Risk factors of hospitalization and readmission of patients with COPD exacerbation – systematic review

Katayoon Bahadori[1]
J Mark FitzGerald[1,2]

[1]Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute, Vancouver, British Columbia, Canada
[2]The Lung Centre, Vancouver General Hospital and University of British Columbia, Vancouver, British Columbia, Canada

Background: Chronic obstructive lung disease (COPD) exacerbations are a significant cause of morbidity and mortality. Data regarding factors which causes or prevents exacerbations is very limited. The aim of this systematic review is to summarize the results from available studies to identify potential risk factors for hospital admission and/or re-admission among patients experiencing COPD exacerbations.

Methods: We undertook a systematic review of the literature. Potential studies were identified by searching the electronic databases: PubMed, EMBASE, BIOSIS, CINAHL, PsycINFO, Cochrane library, reference lists in trial reports, and other relevant articles.

Results: Seventeen articles that met the predefined inclusion criteria were identified. Heterogeneity of study designs, risk factors and outcomes restrict the result to only a systematic review and precluded a formal meta-analysis. In this review, three predictive factors: previous hospital admission, dyspnea and oral corticosteroids were all found to be significant risk factors of readmissions and variables including using long term oxygen therapy, having low health status or poor health related quality of life and not having routine physical activity were all associated with an increased risk of both admission and readmission to hospital.

Conclusions: There are a number of potential modifiable factors that are independently associated with a higher risk of COPD exacerbation requiring admission/readmission to the hospital. Identifying these factors and the development of targeted interventions could potentially reduce the number and severity of such exacerbations.

Keywords: COPD exacerbations, hospitalizations, risk of admission, readmission

Introduction

A systematic review and critical appraisal provides an unbiased and comprehensive synthesis of the best available scientific evidence related to a clinical issue of interest (Slavin 1995; Murlow et al 1998). Findings from a systematic review provide clinicians with an opportunity to examine this clinical evidence and its potential utility in the management of their own patients (Moher et al 1999).

Chronic obstructive pulmonary disease (COPD) is a term referring to a group of lung diseases characterized by fixed airflow obstruction. Exacerbations of COPD are associated with considerable physiologic deterioration and increased airway inflammatory changes that are caused by various factors such as viruses, bacteria, and possibly common pollutants.

Exacerbations of chronic obstructive pulmonary disease are now recognized to be an important cause of the considerable morbidity and mortality associated with COPD (Fletcher et al 1976).

Acute exacerbations are a common reason for hospital admissions and affects health-related quality of life (HRQL) (Seemungal et al 1998), and prognosis (Mannino

Correspondence: J Mark FitzGerald
Centre for Clinical Epidemiology and Evaluation, VGH Research Pavilion, Vancouver General Hospital, 828 West 10th Avenue, Vancouver, BC V5Z 3J5, Canada
Tel +1 604 875 4122
Fax +1 604 875 4595
Email markf@interchange.ubc.ca

2002). Its burden to society, as expressed in disability life years (DALYs), was ranked as eighth for men and seventh for women in 1996. It is predicted to rise to the fifth leading cause worldwide for both sexes by 2020 (Murray and Lopez 1997). A small proportion of COPD patients, approximately 10%, experiencing acute exacerbations, accounts for over 70 percent of costs as a result of COPD due to emergency visits and hospitalizations (Oostenbrink and Rutten-van Molken 2004).

Identifying risk factors for hospitalization and re-admission have important health policy implications, but the knowledge of which factor causes or prevents exacerbation is very limited. The reasons for readmission and, more importantly, how readmissions can be prevented, are not clear.

Some potential factors for COPD exacerbations have been studied.The aim of this systematic review is to summarize the results from available studies to identify potential risk factors for hospital admission and or re-admission among patients experiencing COPD exacerbations. This maybe helpful in allowing us identify intervention strategies.

Materials and methods

Search strategy

The databases used for the selection of the literature were Medline (1966 to Oct 2006), Embase (1988 to Oct 2006), CINAHL, BIOSIS, PsycINFO and the Cochrane library. We did not restrict the search to COPD patients with exacerbation since exacerbation is not indexed as a Medical Subject Heading term (MeSH) for we feared that this could result in a narrow search and we may miss out relevant studies.

We used a broad search strategy using the terms "lung diseases obstructive", "chronic obstructive lung disease", "chronic obstructive pulmonary disease", "COPD exacerbation", "bronchitis", "emphysema", "risk factors", "hospitalization" and "readmission". We added other terms: "smoking", "LTOT", "physical activity" and "early therapy" to capture more studies. The electronic searches were supplemented by scanning the reference lists from retrieved articles to identify additional studies that may have been missed during the initial search.

Study selection

Cohort, retrospective and prospective, cross-sectional and case-control studies were included. We related the citation list to patients with COPD and COPD exacerbation by excluding articles with titles and/or abstracts indicating patients with COPD associated with other concomitant heart/lung disease. Our focus was on studies that analyzed the contribution of risk factors for exacerbation of COPD leading to admission and re-admission to hospital. Limiting our search to English language publications further reduced the list. Studies were selected for inclusion in the review according to definition for exacerbation of COPD, and admission/readmission. Two members of the review team independently scrutinized the titles and abstracts of all identified citations and ordered the full text of any article that was deemed potentially eligible by one of the reviewers. The two reviewers evaluated the full text of all retrieved papers, made a decision on inclusion or exclusion and discussed the decisions. Any disagreement was resolved by consensus with close attention to the inclusion/exclusion criteria.

Data extraction and quality assessment

We selected studies that included COPD exacerbations and the risk factors leading to admission/readmission to hospital. We independently extracted data from the included studies and resolved any differences by discussion. We used a quality scoring system to reduce the effects of confounding often encountered in retrospective and observational studies. We arbitrarily assigned 2 points for each fulfilled criterion (maximum, 10 points). We selected the median score of all the articles as a cutoff point to categorize good and poor quality studies. Authors met to compare assigned scores, and discrepancies were resolved by discussion.

Results

Results of searches for documents

Our primary search yielded more than 1500 articles. Reviewing titles and abstracts, 79 articles possibly fulfilled the inclusion criteria. Among them, 17 articles met the criteria and have been reviewed for this study (Kessler et al 1999; Garcia-Aymerich et al (2000, 2001, 2003); Miravitlles et al (2000, 2006); Pouw et al 2000; Lau et al 2001; Bourbeau et al 2003; Groenewegen et al 2003; Wilkinson et al 2004; Gadoury et al 2005; Gudmundsson et al 2005; Soler-Cataluña et al 2005; (Wang and Bourbeau 2005); Cao et al 2006; Connolly et al 2006). The most common reason for exclusion was that it did not study "exacerbations" of COPD.

Study characteristics

Of the seventeen epidemiological studies, nine were cohorts (Kessler et al 1999; Lau et al 2001; Garcia-Aymerich et al 2003; Groenewegen et al 2003; Wilkinson et al 2004; Soler-Cataluña et al 2005; Wang et al 2005; Gudmundsson et al 2005; Connolly et al 2006), four were cross-sectional studies (Garcia-Aymerich et al 2000; Miravitlles et al (2000, 2006); Cao et al 2006), three were case-controls (Pouw et al 2000; Garcia-Aymerich et al 2001; Bourbeau et al 2003) and one was a randomized clinical

trial (Gadoury et al 2005). Seventy one percent were conducted in Europe, of these, 50% were from Spain. Three of the studies were conducted in Canada (Bourbeau et al 2003; Gadoury et al 2005 and Wang et al 2005).

The study characteristics and demographic of the participants of the included studies are shown in Tables 1 and 2.

Heterogeneity of study designs, risk factors and outcomes restrict our result to only a systematic review and precluded a formal meta-analysis.

Case-control studies

Three case-control studies were included (Pouw et al 2000; Garcia-Aymerich et al 2001; Bourbeau et al 2003) (Table 1). The risk factors that were examined in these studies were: low BMI on admission, weight loss during hospitalization (Pouw et al 2000), inhaled corticosteroids use previous admission (Bourbeau et al 2003), lower FEV_1 and under-prescription of LTOT (Garcia-Aymerich et al 2001). In two studies, there were equal numbers of case and control

Table 1 Study Characteristics of the included studies

No.	First author, Year	Country of origin	Study design	Risk/protective factors	Outcome
1	Pouw 2000	Netherlands	C-C	Low BMI on admission, Weight loss during hospitalization	Readmission
2	Bourbeau 2003	Canada	C-C	Inhaled corticosteroids	Hospitalization
3	Garcia-Aymerich 2001	Spain	C-C	Previous admissions, lower FEV_1, LTOT	Hospitalization
4	Garcia-Aymerich 2003	Spain	P-C	Physical activity	Readmission
5	Groenwegen 2003	Netherlands	P-C	Younger Age, long term oral corticosteroid	Readmission
6	Kessler 1999	France	P-C	Chronic hypercapnic respiratory insufficiency, pulmonary hypertension	Hospitalization
7	Wilkinson 2004	U.K	P-C	Early therapy	Hospitalization
8	Soler-Cataluna 2005	Spain	P-C	Older age, $PaCO_2$	Hospitalization
9	Gudmundsson 2005	Nordic	P-C	Anxiety, low FEV_1, low health status	Readmission
10	Connolly 2006	U.K	P-C	Previous admission, poor performance	Readmission
11	Lau 2001	China	R-C	Pre hospital admission, length of stay >5 days, nursing home residency, self-care activities, right heart strain pattern on ECG, inhaled corticosteroid, bicarbonate level >25 $mmol l^{-1}$	Readmission
12	Wang 2005	Canada	R-C	Living alone, frequency of COPD exacerbation, not having a family doctor	Readmission
13	Garcia-Aymerich 2000	Spain	C-S	No rehabilitation, poor inhaler maneuvers, no influenza vaccination, LTOT, smoking	Hospitalization
14	Miravitlles 2000	Spain	C-S	FEV1 impairment, significant comorbidity	Hospitalization
15	Cao 2006	Singapore	C-S	Disease duration >5 yrs, FEV1 < 50% predicted, use of psychotropic drugs, vaccination status	Readmission
16	Miravitlles 2006	Spain	C-S	Use of LTOT, increasing the number of previous exacerbations, short acting beta-2 agonists, incomplete primary education, impairment in health status	Hospitalization
17	Gadoury 2005	Canada	RCT	Sex (female), increased walking distance, higher education, older age, reduced health status	Hospitalization

R-C = retrospective-cohort, P-C = prospective-cohort, C-S = cross–sectional, C-C = case–control, RCT = randomised control trial

Table 2 Demographic characteristics of the included studies

Study design/First author/year	Sample size (n)		Age (years)		Gender Male (%)	
Case-control	**Case**	**Control**	**Case**	**Control**	**Case**	**Control**
Pouw 2000	14	14	71 (9)	69 (5)	57	57
Bourbeau 2003	843	11030	76 (8)	76 (7)	66	62
Garcia-Aymerich 2001	86	86	70 (8)	69 (9)	91	91
Cohort/cross sectional						
Garcia–Aymerich 2003	340		69 (9)		92	
Lau 2001	551		74 (9)		77	
Soler-Cataluna 2006	304		71 (9)		100	
Wilkinson 2004	128		67 (7)		69	
Kessler 1999	64		64 (9)		84	
Groenwegen 2003	171		71 (9)		61	
Garcia-Aymerich 2000	353		69 (9)		92	
Miravitlles 2000	1001		70 (10)		89	
Cao 2006	186		75 (25)		83	
Miravitlles 2006	1057		67 (9)		95	
Wang 2005	54		71 (10)		61	
Gudmundsson 2005	406		69 (11)		49	
Connolly 2006	7514		71(10)		52	
RCT	**Intervention**	**usual**	**Intervention**	**usual**	**Intervention**	**usual**
Gadoury 2005	96	95	69 (7)	70 (7)	52	59

Age: Mean (SD)

subjects (Pouw et al 2000; Garcia-Aymerich et al 2001). Quality of reporting of case-control studies was evaluated using four questions including whether: exposure assessment was the same for cases and controls; exposure assessors were blind to case-control status; cases and controls were from the same population; and whether the number of and reasons for study withdrawals were reported (Table 3) (Pouw et al 2000). Exposure assessments of cases and controls were assessed to be similar in all three studies (Pouw et al 2000; Garcia-Aymerich et al 2001; Bourbeau et al 2003). As there was no explicit mention whether exposure assessors were blinded or not, we considered them as not blinded. Controls were assessed by the reviewers to be from the same population as the cases in all three studies. Information on withdrawals was reported only in one study (Garcia-Aymerich et al 2001) while in the other study it was partially reported (Pouw et al 2000). Again; these results suggest that there is a risk of bias, particularly interviewer bias, in these studies.

Cohort studies

There were 9 cohort studies included in the review (Table 1), (Kessler et al 1999; Lau et al 2001; Garcia-Aymerich et al 2003; Groenewegen et al 2003; Wilkinson et al 2004; Soler-Cataluña et al 2005; Wang et al 2005; Gudmundsson et al 2005 and Connolly et al 2006). The risk factors that were examined were physical activity, long term oral corticosteroid use, age, chronic hypercapnic respiratory failure,

Table 3 A quality scoring system for case-control studies

First author	Was exposure assessment the same for cases and controls?	Were exposure assessors blind to case-control status?	Were cases and controls from the same population?	Were the number and reasons for study withdrawals reported?
	Yes (2), Partial (1), No (0)	**Yes (2), Partial (1), No (0)**	**Yes (2), Partial (1), No (0)**	**Yes (2), Partial (1), No (0)**
Pouw 2000	2	0	2	1
Bourbeau 2003	2	0	2	0
Garcia-Aymerich 2001	2	0	2	2

pulmonary hypertension, early therapy, hospital admission within 1 year before index admission, poor performance status, total length of stay in index admission >5 days, nursing home residency, dependency in self-care activities, right heart strain pattern on electrocardiogram, on high dose inhaled corticosteroid, actual bicarbonate level >25mmol, frequency of COPD exacerbation, living alone, not having a family doctor, anxiety, low FEV_1 and low health status.

Quality of reporting of cohort studies was evaluated using five questions assessing whether: the studies were prospective or retrospective cohort; exposure assessment was the same for all participants; outcome assessment was the same for all participants; outcome assessors were blind to exposure status; and whether the number of and reasons for study withdrawals were reported (MacKay et al 2003). The score for each question is reported in Table 4. We used the median of the scores to categorize the quality of studies. Based on the median 7, studies that scored seven or more were considered good (Kessler et al 1999; Garcia-Aymerich et al 2003; Groenewegen et al 2003; Wilkinson et al 2004; Soler-Cataluña et al 2005; Gudmundsson et al 2005; Connolly et al 2006) and less than seven were considered poor quality (Lau et al 2001 and Wang et al 2005).

Cross sectional studies

Four cross sectional studies were included in the review (Garcia-Aymeric et al 2000; Miravitlles et al (2000, 2006); Cao et al 2006). The risk factors that were examined in these studies were: no rehabilitation, poor inhaler maneuvers, no influenza vaccination, under prescription of LTOT, smoking, FEV_1 impairment and significant comorbidity, disease duration >5 yrs, use of psychotropic drugs, the increasing number of previous exacerbations, short acting beta-2 agonists, incomplete primary education and health status impairment. No quality assessment of the cross sectional studies were reported in this review.

Randomized control trial

Only one RCT was included in this review (Gadoury et al 2005). The predictive factors of reduced hospitalization for the intervention (self-management) group in this study were sex (female), increased walking distance and higher education and risk factors of increased hospitalizations were older age and reduced health status.

The quality of this trial was assessed using standard criteria (allocation concealment, blinding, analysis by intention to treat, and completeness of follow-up) based on Jadad's quality scale (Jadad et al 1996).

Risk factors for COPD exacerbation resulting in admission/readmission to hospital

Among the many risk factors studied in this review, $PaCO_2$ was reported by most studies (52%) (Kessler et al 1999; Garcia-Aymerich et al 2001; Lau et al 2001; Groenewegen et al 2003; Soler-Cataluña et al 2005). Of these, one was case-control study (Garcia-Aymerich et al 2001) and four were cohort studies (Kessler et al 1999; Lau et al 2001; Groenewegen et al 2003; Soler-Cataluña et al 2005).

Increased $PaCO_2$ has proved to be an independent predictive factor of early hospital admission in two studies (Kessler

Table 4 A quality scoring system for cohort studies

First author	P (2), R (1)	Was exposure assessment the same for all participants?	Was outcome assessment the same for all participants?	Were outcome assessors blind to exposure status?	Were the number of and reasons for study withdrawals reported?
		Yes (2), Partial (1), No (0)	Yes (2), Partial (1), No (0)	Yes (2), Partial (1), No (0)	Yes (2), Partial (1), No (0)
Lau 2001	1	1	2	1	1
Kessler 1999	2	1	2	1	2
Wilkinson 2004	2	1	2	1	2
Garcia-Aymerich 2003	2	2	2	1	2
Groenwegn 2003	2	1	2	1	2
Soler 2005	2	2	0	1	2
Wang 2005	1	1	1	0	2
Gudmundsson 2005	2	1	1	1	2
Connolly 2006	2	1	1	2	1

R = retrospective, P = prospective

et al 1999 and Lau et al 2001) and it has shown to be predictive of reduced survival in another study (Soler-Cataluña et al 2005). One study also reported $PaCO_2$ to be significant in the univariate analysis, (p value 0.025) (OR 1.04, 95% confidence interval [CI] 1.01 to1.08) for hospitalization following an exacerbation of COPD (Garcia-Aymerich et al 2001). But it was not found to be a risk factor for hospital readmission in another prospective study (Groenewegen et al 2003).

Lower FEV_1 was associated with higher risk of COPD readmission in four studies (Garcia-Aymerich et al (2001, 2003); Gudmundsson et al 2005; Cao et al 2006). The result of a study by Miravitlles et al (2000), suggest that FEV_1 impairment explains part of the risk of frequent exacerbations and hospital admissions. Three other studies also looked at FEV_1% predicted at time of admission; however they did not find this to be a significant risk factor (Kessler et al 1999; Garcia-Aymerich et al 2000; Groenewegen et al 2003).

Both oral and inhaled corticosteroids were studied as risk factors for COPD exacerbations (Garcia-Aymerich et al (2001, 2003); Lau et al 2001; Bourbeau et al 2003). Inhaled corticosteroid was a significant risk factor for early hospital admission in both univariate and multivariate analysis in a study by Lau et al (2001). The results from this study supports the previous trial by Burge et al (2000), however no apparent influence from inhaled corticosteroids was found, even at moderate to high doses, on the likelihood of a subsequent hospitalization for COPD exacerbation in two case control studies (Garcia-Aymerich et al 2001; Bourbeau et al 2003).

Use of high dose oral corticosteroid was associated with a significantly increased risk of readmission in a cross sectional study at p value 0.006 with the (OR 1.55, 95% confidence interval [CI] 1.13 to 2.11) (Garcia-Aymerich et al 2003). High dose systematic corticosteroid was reported as a significant factor for shorter time to readmission in the univariate analysis of a retrospective study (Lau et al 2001), and its long term use was reported as a risk factor of hospital readmission in a prospective cohort study (Groenewegen et al 2003). Oral corticosteroid was related to a higher risk of admission in the crude analysis of a case control study (Garcia-Aymerich et al 2001) but its lack of association in the adjusted model was interpreted as a marker of disease severity.

In a study by Garcia-Aymerich et al (2003) two variables: the highest tertile of usual physical activity and a higher score of physical quality of life showed a statistically significant reduced risk of readmission.

In another study by Garcia-Aymerich et al (2001) physical scale of health related quality of life was related to COPD admission in the crude analysis as in two previous studies (Keistinen et al 1996; Seemungal et al 1998) and maintained an association (although non significant) in the clinical model adjusted analysis. But this relationship after including dyspnea in this model was lost, indicating that physical quality of life and admission was confounded by dyspnea.

Dependency for assistance in self-care activities was shown to be an independent risk factor for shorter time to readmission in a retrospective study (Lau et al 2001). Both active and passive smoking was reported by some studies (Kessler et al 1999; Garcia-Aymerich et al (2000, 2001, 2003); Miravitlles et al 2000) to be risk factors. One cross sectional study reported that being a former smoker exposed to passive smoking was associated with a significantly increased risk of readmission (Garcia-Aymerich et al 2003).

In a multivariate logistic regression of a case-control study, current smoking was found to be a protective factor against COPD hospitalization (OR 0.30, p value 0.0222) (Garcia-Aymerich et al 2001). However in two studies no association was found between current smoking and hospital admission (Kessler et al 1999, Miravitlles et al 2000). Long Term use of Oxygen Therapy (LTOT) was reported as a risk factor in five studies (Kessler et al 1999; Lau et al 2001; Garcia-Aymerich et al (2001, 2003); Wang et al 2005).

Lau et al (2001) reported that LTOT was associated with a shorter time to readmission ($P < 0.0001$). Three other studies reported that LTOT significantly increased the risk of hospitalization for acute exacerbations of COPD (Kessler et al 1999; Garcia-Aymerich 2001 et al; Wang et al 2005).

LTOT was also associated with a higher risk of readmission for COPD in a study by Garcia-Aymerich, but this did not reach statistical significance (Garcia-Aymerich et al 2003).

In Garcia-Aymerich et al's (2001) study, low body mass index (BMI) was associated with admission only in the univariate analysis. This was in agreement with another study conducted by Kessler et al (1999). BMI on admission along with weight change during hospitalization were both significantly associated with unplanned early readmission in a study by Pouw et al (2000). While in three other studies there were no significant association between BMI and hospital readmission (Miravitlles et al 2000; Groenewegen et al 2003; Cao et al 2006).

Total length of stay in the index admission of more than 5 days and nursing home residency were the other significant risk factors for early readmission reported by Lau et al. (2001). This study also reported that hospital admission within one year before the index admission was a significant risk factor

for re admission ($p < 0.0001$). Similarly having more than three COPD admissions in the year before recruitment was found to be associated with an increased risk of readmission, in two studies by Garcia-Aymerich et al (2001, 2003) and a recent study by Connolly et al (2006). In contrast to these findings, no association was found between the number of previous hospital admissions and unplanned early readmission in a retrospective study by Pouw et al (2000).

Patients with a longer history of having a COPD diagnosis (more than 5 years) were found to be approximately twice as likely to have frequent readmissions than those with a shorter duration (OR = 2.51, 95% confidence interval [CI] 1.39 to 4.53) (Cao et al 2006).

Co-morbid conditions such as right heart strain on ECG, coronary artery disease, left ventricular failure, diabetes mellitus, were also found to be significant risk factors for admission in the same study (Lau et al 2001) as well as in another cross sectional study (Miravitlles et al 2000). However, surprisingly the presence of comorbidity was not found to be significantly associated with readmission in four other studies (Pouw et al 2000; Garcia-Aymerich et al 2003; Groenewegen et al 2003 and Cao et al 2006).

Older age was considered as a risk factor for hospitalization in two studies (Soler-Cataluña et al 2005; Gadoury et al 2005) but in another study was not associated with an increased risk (Kessler et al 1999). It was also associated with a shorter time to first readmission after discharge in another study (Lau et al 2001). Age related deficiencies in process of care did not predict inpatient or readmission in the recent high sample size study by Connolly et al (2006).

Female gender was reported as a predictive factor for reduced hospitalization in a multicenter, randomised controlled trial (Gadoury et al 2005), but neither age nor gender was found to be an related to COPD admission in a study by Garcia-Aymerich et al (2001). Low health status was found to be an important risk factor for both admission and readmission of COPD patients who experienced an exacerbation (Gudmundsson 2005; Miravitlles et al 2006; Gadoury et al 2005). In a retrospective cohort study it has been reported that patients with poor health related quality of life (HRQoL) had frequent ER visits and readmissions to hospital (Wang et al 2005). Wilkinson et al (2004) demonstrated that patients who habitually fail to seek therapy for their exacerbations have worse HRQoL and are more likely to be hospitalized for the management of an exacerbation. This supports the results and their other study that the patients who had no family doctor were predisposed to readmission (OR 1.435, 95% confidence interval [CI] 0.14 to1.34), p value 0.008) (Wang et al 2005).

Patients with severe dyspnea have been found to be more likely to be readmitted to hospital in a univariate analysis (OR = 1.87, 95% confidence interval [CI] 0.98 to 3.28) (Cao et al 2006). This supports the results of a retrospective cohort study that patients with severe dyspnea and frequent COPD exacerbations had frequent emergency visits and readmissions to hospital (Wang et al 2005). In an earlier study it has been shown that patients with dyspnea of grade 2 never experienced hospital admissions for acute exacerbation, but with a dyspnea of grade 3, 4 or 5 they had a significant risk of hospitalization at one year (Kessler et al 1999).

Characteristics of the risk or protective factors included in this review are shown in Appendix 1.

Discussion

This systematic review evaluated the results of 17 studies for risk factors for admission or readmission in COPD patients who had experienced an exacerbation. Variables including using long term oxygen therapy, having low health status or poor health related quality of life and not having routine physical activity were all associated with an increased risk of admission and readmission to hospital.

$PaCO_2$ was shown to be an independent risk factor for hospital admission for an acute exacerbation of COPD. Higher levels of $PaCO_2$ likely represents a marker of disease severity or less likely that patients with chronic hypercapnia, and hence raised actual bicarbonate, are probably more easily symptomatic than normocapnic patients because of their rapid and shallow breathing pattern (Ringbaek et al 2002), resulting in earlier and more frequent need for acute care.

In this review, three predictive factors: "previous hospital admission", "dyspnea" and "oral corticosteroids" were all found to be significant risk factors of readmissions. Oral corticosteroids are often used in the treatment of acute exacerbations of COPD. In contrast, studies of the utility of inhaled corticosteroids in COPD patients who require hospital admission or emergency department treatment provide conflicting results, with some studies reporting improvement and others reporting no effect. This inconsistency suggests that the results of ongoing clinical trials, designed to look at the specifically possible benefits of inhaled corticosteroids on the risk of exacerbation, should be awaited before recommending their routine use in COPD patients. The most recent such study, paradoxically showed an increased risk of pneumonia in patients with COPD (Calverley et al 2007).

In some studies use of long-term home of supplemental oxygen (LTOT) was independently associated with admission or shorter time to first readmission for acute

exacerbations of COPD. However in other studies, this association was not significant or it did not remain significant after adjustment, indicating that LTOT could be probably a marker of severity in those patients.

The negative association between current smoking and hospital admission was explained by Anthonisen (2000) in that many severely ill patients with COPD spontaneously quit smoking in response to their symptoms and disability, and it is hardly surprising that these patients do not do well afterwards. For this reason studies of patients with well established disease have often not shown a reduction in admission with smoking cessation.

Prospective studies including a wider range of COPD severity would be helpful to clarify this issue.

Low body mass index (BMI) was associated with admission and non elective readmission and consistently with its relation to prognosis of COPD in three studies (Kessler et al 1999; Pouw et al 2000; Garcia-Aymerich et al 2001). It is not clear whether the observed relationships between both low body weight on admission and early readmission are causal relationships or whether these parameters represent epiphenomena of more severe disease. There is a hypothesis that tissue depletion in patients with COPD may be related in part to a systemic catabolic response induced by inflammation, which cannot completely be reversed by nutritional support only (Schols et al 1998). Further studies are indicated to confirm this hypothesis.

In this review, the presence of coexisting comorbidites was not associated with an increased probability of frequent exacerbations, but with an increased risk of admission. This suggests that comorbidity does not appear to be a risk factor for frequent exacerbations, but a risk factor for severe life threatening exacerbations that can provoke admission. We believe that potentially all co-morbidities are important contributing factors to COPD morbidity, and special attention should be paid to the diagnosis of coexisting disease and its association with COPD admission.

Patients with COPD who perform a relatively high level of physical activity in their daily life have been shown a substantially reduced risk of readmission due to exacerbation (Garcia-Aymerich et al 2001; Lau et al 2001).The explanation could be that exercise engages cardiovascular system and helps the body to deliver oxygen to respiratory muscles more efficiently. In addition, endurance training can reduce exercise induced lactic acidosis and improve the oxidative capacity of the muscles in patients with moderate to severe COPD. Therefore such muscles would be more able to tolerate a COPD exacerbation than untrained muscles.

Longer length of stay, nursing home residents (Lau et al 2001), taking anticholinergics (Garcia-Aymerich et al 2003), increasing age and chronic mucus hypersecretion (CMH) (Miravitlles et al 2000), were the other factors associated with early readmission.

Being managed by a respirologist was also associated with higher risk of readmission, contrary to what might have been expected, and it was not totally removed after adjustment for previous admission, suggesting that other mechanisms may be operating. However, in another study (Wilkinson et al 2004), it has been demonstrated that prompt treatment by a physician is associated with better outcomes.

Older age was associated with shorter time to first readmission and increased risk of hospitalization in several studies (Lau et al 2001; Soler-Cataluña et al 2005; Gadoury et al 2005). This may be related to the higher degree of disability and comorbidity in the older population.

Patients who habitually fail to seek therapy for their exacerbations have worse health-related quality of life and are more likely to be hospitalized for the management of an exacerbation. Patients with more symptoms at exacerbation onset tended to present earlier for treatment, and those exacerbations with more symptoms were indeed more severe, as they took longer to recover. Therefore, the milder and less symptomatic exacerbations were in fact presenting slightly later, and when this effect is taken into account, the benefit of early treatment became more pronounced.

In conclusion, our results for this systematic review suggest that there are a number of potential modifiable factors that are independently associated with the higher risk of COPD exacerbation requiring admission/readmission to hospital. Identifying these factors and the development of targeted interventions could potentially reduce the number and severity of such exacerbations.

Limitations of our study

We reviewed only published studies, and unpublished studies may contain valid results that conflict with our conclusions. This is of particular concern in a systematic review of observational studies as there is a greater tendency towards publication bias than there is with randomised controlled trials (Easterbrook et al 1991).

We did not search the gray literature (ie, literature that is difficult to identify, locate and retrieve, examples would include theses, proceedings of workshops etc) extensively. We included only English language papers and since in this

review most of the articles were studied and published in Europe, we might have missed some non-English related articles and also we may have overestimated the methodological limitations of the included studies because we relied on published reports.

There is a chance that we may have missed other studies because of these limitations, but considering the broad nature of our search strategy and the number of citations screened, we believe this risk to be small. In addition, the included studies may have suffered from other design weaknesses such as confounding by variables other than sample size problems, which we did not address. Our challenge in categorizing study design and assigning primary outcomes certainly suggest that design was an issue. To avoid selection bias, a systematic and comprehensive search was conducted and two reviewers independently evaluated trials for inclusion. Because of the wide variation in end points and study design we were not able to do a formal meta analysis.

Implications for policy makers and future research

The evidence related to hospital admission and readmission is currently equivocal and requires further study. Several potentially important outcomes including patients' satisfaction, self management, patients' coping and adherence, smoking cessation, and the effects on social function have not been fully evaluated. There is also a need to evaluate the economic implications of COPD exacerbations and especially hospitalizations.

References

Andersson I, Johansson K, Larsson S, Pehrsson K. 2002. Long-term oxygen therapy and quality of life in elderly patients hospitalized due to severe exacerbation of COPD. A 1 year follow-up study. *Respiratory Medicine*, 96:944–9.

Anthonisen NR. 2000. Smoking, lung function and mortality. *Thorax*, 55: 729–30.

Bourbeau J, Ernst P, Cockcoft D, Suissa S. 2003. Inhaled corticosteroids and hospitalisation due to exacerbation of COPD. *European Respiratory Journal*, 22:286–9.

Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. 2000. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ*, 320:1297–303.

Calverley PMA, Anderson JA, Celli B, et al; for the TORCH investigators. 2007. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *The New England Journal of Medicine*, 356:775–789.

Cao Z, Ong KC, Eng P, Tan WC, Ng TP. 2006. Frequent hospital readmissions for acute exacerbation of COPD and their associated factors. *Respirology*, 11:188–95.

Connolly MJ, Lowe D, Anstey K, Hosker HSR, Pearson MG, Roberts CM. 2006. Admissions to hospital with exacerbations of chronic obstructive pulmonary disease: effect of age related factors and service organization. *Thorax*, 61:843–8.

Connors AF, Dawson NV, Thomas C, Harrell FE, Desbiens N, Fulkerson WJ, Kussin P, Bellamy P, Goldman L, Knaus WA. 1996. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *American Journal of Respiratory & Critical Care Medicine*, 154:959–67.

Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. 1991. Publication bias in clinical research. *Lancet*, 337:867–72.

Fletcher CM, Peto R, Tinker CM, Speizer FE. 1976. Natural history of chronic bronchitis and emphysema. Oxford: Oxford University Press. 272 p.

Gadoury MA , Schwartzman K , Rouleau M, Maltais F , Julien M, Beaupré A, Renzi P, Bégin R, Nault D, Bourbeau J. 2005. Self-management reduces both short-and long-term hospitalisation in COPD. *Eur Respir J*, 26:853–7.

Garcia-Aymerich J, Barreiro E, Farrero E, Marrades RM, Morera J, Anto JM. 2000. Patients hospitalized for COPD have a high prevalence of modifiable risk factors for exacerbation. *European Respiratory Journal*, 16:1037–42.

Garcia-Aymerich J, Monso E, Marrades RM, Escarrabill J, Felez MA, Sunyer J. Anto JM. 2001. Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. EFRAM study. *American Journal of Respiratory & Critical Care Medicine*, 164:1002–7.

Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Marrades RM. Anto JM. 2003. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax*, 58:100–5.

Groenewegen KH, Schols AM, Wouters EF. 2003. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest*, 124:459–67.

Gudmundsson G, Gislason T, Janson C, Lindberg E, Hallin R, Ulrik C S, Brøndum E, Nieminen MM, Aine T, Bakke P. 2005. Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. *Eur Respir J*, 26:414–19.

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*, 17:1–12.

Keistinen T, Vilkman S, Tuuponen T, Kivela SL. 1996. Hospital admissions for chronic obstructive pulmonary disease in the population aged 55 years or over in Finland during 1972–1992. *Public Health*, 110:257–9.

Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. 1999. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine*, 159:158–64.

Lau AC, Yam LY, Poon E. 2001. Hospital re-admission in patients with acute exacerbation of chronic obstructive pulmonary disease. *Respiratory Medicine*, 95:876–84.

MacKay M, Reid DC, Moher D, Klassen T. 2003. Systematic Review of the Relationship Between Childhood Injury and Socio-economic Status. NICE – Public Health Evidence.

Mannino DM. 2002. COPD: Epidemiology, Prevalence, Morbidity and Mortality, and Disease Heterogeneity. *Chest*, 121:121–6.

Miravitlles M, Guerrero T, Mayordomo C, Sanchez-Agudo L, Nicolau F, Segu JL. 2000. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. The EOLO Study Group. *Respiration*, 67:495–501.

Miravitlles M, Calle M, Alvarez-Gutierrez F, Gobartt E, Lo´ pez F , Martı´n A. 2006. Exacerbations, hospital admissions and impaired health status in chronic obstructive pulmonary disease. *Quality of Life Research*, 15: 471–80.

Moher D, Cook DJ, Eastwood S, Olkin L, Rennie D, Stroup DF. 1999. Improving the quality of reports of meta-analysis of randomized controlled trials: the QUOROM statement. *Lancet*, 345:1896–900.

Murlow C, Cook D. 1998. Systematic Reviews: Synthesis of Best Evidence for Health Care Decisions. *Philadelphia American College of Physicians*, 129:759–60.

Murray CJ, Lopez AD. 1997. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet*, 349:1498–504.

Oostenbrink JB, Rutten-van Molken MP. 2004. Resource use and risk factors in high-cost exacerbations of COPD. *Respir Med*, 98:883–91.

Pouw EM, Ten Velde GP,Croonen BH, Kester AD, Schols AM, Wouters EF. 2000. Early non-elective readmission for chronic obstructive pulmonary disease is associated with weight loss. *Clinical Nutrition*, 19:95–9.

Ringbaek TJ, Viskum K, Lange P. 2002. Does long-term oxygen therapy reduce hospitalisation in hypoxaemic chronic obstructive pulmonary disease? *European Respiratory Journal*, 20:38–42.

Schols AMWJ, Slangen J, Volovics L, Wouters EFM. 1998. Weight Loss Is a Reversible Factor in the Prognosis of Chronic Obstructive Pulmonary Disease. Am. J. Respir. *Crit Care Med*, 157:1791–7.

Seemungal T, Donaldson G, Paul E, Bestall J, Jeffries D, Wedzicha. 1998. JADW: Effect of Exacerbation on Quality of Life in Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*, 157:1418–22.

Seemungal TAR, Donaldson GC, Wedzicha JA . 2000. Exacerbations and the risk of hospitalisation in patients with COPD. *Thorax*, 55:A44.

Slavin RE. 1995. Best evidence synthesis: an intelligent alternative to meta-analysis. *J clin Epidemiol*, 48:9–18.

Soler-Cataluña JJ, Martínez-García MÁ, Román Sánchez P, Salcedo E, Navarro M, Ochando R. 2005. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*, 60:925–31.

Wang Q, Bourbeau J. 2005. Outcomes and health-related quality of life following hospitalization for an acute exacerbation of COPD. *Respirology*, 10:334–40.

Wilkinson TMA, Donaldson GC, Hurst JR, Seemungal TAR, Wedzicha JA. 2004. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine*, 169:1298–303.

Appendix 1

Characteristics of the risk/protective factors studied in this systematic review

Risk/Protective Factors	First author	No. of patients	Crude HR/OR/RR (95%CI)	P-value	Adjusted HR/OR/RR (95%CI)	Adjusted p-value	Outcome* A,R,E
Hospital admission in the previous year	Garcia-Aymerich 2003	340	2.27 (1.69–3.04)	0.000	–	–	R
	Garcia-Aymerich 2001	172	3.82 (1.14–2.75)	0.030	6.21 (1.60–24.07)	0.008	A
	Lau 2001	551	1.55 (1.22–1.98)	<0.001	–	–	R
	Gudmundsson 2005	416	1.98 (1.42–2.76)	–	–	-	R
	Connolly 2006	7514	–	–	–	–	R
PCO_2	Garcia-Aymerich 2001	172	1.04 (1.01–1.08)	0.025	–	–	A
	Lau 2001	551	–	0.007	–	–	R
	Kessler 1999	64	2.1 (1.4–3.1)	0.0003	–	–	A
FEV1 Pred%	Garcia-Aymerich 2001	172	0.97 (0.95–0.99)	0.002	0.96 (0.93–0.98)	0.000	A
	Garcia-Aymerich 2003	340	0.97 (0.96–0.98)	0.000	0.97 (0.96–0.99)	0.001	R
	Miravitlles 2000	713	–	–0.72 (0.58–0.88)		–	A
	Cao 2006	186	2.60 (1.18–5.74)	0.018	–	–	R
	Wang 2005	54	2.08 (0.01–0.77)	0.003	–	–	E
	Gudmundsson 2005	416	0.83 (0.76–0.91)	–	–	–	R
LTOT	Garcia-Aymerich 2001	172	–	–	22.6 (2.31–21.88)	0.007	A
	Garcia-Aymerich 2003	340	2.36 (1.79–3.11)	0.000	1.26 (0.87–2.05)	0.223	R
	Lau 2001	551	–	<0.0001	–	–	A
	Miravittles 2006	1057	3.47 (2.35–5.12)	<0.0001	–	–	A
	Wang 2005	54	4.85 (1.33–17.75)	0.014	–	–	E
Health status impairment	Miravittles 2006	1057	1.01 (1.00–1.02)	0.0008	–	–	A
Comorbidity	Lau 2001	551	1.56 (1.19–2.04)	0.001	–	–	R
	Miravitlles 2006	713	–	–	1.97 (1.24–3.14)	–	A
	Wang 2005	54	0.66 (0.45–0.96)	0.031	–	–	E
Oral corticosteroids	Garcia-Aymerich 2003	340	1.55 (1.13–2.11)	0.006	1.59 (1.07–2.37)	0.021	R
	Groenwegen 2003	171	–	0.0026	–	–	R
	Lau 2001	551	–	0.0151	–	–	R
Inhaled corticosteroid	Lau 2001	551	1.35 (1.02–1.80)	0.036	–	–	R
	Miravittles 2006	1057	–	<0.0001	–	–	A
BMI	Pouw 2000	28	–	0.046	–	–	R
	Garcia-Aymerich 2001	172	0.92 (0.86–0.99)	0.023	–	–	A
	Kessler 1999	64	–	0.015	–	–	A
Current smoking	Garcia-Aymerich 2001	172	0.46 (0.20–1.01)	0.053	0.45 (0.19–1.05)	0.063	A
	Gudmundsson 2005	416	0.78 (0.55–1.10)	–	–	–	R
Older age	Lau 2001	551	–	0.0013	–	–	R
	Soler-Cataluna 2006	304	–	–	4.52 (2.31–8.83)	<0.001	A
	Wang 2005	54	0.91 (0.85–0.97)	0.0028	–	–	E
	Gadoury 2005	191	–	–	1.05 (1.03–1.06)	–	E
Living alone	Miravitlles 2006	1057	–	0.007	–	–	A
	Wang 2005	54	0.60 (0.00–0.82)	0.0092	–	–	R
Physical activity/Scale	Garcia-Aymerich 2001	172	0.96 (0.93–0.99)	0.02	0.97 (0.94–1.01)	0.104	A
	Lau 2001	551	1.40 (1.06–1.83)	0.0001	–	–	R
Health related QoL*	Garcia-Aymerich 2003	340	0.46 (0.32–0.68)	0.000	0.49 (0.31–0.79)	0.003	R
			0.97 (0.95–0.98)	0.000	0.98 (0.96–0.99)	0.007	R
Dyspnea	Cao 2006	186	1.80 (0.98–3.28)	<0.05	–	–	R
Family doctor	Wang 2005	54	1.44 (0.14–1.34)	0.008	–	–	R
			4.06 (1.06–10.51)	0.041	–	–	E
Pulmonologist	Garcia-Aymerich 2003	340	2.16 (1.43–3.27)	0.000	1.77 (1.07–2.92)	0.025	R
Influenza vaccination	Cao 2006	186	8.14 (1.77–37.47)	0.002	–	–	R

* Outcome: A= Admission; R= Readmission, E= Exacerbation, QoL= Quality of Life