Risk factors of readmission to hospital for a COPD exacerbation: a prospective study

J García-Aymerich, E Farrero, M A Félez, J Izquierdo, R M Marrades, J M Antó, on behalf of the EFRAM* investigators

Background: Exacerbations of chronic obstructive pulmonary disease (COPD) are a leading cause of admission to hospital among men in many countries, although the factors causing exacerbations are largely unknown. The association between readmission for a COPD exacerbation and a wide range of modifiable potential risk factors, after adjusting for sociodemographic and clinical factors, has been assessed.

Methods: Three hundred and forty patients with COPD recruited during an admission for an exacerbation in four tertiary hospitals in the Barcelona area of Spain were followed for a mean period of 1.1 years. Information on potential risk factors, including clinical and functional status, medical care and prescriptions, medication adherence, lifestyle, health status, and social support, was collected at the recruitment admission. A Cox’s proportional hazards model was used to obtain independent relative risks of readmission for COPD.

Results: During the follow-up period 63% of patients were readmitted at least once, and 29% died. The final multivariate model showed the following risk (or protective) factors: >3 admissions for COPD in the year before recruitment (hazard ratio (HR)=1.66, 95% CI 1.16 to 2.39), forced expiratory volume in 1 second (FEV1) percentage predicted (0.97, 95% CI 0.96 to 0.99), oxygen tension (0.88, 95% CI 0.79 to 0.98), higher levels of usual physical activity (0.54, 95% CI 0.34 to 0.86), and taking anticholinergic drugs (1.81, 95% CI 1.11 to 2.94). Exposure to passive smoking was also related to an increased risk of readmission with COPD after adjustment for clinical factors (1.63, 95% CI 1.04 to 2.57) but did not remain in the final model.

Conclusions: This is the first study to show a strong association between usual physical activity and reduced risk of readmission to hospital with COPD, which is potentially relevant for rehabilitation and other therapeutic strategies.

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of disability and mortality worldwide, and is expected to become the third cause of death and the fifth cause of disability adjusted life years in 2020. Patients with COPD may suffer recurrent exacerbations, with a worsening of symptoms and reduction in lung function that may not be recovered in a small proportion of patients. Moreover, exacerbations are associated with an impaired quality of life, reduced survival, and a high healthcare expenditure. The latter mainly results from admission to hospital which is frequently a consequence of an exacerbation. Prevention of exacerbations is therefore an important goal in the management of stable COPD, although knowledge about which factors relate to COPD exacerbations or hospitals admissions for exacerbations is currently very limited. While influenza vaccination has been shown to reduce the risk of admission in elderly subjects with chronic lung disease, the results for respiratory rehabilitation and inhaled corticosteroids are still controversial. The effect on COPD exacerbations of long term oxygen therapy (LTOT), adherence to medication, consumption of tobacco, alcohol, and sedatives, or usual physical activity has not been directly assessed in either experimental or observational studies.

In the EFRAM project we have previously performed a case-control study to identify risk factors for COPD exacerbations, including a wide range of potential risk factors, and we found that, after adjusting for COPD severity, only underprescription of LTOT was independently associated with admission for a COPD exacerbation. Because selection bias is likely to occur in this type of study, we followed prospectively the 340 patients with COPD recruited in the framework of the EFRAM study. The objective was to assess the association between readmission for a COPD exacerbation and a wide range of modifiable potential risk factors, mainly related to medical care and lifestyle, after adjusting for sociodemographic and clinical factors.

METHODS

Recruitment

A systematic sample of one out of every two patients admitted to hospital or remaining in the emergency room for at least 18 hours for a COPD exacerbation in four tertiary hospitals in the Barcelona area from 1 May 1997 to 30 April 1998 was identified, independently of whether they had previous COPD admissions or not. A diagnosis of COPD was established by the ward pulmonologist based on medical history, current symptoms, and available pulmonary function tests, following the ERS guidelines. An exacerbation was defined as an increase in dyspnoea, sputum production, or sputum purulence. Patients were allowed to enter the study as many times as they were hospitalised during the recruitment period, giving 346 individuals with 404 admissions. In patients with more than one admission during the recruitment period the first one was selected as the beginning of the follow up period. Recruitment methods and diagnosis criteria have been detailed in previous papers in the EFRAM study.

*EFRAM: Estudi dels Factors de Risc d’Agudització de la MPOC (Risk Factors of COPD Exacerbation Study).
approved the protocol and written informed consent was obtained from all patients.

Information about factors potentially related to COPD exacerbations was obtained by an extensive bibliographic search that has been described elsewhere. A large number of potential risk factors—including variables related to clinical status, characteristics of medical care, medical prescriptions, adherence to medication, lifestyle, quality of life, and social support—was identified and has been reported elsewhere. All the variables were considered in the analysis.

During the recruitment hospital admission, patients were asked to complete a questionnaire. Most of the questionnaire content was obtained from previously validated instruments, while some questions were developed and pilot tested. Questions for usual physical activity were adapted from the Spanish validation of the Minnesota Leisure Time Physical Activity Questionnaire, a measure of physical activity in the general population. Each specific activity was assigned an intensity unit based on their rate of energy expenditure expressed as metabolic equivalent value (METs), the ratio of work metabolic rate to resting metabolic rate. The energy expenditure in physical activity was then expressed as the total activity metabolic index per day in kcal/day, taking into account the intensity code for each physical activity, the number of times that this activity was performed in a usual day, and the average time spent in each session. In addition, weight, height and tricipital skinfold thickness were measured. Sputum samples were collected during the first 48 hours after admission and processed within an hour, accepting only those considered suitable for culture according to Murray-Washington criteria, until potentially pathogenic bacteria were identified and quantified. At least 3 months after admission to hospital and during a clinically stable period of COPD, patients performed a forced spirometric test and provided arterial blood to measure gas tensions. Detailed information about all the remaining variables, sources of questions, and methods of spirometric and blood gas measurements have been given in previous papers.

Follow up
Six (1.7%) of the 346 patients recruited did not survive the recruitment admission; 340 patients were therefore followed from the day of discharge after the recruitment admission until 1 May 1999 or the day of death, if earlier. There were no losses to follow up as all patients were either contacted for telephone interview, registered as dead in the mortality registry, or visited in the outpatient clinics or hospitalised after 1 May 1999.

Information on readmissions during the follow up period was obtained from the Minimum Basic Dataset (CMDB), a national administrative database that is monitored to high quality standards. The primary study outcome was the time to readmission for a COPD exacerbation. All admissions with a main or secondary diagnosis fulfilling any of the following code combinations (according to the International Classification of Diseases, 9th revision) were recorded as a COPD exacerbation: (1) 490–496 (COPD group), 480–486 (pneumonia), 487 (influenza), or 518.81 (respiratory failure) as the main diagnosis; (2) 428 (cardiac failure) as the main diagnosis (after admission and processed within an hour, accepting only those considered suitable for culture according to Murray-Washington criteria); (3) any other respiratory problems (011 (tuberculosis), 466 (acute bronchitis), 500–505 (pneumonociosis), 277.6 (deficit α-antitrypsin)) as the main diagnosis if 518.81 or 491.21 was the secondary diagnosis. Criteria of the expert consensus of the American Thoracic Society were used to define such combinations. Vital status was ascertainment through a telephone interview with patients or their proxies and a record linkage with the Catalonia mortality registry for the years 1997–9. Additional institutional ethical approval for the linkage was obtained. Fields used for linkage were full name, sex, and date of birth, as described elsewhere.

Statistical analysis
Time from recruitment (admission) to first event (following admission) was used as the outcome variable in a Cox's proportional hazards model. Sociodemographic and clinical variables were assessed and those with an independent statistically significant association with readmission provided a clinical model. The individual association between all potential risk factors and readmission, adjusted for the variables of the clinical model, was then estimated and those factors considered a priori as clinically relevant, those with a p value of <0.25 after adjusting for the clinical model, and those with a high (≥2) or low (<0.5) hazard ratio (HR) after adjusting for the clinical model were defined as relevant variables. A multivariate model was then built including all relevant variables until the final most parsimonious model was fitted. Poisson regression was used as a complementary approach to obtain relative risks of readmission for COPD, modelling the individual number of readmissions and including the logarithm of the individual person-days at risk as the offset. The analysis was performed using Stata Release 6.0 (StataCorp, Texas, USA, 1999).

RESULTS
Three hundred and forty patients (92% men) of mean (SD) age 69 (9) years were followed; 72% had a low socioeconomic status (IV or V), a mean of 1.5 (2.0) COPD admissions in the previous year, mean forced expiratory volume in 1 second (FEV,) of 36 (16)%, and mean P0 of 8.5 (1.7) kPa; 90% had any comorbid condition and mean body mass index (BMI) of 26 (5) kg/m2. Patients were followed for a mean of 1.1 years; 63% were admitted at least once during the follow up period, and 29% died (table 1). Twenty eight patients (8%) died without having a readmission during the follow up period and were excluded from the study of risk factors for a COPD readmission. The excluded patients were older (74 v 69 years, p=0.003) and slightly thinner (BMI 24 v 26 kg/m2, p=0.070) than the remaining patients. Among all the sociodemographic and clinical variables, having had ≥3 COPD admissions in the year before recruitment, having had ≥3 COPD emergency room visits

### Table 1 Follow up of patients with COPD recruited at an admission for a COPD exacerbation

<table>
<thead>
<tr>
<th>Total number of individuals</th>
<th>340</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) total days of follow up (excluding days in hospital)</td>
<td>410 (181)</td>
</tr>
<tr>
<td>Number of readmissions during follow up, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>126 (37%)</td>
</tr>
<tr>
<td>1</td>
<td>78 (23%)</td>
</tr>
<tr>
<td>2</td>
<td>43 (13%)</td>
</tr>
<tr>
<td>3</td>
<td>32 (9%)</td>
</tr>
<tr>
<td>4</td>
<td>18 (5%)</td>
</tr>
<tr>
<td>≥5</td>
<td>43 (13%)</td>
</tr>
<tr>
<td>Days to first readmission, median (P25–P75)</td>
<td>186 (40–432)</td>
</tr>
<tr>
<td>Vital status: died during follow up, n (%)</td>
<td>98 (29%)</td>
</tr>
<tr>
<td>Respiratory causes (ICD-9 460–519)</td>
<td>73 (24%)</td>
</tr>
<tr>
<td>COPD group (490–496)</td>
<td>54 (15%)</td>
</tr>
<tr>
<td>Respiratory failure (518–519)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Cardiovascular causes (390–459)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Ischaemic heart disease (410–414)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Cancer (140–239)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Lung cancer (162)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Other causes</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Excluded individuals*, n (%)</td>
<td>28 (8%)</td>
</tr>
<tr>
<td>Number of individuals in follow up analysis, n (%)</td>
<td>312 (92%)</td>
</tr>
</tbody>
</table>

*Individuals who died without having a readmission during the follow up period.
without admission in the year before recruitment, a lower percentage predicted FEV₁, and a lower PO2, were independently associated with a significantly increased risk of readmission for COPD, whereas having had ≥3 COPD admissions in the year before recruitment, a lower percentage predicted FEV₁, a lower level of PO2, being controlled by a pulmonologist, and LTOT were also associated with a higher risk of readmission for COPD but did not achieve statistical significance. None of the remaining factors (socioeconomic status, living alone, pneumococcal vaccination, nutritional status, adherence to medication, comorbidity, or bacterial infection at baseline) was significantly associated with readmission.

In a final multivariate model, a high level of usual physical activity was associated with a 46% reduction in the risk of a readmission for COPD, whereas having had ≥3 COPD admissions in the year before recruitment, a lower percentage predicted FEV₁, a lower level of PO2, being controlled by a pulmonologist, and taking anticholinergics were related to an increased risk (table 3). After allowing for inclusion of the individual number of readmissions as the outcome, Poisson regression produced almost identical results as the Cox model.
DISCUSSION

To our knowledge, this is the first study to show that patients with COPD who perform a relatively high level of physical activity in their daily life have a substantially reduced risk of readmission due to exacerbation. Since the third of patients with COPD who reported an activity equivalent to walking \( \geq 60 \) minutes a day had a reduction in risk of readmission to hospital of almost 50\%, this is potentially relevant. Moreover, the association did not change when adjusted for COPD severity, nutritional status factors, or respiratory rehabilitation. Such results are in agreement with the increased risk of COPD admission associated with a limited 6 minute walking test reported in a previous group of COPD patients,\(^{23}\) both studies suggesting that conditioned patients have a lower risk of COPD admission which is independent of the way conditioning is evaluated. Because our finding has not been reported previously, its mechanism can only be speculated. One possible explanation is that exercise leads to a better conditioned cardiovascular system\(^{24}\) that would adapt better to the increase in oxygen intake in respiratory muscles that occurs during a COPD exacerbation.\(^{25}\) In addition, a programme of endurance training can reduce exercise induced lactic acidosis and improve the oxidative capacity of the muscles in patients with moderate to severe COPD,\(^{26}\) suggesting that such muscles would be more able to tolerate a COPD exacerbation than untrained muscles. We found no relationship between physical activity and rehabilitation or nutritional status, which suggests that physical activity in this population depends on other factors. The extent to which these results may have relevance for rehabilitation programmes\(^{27}\) or clinical practice\(^{28}\) is not yet clear.

Several factors related to medical care or prescriptions—such as being controlled by a pulmonologist, taking anticholinergics or oral corticosteroids—were associated with a higher risk of readmission for COPD in the adjusted clinical model, contrary to what had been expected. Similar results were also found in the previous case-control EFRAM study,\(^{11}\) although they were more evident in the follow up analysis. We consider that a previous COPD admission may play a role of “confounding by indication”, a term used when the confounder represents a perceived high risk or poor prognosis that results in an indication for treatment.\(^{29}\) In our study, having had previous admissions fulfils the two conditions necessary to qualify as a confounder.\(^{29}\) Firstly, patients who had had a previous COPD admission at recruitment (82\%) had a higher prevalence of prescriptions of anticholinergics or oral corticosteroids than those who had never had a COPD admission (18\%). Secondly, having had a previous admission (independ-
Longitudinal data can be analysed in different ways and, in our Cox analysis, repeated admissions in the same subject were not taken into account. However, very similar parameter estimates were obtained when repeated admissions were included in a Poisson regression model. Such consistency was expected since Poisson regression can be seen as a special case of a proportional hazards model with a constant baseline hazard.

Patients who died without a readmission were excluded, a decision that could have introduced a degree of survival bias. However, these patients constituted a small proportion (8%) of the total and only showed slight differences in age and BMI. Moreover, when they were included in the analysis by combining death and readmission as the outcome variable, the same risk factors for COPD readmission were obtained and estimates did not change substantially (data available from the authors).

Patients included in our study were mostly men with a mean age of 69 years, mean percentage predicted FEV1 of 36%, who had experienced a mean of 1.5 admissions in the year before recruitment. These characteristics represent the usual pattern of COPD admissions in Barcelona tertiary hospitals and probably elsewhere, with the exception of the male predominance. Generalisation of our results should be restricted to COPD in this stage of the disease since patients in earlier or advanced stages may differ substantially. Another potential problem in the method of recruitment is that some readmissions during the follow up period may not really be new exacerbations but a relapse of the previous one. In order to avoid this the analysis was repeated, excluding those patients whose readmission occurred within 14 days of the previous discharge (n=38), and very similar results were obtained (data available from the authors).

This is the first study to show a strong association between usual physical activity and reduced risk of COPD readmission which is potentially relevant for rehabilitation and other therapeutic strategies. Overall, the analysis yielded results which were consistent with the previous case-control approach—that is, the association of COPD admission with clinical variables (previous admissions, lower FEV1, and lower PaO2) and the lack of an association with most factors relating to smoking history and previous hospitalisation (EFRAM study).

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Authors’ affiliations

J García-Aymerich, J M Antó, Respiratory and Environmental Health Research Unit, IMIM, Barcelona, Spain
E Farrero, Department of Pneumology, Ciutat Sanitària i Universitaria de Bellvitge, L’Hospitalet de Llobregat, Spain
M A Félez, Department of Pneumology, Hospital del Mar, Barcelona, Spain
J Izquierdo, Department of Pneumology, Hospital Germans Trias i Pujol, Badalona, Spain
R M Marrades, Department of Pneumology, Hospital Clinic I Provincial de Barcelona, Barcelona, Spain
J M Antó, Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain
EFRAM investigators: J M Antó, J García-Aymerich, J Sunyer, Respiratory and Environmental Health Research Unit, IMIM, Barcelona, J Alonso, Health Services Research Unit, IMIM, Barcelona; E Barreiro, M A Félez, Department of Pneumology, Hospital del Mar, Barcelona; J Escarraball, E Farrero, J Redondo, Department of Pneumology, Ciutat Sanitària i Universitaria de Bellvitge, L’Hospitalet de Llobregat; R M Marrades, N Soler, A Torres, Department of Pneumology, Hospital Clinic I Provincial de Barcelona, Barcelona; G Bonet, J Izquierdo, E Monsó, J Morera, Department of Pneumology, Hospital Germans Trias i Pujol, Badalona.

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Conflict of interest: none.

REFERENCES


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Leukotriene receptors are overexpressed in aspirin sensitive asthmatics


Patients with aspirin sensitivity, asthma, and nasal polyps exhibit increased synthesis of cysteinyl leukotrienes—both basally and in response to exogenous aspirin—and increased responsiveness to inhaled cysteinyl leukotrienes, in contrast to patients with aspirin tolerant asthma. The authors hypothesised that the latter effect reflects overexpression of the cysteinyl leukotriene receptor CysLT1.

Nasal biopsy specimens were obtained from 22 aspirin sensitive and 12 aspirin tolerant patients with chronic rhinosinusitis and nasal polyposis. The absolute number (and percentage of CD45+ leucocytes) of cells expressing the CysLT1 (but not LTB4) receptor was increased in the aspirin sensitive group, despite no overall difference in numbers of leucocytes. Subsequently, nasal application of lysine aspirin to aspirin sensitive patients caused a reduction in the percentage of CD45+ leucocytes expressing the CysLT1 receptor compared with placebo.

This study raises intriguing questions about the pathogenesis of aspirin sensitive syndromes, providing evidence for overexpression of the CysLT1 receptor in addition to increased leukotriene production. This overexpression is reduced by aspirin desensitisation. Further studies are warranted of leukotriene antagonists and aspirin desensitisation in patients with nasal polyposis with aspirin sensitivity. Variation in the response to leukotriene antagonists may well be related to differences in CysLT1 expression in inflammatory cells in the upper and lower airway.

S Jenkins
Huw.Jenkins@meht.nhs.uk
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