CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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

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

Thorax 2003;**58**:100–105

See end of article for authors' affiliations

Correspondence to: Dr J M Antó, Respiratory and Environmental Health Research Unit, Institut Municipal d'Investigació Mèdica (IMIM), Doctor Aiguader 80, E-08003 Barcelona, Spain; e-mail jmanto@imim.es

Revised version received 25 September 2002
Accepted for publication 21 October 2002

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 (FEV_1) 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% 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.[1] 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.[2] Moreover, exacerbations are associated with an impaired quality of life,[3] reduced survival,[4] and a high healthcare expenditure.[5] 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,[6] although knowledge about which factors relate to COPD exacerbations or hospitals admissions for exacerbations is currently very limited.[7] While influenza vaccination has been shown to reduce the risk of admission in elderly subjects with chronic lung disease,[8] the results for respiratory rehabilitation[9] and inhaled corticosteroids[10] 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,[11] 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,[12] we followed prospectively the 340 patients with COPD recruited in the framework of the EFRAM study.[13] 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.

*EFRAM: Estudi dels Factors de Risc d'Agudització de la MPOC (Risk Factors of COPD Exacerbation Study).

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.[5] An exacerbation was defined as an increase in dyspnoea, sputum production, or sputum purulence.[14] 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.[11 13] The ethics committees of the participating hospitals

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.[13] 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.[11] 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[15] of the Minnesota Leisure Time Physical Activity Questionnaire, a measure of physical activity in the general population.[16] Each specific activity was assigned an intensity unit based on their rate of energy expenditure expressed as metabolic equivalent tax (METs), the ratio of work metabolic rate to resting metabolic rate.[17] 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,[18] until potentially pathogenic bacteria[19] 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 measurementss have been given in previous papers.[11 13]

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 (CMBD), a national administrative database that is monitored to high quality standards.[20] The primary study outcome was the time to readmission for a COPD exacerbation. All admissions with a main and/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 if 518.81 (respiratory failure) or 491.21 (acute exacerbation of chronic bronchitis) were the secondary diagnosis; and (3) any other respiratory problems (011 (tuberculosis), 466 (acute bronchitis), 500–505 (pneumoconiosis), 277.6 (deficit α_1-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[21] were used to define such combinations.

Vital status was ascertained 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.[22]

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

Total number of individuals	340
Mean (SD) total days of follow up (excluding days in hospital)	410 (181)
Number of readmissions during follow up, n (%)	
0	126 (37%)
1	78 (23%)
2	43 (13%)
3	32 (9%)
4	18 (5%)
≥5	43 (13%)
Days to first readmission, median (P_{25}–P_{75})	186 (40–432)
Vital status: died during follow up, n (%)	98 (29%)
Respiratory causes (ICD-9 460–519)	73 (74%)
COPD group (490–496)	54 (55%)
Respiratory failure (518–519)	5 (5%)
Cardiovascular causes (390–459)	12 (12%)
Ischaemic heart disease (410–414)	5 (5%)
Cancer (140–239)	7 (7%)
Lung cancer (162)	5 (5%)
Other causes	6 (6%)
Excluded individuals*, n (%)	28 (8%)
Number of individuals in follow up analysis, n (%)	312 (92%)

*Individuals who died without having a readmission during the follow up period.

Statistical analysis

Time from recruitment (admission) to first event (following admission) was used as the outcome variable in a Cox's proportional hazards model.[23] 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[24] 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 up; 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_1) of 36 (16)%, and mean P_{O_2} of 8.5 (1.7) kPa; 90% had any comorbid condition and mean body mass index (BMI) of 26 (5) kg/m^2. 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/m^2, 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 2 Crude and clinical model adjusted individual associations between relevant variables* and readmission to hospital for an exacerbation in a cohort of 312 patients with COPD (Cox regression)

	Crude HR (95% CI)†	p value	Adjusted HR (95% CI) by clinical model†	p value
Clinical model				
⩾3 COPD admissions in the year before recruitment‡	2.27 (1.69 to 3.04)	0.000		
⩾3 COPD emergency room visits without admission in the year before recruitment‡	1.72 (1.13 to 2.61)	0.012		
% predicted FEV_1§	0.97 (0.96 to 0.98)	0.000		
P_{O_2} (kPa)§	0.78 (0.71 to 0.87)	0.000		
Age	1.00 (0.99 to 1.02)	0.703	1.01 (0.99 to 1.04)	0.163
Sex: women	0.98 (0.60 to 1.61)	0.934	1.43 (0.76 to 2.68)	0.265
Medical care				
Team based primary care‡	0.74 (0.57 to 0.97)	0.029	0.77 (0.56 to 1.07)	0.116
Controlled by a:				
General practitioner	1.00		1.00	
Pulmonologist	2.16 (1.43 to 3.27)	0.000	1.77 (1.07 to 2.92)	0.025
Hospital of recruitment:				
Hospital 1	1.00		1.00	
Hospital 2	1.88 (1.28 to 2.75)	0.001	1.81 (1.14 to 2.88)	0.012
Hospital 3	1.95 (1.32 to 2.88)	0.001	2.08 (1.33 to 3.27)	0.001
Hospital 4	1.07 (0.69 to 1.65)	0.761	1.19 (0.67 to 2.14)	0.550
Medical prescriptions				
Anticholinergics‡	3.52 (2.37 to 5.21)	0.000	2.02 (1.26 to 3.24)	0.004
Oral corticosteroids‡	1.55 (1.13 to 2.11)	0.006	1.59 (1.07 to 2.37)	0.021
Influenza vaccination‡	1.37 (1.01 to 1.87)	0.044	1.43 (0.98 to 2.07)	0.064
Respiratory rehabilitation‡	1.77 (1.23 to 2.57)	0.002	1.32 (0.85 to 2.05)	0.223
Long term oxygen therapy‡	2.36 (1.79 to 3.11)	0.000	1.26 (0.87 to 1.84)	0.224
Compliance				
Correctly performed essential MDI manoeuvres‡	1.17 (0.88 to 1.56)	0.277	1.12 (0.79 to 1.59)	0.526
Lifestyle				
Smoking:				
Ex smoker not exposed to passive smoking	1.00		1.00	
Ex smoker exposed to passive smoking	1.18 (0.81 to 1.70)	0.387	1.63 (1.04 to 2.57)	0.034
Current smoker	0.58 (0.41 to 0.82)	0.002	0.97 (0.64 to 1.47)	0.876
Never smoker	0.93 (0.55 to 1.57)	0.781	1.20 (0.61 to 2.33)	0.598
Usual physical activity (in tertiles)¶				
<79 kcal/day	1.00		1.00	
79–232 kcal/day	0.73 (0.54 to 0.99)	0.043	0.85 (0.59 to 1.24)	0.400
>232 kcal/day	0.46 (0.32 to 0.68)	0.000	0.49 (0.31 to 0.79)	0.003
Other				
Physical scale health related QoL§	0.97 (0.95 to 0.98)	0.000	0.98 (0.96 to 0.99)	0.007

HR=hazard ratio; CI=confidence interval; MDI=metered dose inhaler; QoL=quality of life.
*Relevant variables are: those considered a priori as clinically relevant, those with a p value <0.250 after adjusting for the clinical model, and those with high (>2) or low (<0.5) HR after adjusting for the clinical model.
†Each line is a single model. Clinical model includes: ⩾3 COPD admissions in the year before recruitment, ⩾3 COPD emergency room visits without admission in the year before recruitment, % predicted FEV_1, and P_{O_2}.
‡Reference categories are: <3 COPD admissions in the year before recruitment; <3 COPD emergency room visits without admission in the year before recruitment; not team based primary care; no anticholinergics intake; no oral corticosteroids intake; lack of influenza vaccination; lack of respiratory rehabilitation; lack of long term oxygen therapy; some mistake in any of the essential MDI manoeuvres.
§HR means change in risk for 1 percentual unit in FEV_1, 1 kPa in P_{O_2}, and 1 point increase in physical scale of SF-36 score.
¶First tertile means, for instance, patients walking 20 minutes a day every day ("walking" includes time going to the bar, to buy newspapers, going to the supermarket, or just strolling). Third tertile means patients walking 60 minutes a day every day, or patients walking 20 minutes a day plus practising exercise in a gymnasium 60 minutes a day three days a week.

without admission in the year before recruitment, a lower percentage predicted FEV_1 and a lower P_{O_2} were independently related to a higher risk of readmission for a COPD exacerbation, and constituted the clinical model (table 2). Other clinical factors such as P_{CO_2} (HR 1.15 (95% CI 1.01 to 1.30), p=0.031) and FEV_1/FVC (0.99 (95% CI 0.98 to 1.00), p=0.005) were associated with risk of readmission, but their significance was lost after including P_{O_2} and FEV_1, respectively. The individual associations between each of the potential risk factors and readmission were obtained after adjusting for the clinical model, and those considered relevant—according to criteria defined in the Methods section—are shown in table 2. Only two variables showed a statistically significant reduced risk of readmission: the highest tertile of usual physical activity and a higher score of physical quality of life. Being enrolled in a team based primary care centre was associated with a lower risk of readmission for COPD, although it did not reach statistical significance. In contrast, the following variables were associated with a significantly increased risk of readmission: being controlled by a pulmonologist, being admitted at recruitment in hospitals 2 and 3, taking anticholinergics, taking oral corticosteroids, and being a former smoker exposed to passive smoking. Influenza vaccination, respiratory rehabilitation, 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 FEV_1, a lower level of P_{O_2}, 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 (data not shown; available from the authors).

Table 3 Multivariate adjusted risk factors of readmission to hospital for an exacerbation in a cohort of 312 patients with COPD (Cox regression)

	Adjusted HR (95% CI)	p value
⩾3 COPD admissions in the year before recruitment*	1.66 (1.16 to 2.39)	0.006
% predicted FEV_1	0.97 (0.96 to 0.99)	0.001
P_{O_2} (kPa)	0.88 (0.79 to 0.98)	0.024
Controlled by a:		
General practitioner	1.00	
Pulmonologist	1.66 (0.98 to 2.80)	0.058
Anticholinergics	1.81 (1.11 to 2.94)	0.017
Usual physical activity (in tertiles):		
<79 kcal/day	1.00	
79–232 kcal/day	0.87 (0.60 to 1.27)	0.469
>232 kcal/day	0.54 (0.34 to 0.86)	0.010

HR=hazard ratio; CI=confidence interval; FEV_1=forced expiratory volume in 1 second.
*HR for "COPD admissions as a continuous variable" 1.19 (95% CI 1.10 to 1.30), p=0.000.

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 ⩾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,[25] 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[26] that would adapt better to the increase in oxygen intake in respiratory muscles that occurs during a COPD exacerbation.[27] 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,[28] 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[29] or clinical practice[21] 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.[30] In our study, having had previous admissions fulfils the two conditions necessary to qualify as a confounder.[31] 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 (independent of whether the variable was included as continuous or as categorical with different cut off points) was associated with an increased risk of a subsequent readmission for COPD, as found in previous studies.[3 11] Moreover, in the present analysis the positive association of such variables with further COPD readmissions partially reduced its magnitude and significance when adjusted for having had ⩾3 COPD admissions in the year before recruitment. For example, the crude HR for readmission of taking anticholinergics was 3.52 (95% CI 2.37 to 5.21) compared with 2.40 (95% CI 1.52 to 3.80) when adjusted for $\%FEV_1$ and P_{O_2} and 2.10 (95% CI 1.32 to 3.36) when adjusted for $\%FEV_1$, P_{O_2}, and previous admissions. The increased risk associated with pneumologist care and taking anticholinergics was not totally removed after adjustment for previous admissions, which suggests that other mechanisms such as easier accessibility to hospital or residual confounding[30] may be operating. Consistent with the possibility of bias by indication, our data showed that, after the recruitment admission, LTOT was provided to all patients who fulfilled the necessary criteria with the result that the strong association between underprescription of LTOT and admission for COPD reported in the case-control analysis[11] disappeared after the follow up. With regard to the plausibility of the association between previous admissions and a subsequent readmission, it is possible that "previous admissions" is a surrogate of undefined risk factors. In future, to avoid such biases, the study of the effects of medical care related variables would probably need randomised controlled trials instead of observational studies and/or the use of patients in their first contact with medical care services.

Surprisingly, we found that influenza vaccination was associated with an increased risk of admission. Although randomised trials of influenza vaccination in specific COPD populations have not been reported, the administration of the vaccine in elderly patients with chronic lung disease[8] has been associated with a reduction in the risk of hospital admissions, outpatient visits, and mortality. The fact that only 28% of our population was not vaccinated could confer this group with particular characteristics that were not controlled in the multivariate models.

Exposure to environmental tobacco smoking was associated with an increased risk of readmission with COPD among ex-smokers in the clinical model adjusted analysis. There are no previous studies assessing the effect of passive smoking on patients with COPD.[32] Since there is a moderate prevalence of exposure to passive smoking among non-current smokers with COPD and a low prevalence of advice against passive smoking,[13] these results should be seen as potentially important. A higher score of physical quality of life was associated with a decreased risk of readmission with COPD after adjusting for the clinical model, as in a previous study.[33] Differences in the risk of readmission with COPD between hospitals were found in the crude and the clinical model adjusted analysis. In fact, it would be logical that the lack of an empirical definition of a COPD exacerbation[6] would lead to some variability between centres. Moreover, geographical variations in hospital use both for COPD and other diseases has already been described.[34]

Lower FEV_1 and lower P_{O_2} values were associated with a higher risk of COPD readmission, as in the previous case-control EFRAM analysis.[11] Other studies have not found this association, probably because of the smaller number of subjects[25] and the use of categorised rather than continuous variables.[25 35] Interestingly, FEV_1 and P_{O_2} were not correlated which suggests that, in patients with a low percentage predicted FEV_1, P_{O_2} acts as an independent factor. Higher levels of P_{CO_2} were associated with an increased risk of readmissions, in agreement with the results of Kessler *et al*.[25] Unfortunately, other physiological parameters—such as haemodynamic measurements that have been associated with COPD admission[25] or pulmonary hyperinflation[36]—were not measured.

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.[23]

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 FEV_1 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 FEV_1, and lower Po_2) and the lack of an association with most factors relating to medical care (influenza and pneumococcal vaccination, respiratory rehabilitation, most drug treatments, and adherence to medication).

ACKNOWLEDGEMENTS

The authors thank M Macharé, M Maresma, A Martín, J Rodríguez, S Alonso, R Reinón, R Pedreny, N Soler, and A Roig for their help in the field work, the Registre de Mortalitat de Catalunya (Departament de Sanitat i Seguretat Social) for providing the information on mortality data, and Dr J Gea for his help in the interpretation of results for physical activity.

Authors' affiliations

J Garcia-Aymerich, J M Antó, Respiratory and Environmental Health Research Unit, IMIM, Barcelona, Spain
E Farrero, Department of Pneumology, Ciutat Sanitària I Universitària 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 Clínic 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 Garcia-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 Escarrabill, E Farrero, J Redondo, Department of Pneumology, Ciutat Sanitària I Universitària de Bellvitge, L'Hospitalet de Llobregat; R M Marrades, N Soler, A Torres, Department of Pneumology, Hospital Clínic I Provincial de Barcelona, Barcelona; G Bonet, J Izquierdo, E Monsó, J Morera, Department of Pneumology, Hospital Germans Trias I Pujol, Badalona.

This work was supported in part by grants from Agència d'Avaluació de Tecnologia Mèdica (5/34/96) and Generalitat de Catalunya-CIRIT 1999SGR 00241; J Garcia-Aymerich was a recipient of a grant from Instituto de Salud "Carlos III" (97/4365) from 1997 to 2000 and currently has a fellowship from Institut Municipal d'Investigació Mèdica.

Conflict of interest: none.

REFERENCES

1 **Murray CJL**, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. *Lancet* 1997;**349**:1498–504.
2 **Seemungal TAR**, Donaldson GC, Bhowmik A, *et al*. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;**161**:1608–13.
3 **Seemungal TAR**, Donaldson GC, Paul EA, *et al*. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**:1418–22.
4 **Connors AF**, Dawson NV, Thomas C, *et al*. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am J Respir Crit Care Med* 1996;**154**:959–67.
5 **Siafakas NM**, Vermeire P, Pride NB, *et al*. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995;**8**:1398–420.
6 **Madison JM**, Irwin RS. Chronic obstructive pulmonary disease. *Lancet* 1998;**352**:467–73.
7 **Fabbri L**, Beghé B, Caramori G, *et al*. Similarities and discrepancies between exacerbations of asthma and chronic obstructive pulmonary disease. *Thorax* 1998;**53**:803–8.
8 **Nichol KL**, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalisation, and mortality in elderly persons with chronic lung disease. *Ann Intern Med* 1999;**130**:397–403.
9 **Celli BR**. Is pulmonary rehabilitation an effective treatment for chronic obstructive pulmonary disease? Yes. *Am J Respir Crit Care Med* 1997;**155**:781–3.
10 **Burge PS**. EUROSCOP, ISOLDE and the Copenhagen city lung study. *Thorax* 1999;**54**:287–8.
11 **Garcia-Aymerich J**, Monsó E, Marrades RM, *et al*. Risk factors for hospitalisation for a chronic obstructive pulmonary disease exacerbation. EFRAM study. *Am J Respir Crit Care Med* 2001;**164**:1002–7.
12 **Pearce N**, Grainger J, Atkinson M, *et al*. Case-control study of prescribed fenoterol and death from asthma in New Zealand, 1977–81. *Thorax* 1990;**45**:170–5.
13 **Garcia-Aymerich J**, Barreiro E, Farrero E, *et al*. Patients hospitalised for COPD have a high prevalence of modifiable risk factors for exacerbation (EFRAM study). *Eur Respir J* 2000;**16**:1037–42.
14 **Anthonisen NR**, Manfreda J, Warren CPW, *et al*. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;**106**:196–204.
15 **Elosua R**, Marrugat J, Molina L, *et al*. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish men. The MARATHOM investigators. *Am J Epidemiol* 1994;**139**:1197–209.
16 **Taylor HL**, Jacobs DR Jr, Schucker B, *et al*. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis* 1978;**31**:741–55.
17 **Ainsworth BE**, Haskell WL, Leon AS, *et al*. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 1993;**25**:71–80.
18 **Murray PR**, Washington II JA. Microscopic and bacteriologic analysis of expectorated sputum. *Mayo Clin Proc* 1975;**50**:339–44.
19 **Cabello H**, Torres A, Celis R, *et al*. Bacterial colonization of distal airways in healthy subjects and chronic lung disease: a bronchoscopic study. *Eur Respir J* 1997;**10**:1137–44.
20 **Ayala S**. Análisis de la auditoría del CMBD 1993 en los hospitales del INSALUD. *Papeles Médicos* 1995;**4**:6.
21 **American Thoracic Society**. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;**152**:S77–120.
22 **Sunyer J**, Antó JM, Mcfarlane D, *et al*. Sex differences in mortality of people admitted in emergency rooms for asthma and chronic obstructive pulmonary diseases. *Am J Respir Crit Care Med* 1998;**158**:851–6.
23 **Stürmer T**, Glynn RJ, Kliebsch U, *et al*. Analytic strategies for recurrent events in epidemiologic studies: background and application to hospitalisation risk in the elderly. *J Clin Epidemiol* 2000;**53**:57–64.
24 **Hosmer DW**, Lemeshow S. *Applied logistic regression*. New York: John Wiley & Sons, 1989.
25 **Kessler R**, Faller M, Fourgaut G, *et al*. Predictive factors of hospitalisation for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**159**:158–64.
26 **Patessio A**, Casaburi R, Prefault C, *et al*. Exercise training in chronic lung disease: exercise prescription. In: Roca J, Whipp BJ, eds. *Clinical exercise testing*. European Respiratory Monograph 6. Sheffield: European Respiratory Society Journals, 1997: 129–46.

27 **Barbera JA**, Roca J, Ferrer A, *et al*. Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 1997;**10**:1285–91.
28 **Maltais F**, LeBlanc P, Simard C, *et al*. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**154**:442–7.
29 **Donner CF**, Lusuardi M. Selection of candidates and programmes. In: Donner CF, Decramer M, eds. *Pulmonary rehabilitation*. European Respiratory Monograph 13. Sheffield: European Respiratory Society Journals, 2000: 132–42.
30 **Salas M**, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. *Am J Epidemiol*1999;**149**:981–3.
31 **Rothman KJ**, Greenland S. *Modern epidemiology*. Philadelphia: Lippincott-Raven, 1998.
32 **Coultas DB**. Passive smoking and risk of adult asthma and COPD: an update. *Thorax* 1998;**53**:381–7.
33 **Osman LM**, Godden DJ, Friend JAR, *et al*. Quality of life and hospital re-admission in patients with chronic obstructive pulmonary disease. *Thorax* 1997;**52**:67–71.
34 **Ashton CM**, Petersen NJ, Souchek J, *et al*. Geographic variations in utilization rates in Veterans Affairs hospitals and clinics. *N Engl J Med* 1999;**340**:32–9.
35 **Collet JP**, Shapiro P, Ernst P, *et al*. Effects of an immunostimulant agent on acute exacerbations and hospitalisations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;**156**:1719–24.
36 **Wegner RE**, Jorres RA, Kirsten DK, *et al*. Factor analysis of exercise capacity, dyspnoea ratings and lung function in patients with severe COPD. *Eur Respir J* 1994;**7**:725–9.

LUNG ALERT

Leukotriene receptors are overexpressed in aspirin sensitive asthmatics

▲ Sousa AR, Parikh A, Scadding G, *et al*. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. *N Engl J Med* 2002;**347**:1493–9

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 $CysLT_1$.

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 $CysLT_1$ (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 $CysLT_1$ receptor compared with placebo.

This study raises intriguing questions about the pathogenesis of aspirin sensitive syndromes, providing evidence for overexpression of the $CysLT_1$ 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 $CysLT_1$ expression in inflammatory cells in the upper and lower airway.

S Jenkins
Huw.Jenkins@meht.nhs.uk