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RISK FACTORS OF HOSPITALISATION FOR A COPD EXACERBATION: A PROSPECTIVE STUDY

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ABSTRACT

The association between admission for a COPD exacerbation and a wide range of modifiable potential risk factors, after adjusting for sociodemographic and clinical factors, was assessed. A total of 340 COPD patients recruited during an admission in four tertiary hospitals in the Barcelona area, Spain, were followed for a mean period of 1.1 years. During the follow-up, 63% of patients were admitted at least once, and 29% died. 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. A Cox proportional hazards model was used to obtain independent relative risks of COPD admission. The final multivariate model included the following risk factors: having had 3 or more COPD admissions in the year prior to recruitment (HR=1.66; 95% CI=1.16-2.39), percentage of predicted FEV₁ (0.97, 0.96-0.99), PO₂ level (0.98, 0.97-1.00), being controlled by a pulmonologist rather than by a general practitioner (1.66, 0.98-2.80), taking anticholinergics (1.81, 1.11-2.94), and high levels of usual physical activity compared to low levels (0.54, 0.34-0.86). *Posthoc* analysis strongly suggested that results for factors related to medical care could have been subjected to bias by indication due to the occurrence of previous admissions. This is the first study showing a strong association between usual physical activity and reduced risk of COPD admission, which is potentially relevant for rehabilitation and other therapeutical strategies.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the worldwide leading causes of disability and mortality, and is expected to become the 3rd cause of death and the 5th of disability-adjusted life years in 2020(1). Patients with COPD may suffer recurrent exacerbations, with a worsening of symptoms and lung function that is not recovered in a small proportion of patients(2). Moreover, COPD exacerbation is associated with an impairment of quality of life(3), a reduced survival(4), and a high health care expenditure(5). Prevention of exacerbations is, therefore, an important goal in the management of stable COPD(6), although the knowledge about which factors relate to COPD exacerbation is at present very limited(7). While influenza vaccination has been shown to reduce the risk of admission in elderly subjects with chronic lung disease(8), results are still controversial for respiratory rehabilitation(9) and inhaled corticosteroids(10). The effect on COPD exacerbation 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 experimental nor observational studies.

In the EFRAM project, we previously performed a case-control study to identify risk factors of COPD exacerbation, 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 hard to completely avoid in this type of study(12), we followed prospectively the 340 COPD patients recruited in the framework of the EFRAM study(13). The objective was to assess the association between admission 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 1 out of 2 patients hospitalized or remaining in the emergency room for at least 18 hours for a COPD exacerbation in four tertiary hospitals in the Barcelona area

over 1 year (from May 1, 1997 to April 30, 1998) was identified. Patients were allowed to enter the study as many times as they were hospitalized during the recruitment period, giving 346 individuals with 404 admissions. In patients with more than one admission, the first one was selected as the beginning for the follow-up study. 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 exacerbation was obtained by an extensive bibliographic search that has been detailed elsewhere(13). A list 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 built(11).

During the recruitment hospitalization, patients were asked to complete a questionnaire. Most of its content was obtained from previously validated instruments, while some questions were developed and pilot tested. In addition, weight, height and tricipital skin-fold thickness were measured, and a sputum sample was collected during the first 48 hours after admission. At least three months after hospitalization, and during a clinically stable period of COPD, patients performed a forced spirometric test and provided arterial blood to measure gas pressures. Detailed information about all variables, sources of questions, methods for spirometry and blood gas measures, and collection and processing of sputum samples is available in previous papers(11),(13) and in the Journal's Online-Only Repository.

Follow-up

Follow up comprised the period between the day of discharge after the recruitment for the cross-sectional-EFRAM study and May 1st, 1999, or the day of death, if before. Those patients who did not survive the recruitment admission were not included in the follow-up (n=6 (1,7%)). There were no losses to follow-up.

Information on hospitalizations was obtained from the Minimum Basic Dataset (CMBD), a national administrative database that is monitored with high quality standards(14). The primary study outcome was the time to hospitalization for a COPD exacerbation. An

admission due to COPD exacerbation was defined according to criteria of the expert consensus of the ATS(15). With the purpose of including all COPD exacerbations, even accepting the possibility of false positives, we used main and secondary discharge diagnoses, according to the International Classification of Diseases, 9th revision. The following diagnosis codes defined *a priori*, were included: (1) 490-496 (COPD group), 480-486 (pneumonia), 487 (influenza) and 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 second diagnosis; and (3) 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 were the second diagnosis.

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 to 1999. Additional institutional ethical approval for the linkage was obtained. Fields used for linkage were full name, sex and date of birth, as described elsewhere(16). For people not contacted in the phone interview and not registered as dead in the Mortality Registry, the presence of a doctor's visit or a hospital admission after May 1st 1999 permitted identifying them as alive.

Statistical analysis

To obtain independent relative risks of COPD admission, time from recruitment to first event was used as the outcome variable in a Cox proportional hazards model(17). First, sociodemographic and clinical variables were assessed, and those with an independent statistically significant association with admission provided a *clinical model*. Second, the individual association between all potential risk factors and admission, adjusted by the variables of the *clinical model*, was estimated. Those factors considered *a priori* as clinically relevant, those with a p-value<0.25 after adjusting for the *clinical model*, and those with high (>2) or low (<0.5) HR after adjusting for the *clinical model*(18) were defined as relevant variables. Then, a multivariate model was built including all relevant variables, until the final most parsimonious model was fitted. Poisson regression was used as a second approach to obtain relative risks of COPD admission, modeling the individual number of hospitalizations, and including the logarithm of the individual person-days at risk as the offset. The analysis was performed with Stata, release 6.0 (StataCorp, 1999, College Station, TX, USA).

RESULTS

Three hundred and forty patients were followed during a mean period of 1.1 years, of whom 63% were admitted at least once during the follow-up period, and 29% deceased (table 1). Twenty-eight individuals (8%) died without having an admission during the follow-up period and were excluded from the study of risk factors for a COPD admission. The excluded patients were older (74 vs. 69 years, $p=0.003$) and slightly thinner (body mass index (BMI) 24 vs. 26 kg/m^2 , $p=0.070$) than the remaining patients.

Among all sociodemographic and clinical variables, having had 3 or more COPD admissions in the year prior to recruitment, having had 3 or more COPD emergency room visits without admission in the year prior to recruitment, a lower percentage of predicted FEV₁ and a lower level of PO₂ were independently related to a higher risk of admission for a COPD exacerbation, and constituted the *clinical model* (Table 2). The individual associations between each of the potential risk factors and admission were obtained after adjusting for the *clinical model*. The only variables that showed a statistically significant reduced risk of admission were a high level of usual physical activity and a better physical quality of life. Being enrolled in a team-based primary care center was associated with a lower risk of COPD admission although it did not reach statistical significance. By contrast, the following variables were associated to a statistically significant increased risk of admission: being controlled by a pulmonologist, being admitted in hospitals 2 and 3, taking anticholinergics, taking oral corticosteroids, and being exposed to passive smoking among ex-smokers. Influenza vaccination, respiratory rehabilitation and long-term oxygen therapy were also associated with a higher risk of COPD admission, without achieving statistical significance.

In a final multivariate model, a high level of usual physical activity was associated to a 46% reduction of risk of a COPD admission whereas having had 3 or more COPD admissions in the year prior to recruitment, a lower percentage of predicted FEV₁, a lower level of PO₂, being controlled by a pulmonologist and taking anticholinergics were related to an increased risk (table 3). Results with Poisson regression, allowing inclusion of the individual number of admissions as the outcome showed almost identical results as the Cox model (not shown; data available from the authors).

Since the paradoxical increased risk of COPD admission among patients controlled by the pulmonologist and those taking anticholinergics could have resulted from confounding by indication of the variable “previous admissions”, a *posthoc* analysis of this potential bias was performed. At recruitment, patients who had had some previous COPD admission had a higher prevalence of factors related to medical care (anticholinergics intake, oral corticosteroids intake, influenza vaccination, respiratory rehabilitation, long-term oxygen therapy, and control by the pulmonologist) than patients who had never had a COPD admission, some of the differences being statistically significant (table 4). Table 5 shows that, in the longitudinal analysis, the positive association of such variables with further COPD admission, partially reduced its magnitude and significance when adjusted for having had 3 or more COPD admissions in the year prior to recruitment.

DISCUSSION

The most important finding of the present study is that high levels of usual physical activity were related to a reduction of the risk of COPD admission. In addition, a confounding by indication effect of the variable “previous admissions” was suspected due to the paradoxical increased risk of COPD admission among patients controlled by the pulmonologist and those taking anticholinergics.

Usual physical activity was independently related to a lower risk of COPD admission (almost a 50% reduction of risk in patients walking 60 minutes a day compared to walking 20 minutes a day), and the association did not change when adjusted for COPD severity or nutritional status factors. This is the first time that such an association has been investigated, and results are of interest since this factor seems modifiable through rehabilitation programmes(19) or doctor’s advice(15). Our results are according to the increased risk of COPD admission associated with a limited 6-minutes walking test in a previous panel of COPD patients(20), suggesting that non-deconditioned patients –independently of the way to evaluate deconditioning- have a lower risk of COPD admission. One possible explanation is based on the fact that exercise leads to a better conditioned cardiovascular system(21) that would adapt better to the increase in muscular oxygen intake that occurs during a COPD exacerbation(22). In addition, endurance training can reduce exercise-induced lactic acidosis and improve muscle oxidative capacity in patients with moderate to severe COPD(23), suggesting that such

muscles will be more able to tolerate a COPD exacerbation than not-trained muscles. Nevertheless, it is important to note that our outcome measure was COPD admission due to an exacerbation, used as a surrogate of COPD exacerbation, and the possibility that the reduction of risk is in the admission instead of in the occurrence of an exacerbation, can not be excluded.

Several factors related to medical care or prescriptions, like being controlled by a pulmonologist, taking anticholinergics, and taking oral corticosteroids, were associated with a higher risk of COPD admission in the *clinical model* adjusted analysis, contrary to what could have been expected. Our interpretation of the present results is 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(24). In our study, having had previous admissions (independently of whether the variable was included as continuous or as categorical –with different cut-off points-) was associated to both an increased rate of the prescriptions alluded to above, and to an increased risk of a COPD subsequent admission (as in previous studies(3),(11)), thus fulfilling the two conditions to be qualified as a confounder(25). Consistent with this type of bias, our data showed that, after the recruitment admission, long-term oxygen therapy (LTOT) was provided to all patients who accomplish LTOT indication criteria, with the consequence that the strong association between LTOT underprescription and COPD admission reported in the case-control analysis(11) disappeared after the follow-up. Regarding the association between previous admissions and a subsequent admission, it could be hypothesized that “previous admissions” is not a factor *per se* but an ensemble of factors that can not be measured at a particular point of time. The fact that being controlled by a pneumologist and taking anticholinergics were not totally removed after adjustment by previous admissions could be due to residual confounding(24). In the future, the study of the effects of medical care related variables will probably need randomized controlled trials instead of observational studies to avoid such biases.

Influenza vaccination is a medical care related variable that has been associated with a reduction in the risk of hospitalizations, outpatient visits and mortality in elderly patients with chronic lung disease(8), and its administration is recommended in COPD guidelines(5),(15). However, we found a positive association between influenza vaccination and risk of COPD admission in the *clinical model* adjusted analysis. One possible explanation could be that a

healthier group of COPD patients voluntarily do not attend to receive the vaccine, producing a self-selection bias. Thus, the correct interpretation of our results would not be an increased risk of COPD admission among vaccinated patients, but a reduced risk among non-vaccinated individuals probably because they have a better health status.

Exposure to environmental tobacco smoking was associated with an increased risk of COPD admission among ex-smokers in the *clinical model* adjusted analysis. There are no previous studies assessing the effect of passive smoking on COPD patients(26). Considering that in this population there is a moderate prevalence of exposure to passive smoking among non-current smokers COPD patients, and a low prevalence of advice against passive smoking(13), these results should be seen as potentially important. A better physical scale of quality of life was associated with a decreased risk of COPD admission after adjusting for the *clinical model*, as in a previous work(27). Differences among risks of COPD admission between hospitals were found in the crude and *clinical model* adjusted analysis. In fact, it would be logical that the lack of an empirical definition of COPD exacerbation(6) leads to some variability between centers. Moreover, geographic variations in hospital use both for COPD and other diseases had already been described(28).

Lower FEV₁ and lower PO₂ values were associated with a higher risk of COPD admission, as in the previous case-control-EFRAM analysis(11). Other studies have not found this association, probably due to the smaller number of subjects(20) and the use of categorized variables instead of continuous(20),(29). Interesting additional information is that FEV₁ and PO₂ were not correlated, suggesting that, in patients with low percentage of predicted FEV₁, PO₂ acts as an independent factor. Unfortunately, other physiological parameters were not measured, such as haemodynamic measurements, that have been associated with COPD admission(20), or pulmonary hyperinflation, that has been suggested as a statistical entity independent of airways obstruction in a COPD factor analysis study(30).

Longitudinal data can be analyzed 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 consistence was expected since Poisson regression could be seen as a special case of a proportional hazards model with constant baseline hazard(17).

Patients who died without having had an admission were excluded, a decision that could have introduced a degree of survival bias. However, these patients were a small proportion of the total and only showed slight differences in age and BMI. Moreover, when they were included in the analysis, using death or admission as the outcome variable, we obtained the same risk factors for COPD admission and estimates did not substantially change (data available from the authors). As patients were recruited during an admission, our results can only be extrapolated to COPD patients that have suffered previous admissions. In fact, this limitation is only a matter of generalizability and does not affect validity of results. Another potential problem of the method of recruitment is that some admissions during the follow-up may not be really new exacerbations but a relapse of the previous one. In order to avoid that, the analysis was repeated excluding those patients who's admission was within the 14 days after the previous discharge, and very similar results were obtained (data available from the authors).

This is the first study showing a strong association between usual physical activity and reduced risk of COPD admission, which is potentially relevant for rehabilitation and other therapeutical strategies. Overall, the present analysis showed consistent results with the previous case-control approach, mainly the association of COPD admission with clinical variables (previous admissions, lower FEV₁ and lower PO₂) and the lack of association for most medical care related factors (influenza and pneumococcal vaccination, respiratory rehabilitation, most drug treatments, and adherence to medication). *Posthoc* analysis strongly suggested that results for medical care related factors could have been subjected to bias by indication due to the occurrence of previous admissions, a bias that could have been present in both observational studies but was more evident in the follow-up.

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Table 1. Follow-up experience of COPD patients recruited at an admission for a COPD exacerbation.

Total number of followed individuals	340
Total days of follow-up (excluding days at hospital), m (SD)	410 (181)
Number of admissions 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 admission, median (P25-P75)	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)
Isquemic 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 to follow-up analysis, n (%)	312 (92)

m= mean; SD: standard deviation

* Individuals who died without having an admission during the follow-up period

Table 2. Crude and *clinical model* adjusted individual associations between relevant variables* and hospitalization for an exacerbation in a cohort of 312 COPD patients (Cox regression)

	Crude HR (95% CI)†	p	Adjusted HR (95% CI) by <i>clinical model</i> †	p
<i>CLINICAL MODEL</i>				
≥3 COPD admissions in the year prior to recruitment‡	2.09 (1.79-2.45)	0.000		
≥3 COPD emergency room visits without admission in the year prior to recruitment‡	1.73 (1.40-2.14)	0.000		
Percentage of predicted FEV ₁ §	0.98 (0.97-0.98)	0.000		
PO ₂ (mmHg) §	0.97 (0.97-0.98)	0.000		
<i>MEDICAL CARE</i>				
Team-based primary care‡	0.74 (0.57-0.97)	0.029	0.77 (0.56-1.07)	0.116
Controlled by a:				
General practitioner	1.00		1.00	
Pulmonologist	2.16 (1.43-3.27)	0.000	1.77 (1.07-2.92)	0.025
Hospital of recruitment:				
Hospital 1	1.00		1.00	
Hospital 2	1.88 (1.28-2.75)	0.001	1.81 (1.14-2.88)	0.012
Hospital 3	1.95 (1.32-2.88)	0.001	2.08 (1.33-3.27)	0.001
Hospital 4	1.07 (0.69-1.65)	0.761	1.19 (0.67-2.14)	0.550
<i>MEDICAL PRESCRIPTIONS</i>				
Anticholinergics‡	3.52 (2.37-5.21)	0.000	2.02 (1.26-3.24)	0.004
Oral corticosteroids‡	1.55 (1.13-2.11)	0.006	1.59 (1.07-2.37)	0.021
Influenza vaccination‡	1.37 (1.01-1.87)	0.044	1.43 (0.98-2.07)	0.064
Respiratory rehabilitation‡	1.77 (1.23-2.57)	0.002	1.32 (0.85-2.05)	0.223
Long-term oxygen therapy‡	2.36 (1.79-3.11)	0.000	1.26 (0.87-1.84)	0.224
<i>COMPLIANCE</i>				
Correctly performed essential MDI maneuvers‡	1.17 (0.88-1.56)	0.277	1.12 (0.79-1.59)	0.526
<i>LIFESTYLE</i>				
Smoking:				
Ex-smoker not exposed to passive smoking	1.00		1.00	
Ex-smoker exposed to passive smoking	1.18 (0.81-1.70)	0.387	1.63 (1.04-2.57)	0.034
Current smoker	0.58 (0.41-0.82)	0.002	0.97 (0.64-1.47)	0.876
Never smoker	0.93 (0.55-1.57)	0.781	1.20 (0.61-2.33)	0.598
Usual physical activity¶:				
<550 METs (1st tertile)	1.00		1.00	
550-1625 METs (2nd tertile)	0.73 (0.54-0.99)	0.043	0.85 (0.59-1.24)	0.400
>1625 METs (3rd tertile)	0.46 (0.32-0.68)	0.000	0.49 (0.31-0.79)	0.003
<i>OTHER</i>				
Physical scale health related quality of life§	0.97 (0.95-0.98)	0.000	0.98 (0.96-0.99)	0.007

HR: hazard ratio; CI: confidence interval; MDI: metered-dose-inhaler; MET: metabolic equivalent tax

* 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 prior to recruitment, ≥3 COPD emergency room visits without admission in the year prior to recruitment, percentage of predicted FEV₁, and PO₂.

‡ Reference categories are: <3 COPD admissions in the year prior to recruitment; <3 COPD emergency room visits without admission in the year prior to 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 maneuvers.

§ OR means change in risk for 1 percentual unit in FEV₁, 1 mmHg in PO₂ 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, e.g., 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.

Table 3. Multivariate adjusted risk factors of hospitalization for an exacerbation in a cohort of 312 COPD patients (Cox regression)

	Adjusted HR (95% CI)	p
≥3 COPD admissions in the year prior to recruitment*	1.66 (1.16-2.39)	0.006
Percentage of predicted FEV ₁	0.97 (0.96-0.99)	0.001
PO ₂ (mmHg)	0.98 (0.97-1.00)	0.024
Controlled by a:		
General practitioner	1.00	
Pulmonologist	1.66 (0.98-2.80)	0.058
Anticholinergics	1.81 (1.11-2.94)	0.017
Usual physical activity:		
<550 METs (1st tertile)	1.00	
550-1625 METs (2nd tertile)	0.87 (0.60-1.27)	0.469
>1625 METs (3rd tertile)	0.54 (0.34-0.86)	0.010

HR: hazard ratio; CI: confidence interval; MET: metabolic equivalent tax

* HR for "COPD admissions as a continuous variable" 1.19 (95% CI 1.10-1.30) p=0.000.

Table 4a. *Posthoc* analysis of bias by indication (a). At recruitment prevalence (in percentage) and 95% confidence interval of medical care related variables among patients admitted for a COPD exacerbation, according to previous COPD admissions (Logistic regression)

	Adjusted prevalence (95% CI)*	
	No previous admissions	One or more previous admissions
Controlled by general practitioner	31 (20-46)	14 (10-19)
Controlled by pulmonologist	39 (26-54)	64 (58-70)
Anticholinergics	50 (36-64)	83 (78-87)
Oral corticosteroids	14 (7-27)	24 (19-30)
Influenza vaccination	68 (53-79)	73 (67-78)
Respiratory rehabilitation	6 (2-17)	12 (8-17)
Long-term oxygen therapy	4 (1-15)	38 (31-44)

* Each line is a single model, adjusted by age and FEV₁.

Table 4b. *Posthoc* analysis of bias by indication (b). Change in the association between medical care related variables and admission for a COPD exacerbation after adjustment by severity and previous admissions in a cohort of 312 COPD patients (Cox regression)

	Crude HR (95% CI)*	Adjusted HR (95% CI) by severity*	Adjusted HR (95% CI) by indication*	Adjusted HR (95% CI) by severity and indication*
Controlled by pulmonologist	2.16 (1.43-3.27)	1.73 (1.06-2.82)	2.03 (1.33-3.33)	1.73 (1.05-2.85)
Anticholinergics	3.52 (2.37-5.21)	2.40 (1.52-3.80)	3.08 (2.06-4.60)	2.10 (1.32-3.36)
Oral corticosteroids	1.55 (1.13-2.11)	1.62 (1.14-2.32)	1.40 (1.03-1.92)	1.71 (1.19-2.44)
Influenza vaccination	1.37 (1.01-1.87)	1.28 (0.89-1.84)	1.29 (0.95-1.76)	1.35 (0.93-1.94)
Respiratory rehabilitation	1.77 (1.23-2.57)	1.38 (0.89-2.14)	1.63 (1.12-2.37)	1.28 (0.83-2.00)
Long-term oxygen therapy	2.36 (1.79-3.11)	1.61 (1.12-2.32)	2.00 (1.49-2.69)	1.38 (0.95-2.00)

HR: hazard ratio; CI: confidence interval

* Each line is a single model. *Severity* includes percentage of predicted FEV₁ and PO₂. *Indication* includes having had 3 or more COPD admissions in the year prior to recruitment.

REFERENCES

- 1 Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997;349:1498-1504.
- 2 Seemungal TAR, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:1608-1613.
- 3 Seemungal TAR, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1418-1422.
- 4 Connors AF, Dawson NV, Thomas C, Harrel FE Jr, Desbiens N, Fulkerson WJ, Kussin P, Bellamy P, Goldman L, Knaus WA. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am J Respir Crit Care Med* 1996;154:959-967.
- 5 Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, Rees J. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995;8:1398-1420.
- 6 Madison J M, Irwin RS. Chronic obstructive pulmonary disease. *Lancet* 1998;352:467-473.
- 7 Fabbri L, Beghé B, Caramori G, Papi A, Saetta M. Similarities and discrepancies between exacerbations of asthma and chronic obstructive pulmonary disease. *Thorax* 1998;53:803-808.
- 8 Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, 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;155:781-783.

- 10 Burge PS. EUROSCOP, ISOLDE and the Copenhagen city lung study [editorial]. *Thorax* 1999;54:287-288.
- 11 Garcia-Aymerich J, Monsó E, Marrades RM, Escarrabill J, Félez MA, Sunyer J, Antó JM and the EFRAM investigators. Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. EFRAM study. *Am J Respir Crit Care Med* 2001;164:1002-1007.
- 12 Pearce N, Grainger J, Atkinson M, Crane J, Burgess C, Culling C, Windom H, Beasley R. 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, Marrades RM, Morera J, Antó JM, and the EFRAM investigators. Patients hospitalized for COPD have a high prevalence of modifiable risk factors for exacerbation (EFRAM study). *Eur Respir J* 2000;16:1037-1042.
- 14 Ayala S. Análisis de la auditoría del CMBD 1993 en los hospitales del INSALUD. *Papeles Médicos* 1995;4:6.
- 15 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-S120.
- 16 Sunyer J, Antó JM, Mcfarlane D, Domingo A, Tobías A, Barceló MA, Muñoz A. 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.
- 17 Stürmer T, Glynn RJ, Kliebsch U, Brenner H. Analytic strategies for recurrent events in epidemiologic studies: background and application to hospitalization risk in the elderly. *J Clin Epidemiol* 2000;53:57-64.
- 18 Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons; 1989.

- 19 Donner CF, Lusuardi M. Selection of candidates and programmes. In: Donner CF and Decramer M, editors. Pulmonary rehabilitation. European Respiratory Monograph 13. Sheffield: European Respiratory Society Journals;2000, p.132-142.
- 20 Kessler R, Faller M, Fourgaut G, Menecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159:158-164.
- 21 Patessio A, Casaburi R, Prefault C, Folgering H, Donner C. Exercise training in chronic lung disease: exercise prescription. In: Roca J and Whipp BJ, editors. Clinical exercise testing. European Respiratory Monograph 6. Sheffield: European Respiratory Society Journals;1997, p.129-146.
- 22 Barbera JA, Roca J, Ferrer A, Felez MA, Diaz O, Roger N, Rodriguez-Roisin R. Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 1997;10:1285-1291.
- 23 Maltais F, LeBlanc P, Simard C, Jobin J, Berube C, Bruneau J, Carrier L, Belleau R. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;154:442-447.
- 24 Salas M, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. *Am J Epidemiol.* 1999;149:981-983.
- 25 Rothman KJ, Greenland S. Modern epidemiology. Philadelphia: Lippincott-Raven; 1998.
- 26 Coultas DB. Passive smoking and risk of adult asthma and COPD: and update. *Thorax* 1998;53:381-387.
- 27 Osman LM, Godden DJ, Friend JAR, Legge JS, Douglas JG. Quality of life and hospital re-admission in patients with chronic obstructive pulmonary disease. *Thorax* 1997;52:67-71.

28 Ashton CM, Petersen NJ, Soucek J, Menke TJ, Yu HJ, Pietz K, Eigenbrodt ML, Barbour G, Kizer KW, Wray NP. Geographic variations in utilization rates in Veterans Affairs hospitals and clinics. *N Engl J Med* 1999;340:32-39.

29 Collet JP, Shapiro P, Ernst P, Renzi T, Ducruet T, Robinson A, and the PARI-IS Study Steering Committee and Research Group. Effects of an immunostimulant agent on acute exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;156:1719-1724.

30 Wegner RE, Jorres RA, Kirsten DK, Magnussen H. Factor analysis of exercise capacity, dyspnoea ratings and lung function in patients with severe COPD. *Eur Respir J* 1994;7:725-729.

MEASURES

During the hospitalisation patients were asked to complete a questionnaire and anthropometric measurements were made. At least three months after hospitalisation, and during a clinically stable period of COPD, they performed a forced spirometric test and provided arterial blood to measure gas pressures. Neither spirometry nor blood gases were repeated if the results were already available within the three months prior to hospitalisation, during a period of clinical stability.

Physical examination included weight, height and tricipital skin-fold thickness. Spirometry and the bronchodilator test were measured with standard techniques(1). FEV₁ was expressed as percentage of predicted. Reference FEV₁ values were obtained from selected volunteers from the Barcelona area(2). Blood gas pressures were measured breathing room air. Cut-off points for PO₂ were taken from the guidelines for the administration of LTOT in COPD patients(3),(4).

Questionnaire

Most of the content of the questionnaire was obtained from previously validated instruments, while some questions were developed and pilot tested. Socio-demographic data, and a list of 11 chronic conditions, were obtained from questions used in health surveys in Barcelona(5). Socio-economic status was assigned according to occupation, using an adapted version of the British Registrar General's Social Classes(6). Factors related to health services were as follows: characteristics and content of visits to the physician monitoring the disease, number of hospitalisations and emergency and doctor's visits during the previous year, current pharmacological treatment, influenza and pneumococcal vaccination, pulmonary rehabilitation and long term oxygen therapy (LTOT). For most of the above, we developed an *ad hoc* questionnaire which was piloted for understanding and feasibility. COPD admissions in the previous year were self-reported by the patient and taken from the medical history. Usual medication (that is, previous to the onset of the exacerbation) was self-reported by the patient and taken from tablets and inhalers by the interviewer. It was classified as "yes/no" to the following groups of drugs: β_2 -agonists, anticholinergics, methylxanthines, inhaled and oral corticosteroids, mucolytics and antibiotics. Influenza and pneumococcal vaccinations were self-reported by the patient and taken from the vaccination card, whenever available. Rehabilitation was defined as when the patient reported doing rehabilitation exercises or respiratory gymnastics, including blowing up balloons or balls. Appropriateness of long term oxygen therapy was classified as: appropriate prescription (either "patients with PO₂≤55mmHg using LTOT" or "patients with

PO₂>60mmHg not using LTOT"), underprescription ("patients with PO₂≤55mmHg not using LTOT"), overprescription ("patients with PO₂>60mmHg using LTOT"), and doubtful prescription ("patients with PO₂=55-60mmHg", because no information was available about the presence of pulmonary hypertension, cor pulmonale, polycythaemia or nocturnal hypoxaemia). Non-compliance with LTOT was defined as when the patient reported using it less than 15 hours a day. The Medication Adherence Scale (MAS) and Inhaler Adherence Scale (IAS)(7) were short questionnaires used to measure adherence to oral and inhaled respiratory medication. They were classified in our study as: compliant (all correct answers in the scale), and non-compliant (some mistake in the scale). Inhaler compliance was measured with inhaler-specific checklists(8), and the three items considered essential for metered dose inhalers (MDI) were: "shaking before use", "inhaling slowly while simultaneously activating the canister" and "inhaling slowly throughout discharge"(8). Other exposures included: active and passive smoking(9), alcohol consumption(5), sedative consumption and physical exercise. We defined current smokers as those who had smoked during the month prior to hospitalisation. Passive smoking was defined as when somebody smoked regularly in the patient's house. Smoking was classified as follows: active smoker, ex-smoker exposed to passive smoking, ex-smoker not exposed to passive smoking, and never smoker. Questions for usual physical activity were adapted from the Spanish validation(10) of the Minnesota Leisure Time Physical Activity Questionnaire, developed to measure physical activity in the general population(11). Physical activity was quantified through the number of metabolic equivalent tax (METs) -the ratio of work metabolic rate to resting metabolic rate-(12). It is a continuous scale that includes all physical exercise that the individual practises (including walking or climbing stairs), stratified in tertiles in the present analysis for an easier interpretation of results. No physical activity was defined as when the patient did not walk, climb stairs, do any other physical exercise or attend respiratory rehabilitation. Health related quality of life (SF-12) and the mental health inventory 5-item version included in the SF-36 were measured using the validated Spanish version(13). Difficulty to take medication(14) and social support(15) were also included in the questionnaire.

Collection and processing of sputum samples (From: Monsó E, Garcia-Aymerich J, Soler N, Farrero E, Felez MA, Antó JM and Torres A, for the EFRAM investigators. Risk factors for bacterial infection in exacerbated COPD requiring admission (submitted))

The sputum sample was obtained during the first 48 hours after admission, collected in a sterile vial and processed the following hour in the microbiology laboratory of each hospital. Gram staining was performed and the sample was examined at low magnification (x100) for polymorphonuclear leukocytes and epithelial cells. Only samples with <10 epithelial cells and >25 leukocytes per field were considered suitable for culture, according to Murray-Washington criteria (16). In two patients

who did not produce sputum and for whom fiberoptic bronchoscopy was indicated (pulmonary nodule, hemoptysis) the sputum sample was obtained upon admission using a protected specimen brush (Mill-Rose Laboratories Inc., Mentor, Ohio, USA), as described elsewhere (17).

Samples suitable for culture were processed microbiologically (5% defibrinated sheep blood in Columbia base, 5% defibrinated sheep blood in Columbia base + colistin + nalidixic acid, MacConkey agar, chocolate agar, Sabouraud medium, Wilkins-Chalgren laked blood agar, and Wilkins-Chalgren laked blood agar + vancomycin + kanamycin) and accepted laboratory methods were used for bacterial identification (18). Incubation was carried out at 35 ± 2 °C in aerobic conditions. In the case of the chocolate agar culture, the atmosphere contained 5-7% CO₂. Bacteria were considered potentially pathogenic according to the criteria of Cabello et al (19). A diagnosis of bacteria-related exacerbation was established for all patients whose sputum was suitable for culture and grew one or more potentially pathogenic bacteria. For samples obtained using a protected specimen brush, bacterial cultures were considered positive only when they grew ≥ 1000 colony-forming units per milliliter of one or more potentially pathogenic bacteria.

REFERENCES

- 1 Grupo de trabajo de la SEPAR para la práctica de la espirometría en clínica. Normativa para la espirometría forzada. Ed. Doyma, Barcelona, 1985.
- 2 Roca J, Sanchis J, Agusti-Vidal A, Segarra F, Navajas D, Rodriguez-Roisin R, Casan P, Sans S. Spirometric reference values from a Mediterranean population. *Bull Eur Physiopathol Respir* 1986;22:217-24.
- 3 Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, Rees J. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995;8:1398-1420.
- 4 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-S120.
- 5 Alonso J, Antó JM. Enquesta de Salut de Barcelona 1986. Barcelona, 1989.
- 6 Alvarez-Dardet C, Alonso J, Domingo A, Regidor E. La medición de la clase social en Ciencias de la Salud. SG Editores, Barcelona, 1995.
- 7 Brooks CM, Richards JM, Kohler CL, Soong SJ, Martin B, Windsor RA, Bailey WC. Assessing adherence to asthma medication and inhaler regimens: a psychometric analysis of adult self-report scales. *Med Care* 1994;32:298-307.
- 8 Van der Palen J, Klein JJ, Kerkhoff AHM, Van Herwaarden CLA. Evaluation of the effectiveness of four different inhalers in patients with chronic obstructive pulmonary disease. *Thorax* 1995;50:1183-1187.
- 9 Burney PGJ, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7: 954-960.
- 10 Elosua R, Marrugat J, Molina L, Pons S, Pujol E. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish men. The MARATHOM investigators. *Am J Epidemiol* 1994;139:1197-1209.

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- 11 Taylor HL, Jacobs DR Jr, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chron Dis* 1978;31:741-755.
- 12 Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, Paffenbarger RS Jr. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 1993;25:71-80.
- 13 Alonso J, Prieto L, Ferrer M, Vilagut G, Broquetas JM, Roca J, Batlle JS, Anto JM. Testing the measurement properties of the Spanish version of the SF-36 Health Survey among male patients with chronic obstructive pulmonary disease. Quality of Life in COPD Study Group. *J Clin Epidemiol* 1998;51:1087-1094.
- 14 Ferrer M, Lamarca R, Orfila F, Alonso J. Comparison of performance-based and self-rated functional capacity in Spanish elderly. *Am J Epidemiol* 1999;149:228-35.
- 15 Berkman L, Leo-Summers L, Horwitz RI. Emotional support and survival after myocardial infarction. A prospective, population-based study of the elderly. *Ann Intern Med* 1992;117: 1003-1009.
- 16 Murray PR, Washington II JA. Microscopic and bacteriologic analysis of expectorated sputum. *Mayo Clin Proc* 1975; 50:339-344.
- 17 Monsó E, Ruiz J, Rosell A, Manterola J, Fiz J, Morera J, Ausina V. Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995; 152:1316-1320.
- 18 Balows A, Hausler WJ, Herrmann KL, Isenberg HD, Shadomy HJ. Manual of Clinical Microbiology. 5th ed. American Society of Microbiology. Washington D.C., 1991.
- 19 Cabello H, Torres A, Celis R, El-Ebiary J, Puig de la Bellacasa J, Xaubet A, González J, Agustí C, Soler N. Bacterial colonization of distal airways in healthy subjects and chronic lung disease: a bronchoscopic study. *Eur Respir J* 1997; 10:1137-1144.

Article 4

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RISK FACTORS FOR BACTERIAL INFECTION IN EXACERBATED COPD
REQUIRING ADMISSION.

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ABSTRACT

AIM: To examine individual characteristics as risk factors for bacteria-related COPD exacerbation. **METHOD:** Cross-sectional study of exacerbated COPD patients requiring admission who produced sputum samples for culture. Bacteria-related exacerbation was diagnosed when potentially pathogenic bacteria were cultivated from a good-quality sputum sample. Age, gender, smoking, alcohol, comorbidity, socioeconomic status (SES), lung function, body mass index, medical visits and treatment were the independent variables assessed using logistic regression modelling (OR, 95%CI). The same analysis was repeated to identify risk factors for *Pseudomonas aeruginosa* infection. **RESULTS:** Bacteria-related exacerbation was diagnosed in 57 (38.5%) out of the 148 participating COPD patients (68 SD 10 years, FEV1% 33 SD 15). Multivariable analysis showed bacteria-related exacerbations to be less prevalent among patients with better lung function (FEV1%: 0.97, 0.95-1.00) and *Pseudomonas aeruginosa* infection more prevalent in patients with low SES (8.85, 1.12-69.71). In the subsample of COPD patients who reported increase in sputum production and/or purulence in addition to impairment from dyspnea bacterial infection was significantly related to current smoking (3.66, 1.12-12.00) and poor compliance with the inhaled treatment (4.00, 1.37-11.71). In this subgroup influenza vaccination had a protective effect over *Pseudomonas aeruginosa* infection (0.16, 0.04-0.70) and the previous use of antibiotics was a risk factor for this infection (6.41, 1.39-29.53). **CONCLUSIONS:** The prevalence of bacterial infection is higher in exacerbated COPD patients with severe lung function impairment and *Pseudomonas aeruginosa* is more often recovered from patients with low SES.

Key words: COPD / Exacerbation / Risk factors/ Infection / *Pseudomonas aeruginosa*

INTRODUCTION

General population studies that have used sputum cultures to determine the etiology of bronchial exacerbations have implicated infection in more than half the cases (1). In COPD patients bacterial infection has been confirmed in 45-55% of the exacerbations when researchers have used techniques avoiding contamination of the sample by oropharyngeal secretions, such as the protected specimen brush (2-4). *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* are the most commonly cultured bacteria in this clinical context, but *Pseudomonas aeruginosa* is also a frequent cause of exacerbation in patients with severe disease (4).

Sputum samples may be contaminated by oropharyngeal secretions (5), but are considered representative of lower airway secretions when strict cytologic criteria are used for selecting the sample (6). Although sputum culture has a slightly lower sensitivity and specificity than techniques that bypass the oropharynx, it has the advantage of being widely useable, and in selected populations of exacerbated COPD patients it has diagnosed bacterial infection in a half of them (7,8).

Hospital admission of exacerbated COPD patients is likely to result as a consequence of multiple factors, including severity and treatment. However, the interaction between bronchial infection and these factors has only been sporadically investigated, and risk factors for bacteria-related exacerbation in COPD requiring admission are not known. Recent work has only found the prevalence of bacterial infection to be higher when COPD is severe (7,8). The aim of the present study was to assess a wide range of individual characteristics of COPD patients as possible risk factors for bacteria-related exacerbation in a sample of 148 patients who were part of the EFRAM study, a cross-sectional study that enrolled a systematic sample of exacerbated COPD patients requiring admission.

METHODS

Design and population

The present study of bacterial infection and COPD exacerbation included a representative part of the exacerbated COPD patients who participated in the EFRAM study in the Barcelona area (9,10). The diagnosis of COPD was established by the attending physician based on medical history, current symptoms, chest X-rays and pulmonary function tests, following the European Respiratory Society guidelines (11). Exacerbation of COPD was the first diagnosis upon admission for all cases and was established when an increase in dyspnea, in sputum production or sputum purulence was reported, as defined by Anthonisen et al (12). Patients whose chest X-ray suggested bronchiectasis or with a first diagnosis of pneumonia were not included in the study.

A sputum sample for culture was obtained as part of medical care provided to exacerbated COPD patients in the Barcelona area. The present study included all exacerbated COPD patients enrolled in the EFRAM study for whom sputum cultures were obtained <48 hours after admission and prior to antibiotic treatment. Patients who had received any type of antibiotic treatment over the week prior to admission were not included. For patients who provided more than one episode of exacerbation in the EFRAM study, only the first episode with a sputum sample available was considered. The EFRAM study was approved by the Ethics Committees of the participating centers and written consent was given by all patients.

Measures

Anthropometric data were recorded during admission and all enrolled patients were asked to complete a questionnaire including questions on sociodemography, smoking

habits, alcohol consumption, comorbidity, COPD-related medical visits within the last year, current treatments and characteristics of the exacerbation, as described elsewhere (9,10). Socioeconomic status (SES) was based on the patient's occupation, using an adapted version of the British Registrar General's Social Classes (13). Manual and unskilled laborers were classified in the low SES category. Outpatient and emergency room visits were considered non-admission COPD visits. Rehabilitation was defined as when the patient reported doing respiratory or other rehabilitation exercises. The inhalation technique was assessed using specific checklists as described elsewhere (9,14). At least three months after hospitalization and during a stable period patients performed forced spirometry and reversibility testing according to standard techniques (15). Reference values were obtained from selected volunteers from the Barcelona province (16).

The sputum sample was obtained <48 hours after admission and only samples with <10 epithelial cells and >25 leukocytes per low magnification field were considered suitable for culture (6). In two patients who did not produce sputum for whom a fiberoptic bronchoscopy was indicated (pulmonary nodule, haemoptysis) the sputum sample was obtained upon admission using a protected specimen brush (Mill-Rose Laboratories Inc., Mentor, Ohio, USA) as described elsewhere (3).

Samples suitable for culture were processed microbiologically (17) and bacteria were considered potentially pathogenic according to the criteria of Cabello et al (18). A diagnosis of bacteria-related exacerbation was established for all episodes with sputum samples growing one or more potentially pathogenic bacteria (PPB). For samples obtained using a protected specimen brush, bacterial cultures were considered positive when they grew ≥ 1000 colony-forming units per milliliter of one or more PPB.

Statistical analysis

Data were analyzed using the SPSS software package (Chicago, IL, USA). Results were expressed as absolute and relative frequencies, as means with standard deviations or as medians and interquartile ranges for variables with non-normal distribution. To check for possible selection bias, the COPD exacerbations included in the present study were first compared with the COPD exacerbations in the EFRAM study that did not fulfill the criteria to be included (chi-square, Student *t* or Mann-Whitney U tests). Bacteria-related and non-related COPD exacerbations, defined by the result of the culture obtained from the sputum sample processed (spontaneous sputum or PSB), were analyzed for associations with individual characteristics. Univariate and multivariate analyses were performed using logistic regression modelling, with the following relevant risk factors: age, gender, smoking (current or passive), alcohol consumption, comorbidity, SES (expressed as a dichotomic variables), FEV1%, FVC%, body mass index (expressed as continuous variables), COPD-related admissions within the last year (dichotomized as ≤ 2 or > 2), non-admission COPD visits (outpatient clinic or emergency room) within the last year (dichotomized as ≤ 4 or > 4) and treatments (domiciliary oxygen, corticosteroids, influenza vaccination, antibiotics within the previous three months, rehabilitation and inhalation technique). To identify possible risk factors associated with bronchial infection by *Pseudomonas aeruginosa*, the same analysis was repeated considering *Pseudomonas aeruginosa*-related exacerbation to be the outcome variable. Additionally, the association between bacterial infection and exacerbation criteria (12) was also analyzed, and the analysis of risk factors for bacteria-related COPD exacerbation was repeated after the exclusion of exacerbated patients who only reported one exacerbation criterion, under the assumption that the COPD patients with ≥ 2 exacerbation criteria are a specific population who always report an increase in sputum production and/or purulence and will have

exacerbations more closely related to infection (12,19). Results were given as crude and adjusted odds ratios (OR), with 95% confidence intervals (CI). All variables showing an association with the outcome variables ($p < 0.20$) in the univariable analysis were included in the multivariable models, and the most parsimonious model that still explained the data was accepted as the final multivariable model. All statistical tests were two-sided, and a p -value equal to or less than 0.05 was reported as statistically significant.

RESULTS

Population and microbiology

148 of the 404 (36.6%) COPD exacerbation episodes included in the EFRAM study fulfilled the inclusion criteria for the present study. The studied COPD patients had an average age of 68 years, were mostly men with a high prevalence of current smoking, and had a severe lung function impairment (average FEV1 33%) (table 1). When the COPD exacerbations in the present study were compared with the non-included COPD exacerbations that were part of the EFRAM study, only non-significant differences were found (table 1), suggesting that the sample selected for the present analysis was representative of COPD patients admitted with an exacerbation in the Barcelona area.

55 of the enrolled exacerbated COPD patients produced sputum samples with >25 leukocytes and <10 epithelial cells that grew PPB. Additionally, the 2 patients sampled with a protected specimen brush grew >1000 colony-forming units of PPB per milliliter. Overall, PPB were cultured from 57 of the 148 COPD exacerbations in the present study (38.5%). *Haemophilus influenzae* and *Pseudomonas aeruginosa* were the most commonly recovered bacteria, followed by *Streptococcus pneumoniae* and *Moraxella catarrhalis*. More than one PPB were cultured from sputum in 3 cases (table 2).

Risk factors for bacteria-related exacerbation in COPD

Several differences between the 57 exacerbated COPD patients with PPB in their sputum culture and the 91 patients without evidence of bronchial infection emerged when their individual characteristics were examined. Multivariable analysis revealed that bacteria-related exacerbations were less prevalent in patients with better lung function (FEV1%: OR 0.97, 95%CI 0.95-1.00) and patients vaccinated for influenza (OR 0.54,

95%CI 0.25-1.16), although this second association did not reach statistical significance (table 3). Furthermore, when the 21 exacerbated COPD patients with positive sputum cultures for *Pseudomonas aeruginosa* were examined, infection by this bacteria was associated with low SES (OR 8.85, 95%CI 1.12-69.71) (table 4).

Association between exacerbation criteria and bacterial infection

An increase in dyspnea was reported for most of the patients enrolled in the study (91.2%), whereas an increase in sputum and purulence were reported less frequently (54.7% and 46.3%, respectively). 90 of 148 patients (60.8%) reported two or more exacerbation criteria. Upon univariable analysis positive cultures for PPB were associated with an increase in sputum production (OR 2.23, 95%CI 1.12-4.44) and purulence (OR 1.52; 95%CI 0.78-2.96), although this latter association did not reach statistical significance. An increase in dyspnea emerged as a poor predictor of bacteria-related exacerbation (OR 0.50, 95%CI 0.16-1.58) (table 5). Because this symptom was the only reported criterion for 57 of the 58 COPD patients who reported only one exacerbation criterion (98.3%), an analysis of the subsample of exacerbated COPD patients with ≥ 2 exacerbation criteria was performed, all them reporting an increase in expectoration and/or purulence.

When the subsample of exacerbated COPD reporting ≥ 2 criteria was examined bacterial infection continued to be associated with lung function impairment (FEV1%: OR 0.96, 95%CI 0.93-1.00). However, in this subsample the previously marginal association of current smoking and ineffective inhalation with bacterial infection became statistically significant (current smoking: OR 3.66, 95%CI 1.12-12.00 / ineffective inhalation: OR 4.00, 95%CI 1.37-11.71). The association *Pseudomonas aeruginosa* infection with SES did not reach statistical significance (OR 3.81, 95%CI 0.46-31.54), whereas such infection

was significantly associated with influenza vaccination and previous antibiotic use in this subsample (influenza vaccination: OR 0.16, 95%CI 0.04-0.70 / antibiotics the previous 3 months: OR 6.41, 95%CI 1.39-29.53) (table 6).

DISCUSSION

In the present study we have found that sputum culture demonstrates bacterial infection in 38.5% of COPD exacerbations severe enough to require hospital admission. Bacteria-related exacerbations were more prevalent in COPD patients with severe lung function impairment and low SES emerged as a specific risk factor for *Pseudomonas aeruginosa* infection. For patients with ≥ 2 exacerbation criteria, who reported an increase in sputum and/or purulence in addition to impairment from dyspnea, current smoking and poor compliance with inhalation treatment were significantly associated with bacterial infection. In this population antibiotic use in the previous three months was a risk factor for *Pseudomonas aeruginosa* infection, and influenza vaccination had a protective effect.

In our study lung function was associated with bacterial infection, mainly by *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*, and a higher prevalence of positive cultures was found in patients with severe COPD (FEV1%: OR 0.97, 95%CI 0.95-1.00). Miravittles et al. (7), in a study of exacerbated COPD not requiring hospital admission, also found cultures to be positive in half of their patients for the same bacteria we recovered, and severe lung function impairment was also an independent risk factor for bacterial infection in their study. Eller et al. (8) found positive sputum cultures in 66% of the cases from a population sample of exacerbated COPD patients requiring admission, and cultivated *Pseudomonas aeruginosa* more often from patients with severe disease (11.5%) than from patients with mild COPD (3.3%). Among the wide range of clinically relevant risk factors assessed in our study low SES emerged as a significant predictor of *Pseudomonas aeruginosa* infection (OR 8.85, 95%CI 1.12-69.71), an observation that has important implications for the treatment of exacerbations in this subgroup of COPD patients. Because *Pseudomonas aeruginosa* was often cultivated from exacerbated COPD patients, as we have shown, knowing the

individual characteristics associated with the presence of this bacteria is of great importance, since this microorganism is not well covered by antibiotics currently recommended for treating COPD exacerbation. SES is known to play a role in respiratory diseases (20) and low SES, which can be associated with poor housing conditions and/or other potentially relevant factors, has been related to low lung function and to respiratory symptoms (21,22). To our knowledge, however, ours is the first study to relate SES to bronchial infection by *Pseudomonas aeruginosa* in COPD patients.

Increased dyspnea, sputum production and/or purulence are the criteria currently used to identify COPD exacerbation, and the presence of ≥ 2 of these criteria has been considered to indicate a high probability of bacterial infection (12,23). Wilson et al. (24) studied the prevalence of these three exacerbation criteria in a sample of COPD outpatients, finding that 45% reported increased dyspnea, 77% increased sputum production, and 66% purulence. The prevalence of each exacerbation criterion was clearly different in a study that included exacerbated COPD patients requiring admission, who had a higher prevalence of dyspnea (8). Our study is consistent with this observation, as we found that 92% of the studied patients reported such increase. Bacterial infection was only positively associated with increased sputum production (OR 2.23, 95%CI 1.12-4.44) and purulence (OR 1.52, 95%CI 0.78-2.96) in our study. This observation is consistent with the results of Stockley et al. (19), who found a higher prevalence of bronchial infection when a change in sputum characteristics is reported at the beginning of an episode of COPD exacerbation. These findings support the hypothesis that COPD patients reporting ≥ 2 exacerbation criteria are a specific subgroup for which bacterial infection is more closely related to the pathogenesis of the exacerbation.

We found the prevalence of bacterial infection to be lower in patients vaccinated against influenza than in non-vaccinated patients, and a non-statistically significant

protective effect of influenza vaccination against bacterial infection was found in the multivariable analysis (OR 0.54, 95%CI 0.25-1.16). That protective effect of influenza vaccination was also found in the subsample of COPD patients reporting ≥ 2 exacerbation criteria and the association became statistically significant for *Pseudomonas aeruginosa* infection (OR 0.16, 95%CI 0.04-0.70). Our results suggest that the preventive effect of influenza vaccination on respiratory diseases may be partly mediated through a decrease in the prevalence of bacteria-related COPD exacerbations, consistent with the finding that influenza is a risk factor for pneumonia (25). Unfortunately, our study does not give data about the incidence of influenza infection in the studied sample, since specific tests to detect this virus were not systematically performed.

Among the wide range of clinically relevant risk factors for infection assessed in our study some emerged as statistically significant in COPD patients with ≥ 2 exacerbation criteria, supporting the assumption that this population has specific characteristics that make them different from exacerbated COPD patients reporting only increased dyspnea, as suggested by Stockley et al. (19). In these patients current smoking (OR 3.66, 95%CI 1.12-12.00) and poor compliance with inhalation therapy (OR 4.00, 95%CI 1.37-11.71) were clearly associated with bacterial infection, and antibiotic treatment during the previous three months was related to *Pseudomonas aeruginosa* infection (OR 6.41, 95%CI 1.39-29.53). Current smoking has been said to be related to bronchial colonization by PPB (26,27) and the reported increased prevalence of *Pseudomonas aeruginosa* infection in patients who have received repeated antibiotic treatments (4) is consistent with our observations. Additionally, our findings suggest that a subset of COPD patients with poor compliance with treatment and perhaps inadequate monitoring during stable periods may be at increased risk for bacteria-related exacerbations.

The risk factors found in the present study do not apply to COPD exacerbations related to viral and atypical infections, which may cause up to 25% of the exacerbations (4), given that we did not investigate those pathogens. An additional potential limitation is the diagnosis of bacterial infection by sputum culture, which might be considered less reliable than the protected specimen brush culture. The sputum samples obtained from the patients in the present study were examined according to valid criteria, however. When a sputum sample shows >25 leukocytes and <10 epithelial cells per low magnification field (x100) it is considered to be representative of bronchial secretions, and when a sample with these cytologic characteristics grows PPB a diagnosis of bacterial infection can be established (6). Additionally, good agreement between sputum and protected specimen brush cultures in exacerbated COPD patients requiring admission has recently been reported (28). Finally, we excluded from the study those patients who had received antibiotic treatment the week previous to admission, as such therapy decreases the sensitivity and the specificity of the culture of bronchial secretions in any respiratory infection (4,29).

We conclude that the prevalence of bacteria-related exacerbation in COPD is higher in patients with severe lung function impairment and that low SES is a risk factor for *Pseudomonas aeruginosa* infection. Poor compliance with inhalation treatment is a risk factor for bacterial infection, but influenza vaccination has a protective effect.

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REFERENCES

- 1.-Macfarlane JT, Colville A, Guion A, Macfarlane RM, Rose DH. Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet* 1993; 341:511-514.
- 2.-Fagon JY, Chastre J, Trouillet JL, Domart Y, Dombret MC, Bornet M, et al. Characterization of distal microflora during acute exacerbation of chronic bronchitis. Use of the protected specimen brush technique in 54 mechanically ventilated patients. *Am Rev Respir Dis* 1990; 142:1004-1008.
- 3.-Monsó E, Ruiz J, Rosell A, Manterola J, Fiz J, Morera J, et al. Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995; 152:1316-1320.
- 4.-Soler N, Torres A, Ewig S, Gonzalez J, Celis R, El-Ebiary M, et al. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998;157:1498-1505.
- 5.-Lode H, Schaberg T, Raffenberg M, Mauch H. Diagnostic problems in lower respiratory tract infections. *J Antimicrob Chemother* 1993;32:29-37.
- 6.-Murray PR, Washington II JA. Microscopic and bacteriologic analysis of expectorated sputum. *Mayo Clin Proc* 1975; 50:339-344.
- 7.-Miravittles M, Espinosa C, Fernandez-Laso E, Martos JA, Maldonado JA, Gallego M, et al. Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. *Chest* 1999;116:40-46.
- 8.-Eller J, Ede A, Schaberg T, Niederman MS, Mauch H, Lode H. Infective exacerbations of chronic bronchitis. Relation between bacteriologic etiology and lung function. *Chest* 1998; 113:1542-1548.

- 9.-Garcia-Aymerich J, Barreiro E, Farrero E, Marrades RM, Morera J, Antó J, et al. Patients hospitalized for chronic obstructive pulmonary disease (COPD) have a high prevalence of modifiable risk factors of exacerbation - EFRAM study. *Eur Respir J* 2000; 16:1037-1042.
- 10.-Garcia-Aymerich J, Monsó E, Marrades RM, Escarrabill J, Félez MA, Sunyer J, et al. Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation – EFRAM Study. *Am J Respir Crit Care Med* 2001; 164:1002-1007.
- 11.-Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995; 8:1398-1420.
- 12.-Anthonisen NR, Manfreda J, Warren CPW, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary diseases. *Ann Intern Med* 1987;106:1302-1307.
- 13.-Alvarez-Dardet C, Alonso J, Domingo A, Regidor E. La medición de la clase social en Ciencias de la Salud. SG Editores. Barcelona. 1995.
- 14.-Van der Palen J, Klein JJ, Kerkhoff AHM, Van Herwaarden CLA. Evaluation of the effectiveness of four different inhalers in patients with chronic obstructive pulmonary disease. *Thorax* 1995; 50:1183-1187.
- 15.-Grupo de trabajo de la SEPAR para la práctica de la espirometría en clínica. Normativa para la espirometría forzada. Doyma Ed, Barcelona. 1985.
- 16.-Roca J, Sanchis J, Agustí-Vidal A, Segarra F, Navajas D, Rodríguez-Roisin R, et al. Spirometric reference values from a Mediterranean population. *Bull Eur Physiopathol Respir* 1986; 22:217-224.
- 17.-Balows A, Hausler WJ, Herrmann KL, Isenberg HD, Shadomy HJ. 1991. Manual of Clinical Microbiology. 5th ed. American Society of Microbiology. Washington D.C.

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- 18.-Cabello H, Torres A, Celis R, El-Ebiary J, Puig de la Bellacasa J, Xaubet A, et al. Bacterial colonization of distal airways in healthy subjects and chronic lung disease: a bronchoscopic study. *Eur Respir J* 1997; 10:1137-1144.
- 19.-Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000; 117:1638-1645.
- 20.-Prescott E, Vestbo J. Socioeconomic status and chronic obstructive pulmonary disease. *Thorax* 1999; 54:737-741.
- 21.-Rasmussen FV, Borchsenius L, Winslow JB. Associations between housing conditions, smoking habits and ventilatory function in men with clean jobs. *Scand J Respir Dis* 1978; 59:264-276.
- 22.-Brunekreef B. Damp housing and adult respiratory symptoms. *Allergy* 1992; 47:498-502.
- 23.-Ball P. Epidemiology and treatment of chronic bronchitis and its exacerbations. *Chest* 1995; 108:43s-52s.
- 24.- Wilson R. Outcome predictors in bronchitis. *Chest* 1995; 108: 53s-57s.
- 25.-Nichol L, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. *Ann Intern Med* 1999; 130:397-403.
- 26.-Monsó E, Rosell A, Bonet G, Manterola J, Cardon PJ, Ruiz J, et al. Risk factors for lower airway bacterial colonization in chronic bronchitis. *Eur Respir J* 1999; 13:338-342.
- 27.-Zalacaín R, Sobradillo V, Amilibia J, Barrón J, Achótegui V, Pijoan JL, et al. Predisposing factors to bacterial colonization in chronic obstructive pulmonary disease. *Eur Respir J* 1999; 13:343-348.

28.-Soler N, Torres A, Celis R, Bauer T, Sanchez M, Gonzalez J, Xaubet A. Bronchial microbial patterns in non-severe exacerbations of chronic obstructive pulmonary disease (COPD): a bronchoscopic study. *Eur Respir J* 2000; 16 (suppl 31): 332s.

29.-Montravers P, Fagon JY, Chastre J, Lecso M, Dombret MC, Trouillet JL, et al. Follow-up protected specimen brushes to assess treatment in nosocomial pneumonia. *Am Rev Respir Dis* 1993; 147:38-44.

TABLE 1.-EXACERBATED COPD. DESCRIPTIVE STATISTICS

	Sputum sample		p
	Available	Not-available	
N	148	256	
Continuous variables			
Age, m (SD)	68.0 (10.3)	69.6 (8.1)	0.10
FEV1%, m (SD) (I)	33.0 (14.9)	34.3 (15.6)	>0.20
FVC%, m (SD) (I)	52.4 (17.9)	54.3 (17.5)	>0.20
Categoric variables			
Male, n (%)	132 (89.2)	240 (93.8)	0.10
Current smoking, n (%)	34 (23.0)	70 (27.3)	>0.20
Alcohol previous two weeks, n (%)	42 (28.4)	88 (34.4)	>0.20
Two or more exacerbation criteria, n (%)	90 (60.8)	175 (68.4)	0.12
COPD hospital admissions last year (\$)	1 (0-3)	1 (0-2)	0.10
Non-admission COPD visits last year (#) (\$)	4 (2-7)	4 (2-6)	>0.20
Domiciliary oxygen, n (%)	61 (41.2)	87 (34.0)	0.15
Antibiotics previous month, n (%)	25 (16.9)	54 (21.1)	>0.20

(I) Available from 342 subjects. (#) At emergency room or outpatient clinic. (\$) Continuous variables expressed as medians (interquartile ranges), when the distribution was not normal. Comparison of the two groups using a Student *t* test, a Mann-Whitney U test or chi-square test.

TABLE 2. BACTERIOLOGY OF THE SPUTUM SAMPLE (n=148)

Sample obtained upon admission, n (%)	112 (75.7)
Sample obtained the second day after admission, n (%)	34 (23.0)
Sample obtained upon admission with protected specimen brush, n (%)	2 (1.3)
Potentially pathogenic bacteria recovered (§)	
<i>Haemophilus influenzae</i> , n (%)	17 (11.5)
<i>Streptococcus pneumoniae</i> , n (%)	13 (8.9)
<i>Moraxella catarrhalis</i> , n (%)	5 (3.4)
<i>Staphylococcus aureus</i> , n (%)	1 (0.7)
<i>Pseudomonas aeruginosa</i> , n (%)	21 (14.2)
Enteric gram negative bacilli, n (%)	3 (2.0)
Any potentially pathogenic bacteria, n (%)	57(38.5)

(§) Three cases with polymicrobial cultures (two positive for *Pseudomonas aeruginosa* and gram negative enteric bacilli, and one positive for *Streptococcus pneumoniae* and *Moraxella catarrhalis*).

TABLE 3. RISK FACTORS FOR BACTERIAL INFECTION IN COPD EXACERBATION (N=148).

n	Total	BRE	Non BRE	Crude OR(95%CI)	Adjust. OR(95%CI)	p
	148	57	91	-----	-----	
Age, m (SD)	68(10)	69(10)	67(11)	1.01 (0.98-1.05)	-----	--
Male, n (%)	132(89.2)	53(93.0)	79(86.8)	2.01 (0.62-6.57)	-----	--
Current smoking, n (%)	34(23.0)	16(28.1)	18(19.8)	1.58 (0.73-3.43)	-----	--
Passive smoking, n (%) (@)	27(18.2)	12(21.1)	15(16.5)	1.35 (0.58-3.14)	-----	--
Alcohol, previous two weeks, n (%)	42(28.4)	15(26.3)	27(29.7)	0.85 (0.40-1.78)	-----	--
Comorbidity, n (%)	135(91.2)	52 (91.2)	83(91.2)	1.00 (0.31-3.23)	-----	--
Low socioeconomic status, n (%) (\$)	104(72.7)	39(72.2)	65(73.0)	0.96 (0.45-2.05)	-----	--
FEV1%, m (SD) (l)	33(15)	30(12)	35(16)	0.98 (0.95-1.00)	0.97 (0.95-1.00)	0.04
FVC%, m (SD) (l)	52(18)	50(19)	54(17)	0.99 (0.97-1.01)	-----	--
Body mass index, m (SD)	26(6)	25(5)	26(6)	0.96 (0.90-1.02)	-----	--
COPD-related visits last year						
>2 hospital admissions, n (%)	55(37.2)	19(33.3)	36(39.6)	0.76 (0.38-1.53)	-----	--
>4 non-admiss. visits (+), n (%)	63(42.6)	18(31.6)	45(49.5)	0.47 (0.24-0.94)	0.48 (0.23-1.02)	0.06
Therapy						
domiciliary oxygen, n (%)	61(41.2)	25(43.9)	36(39.6)	1.19 (0.61-2.33)	-----	--
inhaled corticosteroids, n (%)	78(52.7)	29 (50.9)	49(53.8)	0.89 (0.46-1.72)	-----	--
influenza vaccination, n (%)	104(70.3)	35 (61.4)	69(75.8)	0.51 (0.25-1.04)	0.54 (0.25-1.16)	0.11
oral corticosteroids, n (%) (-)	38(25.7)	15 (26.3)	23(25.3)	1.05 (0.50-2.25)	-----	--
antibiotics pr.3 months, n (%)	25(16.9)	11 (19.3)	14(15.4)	1.31 (0.55-3.14)	-----	--
rehabilitation, n (%)	23(15.5)	7 (12.3)	16(17.6)	0.66 (0.25-1.71)	-----	--
ineffective inhalation, n (%)	57(38.5)	26(45.6)	31(34.1)	1.62 (0.82-3.20)	-----	--

BRE: bacteria-related exacerbation. Multivariable logistic regression modelling adjusting for FEV1% and all covariates showing association (p≤0.20). (@) In non-current smokers. (\$) Available from 143 subjects. (l) Available from 132 subjects. (+) At emergency room or outpatient clinic. (-) More than two weeks last year.

TABLE 4. RISK FACTORS FOR *Pseudomonas aeruginosa*-RELATED COPD EXACERBATION (n=148).

N	<i>P. aeruginosa</i>	No <i>P. aeruginosa</i>	CrudeOR(95%CI)	Adjust. OR(95%CI)	p
	21	127			
Age, m (SD)	70(11)	68(10)	1.03 (0.98- 1.08)	-----	--
Male, n (%)	18(85.7)	114(89.8)	0.68 (0.18- 2.64)	-----	--
Current smoking, n (%)	5(23.8)	29(22.8)	1.06 (0.36- 3.13)	-----	--
Passive smoking, n (%) (@)	4 (19.0)	23(18.1)	1.06 (0.33-3.46)	-----	--
Alcohol, previous two weeks, n (%)	7 (33.3)	35(27.6)	1.31 (0.49-3.53)	-----	--
Comorbidity, n (%)	21(100.0)	114(89.8)	-----	-----	--
Low socioeconomic status, n (%) (\$)	19(95.0)	85(69.1)	8.49 (1.10-65.7)	8.85 (1.12-69.71)	0.04
FEV1%, m (SD) (l)	29(10)	34(15)	0.97 (0.94- 1.01)	0.97 (0.93-1.01)	0.17
FVC%, m (SD) (l)	49(16)	53(18)	0.98 (0.96- 1.01)	-----	--
Body mass index, m (SD)	25(6)	26(6)	0.97 (0.89- 1.06)	-----	--
COPD-related visits last year					
>2 hospital admissions, n (%)	5(23.8)	50(39.4)	0.48 (0.17-1.40)	-----	--
>4 non-admiss. visits (+), n (%)	7(33.3)	56(44.1)	0.63 (0.24-1.68)	-----	--
Therapy					
domiciliary oxygen, n (%)	7(33.3)	54(42.5)	0.68 (0.25- 1.79)	-----	--
inhaled corticosteroids, n (%)	9(42.9)	69(54.3)	0.64 (0.25-1.60)	-----	--
influenza vaccination, n (%)	13(61.9)	91(71.7)	0.64 (0.25-1.68)	-----	--
oral corticosteroids, n (%) (-)	8(38.1)	30(23.6)	1.99 (0.75-5.25)	-----	--
antibiotics pr.3 months, n (%)	5(23.8)	20(15.7)	1.67 (0.55-5.08)	-----	--
rehabilitation, n (%)	2(9.5)	21(16.5)	0.53 (0.11-2.45)	-----	--
ineffective inhalation, n (%)	6(28.6)	51(40.2)	0.60 (0.22-1.64)	-----	--

Multivariable logistic regression modelling adjusting for FEV1% and all covariates showing association ($p \leq 0.20$). (@) In current non-smokers. (\$) Available from 143 subjects. (l) Available from 132 subjects. (+) At emergency room or outpatient clinic. (-) More than two weeks last year. (-) More than two weeks last year.

TABLE 5. ASSOCIATION BETWEEN COPD EXACERBATION CRITERIA AND BACTERIA-RELATED EXACERBATION (n=148).

n	Exacerbation criteria	Total 148	Potentially pathogenic bacteria		Crude OR(95%CI)
			present	absent	
			57	91	
	Increase in dyspnea	135 (91.2)	50 (87.7)	85 (93.4)	0.50 (0.16-1.58)
	Increase in sputum	81 (54.7)	38 (66.7)	43 (47.3)	2.23 (1.12-4.44)
	Purulent sputum	68 (46.3)	30 (52.6)	38 (42.2)	1.52 (0.78-2.96)
	Two or more criteria present	90 (60.8)	39 (68.4)	51 (56.0)	1.70 (0.85-3.41)
	Three criteria present	53 (35.8)	23 (40.4)	30 (33.0)	1.37 (0.69-2.73)
	Fever	52 (35.1)	19(33.3)	33 (36.3)	0.88 (0.44-1.76)
					>0.20
					>0.20
					>0.20
					>0.20
					>0.20
					>0.20

TABLE 6.- BACTERIAL INFECTION IN COPD WITH ≥2 EXACERBATION CRITERIA (n=90)

	Bacteria-related exacerbations		<i>P. aeruginosa</i> -related exacerbations		p
	CrudeOR(95%CI)	Adj. OR(95%CI)	CrudeOR(95%CI)	Adj. OR(95%CI)	
Age, m (SD)	1.00 (0.96-1.04)	-----	1.02 (0.96-1.09)	-----	--
Male, n (%)	0.75 (0.10-5.61)	-----	0.44 (0.04-4.61)	-----	--
Current smoking, n (%)	2.69 (0.98-7.35)	3.66 (1.12-12.00)	2.77 (0.77-9.88)	-----	--
Passive smoking, n (%) (@)	0.97 (0.36-2.61)	-----	1.79 (0.48-6.68)	-----	--
Alcohol, previous two weeks, n (%)	0.75 (0.30-1.91)	-----	1.94 (0.55-6.78)	-----	--
Comorbidity, n (%)	0.74 (0.20-2.76)	-----	-----	-----	--
Low socioeconomic status, n (%) (\$)	0.80 (0.30-2.12)	-----	3.81 (0.46-31.54)	-----	--
FEV1%, m (SD) (l)	0.97 (0.94-1.00)	0.96 (0.93-1.00)	0.98 (0.93-1.02)	0.96 (0.91-1.02)	0.19
FVC%, m (SD) (l)	0.98 (0.95-1.01)	-----	0.98 (0.94-1.02)	-----	--
Body mass index, m (SD)	1.00 (0.92-1.08)	-----	0.98 (0.87- 1.11)	-----	--
COPD-related visits last year					
>2 hospital admissions, n (%)	0.66 (0.28-1.57)	-----	0.27 (0.06-1.33)	-----	--
>4 non-admiss. visits (+), n (%)	0.38 (0.15-0.92)	-----	0.43 (0.11-1.72)	-----	--
Therapy					
domiciliary oxygen, n (%)	1.69 (0.71-4.02)	-----	0.53 (0.13- 2.13)	-----	--
inhaled corticosteroids, n (%)	0.84 (0.37-1.94)	-----	0.64 (0.19-2.21)	-----	--
influenza vaccination, n (%)	0.49 (0.20-1.23)	-----	0.25 (0.07-0.86)	0.16 (0.04-0.70)	0.01
oral corticosteroids, n (%) (-)	1.01 (0.39-2.62)	-----	2.38 (0.67-8.42)	-----	--
antibiotics pr.3 months, n (%)	2.17 (0.74-6.34)	3.06 (0.85-11.07)	3.93 (1.07-14.44)	6.41 (1.39-29.53)	0.02
rehabilitation, n (%)	0.66 (0.22-1.98)	-----	0.35 (0.04-2.94)	-----	--
ineffective inhalation, n (%)	2.08 (0.88-4.92)	4.00 (1.37-11.71)	1.14 (0.33-3.93)	-----	--

Multivariable logistic regression modelling adjusting for FEV1% and all covariates showing association ($p \leq 0.20$). (@) In current non-smokers. (\$) Available from 87 subjects. (l) Available from 81 subjects. (+) at emergency room or outpatient clinic. (-) More than two weeks last year.

RESUM GLOBAL DELS RESULTATS

Reclutament i seguiment

Durant el període maig 97-abril 98, es van seleccionar 518 episodis d'ingrés per agudització de la MPOC, dels quals 93 no van donar resposta. Es van excloure els individus que posteriorment mostraren un quocient FEV₁/FVC superior a 88% en els homes i 89% en les dones (criteris de la European Respiratory Society), els que tenien una resposta a la prova broncodilatadora superior al 15% i 200mL (criteris de la British Thoracic Society) i un pacient que posteriorment va ser diagnosticat de fibrosis pulmonar. Finalment, la població estudiada ha estat integrada per 404 episodis de prevalença (corresponents a 346ⁱⁱ individus) i 88 no-respostes (78 no-responents).

Dels 88 episodis (17% respecte al total) en que no es va obtenir resposta al qüestionari, les raons van ser: 79 rebutjos, 2 altes abans de l'entrevista i 7 morts abans de l'entrevista. Els no-responents no diferien en sexe, edat, durada de l'ingrés, percentatge de FEV₁ predit o nombre d'ingressos patits durant el període de reclutament, dels responents. En els no-responents, la proporció de casats era menor (54% vs. 72%, p=0.001), tenien menys comorbiditats (75% vs. 90%, p<0.0005) i utilitzaven més oxigenoteràpia crònica domiciliària (51% vs. 33%, p=0.004). Respecte a la prevalença de factors de risc disponibles, no es van observar diferències en el consum de tabac, alcohol o en la vacunació contra la grip.

Dels 346 responents, 126 individus complien criteris de cas. A partir dels registres hospitalaris, es van reclutar 104 controls. Van ser exclosos els que posteriorment mostraren un quocient FEV₁/FVC superior a 88% en els homes i 89% en les dones (criteris European Respiratory Society), els que tenien una resposta a la prova broncodilatadora superior al 15% i 200mL (criteris British Thoracic Society) i els que havien tingut un ingrés per agudització de la MPOC en els darrers 3 mesos. Finalment, la mostra per a l'estudi cas-control va estar formada per 86 casos i 86 controls.

Respecte al seguiment, 6 individus van morir durant l'ingrés de reclutament, de manera que 340 van ser seguits des del reclutament fins l'1 de maig de 1999.

ⁱⁱ En l'article de l'estudi de prevalença consta que es van incloure 404 episodis corresponents a 353 individus, enlloc de 346 individus (que és el nombre correcte). La raó és que en l'anàlisi de l'estudi de prevalença es va utilitzar el número d'història clínica com a variable per fer l'enllaç entre diferents episodis d'un mateix individu. Posteriorment, en procedir al seguiment dels pacients es va veure que alguns individus tenien diferents números d'història clínica en un mateix hospital. Les anàlisis de prevalença amb el model GEE es van recalculer corregint els números d'història i els resultats no canviaven en absolut. (Dades disponibles dels autors)

La recollida d'esput forma part de l'assistència mèdica habitual en els hospitals implicats a l'estudi. Per al subestudi d'infeccions es van seleccionar les mostres obtingudes en les primeres 48 hores d'estada a l'hospital en pacients que no havien rebut tractament antibiòtic en la setmana prèvia. Per als individus que havien ingressat diverses vegades durant l'estudi, es va considerar només la primera mostra. Seguint aquests criteris es van incloure un total de 148 mostres. Les característiques d'aquests individus es van comparar amb la resta dels inclosos a l'estudi de prevalença i no es van trobar diferències estadísticament significatives.

Dades descriptives

En el primer article es mostren les principals dades sociodemogràfiques i clíniques de la mostra.

De 346 individus inclosos, només 29 (8%) són dones. Un 12% dels individus tenen 2 o més ingressos al llarg de l'estudi. La mitjana d'edat és alta (69 anys). La majoria (73%) són casats. Molt pocs individus són treballadors en actiu (7%). Més de la meitat no han completat l'educació primària i més del 70% dels individus pertanyen a nivells socioeconòmics baixos (IV o V).

Dels 404 episodis, la mediana de dies ingressats per l'agudització ha estat de 9 dies. En el 64% dels episodis, els pacients declaren haver ingressat algun cop per motiu respiratori en l'últim any, amb una mitjana d'ingressos en el darrer any al voltant de 2. Durant el període anterior a l'agudització, els pacients declaren tenir cert grau de dispnea (4-5 sobre una escala de 10) que augmenta amb l'esforç (fins a gairebé 8). L'espirometria forçada i la gasometria arterial basal fetes en situació estable mostren que són pacients greus (mediana de percentatge de FEV₁ predit 31% i mitjana de PO₂ 63mmHg). En el 90% dels episodis, els pacients presenten alguna comorbiditat en una llista de 12 trastorns crònics. El valor de l'índex de massa corporal (mitjana (DE): 26 (5)) suggereix un bon estat nutricional.

Prevalença dels potencials factors de risc

El primer article mostra les proporcions (i intervals de confiança del 95%) dels potencials factors de risc d'agudització modificables, a partir d'estimacions de regressió logística. Es van utilitzar models GEE (*generalized estimating equation*) per permetre als individus amb diferents episodis contribuir amb tota la seva informació, controlant la correlació intraindividu¹⁵⁵. A més, el fet que la unitat d'anàlisi sigui l'individu i no l'episodi facilita la interpretació de resultats.

Vacunació contra la grip i el pneumococ

El 28% dels individus no es vacunen contra la grip, i el 97% no s'han vacunat contra el pneumococ.

Rehabilitació respiratòria i activitat física

El 86% dels pacients declara no haver fet rehabilitació respiratòria durant l'any anterior a l'ingrés.

Oxigenoteràpia crònica domiciliària (OCD)

Destaca que el 28% dels pacients amb $PO_2 \leq 55$ mmHg no porten oxigenoteràpia crònica domiciliària (OCD), el 88% dels quals ha tingut ingressos previs per MPOC i el 42% dels quals fuma actualment. D'altra banda, només el 18% declara que utilitza l'oxigen menys de 15 hores al dia.

Maniobra de la inhalació

El sistema d'inhalador més utilitzat és l'inhalador pressuritzat de dosis controlada (*metered-dose-inhaler* (MDI)) (88% dels episodis vs. 1% Accuhaler i 12% Turbuhaler). El 43% dels pacients falla en algun dels tres ítems essencials amb el MDI ("sacsejar l'inhalador", "inhalar a poc a poc i oprimir el nebulitzador" i "continuar una inhalació lenta i profunda"¹⁴⁸), mentre que només el 16% falla en algun dels ítems essencials del Turbuhaler. El 85% dels pacients declara haver estat ensinistrat pel personal sanitari en el maneig de l'inhalador a l'inici del seu ús, i el 80% declara que aquest maneig és revisat en les visites de control. Estratificant per edat, el grup més jove fa menys errors amb l'inhalador. Després d'ajustar per sexe, edat i gravetat de la malaltia, s'observen diferències estratificant per estat civil: el 37% dels casats fa algun error en la maniobra de la inhalació comparat amb el 57% dels no-casats (soters, vidus o divorciats) ($p=0.002$), i per educació: el 32% dels individus amb educació primària o superior fa algun error en la maniobra de la inhalació comparat amb el 51% dels individus amb menys d'educació primària ($p<0.0005$).

Tabaquisme actiu i passiu

El 26% dels pacients declara fumar actualment o haver-ho deixat en el mes anterior. Encara que el 95% havien rebut consell antitabac en l'any anterior pel metge que controla la malaltia, només el 36% declara haver rebut consell sobre la millor manera per deixar de fumar i, respecte als mètodes,

només el 17% ha rebut informació sobre tractament substitutiu amb nicotina, 13% sobre grups de fumadors i 20% sobre consultes especialitzades. En estratificar per sexe, s'observa que les dones fumen amb menys freqüència que els homes (10% vs. 27%, $p=0.038$). Entre els homes, la prevalença de fumadors actius és major en el grup més jove. Després d'ajustar per sexe i edat, la prevalença de tabaquisme actiu és menor en el grup de pacients amb malaltia més greu segons FEV₁.

El 21% dels individus actualment no-fumadors declara estar exposat al tabac per part d'altres fumadors al seu domicili. Malgrat això, només la meitat del total d'individus declara que el metge havia recomanat que ningú fumés a dins de casa.

Exposició laboral

Només el 5% del total d'individus declara estar exposat en la seva feina a vapors, gasos, pols o fums.

Consum d'alcohol i sedants

El 32% i 15% dels individus van consumir alcohol i sedants, respectivament, en les quatre setmanes anteriors a l'ingrés.

Altres troballes

No s'han trobat diferències en la prevalença d'aquests factors de risc entre els individus pertanyents a nivell socioeconòmic alt (I-III) o baix (IV-V). Tampoc s'han trobat diferències estadísticament significatives entre els pacients amb ingressos previs respecte als que no en tenien, ni entre els ingressos en els mesos d'estiu (d'abril a setembre) respecte als d'hivern (d'octubre a març).

Associació entre els potencials factors de risc i ingrés hospitalari

El segon i tercer article, encara que utilitzen dissenys i mètodes d'anàlisi diferents, responen a la mateixa qüestió: l'associació entre els potencials factors de risc d'agudització de la MPOC i l'ingrés hospitalari per aquesta causa. Per tant, els resultats d'ambdós articles els resumim i interpretem alhora en aquesta secció.

L'anàlisi cas-control compara les prevalences dels factors de risc entre el grup de malalts ingressats per agudització i els clínicament estables, obtenint raons de odds (OR) amb intervals de confiança del 95% a partir d'estimadors de regressió logística.

L'anàlisi longitudinal utilitza la regressió de Cox amb el temps des del reclutament fins a l'ingrés com a variable resultat, proporcionant raons de risc (HR) amb intervals de confiança del 95%. D'altra banda, les dades longitudinals també s'han analitzat amb regressió de Poisson, en la que la variable resultat és el nombre total d'aguditzacions per individu durant el període de seguiment. Els resultats de la regressió de Poisson són gairebé idèntics als de la regressió de Cox, i no estan inclosos a l'article.

Variabls clíniques i sociodemogràfiques

L'obstrucció al flux aeri (menor FEV₁) i la hipoxèmia (menor PO₂) s'han mostrat independentment associades de forma estadísticament significativa amb un augment del risc d'ingrés per agudització de la MPOC en ambdós anàlisis, encara que la PO₂ no es va incloure en el model final del cas-control degut a l'elevat nombre de *missings* per aquesta variable en el grup control. Ambdues variables no estan correlacionades en aquesta mostra de malalts amb MPOC.

Haver tingut ingressos previs per agudització de la MPOC també s'ha vist associada a un major risc d'ingrés, tant si la variable és expressada de forma contínua com categòrica (amb diferents punts de tall). Utilitzant la categorització d'un estudi previ⁵² (3 o més ingressos respecte a menys de 3), obtenim estimadors elevats i estadísticament significatius (OR=6.21 en el cas-control i HR=1.66 en l'estudi longitudinal).

Les visites a urgències (sense posterior ingrés) per causa respiratòria en l'any anterior s'han associat a un augment del risc d'ingressar per agudització de la MPOC en l'anàlisi bivariat d'ambdós estudis, però aquesta associació es perdia en ajustar per altres variables. Igualment, nivells més elevats d'índex de massa corporal (IMC) s'han relacionat amb una reducció del risc d'ingrés només en l'anàlisi bivariat. Les comorbiditats i les variables sociodemogràfiques no s'han associat amb el risc d'ingrés per agudització en cap de les dues aproximacions analítiques.

Variables relacionades amb l'atenció mèdica

Diverses variables relacionades amb l'atenció mèdica “correcta” (és a dir, d'acord amb les guies per al diagnòstic i tractament de la MPOC^{1,2}) han mostrat una associació positiva amb l'ingrés per agudització (per tant, contrari a l'esperat) després d'ajustar per les variables clíniques en l'anàlisi de l'estudi cas-control i, de forma més evident, en l'estudi longitudinal. Aquestes variables inclouen: ser controlat pel pneumòleg comparat amb el metge de capçalera, vacunar-se contra la grip, fer rehabilitació respiratòria, portar oxigenoteràpia crònica domiciliària (OCD), prendre corticosteroids i prendre anticolinèrgics. Aquestes troballes han fet sospitar que la variable ingressos previs juga un paper de biaix per indicació. Per a comprovar-ho, s'han fet anàlisis *posthoc* que han mostrat que haver tingut ingressos previs s'associa tant amb un augment de la prevalença d'aquests factors com amb un augment del risc d'ingrés per agudització. A més, l'associació positiva entre aquests factors i l'ingrés en l'anàlisi bivariada es redueix parcialment i redueix la significació estadística quan s'inclou la variable “ingressos previs” al model. En l'anàlisi longitudinal, però, dues d'aquestes variables mantenen l'associació positiva amb l'ingrés en el model final: ser controlat per l'especialista comparat amb el capçalera (HR=1.66) i prendre anticolinèrgics (HR=1.81).

En l'estudi cas-control s'ha trobat una forta associació entre la infraindicació d'OCD i l'ingrés (OR=22.64), que no s'ha replicat en l'anàlisi longitudinal perquè durant el seguiment es va prescriure OCD a tots aquells pacients que complien criteris d'indicació.

En l'estudi longitudinal, visitar-se en un centre d'atenció primària reformada (és a dir, basada en equips) s'ha associat negativament amb el risc d'ingrés per agudització en l'anàlisi bivariat, però l'associació deixa de ser significativa en ajustar per variables clíniques i desapareix del tot en el model final.

També en l'anàlisi longitudinal dos dels quatre hospitals han mostrat una associació positiva i estadísticament significativa amb l'ingrés, fins i tot després d'ajustar per les variables clíniques, però que no es manté en el model final.

Variables relacionades amb l'estil de vida

En l'anàlisi longitudinal hem trobat que un nivell més alt d'activitat física habitual (per exemple, caminar 1 hora al dia respecte a caminar 20 minuts) redueix un 46% el risc d'ingrés per agudització de la MPOC.

Respecte al tabac, destaquen dues troballes. Prenent com a categoria de referència els exfumadors no exposats a tabac passiu a domicili, els exfumadors sí exposats a tabac passiu a domicili mostren un augment del risc d'ingrés per agudització, només estadísticament significatiu en l'anàlisi longitudinal, encara que en cap dels anàlisis es manté en el model final. D'altra banda, els fumadors mostren en ambdós estudis una associació negativa amb l'ingrés, que, en l'estudi cas-control, es manté estadísticament significativa en el model final (OR=0.30).

Altres

Una millor puntuació en l'escala física del qüestionari de qualitat de vida relacionada amb la salut SF-36 s'ha associat negativament amb l'ingrés per agudització de la MPOC després d'ajustar per variables clíniques (de forma estadísticament significativa només en l'estudi longitudinal), encara que no s'ha mantingut en els models finals.

Associació entre factors de risc i infecció bacteriana

El quart article proporciona dades descriptives de la infecció en una submostra de malalts ingressats per agudització de la MPOC i utilitza la regressió logística per obtenir raons d'odds de l'associació entre certs factors i la infecció bacteriana.

Microbiologia

El 38.5% dels esputs obtinguts han mostrat creixement de gèrmens potencialment patògens, sent els més freqüents *Pseudomonas aeruginosa*, *Haemophilus influenzae* i *Streptococcus pneumoniae*.

Factors de risc de la infecció bacteriana

L'anàlisi multivariat dels factors de risc de la infecció bacteriana en els malalts ingressats per agudització ha mostrat que els malalts amb millor valor en el percentatge de FEV₁ predit tenen menor risc d'ingrés (OR 0.97, 95% IC 0.95-1.00). Els pacients vacunats contra la grip i els que havien acudit més de 4 vegades al metge (consultes externes o urgències) per problemes respiratoris sense haver d'ingressar en l'any anterior al reclutament, han mostrat també un menor risc d'ingrés, encara que l'associació no és estadísticament significativa. Respecte als factors associats amb la infecció per pseudomonas, el baix nivell socioeconòmic (IV-V) ha mostrat una forta associació amb

l'ingrés (OR 8.85, 1.12-69.71), i els nivells més alts de FEV₁ altra vegada s'han associat amb menor risc d'ingrés, encara que no de forma estadísticament significativa.

Quan s'ha restringit l'anàlisi al subgrup d'individus que mostraven 2 o més dels 3 criteris d'agudització (augment de dispnea, augment de la producció d'esput i purulència de l'esput⁵¹), el consum de tabac (OR 3.66), la maniobra de la inhalació incorrecta (OR 4.00) i haver pres antibiòtics en els mesos previs (OR 3.06) s'han mostrat associats a un augment del risc d'infecció bacteriana, només els dos primers de forma estadísticament significativa. Millor FEV₁ s'associa de forma estadísticament significativa amb una reducció d'aquest risc. La vacuna contra la grip i millors nivells de FEV₁ s'han relacionat amb una reducció del risc d'infecció per pseudomonas en aquest subgrup d'individus, només el primer de forma estadísticament significativa. Els pacients que havien pres antibiòtics en els darrers 3 mesos tenen significativament més risc d'infecció per pseudomonas (OR 6.41).

Criteris d'agudització i infecció bacteriana

El 91% dels pacients declara tenir un augment de la dispnea durant l'agudització, un 55% augment de la producció d'esput i un 46% l'esput purulent. L'augment de la producció d'esput s'ha associat de forma estadísticament significativa amb un augment del risc d'infecció bacteriana (OR 2.23, 1.12-4.44). En canvi, ni l'augment de dispnea, la purulència, o la suma de 2 o 3 criteris, han mostrat associació amb la infecció.

DISCUSSIÓ GLOBAL

Els resultats dels estudis i les principals limitacions metodològiques, debatuts en els articles precedents, mereixen una reflexió conjunta. L'objectiu d'aquesta "discussió global" no és repetir allò que ja s'ha dit sinó reflexionar sobre el model d'agudització de la MPOC i el mètode per estudiar-la, aspectes fonamentals i recurrents en les anàlisis i interpretacions dels resultats de l'estudi EFRAM.

Un dels reptes actuals en l'estudi de l'agudització de la MPOC és la formulació d'un model per a la seva descripció consensuat per la comunitat científica, entenent com a "model" la formalització d'una teoria o situació causal obtinguda a partir de dades observacionals¹⁵⁶. L'absència d'aquest marc conceptual dificulta actualment l'estudi de l'agudització de la MPOC i la comparabilitat dels resultats dels treballs existents. Diversos articles, editorials i iniciatives internacionals coincideixen en la conveniència de plantejar un model d'agudització de la MPOC en termes de definició, classificació i etiologia. Aquesta secció ofereix una revisió de diversos treballs que han proposat definicions i/o classificacions de l'agudització, o que han estudiat la seva etiologia. L'elaboració d'un model complet seria el pas següent, però excedeix els objectius d'aquesta discussió.

Respecte a la metodologia per estudiar l'agudització de la MPOC, al llarg de l'estudi EFRAM han anat sorgint discussions sobre diversos aspectes. Aquesta secció fa èmfasi en la selecció dels malalts, per la seva transcendència en la interpretació dels resultats. L'experiència aportada per aquest treball de recerca permet formular algunes propostes útils per a posteriors estudis amb malalts amb MPOC reclutats durant un ingrés hospitalari.

Model d'agudització de la MPOC

L'any 1996, la revisió bibliogràfica sobre l'agudització de la MPOC (prèvia a l'elaboració del protocol del projecte EFRAM), posava de manifest la poca recerca existent sobre la malaltia i, en concret, sobre l'agudització. L'agudització de la MPOC, tot i ser un terme freqüentment utilitzat en la pràctica clínica, no apareixia en les guies per al diagnòstic i tractament de la MPOC de l'ATS¹ o l'ERS². En els anys següents, però, la MPOC i la seva agudització han emergit en les revistes mèdiques com un problema important de salut. L'any 1997, la BTS va incloure un capítol destinat a l'agudització en les seves guies per al diagnòstic i tractament de la malaltia³ i l'any 1998 es van

publicar articles i editorials en defensa de l'estudi de l'agudització^{53,69,157,158,159}, remarcant que la revisió de la literatura revela "més preguntes que respostes"⁶⁹.

Definició de l'agudització de la MPOC

Les guies per al diagnòstic i tractament de la MPOC defineixen l'agudització en termes diversos, coincidint, però, en entendre l'agudització com un empitjorament de la situació clínica (prèviament estable), que es manifesta amb augment i/o aparició de símptomes respiratoris^{1,2,3}. Aquesta no és, però, una definició operativa útil per als estudis epidemiològics, que defineixen l'agudització de la MPOC en funció d'un llistat de símptomes o a partir d'indicadors d'utilització de serveis sanitaris (visites a consultes externes, urgències o hospitalització), tant en assajos clínics com estudis observacionals.

Un article recent proposa una definició d'agudització, consensuada en una reunió d'experts europeus i dels Estats Units: "empitjorament mantingut de la situació del pacient, des de l'estabilitat clínica i més enllà de les variacions diàries normals, que és aguda a l'inici i requereix canvis en la medicació habitual en un pacient amb MPOC subjacent"¹⁶⁰. De moment no hem trobat estudis publicats que hagin utilitzat aquesta definició.

Cal remarcar, per altra banda, la dificultat d'assolir una definició consensuada i alhora operativa de l'agudització de la MPOC degut a les seves pròpies característiques. El fet de presentar-se en pacients amb símptomes variables inter i intraindividu dificulta la definició de l'esdeveniment en termes "absoluts" (per exemple, quantificació de símptomes o signes).

Classificació de l'agudització de la MPOC

Anthonisen i cols⁵¹, en un assaig aleatori controlat (antibiòtics vs. placebo) van classificar les aguditzacions dels pacients inclosos al seu estudi en tres grups: tipus I (augment de dísnea, volum de l'esput i purulència de l'esput), tipus II (dos dels tres símptomes anteriors) i tipus III (un dels tres símptomes anteriors més almenys un símptoma menor: infecció respiratòria de vies altes en els darrers 5 dies, febre, augment de sibilàncies, augment de tos, i augment de freqüència respiratòria o cardíaca en un 20%). Aquests criteris, també anomenats criteris de Winnipeg, s'han utilitzat posteriorment en molts estudis per definir o classificar l'agudització, tot i estar sotmesos a la percepció individual, diferències culturals o a diferències segons el lloc de reclutament dels pacients^{108,161}. Aquesta classificació ha demostrat no ser útil per a mesures de pronòstic, com les

recaigudes de l'agudització o la mortalitat¹⁶¹. En canvi, sí sembla útil per a reconèixer l'etiologia infecciosa de l'agudització: l'associació no descrita prèviament trobada en l'article 4 d'aquesta tesi entre la producció d'esput i el risc d'infecció bacteriana, i la relació entre la purulència de l'esput i el resultat positiu del cultiu trobada per Stockley i cols¹⁶², contribueixen a la creença que els pacients amb augment de la producció d'esput i/o purulència tenen més risc de que l'agudització sigui d'origen infeccios i, per tant, representen el grup d'aguditzats als que s'hauria d'instaurar tractament antibiòtic⁵¹.

Ball i Make⁷⁰ proposaven una classificació de l'agudització en tres estadis de gravetat basant-se en la història del pacient: (1) pacient prèviament sa; (2) pacient amb tos i esput crònics i aguditzacions poc freqüents; i (3) pacient amb aguditzacions freqüents o amb limitació crònica al flux aeri greu. Però fins al moment no s'han publicat treballs que utilitzin o validin aquesta classificació.

També ha estat proposada una classificació de l'agudització basada en la utilització de serveis sanitaris per establir la gravetat: (1) pacient que necessita un augment de la medicació però es pot controlar en el seu ambient; (2) pacient que necessita assistència mèdica; i (3) pacient que pateix deteriorament que requereix ingrés hospitalari¹⁶⁰. Fins al moment tampoc s'han publicat treballs que utilitzin o validin aquesta classificació.

Etiologia de l'agudització de la MPOC

En els termes de Rothman i Greenland¹⁶³, la causa de qualsevol efecte consisteix en un conjunt de "causes components" que actuen alhora, fins assolir la "causa suficient": *un conjunt de condicions i esdeveniments mínims que inevitablement, porta a l'efecte* (la malaltia). A més de les "causes components", s'han de tenir en compte el temps, les dosis i altres aspectes. En aquesta tesi enlloc del terme "causa" hem utilitzat el terme "factor de risc", que es pot definir com *un aspecte de comportament o estil de vida, exposició ambiental o característica hereditària que, segons l'evidència epidemiològica s'associa amb un esdeveniment relacionat amb la salut que és important prevenir*¹⁵⁶.

Durant la revisió bibliogràfica inicial, no vam identificar cap estudi destinat a conèixer quins són els factors de risc d'agudització de la MPOC. A partir de la revisió de tots els estudis identificats, i de les propostes dels investigadors participants en el projecte, vam elaborar una llista de "potencials factors de risc (o protectors)" per a estudiar-los amb profunditat en l'EFRAM.

VARIABLES SOCIODEMOGRÀFIQUES**VARIABLES CLÍNiques**

Ingressos per MPOC en l'any previ
Percentatge de FEV₁ predit
Percentatge de FEV₁/FVC predit
PO₂
PCO₂
Comorbiditats autodeclarades
Índex de massa corporal

ATENCIÓ MÈDICA

Atenció primària reformada o no reformada
MPOC controlada pel metge de capçalera o el pneumòleg

ADEQUACIÓ TERAPÈUTICA

Fàrmacs: agonistes β₂, anticolinèrgics, metilxantines,
corticoids inhalats i orals, i antibiòtics
Vacuna contra la grip i el pneumococ
Rehabilitació respiratòria
Utilització d'oxigenoteràpia crònica domiciliària (OCD)
Adequació de l'OCD

COMPLIMENT**ESTIL DE VIDA**

Tabaquisme actiu i passiu
Consum d'alcohol
Consum de sedants
Activitat física habitual (Metabolic Equivalent Tax
(METs))

INFECCIONS RESPIRATÒRIES**CONTAMINACIÓ ATMOSFÈRICA****ALTRES**

Qualitat de vida relacionada amb la salut
Estat mental
Suport social i familiar

Donat que l'agudització de la MPOC és un fenomen agut o subagut superposat a una malaltia progressiva, els potencials factors de risc poden actuar de forma crònica o com a desencadenants de l'agudització. Però no hem trobat evidències sobre els possibles mecanismes d'acció per a molts dels factors esmentats i és difícil situar la seva acció en el temps al llarg de l'evolució d'un malalt amb MPOC. És possible, a més, que alguns factors actuïn en les fases finals de la malaltia crònica, quan els individus estan més greus i per tant són més susceptibles davant qualsevol "atac", el que es coneix amb el terme *frailty*. Una darrera conseqüència d'aquesta situació és l'efecte *harvesting* descrit en els estudis sobre contaminació atmosfèrica, on es suggereix que els seus efectes es produeixen en persones que, sense la contaminació, igualment haurien mort o ingressat a l'hospital al cap de poc temps¹⁶⁴.

La llista de potencials factors de risc no inclou un ampli espectre de variables clíniques, ja que l'estudi EFRAM (promogut per l'AATM) pretenia estudiar les associacions entre diversos factors i l'agudització, després d'ajustar pels principals factors sociodemogràfics i clínics. L'estudi de Kessler i cols⁵⁶, publicat l'any 1999, que segueix 64 malalts amb MPOC durant 2 anys i mig, estava orientat directament a avaluar els factors fisiopatològics associats a l'agudització de la MPOC, i mostra, en l'anàlisi multivariat, que només la $PCO_2 > 44 \text{ mmHg}$ i la pressió de l'artèria pulmonar $> 18 \text{ mmHg}$ s'associen amb l'ingrés per agudització de forma estadísticament significativa. A la vista d'aquests resultats, caldria incorporar a la llista anterior un grup més ampli de "factors de gravetat".

Els resultats de l'estudi EFRAM, tant en l'anàlisi cas-control com el longitudinal, no presenten tantes associacions com esperàvem. Una correcta interpretació dels resultats ha d'oferir la mateixa importància a les troballes positives que a les negatives. Per primera vegada es suggereix una forta reducció del risc d'ingrés per agudització de la MPOC associada a l'activitat física habitual. Alguns factors, classificats en la introducció com a "controvertits" o "poc estudiats", s'associen amb un augment del risc d'ingrés per agudització: ingressos previs per MPOC⁵², menor FEV_1 ⁷¹ i menor PO_2 ⁵⁶. Cal destacar també la manca d'associació per a la majoria de variables relacionades amb l'atenció mèdica (vacunes de la grip i el pneumococ, rehabilitació respiratòria, la majoria de tractaments farmacològics, i compliment amb la medicació), fins i tot contrària en algun cas a resultats d'estudis experimentals¹²⁶ i observacionals¹²⁷.

Els resultats obtinguts suggereixen la conveniència d'incloure més variables fisiopatològiques entre els potencials factors de risc d'agudització de la MPOC. Aquestes variables, a més d'estar relacionades amb l'agudització, podrien estar confonent el paper d'altres factors. Així mateix, no s'haurien d'excloure els factors relacionats amb l'atenció mèdica o amb l'estil de vida fins que assajos clínics o estudis longitudinals descartin tota relació amb l'agudització després d'ajustar pels potencials confusors.

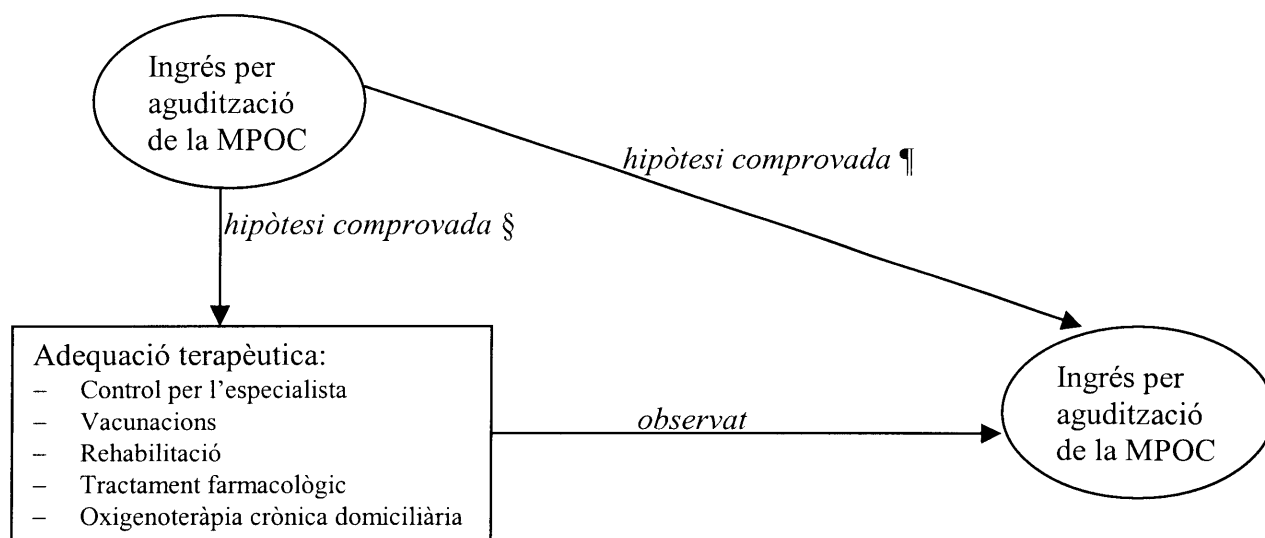
Selecció dels individus

Tots els pacients de l'estudi EFRAM van ser reclutats durant o després d'haver patit un ingrés hospitalari per agudització de la seva MPOC. Aquest fet impedeix extrapolar els resultats obtinguts a tots els individus amb MPOC, i constitueix una limitació de l'estudi. Aquesta limitació, en principi, afecta només la generalitzabilitat i no la validesa interna dels resultats de l'estudi, però

algunes troballes paradoxals podrien trobar explicació en el fet d'haver reclutat aquest tipus de malalts.

L'associació negativa entre fumar actualment i el risc d'ingrés per agudització, trobada en l'anàlisi cas-control, exemplifica aquesta circumstància. S'han descrit també altres associacions paradoxals amb el tabac i la MPOC, com la millor supervivència associada a continuar fumant en les fases finals de la malaltia^{165,166}. Anthonisen explica aquest fet suggerint que els individus amb MPOC més greu deixen de fumar de forma espontània en resposta als símptomes i discapacitat que els produeix la malaltia, i després no millora el seu estat¹¹¹. Per tal d'evitar aquests resultats caldrien estudis longitudinals amb un ventall més ampli de gravetat i una millor caracterització clínica dels individus.

Un altre cas paradoxal és el de l'associació positiva entre diverses variables relacionades amb l'atenció mèdica "correcta" i l'ingrés per agudització, observada en l'estudi cas-control i, de forma més evident, en l'estudi longitudinal. L'article 3 explica aquest efecte com un possible biaix d'indicació per part de la variable "ingressos previs". El gràfic següent esquematitza aquest concepte:



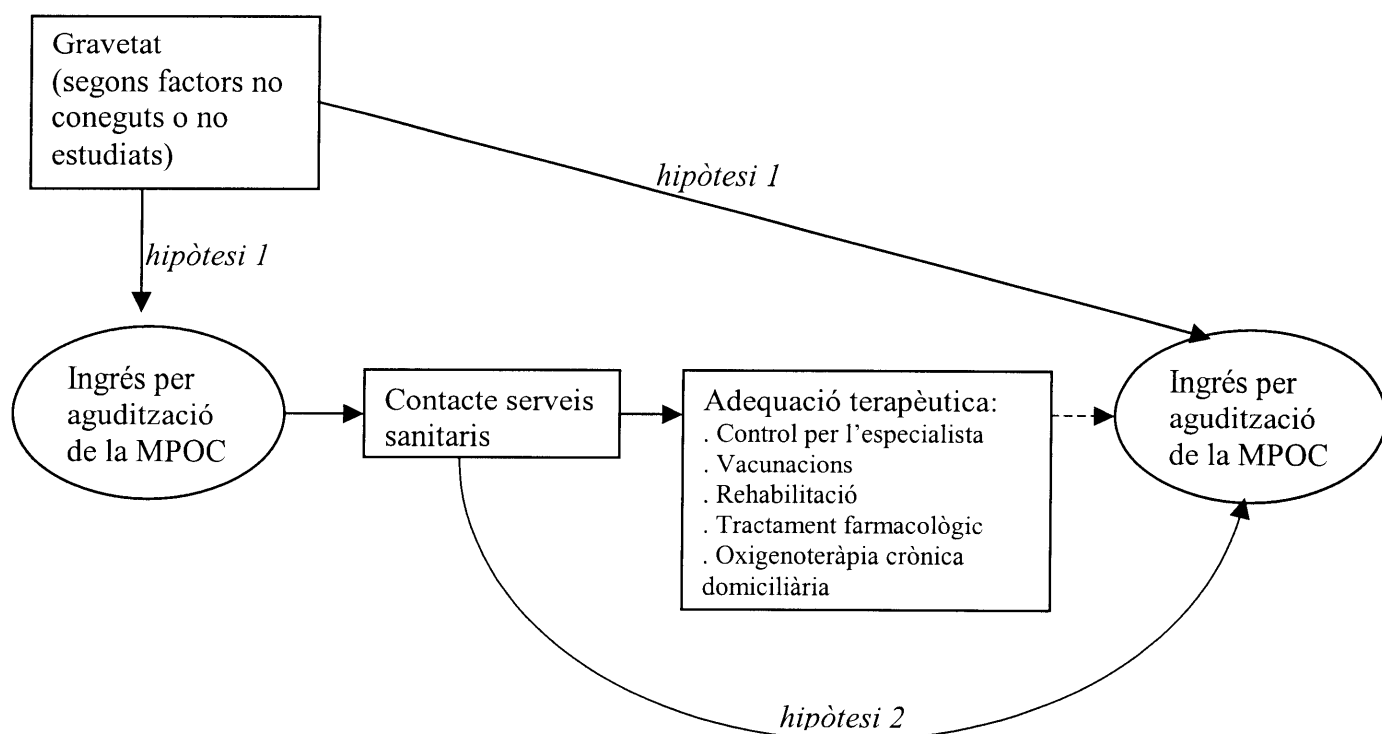
§ Taula 4a de l'article 3: haver tingut ingressos previs s'associa amb un augment de la prevalença dels factors relacionats amb l'atenció mèdica.

¶ Haver tingut ingressos previs s'associa amb un augment del risc d'ingrés per agudització en el nostre estudi (veure "Resultats", pàgina 101) i en estudis anteriors⁵².

Donat que no és plausible que "haver tingut ingressos previs" sigui un pas intermig entre aquests factors i l'ingrés per agudització, aquesta variable compleix les característiques d'una variable confusora¹⁶³.

La reducció parcial de la magnitud de l'associació positiva entre aquests factors i l'ingrés per agudització en ajustar per ingressos previs (taula 4b de l'article 3) fa més plausible la hipòtesi de variable confusora. El fet que les associacions no desapareguin totalment i que, en l'anàlisi longitudinal, dues variables mantinguin una associació positiva i estadísticament significativa en el model final pot ser degut a un biaix residual¹⁶⁷.

Tot i que les evidències sobre aquest possible efecte confusor no siguin del tot concloents, un aspecte important a considerar és el mecanisme mitjançant el qual es produiria l'associació entre haver tingut ingressos previs i reingressar. Una possible explicació és que la variable "ingressos previs" actuï com a "substitut" d'un conjunt de factors no coneguts o no mesurats. Una altra possible explicació és que els malalts amb MPOC que ingressen per agudització de la seva malaltia entren en un circuit assistencial on, paral·lelament a rebre els tractaments adequats (vacunacions, rehabilitació, tractament farmacològic, oxigenoteràpia crònica domiciliària, seguiment per l'especialista), tenen més accés a l'ingrés hospitalari com a via de tractament preferent de les seves aguditzacions. L'esquema següent mostra ambdues hipòtesis:



Així doncs, la presència d'ingressos previs per agudització de la MPOC en malalts de l'estudi ha passat de ser un criteri de restricció (per tal d'augmentar la validesa interna) a ser un important factor de risc i un possible confusor d'altres factors. De cara a estudis futurs, caldria, en primer lloc, comprovar la possible existència d'un biaix d'indicació per part de la variable "ingressos previs". Convindria, en aquest cas, emprar una mesura vàlida i fiable dels ingressos previs (incloent

informació sobre la seva gravetat). Per altra banda, els estudis destinats a avaluar factors de risc de l'agudització de la MPOC haurien de reclutar els pacients en fases incipients de la malaltia i/o amb poc (o gens) contacte amb els serveis sanitaris. A més, els estudis destinats a avaluar els efectes de factors relacionats amb l'atenció mèdica haurien de tenir en compte com a possible confusor el contacte entre els individus seleccionats i els serveis sanitaris.

Recerca futura

La necessitat d'establir un model d'agudització de la MPOC defensada en aquesta discussió i compartida també per altres autors^{53,69}, ha estat inclosa entre les recomanacions per a recerca futura sobre la MPOC de la iniciativa GOLD (*assolir un millor coneixement de la història natural de la malaltia, estudiar els mecanismes inflamatoris implicats en l'agudització, estudiar prospectivament les interaccions gen-ambient que poden actuar en l'evolució de la MPOC i classificar les aguditzacions segons la gravetat amb mesures resultat estandarditzades*, entre d'altres recomanacions)⁴. La formulació d'un model d'agudització de la MPOC acceptat pel conjunt de la comunitat científica és fonamental per millorar la qualitat i comparabilitat de la recerca sobre aquest esdeveniment i, en definitiva, per millorar la situació dels pacients amb MPOC en termes de supervivència i qualitat de vida.

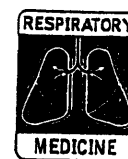
CONCLUSIONS

1. La prevalença de factors de risc d'agudització de la MPOC en pacients ingressats per aquesta causa és moderada a alta, el que suggereix un maneig insatisfactori d'aquests pacients.
 - Per als factors amb rellevància establerta sobre l'agudització, cal fer més esforços per monitoritzar i millorar els patrons d'atenció mèdica.
 - Per als factors que se sospita que són rellevants per l'agudització, les prevalences observades revelen la necessitat d'investigar el seu impacte real en l'agudització.
2. L'activitat física habitual s'associa a una reducció del risc d'ingrés per agudització de la MPOC.
3. La infraprescripció d'oxigenoteràpia crònica domiciliària (OCD) és un important factor de risc d'ingrés per agudització de la MPOC.
 - La prescripció de l'OCD als pacients en els que està indicat porta a la desaparició de l'associació entre la infraprescripció d'OCD i l'ingrés hospitalari, i posa de manifest la importància de fer un bon seguiment dels pacients després de l'ingrés per agudització.
4. Les variables clíniques indicadores de la gravetat de la malaltia, com els ingressos previs, nivells baixos de FEV₁ i nivells baixos de PO₂ es relacionen amb un augment del risc d'ingrés per agudització de la MPOC.
5. L'associació entre els factors relacionats amb l'atenció mèdica i l'ingrés per agudització és difícil d'estudiar en una mostra de pacients prèviament ingressats degut al paper confusor d'haver tingut ingressos previs per agudització de la MPOC.
6. La resta de potencials factors de risc estudiats no mostra associació amb l'ingrés per agudització de la MPOC.
7. Els nivells baixos de FEV₁ s'associen a un augment de risc d'infecció bacteriana en els pacients ingressats per agudització de la MPOC. El baix nivell socioeconòmic s'associa a un major risc d'infecció per pseudomones en aquests pacients.

8. L'absència d'un model d'agudització de la MPOC dificulta l'estudi d'aquest esdeveniment i la comparabilitat entre els treballs existents. Cal aprofundir en els coneixements sobre l'agudització, especialment en la seva etiologia, i intentar formalitzar una teoria causal.

ANNEX**Article 5**

Garcia-Aymerich J, Sunyer J, Domingo-Salvany A, Mcfarlane D, Montellà N, Pérez G, Antó JM. Differences in mortality between patients attending the emergency room services for asthma and chronic obstructive pulmonary disease. *Respir Med* 1999; 93: 822-826.



Differences in mortality between patients attending the emergency room services for asthma and chronic obstructive pulmonary disease

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Asthma has a more favourable prognosis than chronic obstructive pulmonary disease (COPD), based on studies including few asthmatics and few women with COPD. We assessed differences in mortality between people attending the emergency room for asthma and for COPD in a population-based cohort.

We recruited all the men and women, who were residents of Barcelona (Spain) over 14 years of age, who attended emergency room services for an obstructive lung disease during the period 1985-1989. Vital status was followed up to the end of 1995. A total of 15 517 individuals (including 4555 asthmatics and 2194 females with COPD) were studied. Mortality was ascertained using a record linkage with the regional Mortality Registry.

Overall, 43.6% people died during the follow-up period. Mortality was higher among individuals with COPD than with asthma, in males and females, for all causes of death, as well as for cancer, cardiovascular and respiratory causes. After adjusting for age, the relative risk (RR) of dying of a male attending for COPD and discharged home was 1.50 (1.29-1.74) in comparison with a male attending for asthma, and 3.06 (2.66-3.51) for a male attending for COPD and admitted into the hospital. Similar figures were found for females. The increased risk for patients with COPD was significantly higher than for asthma in all age groups.

Both males and females with asthma have a more favourable prognosis than patients with COPD, for all age groups.

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Introduction

It is generally accepted that patients with an obstructive lung disease have a poorer survival than expected (1) and that degree of bronchial obstruction (indicated by reduced forced expiratory volume in the first second) is a risk factor of mortality (2). Most studies on the natural history of chronic obstructive pulmonary disease (COPD) have included a preponderance of men and excluded patients with asthma (3-6). Although longitudinal studies in The Netherlands (7) and in Tucson (8) did not exclude individuals with asthma, these studies included a relatively small number of subjects with the disease and, particularly, of females with COPD. These studies reported that the overall course in patients with an asthmatic type of chronic non-specific lung disease was more favourable than in

patients with a combination of emphysematous changes and permanent bronchial obstruction (7,8).

We performed an 11-year retrospective follow-up of the vital status of a large cohort consisting of individuals attending emergency room services in Barcelona for asthma and COPD during the period 1985-89. We assessed the mortality of this cohort both in males and females, particularly the relative risk of dying among patients with COPD in comparison to patients with asthma.

Methods

Daily emergency room visits of Barcelona residents with asthma or chronic obstructive pulmonary disease (COPD), over 14 years of age, were recorded during the years 1985-1989. Data were collected from the clinical records of the four largest urban hospitals, which covered around 80% of all Barcelona asthma and COPD emergency room visits (9). The clinical records of all daily visits were reviewed and those in the diagnostics section which matched a list drawn up by a panel of chest physicians were selected. Using this information, and if necessary other data contained in the clinical records, emergency room visits were classified as

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asthma, COPD or other respiratory causes as explained elsewhere (9,10). Briefly, asthma referred to an attack of asthma, shortness of breath, or bronchospasm, whereas COPD referred to an exacerbation of chronic bronchitis or emphysema. Subjects with bronchospasm or an attack of shortness of breath and a concomitant diagnosis of COPD were classified as COPD. A reliability study of the register showed that identification of asthma emergencies was highly reliable (Kappa value, $\kappa=0.81$), as was the agreement after restriction to only individuals with asthma or COPD ($\kappa=0.91$) (9). A validity study showed that 92% of individuals classified as asthmatics were patients with asthma (unpublished data). In order to group together episodes referring to the same individual we employed a 'flexible deterministic record linkage', described elsewhere (11). Follow-up started at the first visit to emergency room services during the period 1985-89. Mortality was ascertained using a record linkage of the cohort individuals with the Catalonia Mortality Registry for the years 1985-95 (11). Fields used for linkage were full name, sex and year of birth. People not detected as dead in the Mortality Registry were considered alive at the end of the study period (31 December 1995).

All analyses were stratified by sex, due to the marked differences in diagnosis and mortality by sex. Mortality rate ratios were calculated using the person-year method. Specific mortality rates per age group were compared by diagnosis using the Poisson regression (12). The assessment of relative risks of dying by diagnosis was repeated using survival analyses (Cox regression), which allow controlling for age in a much finer way. Survival methods employed age as the time scale with staggered entry (12), using the STATA statistical package. In accordance with the study design we carried out two distinct analyses corresponding to the periods 1985-89 and 1990-95. During 1985-89, the units of analysis were the individual periods corresponding to the age spans after an individual had had a visit with a

given diagnosis and severity (discharge or referral). An individual contributed in as many individual periods as visits to emergency services. The analysis carried out in the second period allowed determination of the effect of the individual history experienced during the period 1985-89 on the hazard of death between 1990 and 1995, after restriction to individuals alive at 31 December 1989. This analysis allowed adjustment within the same subject for discordant diagnosis of asthma or COPD (13).

Results

Overall, 15 517 individuals were followed up, including 4555 who were diagnosed with asthma, 9987 of COPD (2194 females) and 975 of both diagnoses in repeated visits. The proportion of individuals diagnosed with COPD in emergency rooms increased significantly with age, coinciding with a decrease in asthma, both in males and females (Table 1). The proportion of individuals with a diagnosis of COPD was larger in males than females. The proportion of subjects who had received both diagnoses in repeated visits was not related to age, but their average number of visits per individual was higher (5.2 per individual) than among individuals always diagnosed with asthma (1.5) or COPD (1.7). Among men and women, 51% of patients were discharged home (around 60% of asthmatics and 45% of patients with COPD). Only 0.9% of males and 0.6% of females were admitted in the Intensive Care Unit (ICU).

Overall, 43.6% (6759 out of 15 517) of the individuals died during the follow-up period. Most deaths (90% in males and 65% in females) occurred among individuals with COPD. Mortality was higher among individuals with COPD than among individuals with asthma in both sexes, and this occurred at all ages, although the relative risk decreased with age in males and females (Table 1).

TABLE 1. Mortality rate due to all causes by age group, sex and diagnosis in emergency visit (Barcelona 1985-1995)

Sex	Age	Emergency visits Percent by diagnosis*		Mortality rate $\times 1000 \times$ year		COPD/Asthma ratio		
		n	COPD	Asthma	COPD	Asthma	Rate ratio [†]	Adjusted risk ratio [‡]
Male	15-44	1312	26%	70%	23.64	5.83	4.05 (2.64-6.22)	4.53 (2.47-8.30)
	45-64	3381	78%	14%	60.01	18.28	3.28 (2.56-4.20)	3.62 (2.55-5.13)
	65-74	2527	90%	5%	105.34	44.33	2.38 (1.79-3.16)	2.41 (1.63-3.54)
	>74	2698	94%	3%	174.48	106.77	1.68 (1.30-2.17)	1.60 (1.16-2.21)
Female	15-44	1384	7%	92%	12.60	2.46	5.12 (2.29-11.4)	3.20 (0.66-15.4)
	45-64	1538	24%	66%	39.47	10.55	3.74 (2.77-5.05)	4.66 (3.03-7.16)
	65-74	1100	53%	34%	72.32	29.40	2.46 (1.93-3.13)	2.91 (2.04-4.13)
	>74	1577	72%	20%	141.82	87.51	1.62 (1.40-1.88)	1.77 (1.42-2.20)

*Percentages do not sum to 100% due to the presence of subjects with both diagnoses.

[†]Rate ratio and 95% confidence intervals after exclusion of subjects with both diagnoses, using Poisson regression. Period 1985-95.

[‡]Relative risk adjusted for severity and age, using Cox regression. Period 1985-89.

Increased risk of dying among COPD patients was observed for cancer, cardiovascular and respiratory causes (Table 2). After adjusting for severity of illness at each visit, mortality remained higher in COPD patients than in asthmatics (Table 3). In addition, for the period 1985–89, the relative risk increased consistently with increasing severity of COPD. Among asthmatics, being admitted into hospital (females) and being admitted into the Intensive Care Unit (ICU) (both sexes), was associated with an increased risk of dying in comparison to being discharged home. Analysis of the period 1990–95 also showed a higher relative risk for COPD than asthma and increasing risks by severity of the COPD visit.

Discussion

Mortality was higher among subjects with COPD than with asthma, both in males and in females, and this occurred for cancer, cardiovascular and respiratory causes. As Burrows (8) has stated, the finding of important differences in survival between asthma and COPD suggests that one should not group all types of persistent airflow obstruction under the same heading. Our study included a large population of women, which allows us to extend the Burrows view to females, with sufficient confidence. In addition, our results coincide with the finding in a follow-up study of asthmatics, that a concomitant diagnosis of bronchitis increased the risk of dying in asthmatics (14). The external validity of these

findings is limited to severe patients with asthma and COPD (i.e. those needing emergency room attendance). Misclassification of diagnosis between asthma and COPD in emergency rooms may be claimed as a limiting factor in the present study. However, our register has been shown to be of high reliability and validity in terms of distinguishing COPD from asthma (9). In addition, the fact that asthma patients had a higher risk of dying due to asthma than COPD patients, gave support to the validity of the diagnosis in emergency rooms. Moreover, we used analytical methods that overcome in part problems of misclassification between asthma and COPD, since we allowed subjects to contribute to the analysis even with discrepant diagnosis at repeated visits.

We found that an emergency room visit for COPD at ages younger than 45 is already an important cause of death when comparing with asthmatics. The mortality rate ratios between our young males and females with COPD and those from the general population were 11.8 and 14.8, respectively ($P < 0.01$ in both cases). Thus, visiting an emergency service for a COPD exacerbation increased the risk of dying not only at old ages (where the rate difference between COPD and asthma was around 60 deaths per 1000 individuals per year according to Table 1), but also in young and middle age groups. At older ages, patients with asthma still had a more favourable prognosis than patients with COPD, although the relative risk of dying between COPD and asthma decreased after the age of 45 years. These changes could be due to an increased concomitance of the two entities with age, or alternatively because of a

TABLE 2. Mortality rate by cause of death and diagnosis in emergency visit

Causes	Mortality rate $\times 1000 \times$ year		COPD/Asthma age-adjusted rate ratio
	COPD	Asthma	
Male			
All	109.4	17.6	2.89 (2.51–3.24)
Cancer	21.1	4.5	2.94 (2.21–3.91)
Lung cancer	8.4	1.8	3.47 (2.22–5.40)
Cardio-vascular	27.3	3.6	1.82 (1.49–2.23)
Myocardial infarction	8.4	1.5	2.30 (1.42–3.73)
Respiratory	43.8	5.0	3.70 (2.85–4.80)
COPD	34.7	2.1	6.95 (4.68–10.3)
Asthma	0.9	1.8	0.30 (0.16–0.57)
Other	17.7	4.5	1.84 (1.37–2.48)
Female			
All	99.0	18.1	1.93 (1.70–2.18)
Cancer	8.3	2.6	1.52 (1.05–2.21)
Lung cancer	0.9	0.1	6.17 (1.11–34.1)
Cardio-vascular	39.1	6.0	2.81 (2.07–3.03)
Myocardial infarction	7.6	1.4	1.54 (1.00–2.37)
Respiratory	32.9	5.4	2.33 (1.85–2.92)
COPD	22.1	1.9	4.32 (3.05–6.12)
Asthma	2.1	2.8	0.29 (0.17–0.46)
Other	18.8	4.2	1.62 (1.24–2.13)

TABLE 3. Age adjusted mortality hazard by diagnosis and severity

Period	Variable	Male	Female
1985-1989 [†]	Asthma visit	1	1
	Asthma admission	0.98 (0.80-1.20)	1.39 (1.05-1.84)*
	Asthma ICU	2.19 (1.13-4.28)*	6.13 (2.75-13.6)*
	COPD visit	1.50 (1.29-1.74)*	1.68 (1.31-2.16)*
	COPD admission	3.06 (2.66-3.51)*	3.34 (2.68-4.16)*
	COPD ICU	4.76 (3.42-6.62)*	3.50 (1.40-8.70)*
1990-1995 [‡]	Asthma visit	1	1
	Asthma admission	0.78 (0.55-1.09)	1.22 (0.96-1.56)
	COPD visit	1.35 (1.12-1.61)*	1.35 (1.09-1.67)*
	COPD admission	1.93 (1.62-2.31)*	1.80 (1.46-2.20)*
	Number of episodes	1.04 (1.02-1.05)*	1.04 (1.02-1.06)*

[†]Episode-based analysis: death after an episode between 1985 and 1989.

[‡]Person-based analysis: death for those who survive 31/12/89 up to 1995 (77.2% of the cohort), adjusted for number of visits during the period 1985-89, % of asthma or COPD visits, and type of referral of each visit. 'Admission' includes 'admission' and 'ICU'.

* $P < 0.05$

disproportionate increase in severity of asthma with age. The possibility that a survival bias could explain such a decrease was excluded with the use of survival methods that split the follow-up time into narrower bands of time. The expected reduction of the relative risk in the oldest group due to the biological occurrence of death in all subjects did not explain the reduction of the relative risk observed in the middle age groups, as was shown in a study on the mortality effects of smoking (15).

Causes of death among COPD patients were similar to those reported by other studies, although our patients were less likely to die of lung cancer (16,17). Our asthmatic patients were more likely to die of asthma than asthmatics selected from the general population in Denmark (18), while lung cancer was a more frequent cause of death in our men than in other studies but less frequent in women (18,19). These differences, mainly in lung cancer, can be attributed to differences in smoking patterns between countries (20).

We found a decrease in the relative risk of dying between the analysis of the period 1985-89 and 1990-95. However, the two analyses are complementary but not identical. The relative risk of the first period refers to the short term risk of dying for an individual after receiving a certain diagnosis at a given visit, irrespective of the number and diagnosis of previous visits. An individual contributes in as many episodes as visits to emergency services. However, the relative risk of the second analysis, limited to those who survived to a given date, refers to the risk of dying in a longer period of time taking into account the personal history (number of visits and variation in the diagnosis within the same subject). Thus, the results of the second analysis suggest that an asthmatic with a

concomitant diagnosis of COPD was at higher risk of dying than an asthmatic without COPD, and this remained true during a long period after the visit to emergency rooms. In addition, the second analysis showed that the number of admissions (whatever the diagnosis) slightly increased the risk of death.

Our study illustrates that patients admitted for COPD in emergency services had a high mortality rate, even at young ages. Murray and López have estimated that COPD was the sixth biggest cause of death in the world in 1990, with 2.2 million deaths and will move up three places by 2020 (21). We did not have data on specific risk factors of COPD at an individual level, but since smoking accounted for 90% of COPD, we may claim for a more stringent policy against cigarette production and distribution.

In conclusion, this study with a large population of patients visited for an obstructive airways disease confirms that patients with a diagnosis of asthma have a more favourable prognosis than patients classified as COPD, and this occurred in a similar magnitude in males and females. As Burrows stated (22), it seems essential to distinguish these forms of disease in clinical and epidemiological studies on aetiology and natural history.

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References

1. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease: a prospective study of 200 patients. *N Eng J Med* 1969; **280**: 397-404.
2. Speizer FE, Fay ME, Dockery W, Ferris BG Jr. Chronic obstructive pulmonary disease mortality in six US cities. *Am Rev Respir Dis* 1989; **140**: s49-s55.
3. Jones NL, Burrows B, Fletcher CM. Serial studies of 100 patients with chronic airways obstruction in London and Chicago. *Thorax* 1967; **22**: 327-335.
4. Kanner RE, Renzetti AD Jr, Klauber MR, Smith CB, Golden CA. Variables associated with changes in spirometry in patients with obstructive lung diseases. *Am J Med* 1979; **67**: 44-50.
5. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease: a 15 year follow-up study. *Am Rev Respir Dis* 1979; **119**: 895-902.
6. Anthonisen NR, Wright EC, Hodgkin JE, IPPB Trial Group. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; **133**: 14-20.
7. Postma DS, Sluiter HK. Prognosis of chronic obstructive pulmonary disease: the Dutch experience. *Am Rev Respir Dis* 1989; **140**: s100-s105.
8. Burrows B, Bloom JW, Traver GA *et al*. The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. *N Eng J Med* 1987; **317**: 1309-1314.
9. Martínez F, Sunyer J, Antó JM. Reliability study of a monitoring system for respiratory emergency room admissions. *Eur Respir J* 1993; **6**: 337-341.
10. Antó JM, Sunyer J. Epidemiologic studies of asthma epidemics in Barcelona. *Chest* 1990; **98**: 185S-190S.
11. Sunyer J, Antó JM, Mcfarlane D, Domingo A, Tobias A, Barceló MA, Muñoz A. Sex differences in mortality of people admitted in emergency rooms for asthma and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 1998; **158**: 851-856.
12. Clayton D, Hills M. *Statistical models in epidemiology*. London: Oxford University Press, 1993.
13. Donahue JG, Muñoz A, Ness PM *et al*. The declining risk of post-transfusion hepatitis C virus infection. *N Eng J Med* 1992; **327**: 369-373.
14. Silverstein MD, Reed Ch E, O'Connell EJ, Melton LJ, O'Fallen M, Yunginger JW. Long-term survival of a cohort of community residents with asthma. *N Eng J Med* 1994; **331**: 1537-1541.
15. LaCroix AZ, Lang J, Scherr P *et al*. Smoking and mortality among older men and women in three communities. *N Eng J Med* 1991; **324**: 1619-1625.
16. Kuller LH, Ockene JK, Townsend M, Browner W, Meilahn E, Wetworth DN. The epidemiology of pulmonary function and COPD mortality in the Multiple Risk Factor Intervention Trial. *Am Rev Respir Dis* 1989; **140**: s76-s81.
17. Vilkinen S, Keistinen T, Tuuponen T, Kivela S-L. Survival and causes of death among elderly Chronic Obstructive Pulmonary Disease patients after first admission to hospital. *Respiration* 1997; **64**: 281-284.
18. Lange P, Ulrik Ch S, Vestbo J. Mortality in adults with self-reported asthma. *Lancet* 1996; **347**: 1285-1289.
19. Ulrik Ch S, Frederiksen J. Mortality and markers of risk of asthma death among 1075 outpatients with asthma. *Chest* 1995; **108**: 10-15.
20. Peto R, López AD, Boreham J, Thun M, Health CJ. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *Lancet* 1992; **339**: 1268-1278.
21. Murray ChJL, López AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997; **349**: 1498-1504.
22. Burrows B. The course and prognosis of different type of chronic airflow limitation in a general population sample from Arizona: comparisons with the Chicago COPD series. *Am Rev Respir Dis* 1989; **140**: s92-s94.

Article 6

Garcia-Aymerich J, Tobías A, Antó JM, Sunyer J. Air pollution and mortality in a cohort of patients with chronic obstructive pulmonary disease (COPD) - A time-series analysis. *J Epidemiol Community Health* 2000; 54: 73-74.

Air pollution and mortality in a cohort of patients with chronic obstructive pulmonary disease: a time series analysis

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Many studies have shown an association between current daily levels of air pollution and daily mortality by respiratory and cardiovascular causes in the general population.¹ However, the weak associations observed and the ecological nature of the exposure to air pollutants have created some doubts about plausibility of a causal relation. Specificity, which increases the plausibility of causal inference although its lack does not negate it, could be increased using a population more susceptible a priori.² Hence, we assessed the association between daily levels of air pollutants and daily mortality in a cohort of chronic obstructive pulmonary disease (COPD) patients in Barcelona for the years 1985 to 1989. We hypothesised that patients with COPD are more likely to die after increased exposure to urban air pollution than the general population.²

Methods

All patients attending emergency room services for either asthma or COPD were recruited during the years 1985 to 1989 in Barcelona. Vital status was obtained through record linkage of the people of the cohort with the Catalonia Mortality Registry for the years 1985 to 1989.³ A total of 9987 people (of the 15 517 in the initial cohort) had a diagnosis of COPD, 3245 of whom died in the period 1985 to 1989 and were used in this analysis. Cardiovascular mortality refers to codes 390 to 459 and respiratory mortality to codes 460 to 519 of the International Classification of Diseases (ICD-9).

Daily information on levels of black smoke, sulphur dioxide (SO₂), nitrogen dioxide (NO₂), ozone (O₃), temperature and relative humidity was collected from the city network.⁴

Poisson regression time series models were fitted for each pollutant (in a log-linear form)

and each different category of mortality following the APHEA methodology⁵ and adding the natural logarithm of the number of subjects at risk (that is, those still alive) as an offset. The analyses were done using Stata, release 5.0.

Results

The daily mean number of deaths was 1.8 for all causes mortality, ranging from 0 to 9, and 0.7 (0 to 5) and 0.5 (0 to 4) for respiratory and cardiovascular mortality, respectively. Levels of air pollutants have been published elsewhere.⁴

Table 1 shows the estimated association between air pollutants and mortality in our cohort compared with the estimates for the general population in Barcelona. Associations between one hour maximum of SO₂, 24 hours average of NO₂ and one hour maximum of NO₂, and mortality among COPD patients were stronger than associations obtained with the general population, mainly related to respiratory diseases.

Discussion

Daily mortality in COPD patients is related to daily levels of all six pollutants, for all, respiratory and cardiovascular causes. This association is stronger than in the general population only for peaks of SO₂ and daily means and peaks of NO₂. Particles, measured as black smoke, and daily mean of SO₂, the pollutants classically associated with mortality,⁶ showed similar or weaker associations for COPD patients than for the general population. Changes in the profile of urban air pollutants, with a currently more pronounced photochemical component, could explain in part these effects.

Caution is necessary when comparing with the general population given the small range of

Table 1 Estimated relative risks and 95% confidence limits for total, respiratory and cardiovascular mortality for an increase of 50 µg/m³ in air pollutants, in the general population and a cohort of COPD patients in Barcelona

	Black smoke 24 h	lag	SO ₂ 24 h	lag	SO ₂ 1 h	lag	NO ₂ 24 h	lag	NO ₂ 1 h	lag	O ₃ 1 h	lag
Total mortality												
general population*	1.056 1.027, 1.087	0-3	1.078 1.041, 1.116	0-3	1.013 1.004, 1.021	1	1.043 1.011, 1.076	0-3	1.017 1.006, 1.027	1	1.024 1.006, 1.042	5
COPD	1.023 0.915, 1.145	0-2	1.045 0.914, 1.193	0-2	1.036 0.999, 1.074	2	1.145 1.006, 1.304	0-2	1.023 0.975, 1.115	2	1.040 0.953, 1.134	3
Respiratory mortality												
general population*	1.051 0.975, 1.134	0-3	1.062 0.989, 1.141	0-1	1.017 0.994, 1.039	0	1.043 0.970, 1.122	0-1	1.013 0.983, 1.044	0	1.035 0.981, 1.092	5
COPD	1.071 0.903, 1.271	0-2	1.041 0.849, 1.276	0-2	1.050 0.993, 1.110	2	1.161 0.944, 1.428	0-2	1.084 1.005, 1.169	2	1.057 0.921, 1.214	3
Cardiovascular mortality												
general population*	1.059 1.019, 1.101	0-3	1.091 1.040, 1.144	0-3	1.016 1.005, 1.028	1	1.031 0.988, 1.076	0-3	1.019 1.004, 1.034	1	1.029 1.004, 1.054	1
COPD	0.908 0.733, 1.124	0-2	1.035 0.808, 1.325	0-2	1.067 0.999, 1.140	3	1.056 0.827, 1.348	0-2	1.032 0.942, 1.130	3	1.011 0.858, 1.192	3

*Partially published in reference 4.

daily deaths that led to wide confidence intervals. This also precluded an adequate fit using time series models, according to the analysis of residuals. Results did not change using generalised additive models (not shown).

Respiratory mortality showed stronger associations for COPD patients than for the general population for all pollutants excepting averages of SO₂, while cardiovascular mortality did so only for peaks of SO₂ and the two measures of NO₂. This suggests that the susceptibility of COPD patients to air pollution is mainly related to their respiratory condition.

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- 1 Zmirou D, Schwartz J, Saez M, et al. Time-series analysis of air pollution and cause-specific mortality. *Epidemiology* 1998;9:495-503.
- 2 Schwartz J. What are people dying of on high air pollution days? *Environ Res* 1994;64:26-35.
- 3 Sunyer J, Anto JM, McFarlane D, et al. Sex differences in mortality of people who visited emergency rooms for asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:851-6.
- 4 Sunyer J, Castellsague J, Saez M, et al. Air pollution and mortality in Barcelona. *J Epidemiol Community Health* 1996;50:S76-80.
- 5 Katsouyanni K, Schwartz J, Spix C, et al. Short term effects of air pollution on health: a European approach using epidemiologic time series data: the APHEA protocol. *J Epidemiol Community Health* 1996;50:S12-18.
- 6 Katsouyanni K, Touloumi G, Spix C, et al. Short-term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. *Air Pollution and Health: a European Approach*. *BMJ* 1997;314:1658-63.

REFERÈNCIES

- ¹ 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-S120.
- ² Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, Rees J. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995;8:1398-1420.
- ³ The COPD Guidelines Group of the Standards of Care Committee of the BTS. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997;52:S1-S28.
- ⁴ National Heart, Lung, and Blood Institute/World Health Organization Workshop. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available at <http://www.goldcopd.com/workshop>.
- ⁵ McConell WD, Holgate ST. The definition of asthma: its relationship to other chronic obstructive lung diseases. In: Clark TJH, Godfrey S, Lee TH, Thomsom NC, editors. *Asthma*. London: Oxford University Press, 2000. Fourth edition.
- ⁶ Pla de Salut de Catalunya 1996-1998. 1997.
- ⁷ Tirimanna PR, van Schayck CP, den Otter JJ, van Weel C, van Herwaarden CL, van den Boom G, van Grunsven PM, van den Bosch WJ. Prevalence of asthma and COPD in general practices in 1992: has it changed since 1977? *Br J Gen Pract* 1996;46:277-281.
- ⁸ Chronic obstructive pulmonary disease. Epidemiology, aetiology and natural history. In: Brewis MAL, Gibson GJ, Geddes DM, eds. *Respiratory Medicine*. London: Baillière Tindall, 1990.
- ⁹ Peto R, Lopez AD, Boreham J, Thun M, Heath CJ. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *Lancet* 1992;339:1268-1278.
- ¹⁰ Jaén A, Ferrer A, Ormaza I, Rué M, Domingo C, Marín A. Prevalencia de bronquitis crónica, asma y obstrucción al flujo aéreo en una zona urbano-industrial de Cataluña. *Arch Bronconeumol* 1999;35:122-128.
- ¹¹ Mannino DM, Brown C, Giovino GA. Obstructive lung disease deaths in the United States from 1979 through 1993. *Am J Respir Crit Care Med* 1997;156:814-818.
- ¹² Murray CJL, Lopez A. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997;349:1269-1276.
- ¹³ Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997;349:1498-1504.
- ¹⁴ Salut en xifres. Aplicacions de sèries temporals a l'estudi de les causes de mort a Catalunya 1983-93. Barcelona: Departament de Sanitat i Seguretat Social, Generalitat de Catalunya, 1995.
- ¹⁵ Bolívar B, Carrillo E, García A, Juncosa S, Martínez C. Morbiditat atesa en l'atenció primària. Informe del registre ANAC-II. 1996.

- ¹⁶ Murray CJL, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997;349:1436-1442.
- ¹⁷ Grasso ME, Weller WE, Shaffer TJ, Diette GB, and Anderson GF. Capitation, managed care, and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:133-138.
- ¹⁸ Löfdahl C-G. Cost development of obstructive airway disease in Sweden. *Eur Respir Rev* 1996;35:113-115.
- ¹⁹ Rutten-Van Mólken MPMH, Van Doorslaer EKA, Rutten FFH. Economic appraisal of asthma and COPD care: a literature review 1980-1991. *Soc Sci Med* 1992;35:161-175.
- ²⁰ Rutten Van-Molken MP, Feenstra TL. The burden of asthma and chronic obstructive pulmonary disease: data from the Netherlands. *Pharmacoeconomics* 2001;19 suppl2:1-6.
- ²¹ Gold D, Wang X, Wypij D, Speizer F, Ware J, Dockery D. Effects of cigarette smoking on lung function in adolescent boys and girls. *N Eng J Med* 1996; 335: 931-937.
- ²² Silverman EK, Chapman HA, Drazen JM, Weiss ST, Rosner B, Campbell EJ, O'Donnell WJ, Reilly JJ, Ginns L, Mentzer S, Wain J, Speizer FE. Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease. Risk to relatives for airflow obstruction and chronic bronchitis. *Am J Respir Crit Care Med* 1998;157:1770-1778.
- ²³ McCloskey SC, Patel BD, Hinchliffe SJ, Reid ED, Wareham NJ, Lomas DA. Siblings of patients with severe chronic obstructive pulmonary disease have a significant risk of airflow obstruction. *Am J Respir Crit Care Med* 2001;164:1419-1424.
- ²⁴ Redine S, Weiss ST. Genetic and perinatal risk factors for the development of chronic obstructive pulmonary disease. In: *Clinical Epidemiology of Chronic Obstructive Pulmonary Disease*. New York: Hensley MJ, 1989.
- ²⁵ Schellenberg D, Pare PD, Weir TD, Spinelli JJ, Walker BA, Sandford AJ. Vitamin D binding protein variants and the risk of COPD. *Am J Respir Crit Care Med* 1998;157:957-961.
- ²⁶ Koyama H, Geddes DM. Genes, oxidative stress, and the risk of chronic obstructive pulmonary disease. *Thorax* 1998;53:S10-S14.
- ²⁷ Siafakas NM. Microsatellite DNA instability in COPD. *Chest* 1999;116:47-51.
- ²⁸ Ishii T. Glutathione S-transferase P1 (GSTP1) polymorphism in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:693-696.
- ²⁹ Xu X, Rijcken B, Schouten JP, Weiss ST. Airways responsiveness and development and remission of chronic respiratory symptoms in adults. *Lancet* 1997;350:1431-1434.
- ³⁰ Sparrow D, O'Connor G, Weiss ST. The relation of airways responsiveness and atopy to the development of chronic obstructive lung disease. *Epidemiol Rev* 1988; 10: 29-47.
- ³¹ Rijcken B, Schouten JP, Xu X, Rosner B, Weiss ST. Airway hyperresponsiveness to histamine associated with accelerated decline in FEV1. *Am J Respir Crit Care Med* 1995;151:1377-82.

- ³² Kauffmann F, Neukirch F, Korobaeff M, Marne MJ, Claude JR, Lellouch J. Eosinophils, smoking, and lung function. An epidemiologic survey among 912 working men. *Am Rev Respir Dis* 1986;134:1172-5.
- ³³ Burrows B, Knudson RJ, Cline MG, Lebowitz MD. A reexamination of risk factors for ventilatory impairment. *Am Rev Respir Dis* 1988;138:829-36.
- ³⁴ Lange P, Parner J, Vestbo J, Jensen G, Schnohr P. A 15-year follow-up of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194-1200.
- ³⁵ Lange P, Ulrik CS, Vestbo J, Copenhagen City Heart Study Group. Mortality in adults with self-reported bronchial asthma. A study of the general population. *Lancet* 1996;347:1285-1289.
- ³⁶ Iribarren C, Tekawa IS, Sidney S, and Friedman GD. Effect of cigar smoking on the risk of cardiovascular disease, chronic obstructive pulmonary disease, and cancer in men. *N Engl J Med* 1999;340:1773-1780.
- ³⁷ Fletcher CM, Peto R, Tinker C. The natural history of chronic bronchitis and emphysema. New York: Oxford University Press, 1976.
- ³⁸ Robbins AS, Abbey DE, Lebowitz MD. Passive smoking and chronic respiratory disease symptoms in non-smoking adults. *Int J Epidemiol* 1993;22:809-17.
- ³⁹ Hanrahan JP, Tager IB, Segal MR. The effects of maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis* 1992;145:1129-1135.
- ⁴⁰ Coultas DB. Passive smoking and risk of adult asthma and COPD: an update. *Thorax* 1998;53:381-387.
- ⁴¹ Becklake MR. Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989;140(3 Pt 2):S85-91.
- ⁴² Oxman AD, Muir DCF, Shanon HS, Stock SR, Hnizdo E, Lange HJ. Occupational dust exposure and chronic obstructive pulmonary disease. A systematic overview of the evidence. *Am Rev Respir Dis* 1993;148:38-48.
- ⁴³ Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Health effects of outdoor air pollution (part 1). *Am J Respir Crit Care Med* 1996;153:3-50.
- ⁴⁴ Sunyer J. Urban air pollution and chronic obstructive pulmonary disease: a review. *Eur Respir J* 2001;17:1024-1033.
- ⁴⁵ Prescott E, Vestbo J. Socioeconomic status and chronic obstructive pulmonary disease. *Thorax* 1999;54:737-741.
- ⁴⁶ Gold DR, Tager IB, Weiss ST, Tosteson TD, Speizer FE. Acute lower respiratory illness in childhood as a predictor of lung function and chronic respiratory symptoms. *Am Rev Respir Dis* 1989; 877-885.
- ⁴⁷ Martinez FD. Role of viral infections in the inception of asthma and allergies during childhood: could they be protective? [editorial] *Thorax* 1994;49:1189-91.

- ⁴⁸ Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease. A prospective study of 200 patients. *N Engl J Med* 1969;280:397-404.
- ⁴⁹ Decramer M, Gosselink R, Troosters T, Verschueren M, Evers G. Muscle weakness is related to utilization of health care resources in COPD patients. *Eur Respir J* 1997;10:417-423.
- ⁵⁰ Poole PJ, Bagg B, Brodie SM, Black PN. Characteristics of patients admitted to hospital with chronic obstructive pulmonary disease. *N Z Med J* 1997;110:272-275.
- ⁵¹ Anthonisen NR, Manfreda J, Warren CPW, Hershfield ES, Harding GKM, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196-204.
- ⁵² Seemungal TAR, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1418-1422.
- ⁵³ Madison JM, Irwin RS. Chronic obstructive pulmonary disease. *Lancet* 1998;352:467-473.
- ⁵⁴ Sachs APE, Koëter GH, Groenier KH, van der Waaij D, Schiphuis J, Meyboom-de Jong B. Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease in general practice. *Thorax* 1995;50:758-763.
- ⁵⁵ Vitacca M, Clini E, Porta R, Foglio K, Ambrosino N. Acute exacerbations in patients with COPD: predictors of need for mechanical ventilation. *Eur Respir J* 1996;9:1487-1493.
- ⁵⁶ Kessler R, Faller M, Fourgaut G, Menecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159:158-164.
- ⁵⁷ Osman LM, Godden DJ, Friend JAR, Legge JS, Douglas JG. Quality of life and hospital re-admission in patients with chronic obstructive pulmonary disease. *Thorax* 1997;52:67-71.
- ⁵⁸ Murata GH, Gorby MS, Kapsner CO, Chick TW, Halperin AK. A multivariate model for the prediction of relapse after outpatient treatment of decompensated chronic obstructive pulmonary disease. *Arch Intern Med* 1992;152:73-77.
- ⁵⁹ Sunyer J, Sáez M, Murillo C, Castellsague J, Martínez F, Antó JM. Air pollution and emergency room admissions for chronic obstructive pulmonary disease: a 5-year study. *Am J Epidemiol* 1993;137:701-705.
- ⁶⁰ Anderson HR, Spix C, Medina S, Schouten JP, Castellsague J, Rossi G, Zmirou D, Touloumi G, Wojtyniak B, Ponka A, Bacharova L, Schwartz J, Katsouyanni K. Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. *Eur Respir J* 1997;10:1064-1071.
- ⁶¹ Seemungal TAR, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:1608-1613.

- ⁶² Niewoehner DE, Collins D, Erbland ML, for the Department of Veterans Affairs Cooperative Study Group. Relation of FEV1 to clinical outcomes during exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:1202-1205.
- ⁶³ Emerman CL, Effron D, Lukens TW. Spirometric criteria for hospital admission of patients with acute exacerbation of COPD. *Chest* 1991;99:595-9.
- ⁶⁴ McCrory DC, Brown C, Gelfand SE, Bach PB. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. *Chest* 2001;119:1190-1209.
- ⁶⁵ Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *JAMA* 1995;274:1852-1857.
- ⁶⁶ Connors AF, Dawson NV, Thomas C, Harrel FE Jr, Desbiens N, Fulkerson WJ, Kussin P, Bellamy P, Goldman L, Knaus WA. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am J Respir Crit Care Med* 1996;154:959-967.
- ⁶⁷ Cydulka RK, McFadden ER, Emerman CL, Sivinski LD, Pisanelli W, Rimm AA. Patterns of hospitalization in elderly patients with asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;156:1807-1812.
- ⁶⁸ Grasso ME, Weller WE, Shaffer TJ, Diette GB, Anderson GF. Capitation, managed care, and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:133-138.
- ⁶⁹ Fabbri L, Beghé B, Caramori G, Papi A, Saetta M. Similarities and discrepancies between exacerbations of asthma and chronic obstructive pulmonary disease. *Thorax* 1998;53:803-808.
- ⁷⁰ Ball P, Make B. Acute exacerbations of chronic bronchitis. An international comparison. *Chest* 1998;113:199S-204S.
- ⁷¹ Collet JP, Shapiro P, Ernst P, Renzi T, Ducruet T, Robinson A, the PARI-IS Study Steering Committee and Research Group. Effects of an immunostimulant agent on acute exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;156:1719-1724.
- ⁷² Sahebajami H, Doers JT, Render ML, Bond TL. Anthropometric and pulmonary function test profiles of outpatients with stable chronic obstructive pulmonary disease. *Am J Med* 1993;94:469-474.
- ⁷³ Wilson DO, Rogers RM, Wright EC, Anthonisen NR. Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. *Am Rev Respir Dis* 1989;139:1435-1438.
- ⁷⁴ Braun SR, Keim NL, Dixon RM, Clagnaz P, Anderegg A, Shrago ES. The prevalence and determinants of nutritional changes in chronic obstructive pulmonary disease. *Chest* 1984;86:558-563.
- ⁷⁵ Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J* 1994;7:1793-1797.

- ⁷⁶ Hunter ABM, Carey MA, Larsh HW. The nutritional status of patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1981;124:376-381.
- ⁷⁷ Braun SR, Dixon RM, Keim NL, Luby M, Anderegg A, Shrago ES. Predictive clinical value of nutritional assessment factors in COPD. *Chest* 1985;85:353-357.
- ⁷⁸ Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. *Am Rev Respir Dis* 1982;126:5-8.
- ⁷⁹ Schols AM, Burman WA, Staal-van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangement and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 1996;51:819-824.
- ⁸⁰ Schwartz J. What are people dying of on high air pollution days? *Environ Res* 1994;64:26-35.
- ⁸¹ Lawther PJ, Waller RE, Henderson M. Air pollution and exacerbation of bronchitis. *Thorax* 1970;25:525-39.
- ⁸² Harre ES, Price PD, Ayrey RB, Toop LJ, Martin IR, Town GI. Respiratory effects of air pollution in chronic obstructive pulmonary disease: a three month prospective study. *Thorax* 1997;52:1040-1044.
- ⁸³ Higgins BG, Francis HC, Yates CJ, Warburton CJ, Fletcher AM, Reid JA, Pickering CA, Woodcock AA. Effects of air pollution on symptoms and peak expiratory flow measurements in subjects with obstructive airways disease. *Thorax* 1995;50:149-155.
- ⁸⁴ Sunyer J, Antó JM, Murillo C, Saez M. Effects of urban air pollution on emergency room admissions for chronic obstructive pulmonary disease. *Am J Epidemiol* 1991;134:277-286.
- ⁸⁵ Schwartz J. Air pollution and hospital admissions for the elderly in Detroit, Michigan. *Am J Respir Crit Care Med* 1994;150:648-655.
- ⁸⁶ Burnett RT, Dales R, Krewski D, Vincent R, Dann T, Brook JR. Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. *Am J Epidemiol* 1995;142:15-22.
- ⁸⁷ Gilmour PS, Brown DM, Lindsay TG, Beswick PH, MacNee W, Donaldson K. Adverse health effects of PM₁₀ particles: involvement of iron in generation of hydroxyl radical. *Occup Environ Med* 1996;53:817-822.
- ⁸⁸ Li XY, Gilmour PS, Donaldson K, MacNee W. Free radical activity and pro-inflammatory effects of particulate air pollution (PM₁₀) in vivo and in vitro. *Thorax* 1996;51:1216-1222.
- ⁸⁹ Gong H. Health effects of air pollution. A review of clinical studies. *Clin Chest Med* 1992;13:201-214.
- ⁹⁰ Aris RM, Christian D, Hearne PQ, Kerr K, Finkbeiner WE, Balmes JR. Ozone-induced airway inflammation in human subjects as determined by airway lavage and biopsy. *Am Rev Respir Dis* 1993;148:1363-1372.

- ⁹¹ Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Health effects of outdoor air pollution (part 2). *Am J Respir Crit Care Med* 1996;153:477-98.
- ⁹² Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD and smokers. *Am J Respir Crit Care Med* 1996;154:1055-1060.
- ⁹³ Kim CS, Kang TC. Comparative measurement of lung deposition of inhaled fine particles in normal subjects and patients with obstructive airway disease. *Am J Respir Crit Care Med* 1997;155:899-905.
- ⁹⁴ Tager I, Speizer FE. Role of infection in chronic bronchitis. *N Engl J Med* 1975;292:563-571.
- ⁹⁵ Carilli AD, Gohd RS, Gordon W. A virologic study of chronic bronchitis. *N Engl J Med* 1964;270:123-127.
- ⁹⁶ Fagon JY, Chastre J. Severe exacerbations of COPD patients: the role of pulmonary infections. *Semin Respir Infect* 1996;11:109-118.
- ⁹⁷ Sachs APE, van der Waaij D, Groenier KH, Koëter GH, Schiphuis J. Oropharyngeal flora in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993;148:1302-1307.
- ⁹⁸ Cabello H, Torres A, Celis R, El-Ebiary M, Puig de la Bellacasa J, Xaubet A, González J, Agustí C, Soler N. Bacterial colonization of distal airways in healthy subjects and chronic lung disease: a bronchoscopic study. *Eur Respir J* 1997;10:1137-1144.
- ⁹⁹ Irwin RS, Erickson AD, Pratter MR, Corrao WM, Garrity FL, Myers JR, Kaemmerlen JT. Prediction of tracheobronchial colonization in current cigarette smokers with chronic obstructive bronchitis. *J Infect Dis* 1982;145:234-241.
- ¹⁰⁰ Monsó E, Ruiz J, Rosell A, Manterola J, Fiz J, Morera J, Ausina V. Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995;152:1316-1320.
- ¹⁰¹ Zalacain R, Sobradillo V, Amilibia J, Barrón J, Achótegui V, Pijoan JI, Llorente JL. Predisposing factors to bacterial colonization in chronic obstructive pulmonary disease. *Eur Respir J* 1999;13:343-348.
- ¹⁰² Monsó E, Rosell A, Bonet G, Manterola J, Cardona PJ, Ruiz J, Morera J. Risk factors of lower airway bacterial colonization in chronic bronchitis. *Eur Respir J* 1999;13:338-42.
- ¹⁰³ Riise GC, Larsson S, Larsson P, Jeansson S, Andersson BA. The intrabronchial microbial flora in chronic bronchitis patients: a target for N-acetylcysteine therapy? *Eur Respir J* 1994;7:94-101.
- ¹⁰⁴ Sportel JH, Koëter GH, van Altena R, Löwenberg A, Boersma WG. Relation between beta-lactamase producing bacteria and patient characteristics in chronic obstructive pulmonary disease (COPD). *Thorax* 1995;50:249-253.
- ¹⁰⁵ Barreiro B, Esteban L, Prats E, Verdaguer E, Dorca J, Manresa F. *Branhamella catarrhalis* respiratory infections. *Eur Respir J* 1992;5:675-679.

- ¹⁰⁶ Fagon JY, Chastre J, Trouillet JL, Domart Y, Dombret MC, Bornet M, Gibert C. Characterization of distal bronchial microflora during acute exacerbation of chronic bronchitis. Use of the protected specimen brush techniques in 54 mechanically ventilated patients. *Am Rev Respir Dis* 1990;142:1004-1008.
- ¹⁰⁷ Blasi F, Legnani D, Lombardo VM, Negretto GG, Magliano E, Pozzoli R, Chiodo F, Fasoli A, Allegra L. Chlamydia pneumoniae infection in acute exacerbations of COPD. *Eur Respir J* 1993;6:19-22.
- ¹⁰⁸ Eller J, Ede A, Schaberg T, Niederman MS, Mauch H, Lode H. Infective exacerbations of chronic bronchitis: relation between bacteriologic etiology and lung function. *Chest* 1998;113:1542-1548.
- ¹⁰⁹ Miravittles M, Espinosa C, Fernandez-Laso E, Martos JA, Maldonado JA, and Gallego M. Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Study group of bacterial infection in COPD. *Chest* 1999;116:40-46.
- ¹¹⁰ Jansen HM, Sachs APE, van Alphen L. Predisposing conditions to bacterial infections in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;151:2073-2080.
- ¹¹¹ Anthonisen NR. Smoking, lung function, and mortality. *Thorax* 2000;55:729-734.
- ¹¹² Easton PA, West P, Meatherall RC, Brewster JF, Lertzman M, Kryger MH. The effect of excessive ethanol ingestion on sleep in severe chronic obstructive pulmonary disease. *Sleep* 1987;10:224-233.
- ¹¹³ Fernández-Solá J, Junqué A, Estruch R, Monforte R, Torres A, Urbano-Márquez A. High alcohol intake as a risk and prognostic factor for community-acquired pneumonia. *Arch Intern Med* 1995;155:1649-1654.
- ¹¹⁴ Casaburi R. Rationale for anabolic therapy to facilitate rehabilitation in chronic obstructive pulmonary disease. *Baillieres Clin Endocrinol Metab* 1998;12:407-418.
- ¹¹⁵ Patessio A, Casaburi R, Prefault C, Folgering H, Donner C. Exercise training in chronic lung disease: exercise prescription. In: Roca J and Whipp BJ, editors. Clinical exercise testing. European Respiratory Monograph 6. Sheffield: European Respiratory Society Journals, 1997.
- ¹¹⁶ Maltais F, LeBlanc P, Simard C, Jobin J, Berube C, Bruneau J, Carrier L, Belleau R. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;154:442-447.
- ¹¹⁷ Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, and Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;320:1297-1303.
- ¹¹⁸ Sin DD, Tu JV. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:580-584.
- ¹¹⁹ Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, and Efthimiou J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. *Lancet* 1998;351:773-780.

- ¹²⁰ Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;353:1819-23.
- ¹²¹ Poole PJ, Black PN. Oral mucolytic drugs for exacerbations of chronic obstructive pulmonary disease: systematic review. *BMJ* 2001;322:1271-1274.
- ¹²² Rothbarth PH, Kempen BM, Sprenger MJW. Sense and nonsense of influenza vaccination in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;151:1682-1686.
- ¹²³ Alling DW, Blackwelder WC, Stuart-Harris CH. A study of excess mortality during influenza epidemics in the United States, 1968-1976. *Am J Epidemiol* 1981;113:30-43.
- ¹²⁴ Sprenger MJ, Mulder PG, Beyer WE, Van Strik R, Masurel N. Impact of influenza on mortality in relation to age and underlying disease, 1967-1989. *Int J Epidemiol* 1993;22:334-340.
- ¹²⁵ Scragg R. Effect of influenza epidemics on Australian mortality. *Med J Aust* 1985;142:98-102.
- ¹²⁶ Gross PA, Hermogenes AW, Sacks HS, Lau J, Levadowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. *Ann Intern Med* 1995;123:518-527.
- ¹²⁷ Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. *Ann Intern Med* 1999;130:397-403.
- ¹²⁸ Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(No. RR-8).
- ¹²⁹ Fine MJ, Smith MA, Carson CA, Meffe F, Sankey SS, Weissfeld LA, Detsky AS, Kapoor WN. Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomized controlled trials. *Arch Intern Med* 1994;154:2666-2677.
- ¹³⁰ Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA* 1993;270:1826-31.
- ¹³¹ Celli BR. Is pulmonary rehabilitation an effective treatment for chronic obstructive pulmonary disease? Yes. *Am J Respir Crit Care Med* 1997;155:781-783.
- ¹³² Lacasse Y, Wong E, Guyatt GH, King D, Cook DJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *Lancet* 1996;348:1115-1119.
- ¹³³ Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995;122:823-832.

- ¹³⁴ Griffiths TL, Burr ML, Campbell IA, Mullins J, Shiels K, Turner-Lawlor PJ, Payne N, Newcombe RG, Lonescu AA, Thomas J, Tunbridge J. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;355:362-68.
- ¹³⁵ Guell R, Casan P, Belda J, Sangenis M, Morante F, Guyatt GH, and Sanchis J. Long-term effects of outpatient rehabilitation of COPD: A randomized trial. *Chest* 2000;117:976-983.
- ¹³⁶ Medical Research Council. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981;1:681-686.
- ¹³⁷ Nocturnal Oxygen Therapy Group. Continuous or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease. A clinical trial. *Ann Intern Med* 1980;93:391-398.
- ¹³⁸ Tougaard L, Krone T, Sorknaes A, Ellegaard H, PASTMA group. Economic benefits of teaching patients with chronic obstructive pulmonary disease about their illness. *Lancet* 1992;339:1517-1520.
- ¹³⁹ Lacasse Y, Guyatt GH, Goldstein RS. The components of a respiratory rehabilitation program: a systematic overview. *Chest* 1997;111:1077-1088.
- ¹⁴⁰ Folgering H, Rooyackers J, Herwaarden C. Education and cost/benefit ratios in pulmonary patients. *Monaldi Arch Chest Dis* 1994;49:166-168
- ¹⁴¹ Rand CS, Wise RA. Measuring adherence to asthma medication regimens. *Am J Respir Crit Care Med* 1994;149:s69-s76.
- ¹⁴² Wright EC. Non-compliance or how many aunts has Matilda? *Lancet* 1993;342:909-913.
- ¹⁴³ Canadian Thoracic Society. Guidelines for the assessment and management of chronic obstructive pulmonary disease. *Can Med Assoc J* 1992;147:420-428.
- ¹⁴⁴ Soto J, Sacristán JA, Alsar MJ. Incumplimiento terapéutico con los preparados de teofilina en régimen ambulatorio. *Rev Clin Esp* 1992;191:457
- ¹⁴⁵ Dolce JJ, Crisp C, Manzella B, Richards JM, Hardin M, Bailey WC. Medication adherence patterns in chronic obstructive pulmonary disease. *Chest* 1991;99:837-841.
- ¹⁴⁶ Pépin JL, Barjhoux CE, Deschaux C, Brambilla C, ANTADIR. Long-term oxygen therapy at home. Compliance with medical prescription and effective use of therapy. *Chest* 1996;109:1144-1150.
- ¹⁴⁷ Morrison D, Skwarski K, MacNee W. Review of the prescription of domiciliary long term oxygen therapy in Scotland. *Thorax* 1995;50:1103-1105.
- ¹⁴⁸ van der Palen, Klein JJ, Kerkhoff AHM, van Herwaarden CLA. Evaluation of the effectiveness of four different inhalers in patients with chronic obstructive pulmonary disease. *Thorax* 1995;50:1183-1187.
- ¹⁴⁹ Larrión JL, Martí M, Mareque M, Daimiel R, Luengo C, Grupo de Trabajo sobre incumplimiento. Incumplimiento terapéutico en los ancianos. *Med Clin (Barc)* 1993;100:736-740.

-
- ¹⁵⁰ Assessing and ensuring drug compliance in chronic respiratory disease. SEPCR-ERS Workshop. Wiesbaden, 1990. *Eur Respir J* 1992;5:122-45.
- ¹⁵¹ Siafakas NM, Bouros D. Consequences of poor compliance in chronic respiratory diseases. *Eur Respir J* 1992;5:134-136.
- ¹⁵² Naberan Tona C. Survey about Barcelona Health Center General Practitioners' therapeutic attitude and control criteria of patients with respiratory chronic diseases. *Aten Primaria* 1994;13:112-116.
- ¹⁵³ Strauss MJ, Conrad D, LoGerfo JP, Hudson LD, Bergner M. Cost and outcome of care for patients with chronic obstructive lung disease. Analysis by physician specialty. *Med Care* 1986;24:915-924.
- ¹⁵⁴ Regueiro CR, Hamel MB, Davis RB, Desbiens N, Connors AF, Phillips RS. A comparison of generalist and pulmonologist care for patients hospitalized with severe chronic obstructive pulmonary disease: resource intensity, hospital costs, and survival. *Am J Med* 1998;105:366-372.
- ¹⁵⁵ Diggle P, Liang K, Zeger SL. Analysis of longitudinal data. New York: Oxford Science Publications, 1994.
- ¹⁵⁶ Last JM. A dictionary of epidemiology. New York: Oxford University Press, 1995.
- ¹⁵⁷ Gravil JH, Al-Rawas OA, Cotton MM, Flanigan U, Irwin A, Stevenson RD. Home treatment of exacerbations of chronic obstructive pulmonary disease by an acute respiratory assessment service. *Lancet* 1998;351:1853-55.
- ¹⁵⁸ Postma DS. When can a exacerbation of COPD be treated at home? *Lancet* 1998;351:1827-28.
- ¹⁵⁹ Taylor R. Chronic obstructive pulmonary disease. No longer any justification for therapeutic nihilism. *BMJ* 1998;316:1475-80.
- ¹⁶⁰ Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000;117:398S-401S.
- ¹⁶¹ Ball P, Harris JM, Lowson D, Tillotson G, Wilson R. Acute infective exacerbations of chronic bronchitis. *QJM* 1995;88:61-68.
- ¹⁶² Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000; 117:1638-1645.
- ¹⁶³ Rothman KJ, Greenland S. Modern epidemiology. Philadelphia: Lippincott-Raven, 1998.
- ¹⁶⁴ Schwartz J. Is there harvesting in the association of airborne particles with daily deaths and hospital admissions? *Epidemiology* 2001;12:55-61.
- ¹⁶⁵ Burrows B, Earle RH. Prediction of survival in patients with chronic airway obstruction. *Am Rev Respir Dis* 1969;99:865-71.
- ¹⁶⁶ Anthonisen NR, Wright EC, Hodgkin JE, IPPB Trial Group. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;133:14-20.

¹⁶⁷ Salas M, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. *Am J Epidemiol* 1999;149:981-983.