

## RESEARCH PAPER

# Management of COPD exacerbations in primary care: a clinical cohort study

\*Josefin Sundh<sup>1</sup>, Eva Österlund Efraimsson<sup>2†</sup>, Christer Janson<sup>3</sup>, Scott Montgomery<sup>4,5</sup>, Björn Ställberg<sup>6</sup>, Karin Lisspers<sup>6</sup>

<sup>1</sup> Department of Respiratory Medicine, Örebro University Hospital & School of Health and Medical Science, Örebro University, 701 85 Örebro, Sweden

<sup>2</sup> School of Health and Social Studies, Dalarna University, 79188 Falun, Sweden

<sup>3</sup> Department of Medical Sciences, Respiratory Medicine and Allergology, Uppsala University, 75105 Uppsala, Sweden

<sup>4</sup> Clinical Epidemiology and Biostatistics, Örebro University Hospital & School of Health and Medical Science, Örebro University, 701 85 Örebro, Sweden

<sup>5</sup> Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institute, 171 76 Stockholm, Sweden

<sup>6</sup> Department of Public Health and Caring Science, Family Medicine and Preventive Medicine, Uppsala University, 75122 Uppsala, Sweden

† Eva Österlund Efraimsson deceased May 2013

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### Abstract

**Background:** Chronic obstructive pulmonary disease (COPD) exacerbations are associated with lung function decline, lower quality of life, and increased mortality, and can be prevented by pharmacological treatment and rehabilitation.

**Aims:** To examine management including examination, treatment, and planned follow-up of COPD exacerbation visits in primary care patients and to explore how measures and management at exacerbation visits are related to subsequent exacerbation risk.

**Methods:** A clinical population of 775 COPD patients was randomly selected from 56 Swedish primary healthcare centres. Data on patient characteristics and management of COPD exacerbations were obtained from medical record review and a patient questionnaire. In the study population of 458 patients with at least one exacerbation, Cox regression analyses estimated the risk of a subsequent exacerbation with adjustment for age and sex.

**Results:** During a follow-up period of 22 months, 238 patients (52%) had a second exacerbation. A considerable proportion of the patients were not examined and treated as recommended by guidelines. Patients with a scheduled extra visit to an asthma/COPD nurse following an exacerbation had a decreased risk of further exacerbations compared with patients with no extra follow-up other than regularly scheduled visits (adjusted hazard ratio 0.60 (95% confidence interval 0.37 to 0.99),  $p=0.045$ ).

**Conclusions:** Guidelines for examination and emergency treatment at COPD exacerbation visits are not well implemented. Scheduling an extra visit to an asthma/COPD nurse following a COPD exacerbation may be associated with a decreased risk of further exacerbations in primary care patients.

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**Keywords** primary care, COPD, exacerbation, management, nurse

### Introduction

Chronic obstructive pulmonary disease (COPD) exacerbations are a major global cause of morbidity.<sup>1,2</sup> They are known to cause lung function decline,<sup>1</sup> frequent hospital admission<sup>2</sup> generating a substantial financial burden for society,<sup>3</sup> worsening quality of life,<sup>4,5</sup> and increased mortality.<sup>2,6,7</sup> Previous studies have shown that

exacerbation risk can be reduced by pharmacological<sup>8-10</sup> and non-pharmacological<sup>11,12</sup> interventions during the stable phase.

International guidelines for COPD exacerbations recommend careful examination and treatment with inhaled bronchodilators, antibiotics, and oral steroids.<sup>13-15</sup> Studies of exacerbation management in hospitalised COPD patients have shown that

\* **Corresponding author:** Dr Josefin Sundh, Department of Respiratory Medicine, Örebro University Hospital & School of Health and Medical Science, Örebro University, 701 85 Örebro, Sweden. Tel +46 196025597, +46 702349517 Fax +46 19186526 E-mail: josefin.sundh@orebroll.se

management is not always optimal,<sup>16,17</sup> indicating a need to explore the management of COPD exacerbations in primary care patients.

In Sweden, management of the majority of COPD patients involves regular visits in primary care and a smaller number involves regular visits to secondary care outpatient clinics.<sup>18</sup> During acute exacerbations, patients with regular visits in primary care might present either at their primary healthcare centre (PHCC) or in the accident and emergency department of the nearest hospital.

The first aim of this study was to examine the management of exacerbations in Swedish primary care COPD patients during emergency visits in PHCCs or in hospitals by describing examinations, treatment, and planned follow-up. The second aim was to study the associations of these measures with the risk of a subsequent exacerbation.

## Methods

### Setting

In Sweden it is recommended that PHCCs have a specific asthma/COPD clinic with access to spirometry, pulse oximeters, nebulisers, and oxygen.<sup>19</sup> Each general practitioner (GP) is responsible for the diagnosis, treatment, and follow-up of COPD patients and can refer patients to the asthma/COPD clinic for spirometry and patient education. A Swedish asthma/COPD clinic should involve a responsible GP and a trained specialist nurse.<sup>18-21</sup> The role of the asthma/COPD nurse is to perform and interpret spirometry, peak expiratory flow (PEF) and pulse oximetry, to provide patient education comprising pathophysiology, treatment, inhalation technique and smoking cessation,<sup>22</sup> and to cooperate with the patient's GP in planning treatment and follow-up.<sup>21</sup> In secondary care, an asthma/COPD nurse is often available for outpatients.

### Population and data collection

Participants were sampled from a larger cohort of COPD patients at 56 PHCCs in seven Swedish counties.<sup>23-26</sup> Data were obtained from medical record review and a patient questionnaire, and the procedures are presented in Figure 1. The final study population included the 458 (59.1%) primary care COPD patients who

presented with one or more exacerbations in PHCCs or at the accident and emergency department of a hospital during 2000-2003. Information on exacerbation visits was obtained using records from both PHCCs and nearby hospitals. Information on clinical resources was obtained in 2005 using a clinical questionnaire to the clinical directors of the participating centres.

### Measures

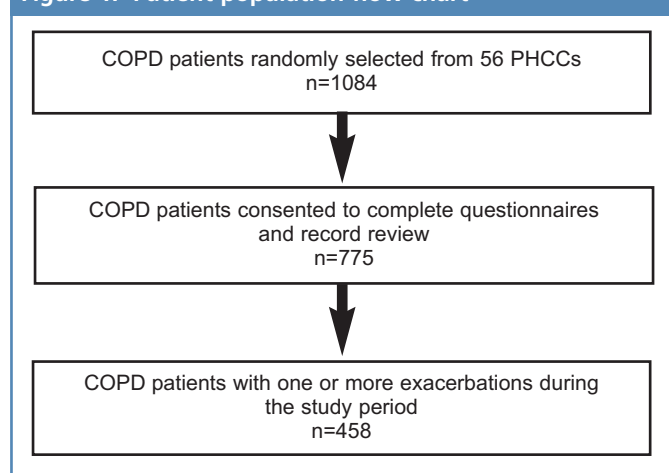
Sex, age, level of education, and smoking status were obtained from patient questionnaires. The dichotomous education variable identified education for at least two years beyond the compulsory period of nine years. Information about co-morbidity, lung function, and exacerbations was obtained from medical records. All first and second exacerbations were identified by careful record review of characteristics of patient visits. An exacerbation was defined as an unscheduled or emergency visit at a PHCC or hospital due to increased dyspnoea, increased cough, increased sputum production, purulent sputum, or an airway infection. In addition, the visit should result in either treatment with oral or parenteral steroids, inhalation using nebulised bronchodilators, treatment with antibiotics, hospital admission due to COPD symptoms, or alteration to maintenance or rescue medication. A minimum of 14 days was the defined period between exacerbations, as previously used in a Swedish study.<sup>27</sup> Information was collected on examination, treatment, and planned extra follow-up at exacerbation visits (Table 1). Heart disease (ischaemic heart disease or heart failure), type 1 or 2 diabetes mellitus, and depression (diagnosis combined with pharmaceutical therapy) were identified. Lung function data were available for 184 patients (40.2%). Forced expiratory volume in one second (FEV<sub>1</sub>) was expressed as percentage of predicted using the European Community for Steel and Coal reference value.<sup>28</sup> The subgroup of patients with spirometry data was divided by COPD stage according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations.<sup>15</sup> Information about nurse-led asthma/COPD clinics, nebulisers, pulse oximeters, and spirometers was obtained from the clinical questionnaires.

### Statistical analysis

The analyses were performed using PASW Version 20.0 (SPSS Inc, Chicago, Illinois, USA) and Stata (StataCorp LP, College Station, Texas, USA). Cross-tabulations and the  $\chi^2$  test examined differences in measures at exacerbation visits in primary versus secondary care, and between patients with one and more than one exacerbation visits. Kaplan-Meier and Cox regression analyses assessed time from first to second exacerbation, with adjustment for age and sex. The proportional hazards assumption was violated for the following measures: added rescue medication, altered maintenance treatment, and extra scheduled visits to nurse and doctor as tested by Schoenfeld residuals and graphically. For this reason, all analyses were right-truncated for follow-up to 22 months as hazards were proportional to this time.

The analyses were repeated with further adjustment for lung function in a subgroup of 184 patients with spirometry data. Associations with follow-up by doctor or nurse were further investigated through stratification and interaction by sex, age, prescribed steroid course, and lung function. Hazard ratios (HR) with

Figure 1. Patient population flow chart



**Table 1. Measures at exacerbation visit 1**

Examinations and measures	N (%)	Exacerbation visit PHCC (n = 391, 85%)	Exacerbation visit hospital (n = 67, 15%)	p Value
PEF				
Before inhalation of bronchodilators	213 (47.5%)	179 (46.9%)	34 (51.5%)	0.484
After inhalation of bronchodilators	121 (26.6%)	103 (26.4%)	18 (27.7%)	0.829
Saturation	65 (14.3%)	18 (4.6%)	47 (72.3%)	<0.0001
Lung auscultation	440 (96.7%)	375 (96.4%)	65 (98.5%)	0.381
Heart rate	135 (29.6%)	82 (21.0%)	53 (80.3%)	<0.0001
Arterial blood gas	23 (5.0%)	1 (0.3%)	22 (33.3%)	<0.0001
X-ray lungs	64 (14.0%)	30 (7.7%)	34 (51.5%)	<0.0001
CRP	237 (52.0%)	191 (49.0%)	46 (69.7%)	0.002
Electrocardiogram	37 (8.1%)	20 (5.1%)	17 (25.8%)	<0.0001
Hospital admission or acute referral to hospital	39 (8.6%)	12 (3.1%)	27 (40.9%)	<0.0001
Inhaled nebulised bronchodilators	186 (40.6%)	144 (36.8%)	42 (62.7%)	<0.0001
Course of steroids	128 (27.9%)	93 (23.8%)	35 (52.2%)	<0.0001
Course of antibiotics	274 (59.8%)	233 (59.6%)	41 (61.2%)	0.805
Planned extra follow-up				
No extra visit	324 (70.7%)	278 (71.1%)	46 (68.7%)	Ref
Extra visit or call doctor	86 (18.8%)	65 (16.6%)	21 (31.3%)	0.034
Extra visit nurse	48 (10.5%)	48 (12.3%)	0 (0%)	<0.0001

Examinations performed and measures taken at exacerbation visit 1 according to medical records, in total and distributed over level of care. CRP=C reactive protein, PEF=peak expiratory flow.

95% confidence intervals (95% CI) were presented and a p value <0.05 was considered statistically significant.

**Ethics**

The study was approved by the Regional Ethical Review Board of Uppsala University (Dnr 2010/090). Written consent to use the information for future analysis was obtained for all participating patients in 2005.

**Results**

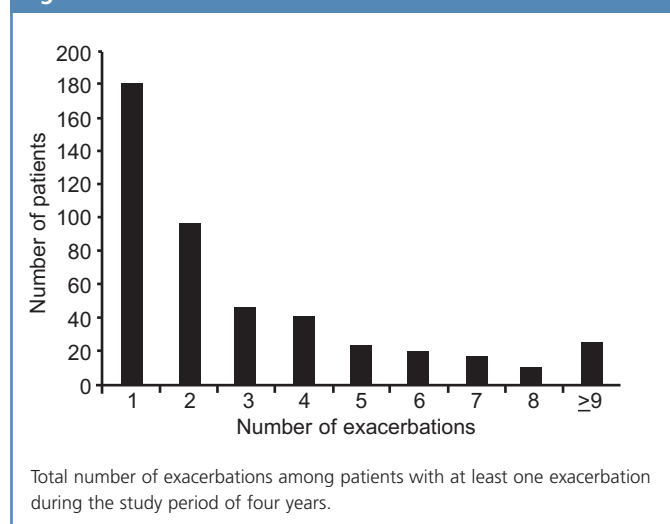
A median number of 2 (range 1–49) exacerbations was observed over the four-year study period, and the distribution is presented in Figure

2. Examinations and prescriptions by first emergency visit in a PHCC and in a hospital are described in Table 1 and Figure 3.

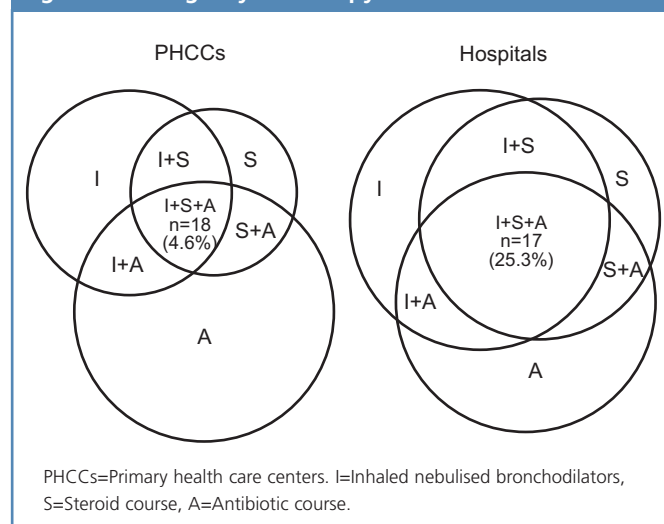
Of the 458 patients with at least one exacerbation, 238 patients had a second exacerbation within 22 months (Table 2). The analyses were repeated without the 22-month right-truncation with no material alteration of the results (data not shown). Table 2 shows the characteristics of patients with one or more than one exacerbations.

Female sex and treatment with a course of oral steroids were both statistically significantly and independently associated with an increased risk of a subsequent exacerbation (Table 3). Added maintenance and rescue medication and an extra planned visit to a

**Figure 2 Number of exacerbation visits**



**Figure 3 Emergency at therapy exacerbation visits**



**Table 2. Comparison of patients with and without an additional exacerbation**

Characteristics and measures	Patients with 1 exacerbation	Patients with $\geq 2$ exacerbations	p Value
All (n=458)	220 (48%)	238 (52%)	
Sex (n=458)			
Male	92 (41.8%)	73 (30.7%)	Ref
Female	128 (58.2%)	165 (69.3%)	0.013
Educational level*			
Lower	151 (69.6%)	169 (72.8%)	Ref
Higher	66 (30.4%)	63 (27.2%)	0.446
Current daily smoker**			
No	146 (66.7%)	165 (69.3)	Ref
Yes	73 (33.3%)	73 (30.7%)	0.542
Age (years)			
<50	18 (8.2%)	16 (6.7%)	0.876
51-60	51 (23.2%)	60 (25.2%)	0.204
61-70	90 (40.9%)	111 (46.6%)	0.101
>70	61 (27.7%)	51 (21.4%)	Ref
Comorbidity			
Heart disease	50 (22.7%)	45 (18.9%)	0.314
Depression	35 (15.9%)	32 (13.4%)	0.456
Diabetes	19 (8.6%)	23 (9.2%)	0.703
Lung function ***			
Stage 1	38 (42.2%)	22 (23.4%)	Ref
Stage 2	30 (33.3%)	41 (43.6%)	0.017
Stage 3	20 (22.2%)	27 (28.7%)	0.034
Stage 4	2 (2.2%)	4 (4.3%)	0.171
Level of care exacerbation visit 1			
PHCC	197 (89.5%)	194 (81.5%)	Ref
Hospital	23 (10.5%)	44 (18.5%)	0.015
Added maintenance therapy	76 (34.5%)	51 (21.4%)	0.002
Added rescue therapy	28 (12.7%)	14 (5.9%)	0.011
Acute inhalation therapy	90 (40.9%)	96 (40.6%)	0.901
Course of steroids	46 (20.9%)	82 (34.5%)	0.001
Course of antibiotics	128 (58.2%)	146 (61.3%)	0.490
Planned extra follow-up			
No extra visit	147 (66.8%)	177 (74.4%)	Ref
Extra visit or call doctor	43 (19.5%)	43 (18.1%)	0.444
Extra visit nurse	30 (13.6%)	18 (7.6%)	0.029

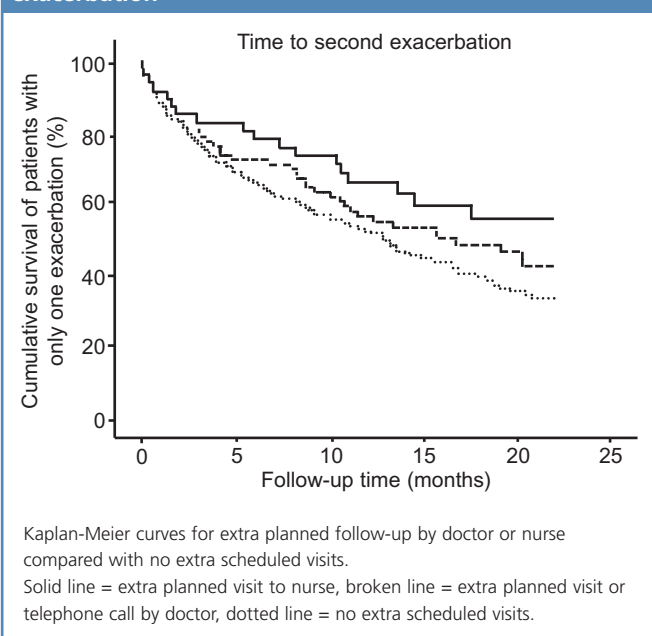
Study period truncated at 22 months.

Number with available information: \*n=449, \*\*n=457, \*\*\*n=184.

nurse compared with no extra scheduled visits were statistically significantly and independently associated with a decreased risk of a subsequent exacerbation (Table 3, Figure 4).

When examining only patients with the first visit in primary care, the HR for the association between an extra planned visit to a nurse and reduced risk for subsequent exacerbation was 0.64 (95% CI 0.39 to 1.05),  $p=0.077$ .

In the subgroup of 184 patients with lung function data, the association of a steroid course with increased risk of a new exacerbation remained both after adjustment for sex and age (HR 1.94 (95% CI 1.25 to 3.02),  $p=0.003$ ) and additional adjustment for

**Figure 4 Planned follow-up and time to second exacerbation**

lung function (HR 1.88 (95% CI 1.20 to 2.94),  $p=0.006$ ). The association of female sex with a higher risk of a subsequent exacerbation remained after adjustment for age (HR 1.65 (95% CI 1.04 to 2.61),  $p=0.032$ ) and was somewhat attenuated after adjustment for lung function (HR 1.59 (95% CI 1.01 to 2.52),  $p=0.050$ ). The same pattern was shown for an extra planned visit to a nurse; the association with a reduced exacerbation risk was statistically significant after adjustment for age and sex (HR 0.48 (95% CI 0.25 to 0.91),  $p=0.025$ ) but not after additional adjustment for lung function (HR 0.55 (95% CI 0.28 to 1.07),  $p=0.77$ ). The associations with the risk of a second exacerbation for added rescue medication and maintenance medication were eliminated by further adjustment for lung function (data not shown). Higher COPD stage was associated with a higher risk of a subsequent exacerbation (data not shown).

Patients treated with a steroid course statistically significantly more often had a planned follow-up by a doctor (39.5%) than by a nurse (20.8%) ( $p=0.027$ ;  $p$  for interaction=0.043). Stratification and interaction analyses by sex, age, and lung function showed no differences in the adjusted associations with second exacerbation risks for extra scheduled visits to a doctor or nurse (data not shown).

The clinical questionnaire revealed that 36 of the participating 56 PHCCs (64%) and seven of the 14 secondary care clinics (50%) had a specific nurse-led asthma/COPD clinic. In the PHCCs, nebulisers for inhalation of bronchodilators were available in 50 centres (89%), pulse oximeters in 46 centres (82%), and spirometers in 52 centres (93%). All 14 secondary care clinics had access to pulse oximetry and nebulisers, and 13 (93%) had their own spirometer.

## Discussion

### Main findings

The main finding of this multicentre study of primary care COPD

**Table 3. Cox regression analyses for preventive measures**

Characteristics and measures	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Sex				
Male	Ref		Ref	
Female	1.40 (1.06 to 1.85)	0.016	1.40 (1.06 to 1.86)	0.019
Acute inhalation treatment	1.14 (0.88 to 1.48)	0.307	1.16 (0.89 to 1.50)	0.267
Course of steroids	1.56 (1.19 to 2.04)	0.001	1.58 (1.21 to 2.07)	0.001
Course of antibiotics	1.08 (0.83 to 1.40)	0.580	1.05 (0.81 to 1.36)	0.734
Added rescue treatment	0.54 (0.31 to 0.93)	0.025	0.53 (0.31 to 0.91)	0.022
Added maintenance treatment	0.72 (0.53 to 0.98)	0.038	0.73 (0.54 to 1.00)	0.048
Planned extra follow-up				
No extra scheduled visit	Ref		Ref	
Extra visit or call to doctor	0.81 (0.58 to 1.13)	0.214	0.82 (0.59 to 1.15)	0.254
Extra visit nurse	0.58 (0.36 to 0.94)	0.026	0.60 (0.37 to 0.99)	0.045

Study period truncated to 22 months. Adjusted for sex and age.

patients is that a considerable proportion of patients consulting for an exacerbation were not examined, treated, and planned for follow-up as recommended in the guidelines.

Furthermore, we found that female sex and treatment with steroid courses were associated with a higher risk of a subsequent exacerbation, and that added rescue or maintenance medication and an extra planned visit to an asthma/COPD nurse following an exacerbation were associated with a reduced risk of subsequent exacerbations.

### Interpretation of findings in relation to previously published work

Interestingly, not only patients in COPD stage 3 but also those in stage 2 statistically significantly more often had two or more exacerbations compared with patients in COPD stage 1. Thus, even patients with moderate disease might often have exacerbations, which supports the intention of the recent GOLD updates to consider exacerbation frequency as well as symptoms and lung function when assessing the disease.<sup>15</sup> The number of patients in stage 4 is too small to draw firm conclusions.

National and international guidelines support careful examination at exacerbation visits.<sup>13-15</sup> This study suggests that management should be improved – especially with respect to measuring oxygen saturation and heart rate – in order to identify patients with severe exacerbations in need of hospital admission. Recommendations were better followed when primary care patients with exacerbations were managed in hospitals, but management was not optimal at any level of care.

It is interesting that courses of oral steroids and nebulised bronchodilators were more often used in secondary care while antibiotics were equally common in primary and secondary care. The difference in treatment of exacerbations in PHCCs and hospitals might at least partly reflect differences in the severity of the exacerbations, but is still unexpected. However, treating exacerbations with antibiotics and steroids is evidence-based<sup>29-32</sup> and recommended in international guidelines.<sup>13-15</sup> Our study showed no association between treatment with antibiotics and subsequent exacerbation, and an increased risk of treatment with a course of oral steroids. We believe that this is at least partly because the patients receiving steroids had more severe disease with greater risk of new exacerbations.

Our findings are consistent with studies of exacerbation management in hospitalised COPD patients,<sup>16,17</sup> but we are not aware of other similar studies describing the management of COPD exacerbations in primary care patients in both PHCCs and hospitals.

Women are known to have an increased susceptibility to develop COPD.<sup>33</sup> Biological explanations such as through hormones have been suggested.<sup>34</sup> The association with a higher risk for a subsequent exacerbation among women in this study is consistent with several studies of secondary care patients<sup>35,36</sup> but has not been shown previously for primary care patients.

Information from the clinical questionnaires revealed that only about two-thirds of the participating PHCCs and about half of the participating hospital clinics in this study had specific nurse-led asthma/COPD clinics. A Swedish study examining resources in PHCCs in western Sweden found that 82% of PHCCs had a nurse specifically responsible for COPD,<sup>37</sup> and a more recent Swedish study found that the proportion of asthma/COPD clinics was even higher (87%).<sup>18</sup> In the same studies, the presence of pulse oximeters and nebulisers was equal or slightly higher than in our study. Since our study examines management in an earlier calendar period than the other Swedish studies, this indicates that national recommendations regarding structure of COPD care have been better implemented over time.

The organisation of COPD care has been studied in several countries. Nurse-led asthma/COPD clinics are common in the UK,<sup>38,39</sup> and nurse-based information programmes have been used in the Netherlands with a beneficial effect on exacerbation frequency.<sup>40</sup> An integrated care system including a nurse case manager associated with a reduced risk of hospital admissions due to COPD exacerbations has been described in Spain and Belgium.<sup>41</sup> A previous meta-analysis in the UK examined nurse-led management interventions for COPD with no certain positive effects.<sup>42</sup> However, the organisation of nurse-led asthma/COPD clinics might differ between countries. Our finding that an extra scheduled visit to a nurse after an exacerbation might be associated with a reduced risk of a subsequent exacerbation is consistent with a Swedish study where patients in PHCCs with nurse-led asthma/COPD clinics had fewer exacerbations.<sup>18</sup>

A possible explanation for the decreased exacerbation risk following an extra scheduled visit to a nurse could be selection bias, if patients chosen for follow-up by nurse were generally healthier

than patients with planned doctor follow-up. This could be consistent with the higher rate of steroid courses among those with planned follow-up by a doctor. On the other hand, COPD stage did not differ significantly between the doctor and nurse follow-up groups. Thus, our findings are unlikely to be explained entirely by selection bias.

Another possible explanation is that patients with a first exacerbation visit at a hospital could have more severe exacerbations and none of these patients had an extra planned nurse visit. A sub-analysis of patients with the first exacerbation visit in a PHCC was examined. This resulted in a HR of similar magnitude but was no longer statistically significant, which is partially explained by reduced power due to fewer patients. We believe that exacerbation visits at hospitals do not necessarily signal more severe exacerbations. In Sweden, primary care patients have limited access to GPs during evenings and weekends and so may present at hospitals.

We believe the association between an extra planned nurse visit could indicate reactivity of the PHCC management team to the exacerbation to optimise care. It could be a marker for generally better COPD care with integrated management. The nurse may have more time to develop a comprehensive view of the patient and help to implement strategies to reduce exacerbation risk.

### Strengths and limitations

Strengths of this study are that it is longitudinal and comprises a real clinical population of COPD patients without exclusion criteria, randomly sampled from multiple centres. This ensures a high level of generalisability. Further, the data from medical records were initially recorded prospectively and should be reliable and not subject to different recall bias.

A limitation is that lung function data were only available for a subset of the study population, although most clinics had access to spirometry. Possible explanations might be that spirometry had been performed but not reported in the records or that patients had a diagnosis confirmed by spirometry before the study. Patients with severe disease might have been particularly unable or unwilling to perform a lung function test. It has been demonstrated that many COPD diagnoses are based on clinical findings rather than spirometry.<sup>23</sup>

We did not have access to records prior to the study period 2000-2003 so earlier spirometry data were unavailable. Another potential issue is that 32% of the spirometry measurements were based on pre-bronchodilator values but we speculate that, in most of these cases, spirometry with reversibility test had also been performed previously.

Only exacerbation visits in PHCCs and hospitals in the seven counties of the study area were examined. However, we believe that failure to identify exacerbation visits abroad or in other parts of the country must constitute a very small number, not influencing the results of the study. COPD exacerbations may sometimes be labelled and treated incorrectly, and we may have missed some exacerbations or included non-exacerbation events. However, our standardised definition should ensure accurate identification of the vast majority of exacerbations. The exacerbations were not graded by severity, but our definition captured exacerbations associated with a healthcare visit and prescribed treatment, indicating severity relevant to use of

healthcare resources and patient well-being.

Finally, in our investigation of extra planned visits we cannot be certain that the visits occurred. However, we believe an extra scheduled visit could still serve as a surrogate marker for fulfilled visits and responsive COPD management.

### Implications for future research, policy and practice

This study shows that the guidelines for exacerbation management should be better implemented, especially in PHCCs where the majority of exacerbation visits among primary care patients take place. Previous studies have shown that educational programmes of management in stable COPD have improved compliance with guidelines,<sup>43,44</sup> and it should also be possible to apply this to the management of exacerbations.

The issue of how COPD care should be organised is very important, and this study showed that very few patients were scheduled for extra follow-up. We believe that the finding that an extra scheduled visit to a nurse is as good as a scheduled visit to a doctor and even might reduce the risk of subsequent exacerbation is important and could be a way of optimising resources in COPD care. However, the findings should be confirmed in appropriate studies with adequate statistical power.

### Conclusions

Guidelines for management of COPD exacerbation visits are not followed optimally and ought to be better implemented. Integrated management including nurse-led asthma/COPD clinics might assist in optimising COPD care relevant to exacerbation risk.

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