ expectations and—in some cases—to the previous literature, in the follow-up of 340 COPD patients included in the study of the risk factors of COPD exacerbation (EFRAM study).\(^5\) This association between medical care related factors and COPD re-admission had also been found in the previous case-control EFRAM study,\(^1\) although it was more evident in the follow-up analysis.

As all unexpected findings alluded to above have been found in observational studies, it is likely that they can be partly attributed to the lack of randomisation of factors that affect the outcome under study. Anthonissen explained paradoxical results regarding smoking cessation as a situation of self-selection bias, in which patients who are severely ill spontaneously quit smoking in response to their symptoms and disability and do not do well afterwards.\(^6\) The increased mortality associated with glucocorticoids use was attributed by Schols et al.\(^4\) to a confounder by indication, such as frequent disease exacerbations. Surprisingly, so far no formal analysis has been focused on the identification and control of potential confounders in observational studies on the course of COPD.

In the present analysis, we aimed to test the confounding effect of FEV\(\text{subscript}1\), PO\(\text{subscript}2\) and previous COPD admissions in the reported association between medical care related factors (being controlled by a pulmonologist, taking anticholinergics, taking oral corticosteroids, influenza vaccination, respiratory rehabilitation and long-term oxygen therapy) and COPD re-admission.\(^5\)

Methods

Patients and methods

A systematic sample of 1 out of every 2 patients hospitalised or remaining in the emergency room for at least 18 h for a COPD exacerbation (index-admission) in four tertiary hospitals in the Barcelona area over 1 year (from May 1, 1997 to April 30, 1998) was identified. A total of 404 episodes of admission corresponding to 346 patients were obtained. In patients with more than one admission during the recruitment period, the first one was selected as the beginning of the follow-up period. COPD diagnosis was established by the ward pulmonologist and based on medical history, current symptoms and available pulmonary function tests, following the ERS guidelines.\(^7\) An exacerbation was defined when the patient reported an increase in dyspnea, in sputum production or sputum purulence.\(^8\) Recruitment methods and diagnosis criteria have been detailed in previous papers.\(^1,9\)

Information about potential risk factors was collected at baseline, including clinical status, medical care and prescriptions, medication adherence, lifestyle, quality of life and social support. Medical care related factors included: being controlled by a pulmonologist or by the general practitioner, taking anticholinergics, taking oral corticosteroids, influenza vaccination, respiratory rehabilitation and long-term oxygen therapy. COPD admissions in the previous year were reported by the patient and taken from the clinical records. Lung function and blood gases were measured at least 3 months after admission and during a period of clinical stability. Three hundred and forty patients were followed for a mean period of 1.1 years and information on further hospitalisations was obtained.\(^5\) The Ethics Committees of the participating hospitals approved the protocol and written informed consent was obtained from all patients.

Statistical analysis

The term confounding refers to a situation in which a non-causal association between a given exposure and an outcome is observed as a result of the influence of a third variable (or group of variables).\(^10\) Residual confounding may occur when the control for confounders is incomplete or when some confounding variables remain unaccounted for. In order to assess confounding, we followed the strategy suggested by Szklo and Nieto.\(^10\)
First, the association between a confounding variable (FEV1, PO2 or previous COPD admissions) and the exposure (medical care related factors) was assessed. Thus, we estimated the prevalence at index-admission of medical care related factors stratified by FEV1, PO2, and previous COPD admissions. Second, the association of the confounding variable (FEV1, PO2 or previous admissions) with the outcome (COPD re-admission) was estimated using time from recruitment (index-admission) to first event (following COPD re-admission) as the outcome variable in a Cox proportional hazards model, as has been reported elsewhere. Finally, we assessed the associations, both crude and adjusted for FEV1, PO2 and previous admissions, between medical care related factors and COPD re-admission using Cox regression, looking for changes in direction and magnitude of the association. Percent excess risk explained by the confounders was computed as: "((unadjusted HR-adjusted HR)/(unadjusted HR-1.00))*100". Age and hospital of recruitment were tested as possible effect modifiers of the association between medical care related factors and COPD re-admission using stratification in the Cox regression. All analyses were performed with Stata, release 6.0 (StataCorp, 1999, College Station, TX, USA).

Results

First, the association between the confounding variable (FEV1, PO2 or previous COPD admissions) and the exposure (medical care related factors) was assessed by estimating the prevalence at index-admission of medical care related factors stratified by FEV1, PO2, and previous COPD admissions. Second, the association of the confounding variable (FEV1, PO2 or previous admissions) with the outcome (COPD re-admission) was estimated using time from recruitment (index-admission) to first event (following COPD re-admission) as the outcome variable in a Cox proportional hazards model, as has been reported elsewhere. Finally, we assessed the associations, both crude and adjusted for FEV1, PO2 and previous admissions, between medical care related factors and COPD re-admission using Cox regression, looking for changes in direction and magnitude of the association. Percent excess risk explained by the confounders was computed as: "((unadjusted HR-adjusted HR)/(unadjusted HR-1.00))*100". Age and hospital of recruitment were tested as possible effect modifiers of the association between medical care related factors and COPD re-admission using stratification in the Cox regression. All analyses were performed with Stata, release 6.0 (StataCorp, 1999, College Station, TX, USA).

Confounding by indication in COPD

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### Table 1 At recruitment age adjusted prevalence (in percentage) and 95% confidence interval of medical care related factors among patients admitted for a COPD exacerbation, according to FEV1, ATS stages and PO2 levels.

<table>
<thead>
<tr>
<th>Factors at recruitment (index-admission)</th>
<th>FEV1 ATS stages</th>
<th>PO2 levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV1 ≥50%</td>
<td>FEV1 = 35–49%</td>
</tr>
<tr>
<td></td>
<td>n = 42 (14%)</td>
<td>n = 71 (25%)</td>
</tr>
<tr>
<td>Controlled by pulmonologist</td>
<td>41 (27–56)</td>
<td>56 (44–67)</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>55 (40–69)</td>
<td>73 (62–82)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>12 (5–26)</td>
<td>27 (18–38)</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>69 (54–81)</td>
<td>75 (63–84)</td>
</tr>
<tr>
<td>Respiratory rehabilitation</td>
<td>5 (1–17)</td>
<td>10 (5–19)</td>
</tr>
<tr>
<td>Long-term oxygen therapy</td>
<td>21 (12–36)</td>
<td>23 (14–34)</td>
</tr>
</tbody>
</table>

*ATS: American Thoracic Society.*
### Table 2
At recruitment age adjusted prevalence (in percentage) and 95% confidence interval of medical care related factors among patients admitted for a COPD exacerbation, according to previous COPD admissions.

<table>
<thead>
<tr>
<th>Factors at recruitment (index-admission)</th>
<th>COPD admissions ever</th>
<th>COPD admissions in the year prior to recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No ( n = 67 ) (19%)</td>
<td>Yes ( n = 279 ) (81%)</td>
</tr>
<tr>
<td>Controlled by pulmonologist</td>
<td>28 (19–40)</td>
<td>63 (57–69)</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>43 (32–55)</td>
<td>82 (77–86)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>13 (7–24)</td>
<td>23 (18–28)</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>64 (52–75)</td>
<td>73 (68–78)</td>
</tr>
<tr>
<td>Respiratory rehabilitation</td>
<td>6 (2–14)</td>
<td>14 (11–19)</td>
</tr>
<tr>
<td>Long-term oxygen therapy</td>
<td>4 (1–13)</td>
<td>39 (34–45)</td>
</tr>
</tbody>
</table>

### Table 3
Change in the association between medical care related factors and admission for a COPD exacerbation after adjustment by severity and previous admissions in a cohort of COPD patients.

<table>
<thead>
<tr>
<th></th>
<th>Crude HR (95% CI)</th>
<th>Adjusted HR (95% CI) by FEV(_1)</th>
<th>Adjusted HR (95% CI) by PO(_2)</th>
<th>Adjusted HR (95% CI) by previous admissions</th>
<th>Adjusted HR (95% CI) by FEV(_1), PO(_2) and previous admission</th>
<th>% excess risk* explained by FEV(_1), PO(_2) and previous admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled by pulmonologist</td>
<td>2.16 (1.43–3.27)</td>
<td>2.11 (1.33–3.33)</td>
<td>1.76 (1.10–2.83)</td>
<td>2.03 (1.33–3.33)</td>
<td>1.73 (1.05–2.85)</td>
<td>37%</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>3.52 (2.37–5.21)</td>
<td>2.62 (1.69–4.05)</td>
<td>2.74 (1.76–4.28)</td>
<td>3.08 (2.06–4.60)</td>
<td>2.10 (1.32–3.36)</td>
<td>56%</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>1.55 (1.13–2.11)</td>
<td>1.47 (1.05–2.04)</td>
<td>1.71 (1.21–2.41)</td>
<td>1.40 (1.03–1.92)</td>
<td>1.71 (1.19–2.44)</td>
<td>—(^\dagger)</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>1.37 (1.01–1.87)</td>
<td>1.26 (0.90–1.75)</td>
<td>1.27 (0.89–1.82)</td>
<td>1.29 (0.95–1.76)</td>
<td>1.35 (0.93–1.94)</td>
<td>6%</td>
</tr>
<tr>
<td>Respiratory rehabilitation</td>
<td>1.77 (1.23–2.57)</td>
<td>1.38 (0.92–2.08)</td>
<td>1.58 (1.03–2.42)</td>
<td>1.63 (1.12–2.37)</td>
<td>1.28 (0.83–2.00)</td>
<td>64%</td>
</tr>
<tr>
<td>Long-term oxygen therapy</td>
<td>2.36 (1.79–3.11)</td>
<td>1.91 (1.40–2.60)</td>
<td>1.62 (1.14–2.31)</td>
<td>2.00 (1.49–2.69)</td>
<td>1.38 (0.95–2.00)</td>
<td>72%</td>
</tr>
</tbody>
</table>

HR: hazard ratio; CI: confidence interval. Each line is a single model.

*Percent excess risk explained by the variables adjusted for is computed as: ((unadjusted HR-adjusted HR)/(unadjusted HR-1.00))*100 (reference 10).

\(^\dagger\)Not applicable.
recruitment, thus excluding a possible role of effect modifier by age or hospital (results available from the authors).

Discussion

The present finding of significant associations between medical care related factors and a group of severity factors \( (FEV_1, PO_2 \) and previous admissions), together with the previously reported associations between these particular severity factors and COPD re-admission,\(^1\) strongly suggest that \( FEV_1, PO_2 \) and previous admissions may be confounders of the previously reported \(^3\) associations between medical care related factors and COPD re-admission. The fact that these associations were substantially reduced after adjusting for the severity related variables alluded to above, and the homogeneity of the pattern of confounding for a large number of medical care related factors, strongly suggest the presence of confounding by severity or by indication.\(^12\) Although the mechanism of confounding is usually not directly observable, the bi-directional nature of our study allowed us to elucidate it. Such mechanism is clear with the experience of 22 patients that at recruitment \( (\text{index-admission}) \) showed \( PO_2 \leq 55 \text{ mm Hg} \) and were not using LTOT. As a consequence of the index-admission, two-thirds of them were prescribed LTOT. Since \( PO_2 \) is a relevant variable for the indication of LTOT in a COPD patient, it was not surprising that in our data the association between LTOT and COPD re-admission changed from an unadjusted OR of 2.36 (1.79–3.11) to an OR of 1.62 (1.14–2.31) after adjustment for \( PO_2 \) and to 1.38 (95% IC: 0.95–2.00) after further adjustment for \( FEV_1 \) and previous admissions.

The fact that even after adjustment for \( FEV_1, PO_2 \) and previous admissions some medical care related factors were still associated to COPD re-admission was not surprising since residual confounding is easy to remain.\(^10\) Possible explanations for residual confounding in our study are: the existence of other confounders in the association between medical care related factors and COPD re-admission, measurement error in questionnaires and lung function testing, and the lack of information on longitudinal changes of the relevant variables.\(^13\) Pulmonary hypertension is one of the possible co-confounders, because patients suffering it have a higher risk of COPD re-admission\(^14\) and probably have a higher proportion of medical care related factors.\(^15\) Similar associations could be speculated for chronic mucus hypersecretion\(^16\) or muscular weakness.\(^17\) Unfortunately neither these factors—nor proxy measures of them—were measured in our study. Other non-respiratory comorbidities such as cardiac disease could also be co-confounders by indication, because they can direct or indirectly modify both the physician control or prescriptions, and the risk of COPD admission. In our study, the analysis of the confounding effect of a list of self-reported chronic comorbid conditions did not show a confounder pattern for "having at least one comorbidity" nor for "cardiac comorbidity", although misclassification due to self-reporting cannot be discarded. In the present study we performed classical confounding analysis, but several alternative designs and analytical strategies have been proposed to deal with time-dependent variables, and specifically to avoid confounding by indication. Thus, case-crossover\(^18\) and case-time-control\(^19\) designs, as well as G-estimation\(^20\) and marginal structural\(^21\) models should be considered for future studies in COPD patients. Because confounding by indication may be related to specific hospitals within the same study, multilevel analysis including hospital as an ecological treatment variable has been proposed to reduce confounding,\(^22\) although this approach would require the inclusion of about 50 groups (hospitals).\(^23\) We have previously reported differences in the risk of COPD re-admission between the hospitals involved in our study although these differences were removed after adjustment for type of physician and use of anticholinergics.\(^5\)

Previous studies have also found unexpected associations between medical care related factors and COPD outcomes. Treatment with anticholinergics (ipratropium) was independently associated with an increased risk of death from asthma and COPD in a large cohort of asthmatic patients.\(^24\) The authors attributed these results to the lack of information about coexisting COPD, which could be acting as a confounder by indication. However, they also suggested that the difficulty to expectorate due to the drying effect of ipratropium on lung secretions, and the development of tachycardia, are possible mechanisms for a causal relationship. A subsequent large database study of elderly asthmatic and COPD patients was unable to reproduce these results.\(^25\) In the 5-year follow-up of the Lung Health Study, a randomised clinical trial involving 5887 smokers aged 35–60, there was a tendency for coronary and cardiovascular disease morbidity to be more common among smoking-intervention- ipratropium participants than smoking-intervention-placebo participants, which was attributed to side-effects of ipratropium bromide.\(^26\) Another study found an increased mortality in
severe COPD patients independently related to oral corticosteroids. The authors suggested that previous admissions—a factor not measured—could be acting as a confounder by indication, although the association could also be due to the side-effects of sustained use of systemic corticoids, mainly myopathy and immunosuppressive effects. In our study, none of the severity variables accounted for any part of the excess risk of re-admission among oral corticosteroids users, as is shown in Table 3, pointing to the "side-effects explanation" rather than to the "confounding explanation". The interpretation of unexpected findings is more difficult in the case of pharmacological treatments than in the remaining medical care related factors, because true adverse effects are frequently a plausible explanation, and which can even coexist with confounding. In our study, the inclusion of a wide range of potential risk factors of COPD exacerbation allowed us to find that several paradoxical associations were clustered in the same group of medical care related factors, suggesting a single common explanation. Further observational studies on COPD outcomes should include a variety of medical care related factors to better understand the paradoxical associations if present, although adverse drug side-effects must always be considered for the sake of the patients.

In conclusion, the present study supports the hypothesis that the excess risk of COPD re-admission associated with medical care related factors might be partially due to confounding by indication. Residual confounding may still account for part of the remaining excess risk. True adverse effects of some pharmacological treatments cannot be excluded. Moreover, our results show that the magnitude of the confounding effect of FEV1, PO2 and previous COPD admissions can be large, and so the lack of adjustment for such factors, even when the crude association between the exposure and the outcome is large (e.g., relative risk higher than two and statistically significant) may lead to biased estimates. Both conclusions strongly suggest that further studies on COPD prognosis should include a broader characterisation of patients, not only based on lung function impairment. In addition, patients should be recruited at a similar point in the course of the disease, according to recommendations of Evidence-Based Medicine for studies of prognosis.

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