The costs of exacerbations in chronic obstructive pulmonary disease (COPD)

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Abstract   Exacerbations are the key drivers in the costs of chronic obstructive pulmonary disease (COPD). The objective was to examine the costs of COPD exacerbations in relation to differing degrees of severity of exacerbations and of COPD. We identified 202 subjects with COPD, defined according to the BTS and ERS criteria. Exacerbations were divided into mild (self-managed), mild/moderate (telephone contact with a health-care centre and/or the use of antibiotics/systemic corticosteroids), moderate (health-care centre visits) and severe (emergency care visit or hospital admission). Exacerbations were identified by sending the subjects a letter inquiring whether they had any additional respiratory problems or influenza the previous winter. At least one exacerbation was reported by 61 subjects, who were then interviewed about resource use for these events. The average health-care costs per exacerbation were SEK 120 (95% CI=39–246), SEK 354 (252–475), SEK 2111 (1673–2612) and SEK 21852 (14436–29825) for mild, mild/moderate, moderate and severe exacerbations, respectively. Subjects with impaired lung function experienced more severe exacerbations, which was also reflected in the cost of exacerbations per severity of the disease during the $4\frac{1}{2}$ month study period (ranging from SEK 224 for mild to SEK 13708 for severe cases, median SEK 940). Exacerbations account for 35–45% of the total per capita health-care costs for COPD. In conclusion, costs varied considerably with the severity of the exacerbation as well as with the severity of COPD. The prevention of moderate-to-severe exacerbations could be very cost-effective and improve the quality of life. © 2002 Elsevier Science Ltd. All rights reserved.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease among adults and the elderly. In developed countries the estimated prevalence is 4–6% among adult males and 1–3% among adult females, and this prevalence, particularly among women, is increasing (1–3). The dominant risk factor is smoking, a widely accepted figure being the development of COPD by 15% of smokers. However, according to the recent U.S. National Health and Nutrition Study (NHANES) III and the Obstructive Lung Diseases in Northern Sweden Studies (OLIN), sooner or later as many as 50% of smokers may develop COPD (4,5). COPD is also a disease which is

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demanding in terms of health-care resources consumed (6,7), the key cost driver being acute exacerbations (7,8).

COPD is a slowly progressive disease. Acute exacerbations, or acute worsening of respiratory symptoms, occur commonly in subjects with COPD (8). These exacerbations differ in severity. It has been estimated that the average COPD patient experiences about one to four acute exacerbations per year (9). Health-care utilisation is usually significantly increased during an exacerbation (7,8,10,11) and the quality of life of the individual is considerably reduced (12). Furthermore, exacerbations are the most frequent cause of hospital admission and death among subjects with COPD (13).

A reduction in the number of exacerbations of COPD has been identified as an important outcome in national and international guidelines and in the clinical literature (8,14–18). Unfortunately, exacerbations are described

rather than defined in the guidelines and these descriptions are of limited consistency. Hence, at present there is no universally accepted clinical definition of what constitutes an acute exacerbation of COPD or of how to grade the severity of such an exacerbation. There are limited data about the incidence of exacerbations of differing severity. Moreover, data on the economic consequences of exacerbations are very scarce.

The purpose of this paper is to examine the costs of COPD exacerbations in relation to differing degrees of severity of exacerbations and of COPD.

MATERIAL AND METHODS

Sample

Details of the study sample were described in a previous publication (6). Briefly, the sample was generated from large-scale studies, which started in 1985, of the epidemiology of obstructive pulmonary diseases and type I allergy in northern Sweden (the OLIN studies). Today, longitudinal studies of a number of cohorts are under way, including a total of approximately 40 000 children, adults and elderly individuals (19–23).

The inclusion criterion, a diagnosis of COPD, was based on spirometry testing. This diagnosis was primarily defined according to the British Thoracic Society's (BTS) criteria: an FEV_1/VC ratio $<70\%$ and an FEV_1 $<80\%$ of predicted values. BTS divides COPD into mild, moderate and severe disease (16). In addition, persons with an FEV_1/VC ratio $<70\%$ and an FEV_1 $\geqslant 80\%$ of the predicted value were also included in the study. The inclusion of this mild type of COPD is in full agreement with the recent Global Initiative of Chronic Obstructive Pulmonary Disease (GOLD) guidelines (14) and corresponds approximately to the criteria of the European Respiratory Society

(ERS) for mild COPD (17). Subjects with other diseases which explained their impaired pulmonary function were excluded. Those with chronic pulmonary obstruction who referred to themselves as asthmatics were included, which is supported by the BTS guidelines (16).

The number of patients diagnosed with COPD in the OLIN studies is about 800, although when stratifying by age (range 28–80 years) and disease severity ($FEV_1\%$ predicted 18–118), some strata contain relatively few subjects. Accordingly, all subjects with an FEV_1 $<60\%$ of predicted values were included in the study cohort. In the case of subjects with an FEV_1 $\geqslant 60\%$ of the predicted value, a random sample was drawn from each stratum to give a study cohort of a sufficient size to allow the measurement of significant differences between different groups of severity. By subsequently assigning weights to our strata based on prevalence, we avoided bias originating from our selection, since the weighted strata generated the weighted results according to the prevalence of subjects of a similar age and degree of severity. The study population is shown in Table I. As can be seen from the table, the random sample was first used in a recently completed cost-of-illness study (6). This very same sample was subsequently used for the present cost of exacerbation study.

The study was approved by the ethics committee at the Umeå University and the University Hospital of Northern Sweden in Umeå.

Study design

The 202 subjects with COPD were sent a letter in March 2000, which asked them whether they had needed to do any of the following because of additional respiratory

TABLE I. Study sample by severity of COPD. Number of subjects with and without exacerbation

	FEV$_1$ % predicted				
	< 40%	40–59%	60–79%	$\geqslant$ 80%	All
Subjects diagnosed with COPD-OLIN	41	105	294	339	779
Contacted subjects for the COI study (6)[a]	37	99	108	49	293
Enrolled subjects for the COI study (6)[b]	28	72	79	34	213
Completing subjects in the COI study (6)	24	68	76	34	202
Study sample					
Subjects receiving questionnaire	24	68	76	34	202
Non-responders, dead	0	1	1	0	2
Non-responders, other reason[b]	0	4	3	2	9
Participated in the exacerbation study	24	63	72	32	191

[a]Alive.
[b]The individuals who did not participate were too ill, were not living at the given address, could not be reached by telephone, did not speak Swedish or refused to participate in the COI study.

problems or influenza during the previous winter (November–March):

- take more medication for respiratory disease,
- take time off work,
- make an unplanned visit to a nurse or doctor (at a GP's surgery or hospital),
- visit an emergency care unit, or
- stay overnight in a hospital.

Two weeks later a reminder was sent out. The subjects who answered 'yes' to any of these questions were included in the study.

Methods

A structured telephone interview, using a specially designed and pilot-tested questionnaire, was conducted by a registered nurse (A-C J). The questionnaire focused strictly on extra resources use in connection with the respiratory problems. The incremental costs due to an exacerbation were included, while the costs of day-to-day COPD treatment were excluded. Visits and hospitalisations were verified by the patient records since these two items have been found to account for a large proportion of the total health-care costs for COPD, irrespective of the country involved (24–27).

The following definitions of exacerbation were used:

- *Mild exacerbations* were defined as those self-managed by the subject by increasing the dose of the current medication (including adding OTC medication).
- *Mild/moderate exacerbations* were those requiring telephone contact with a health-care centre and/or treatment with antibiotics or systemic corticosteroids.
- *Moderate exacerbations* required a visit to a GP or to an outpatient clinic.
- *Severe exacerbations* required visits to an A&E department or hospital admission.

An exacerbation was classified according to the highest level of resource use, e.g. a telephone call followed by a visit to a GP was classified as moderate. The definitions resemble the definitions proposed by a working group convened following the 1999 Aspen Lung Conference (8), with the exception of the two milder types, which were combined into one type of exacerbation.

We used the BTS and ERS staging systems to divide the severity of COPD into: <40, $40–59$, $60–79$ and $\geqslant 80\%$ FEV_1 predicted.

Analysis

The resources recorded were medicine, health-care contacts, visits to A&E departments, hospitalisation and transportation to the health-care provider. Resource use was multiplied by the 1999 unit prices shown in Table 2, which reflect local prices in northern Sweden. The exchange rates on January 3, 2002 were USD 1 = SEK 10.23 and one euro = SEK 9.25.

Homogeneity of categorical data was tested using chi-square tests (e.g. differences in occupation, smoking habits, risk of experiencing exacerbations, etc). Comparisons of cost data between several groups were made using analyses of covariance (ANOVA model). Simultaneous comparisons of group means were made using multiple comparison analysis (MCA) (29). A *P*-value less than 0.05 was considered to be statistically significant.

In calculating prevalence-weighted average costs as well as societal costs, we used previously estimated national prevalence estimates, broken down by disease severity and official population data (6,30,31). The estimated Swedish total COPD prevalence was about 678 000 individuals (6). These detailed prevalence numbers were used to weight our sample, as we sampled all patients below FEV_1 60%. In this way, we arrived at average values that should reflect the distribution of COPD patients in Sweden (4,6,31).

RESULTS

Patient description

The final response rate was 95% (Table 1). Of the 11 non-participants, two had died since the previous contact. The remaining nine subjects did not respond or were unwilling to participate even after a second reminder. A total of 61 subjects (32%) reported that they had needed to do one or more of the activities listed under study design (Fig. 1).

Five additional subjects reported having experienced additional respiratory problems and/or influenza,

TABLE 2. Unit costs (SEK, 1999)

Resource	Costs
Medicine (28)	According to specified use
Visit/contact, physician, per visit or contact	1170
Visit/contact, other personnel, per visit or contact	340
Hospitalisation	
Respiratory	2810
General	3650
Intensive care unit	5440
Primary care centre	3030
Transportation, per 10 km	15
Ambulance transport, per transport	2479

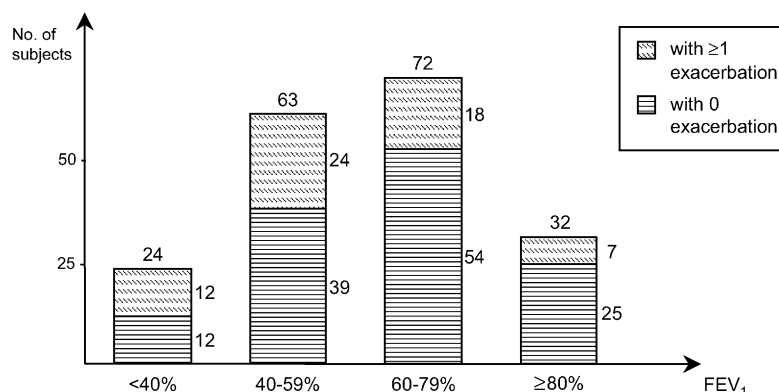*Sources:* County council, Norrbotten, Sweden and (6).

FIG. I. Exacerbation rate by severity of COPD.

giving rise to an additional seven exacerbations. They were excluded from the analysis, however, because it was later established that they either did not consume any additional resources (hence by our definition did not experience an exacerbation, three subjects reporting in total four exacerbations) or were mentally confused and therefore unable to provide any reliable information (two subjects reporting four exacerbations).

Exacerbations in relation to demography

The analyses are based on 61 subjects (out of the 191 responders), who accounted for a total of 75 exacerbations. There were no significant differences in age, gender and smoking habits among those who experienced an exacerbation and those who did not. Subjects who experienced one or more exacerbations had a significantly lower FEV_1 as a percentage of that predicted than those who did not experience any exacerbations ($P=0.028$, Table 3). In addition, they were to a lesser extent part of the labour market. About 5% of the subjects without exacerbations were registered as disabled due to their disease, compared with 21% of the 61 subjects with exacerbations ($P<0.001$).

Half of those with severe COPD reported having had one or more exacerbations, compared with only 25% of those with very mild or mild COPD (Fig. I). On average, 32% of the subjects reported an exacerbation during this period.

The risk of experiencing exacerbations differed significantly between the FEV_1 classes when adjusting for exacerbation types ($P=0.002$). For example, subjects with severe COPD reported on average one severe exacerbation during the study period, compared with $0-0.125$ for the very mild-to-moderate subjects (Table 4).

TABLE 3. Study sample demography in subjects with and without exacerbations

	Subjects with no exacerbations	Subjects with one or more exacerbation	Difference
Number of subjects	130	61	
Mean age in years (STD)	63.3 (12.9)	64.6 (10.8)	ns
Min – max	28–80	43–80	
Mean FEV_1% of predicted (STD)	64.1 (18.8)	56.9 (20.8)	$P=0.028$
Min – max	25–118	18–100	
Gender (% male/female)	62/38	51/49	ns
Smoking habits			ns
Non-smokers (%)	18	13	
Ex-smokers (%)	43	56	
Smoker (%)	38	31	
Occupation			
Employed, full-time (%)	28	13	
Employed, part-time (%)	1	3	
Other (retired, unemployed, etc.) (%)	71	84	$P=0.004$

TABLE 4. Number and severity of exacerbations by severity of COPD

Exacerbations	FEV$_1$				
	< 40% (n=12)	40–59% (n=24)	60–79% (n=18)	⩾ 80% (n=7)	All (n=61)
Mild (self-managed)	2	7	8	6	23
Mild/moderate (telephone contact and/or antibiotic and/or oral steroid)	4	5	1	0	10
Moderate (health-care outpatient visit)	5	10	8	2	25
Severe (emergency visit or hospitalisation)	12	3	2	0	17
All	23	25	19	8	75

Exacerbations in relation to costs

As expected, resource use for the four different types of exacerbations differed. The average number of medicines used during a mild exacerbation was 1.6, slightly lower than during mild/moderate (2.7) and moderate (2.6) exacerbations, but much lower than for severe exacerbations (4.2). Some medications were added compared to regular treatment (e.g. antibiotics), whereas for some the dose was increased (e.g. short-acting β_2-agonists). The main groups of medicines were short- and long-acting β_2-agonists (80% of exacerbations, mainly salbutamol), antibiotics (36%, mainly doxycycline), closely followed by systemic corticosteroids (34%, prednisolone). Inhaled corticosteroids, anticholinergics and xanthines were used in 23, 21 and 17% of the exacerbations, respectively. OTC medication (e.g. painkillers,

cough & cold remedies) was also used to a large extent (48% of exacerbations).

The number of phone contacts ranged from 0.29 for severe exacerbations to 1.2 for mild/moderate exacerbations. The number of health-care visits was 0.65 for severe exacerbations and 1.56 for moderate exacerbations. Thus, we find a certain interchangeability between different forms of resource use. The average length of stay in hospital for a severe exacerbation was 6.6 days (median 6 days).

The costs of treating COPD exacerbations increased considerably with severity (Table 5). Severe exacerbations were on average about 10 times more expensive than moderate and 60 times more expensive than mild/ moderate exacerbations. Weighted average exacerbation costs show that hospitalisation accounts for two-thirds of the total costs (Fig. 2).

TABLE 5. Mean (median) costs per exacerbation according to severity (SEK, 1999)

	Exacerbation type				
	Mild (n=23)	Mild/Moderate (n=10)	Moderate (n=25)	Severe (n=17)	Weighted average, per exacerbation (%)
Cost of medicine	120 (36)	252 (265)	291 (203)	400 (271)	181 (6%)
Cost of visits/contacts	N/A	102 (110)	1778 (1170)	576 (0)	769 (24%)
Transportation	N/A	N/A	41 (9)	523 (158)	80 (3%)
Hospitalisation cost	N/A	N/A	N/A	20 352 (21 900)	2106 (67%)
Direct costs					
Mean	120	354	2111	21852	3163 (100%)
95% CI	39–246	252–475	1673–2612	14 436–29 825	2649–3657
Median	36	375	1483	22 869	–
STD	264	194	1235	16 645	–

Note: Combining the two milder types of exacerbations results in an average cost of SEK 191 (median SEK 69). The weighted average takes into account the proportion of each severity grade in the general Swedish COPD population. N/A: due to definition not applicable.
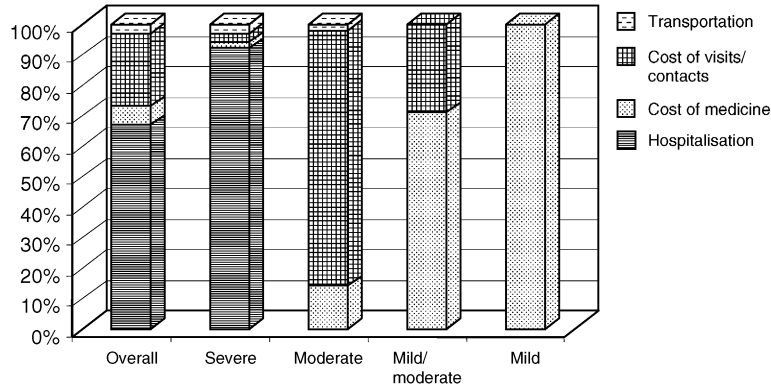
Fig. 2.   Per cent of total costs of exacerbations.

Exacerbations in relation to severity of COPD

During the $4\frac{1}{2}$ month study period, the total per capita costs due to exacerbations, i.e. including all types of exacerbations and weighting them according to frequency, varied from SEK 13 708 in subjects with severe COPD to SEK 294 in those with very mild COPD (Table 6). The subjects with the lowest FEV_1% predicted were a source of significantly higher costs than those in the three other groups of disease severity, mainly because they experienced a higher rate of severe exacerbations. The prevalence-weighted $4\frac{1}{2}$ month cost of all (weighted) exacerbations for the average COPD subject was SEK 940 (95% CI=428–1 555). This means that during this particular winter the average COPD subject in this sample (and also in Sweden since we weighted the cost by national prevalence estimates) consumed extra resources amounting to SEK 940, all due to exacerbations.

At a national level, using recent prevalence estimates for each severity category (4,6,31) plus official population data (30) and assuming no seasonal variation, the estimated annual cost of exacerbations for all individuals with COPD in Sweden was about SEK 1.7 billion (95% CI; SEK 0.77–2.8).

DISCUSSION

This study examined the costs of COPD exacerbations in clinical practice from various aspects. Firstly, there was a difference between the population reporting an exacerbation and those who did not. Subjects reporting a recent exacerbation had lower lung capacity and were to a lesser extent part of the labour market. Secondly, subjects with a lower level of lung function experienced more, though also more severe, exacerbations. As a consequence, this also resulted in higher costs due to exacerbations in general. Thirdly, there were large cost differences between differing degrees of severity, with severe exacerbations having health-care costs more than 10 times higher than for moderate exacerbations and about 60 times higher than for mild/moderate exacerbations. Finally, the total cost due to exacerbations during the $4\frac{1}{2}$ month study period varied substantially between different levels of disease severity — for instance, severe COPD subjects experienced costs that were more than 45 times higher than those for mild COPD subjects.

The fact that subjects with impaired lung function reported more, but also more severe, exacerbations is in line with Rodriguez-Roisin (8), who claimed that the

Table 6.   Mean (median) costs per $4\frac{1}{2}$ months according to severity (SEK, 1999).

	COPD Severity Degree (FEV_1)				
	< 40%	40–59%	60–79%	⩾ 80%	Weighted average, per 4.5 months (%)
Cost of medicine	514	60	30	35	54 (6%)
Cost of visits/contacts	422	367	222	189	230 (24%)
Transportation	263	13	39	1	24 (3%)
Hospitalisation cost	12 510	263	406	0	631 (67%)
Direct costs: Mean	13 708	702	697	224	940
95% CI	3 580–27 509	334–1 203	189–1 469	6–584	428–1 555

classification and costs of an exacerbation are largely related to the underlying severity of the subject's condition. Furthermore, Miravitlles *et al.* (32) found FEV₁ to be an important explanatory variable in both their hospital admission and their exacerbation explanatory models.

Only limited previous data are available for the costs of exacerbations in COPD. An abstract was presented at the 1999 ERS meeting, with data from a randomised clinical study (33). Using definitions that are similar to the present study, its direct cost estimates of £15 for a mild exacerbation (self-managed), £95 for a moderate exacerbation (treated by a family physician or outpatient clinic) and £1659 for a severe exacerbation (requiring hospitalisation) are similar to our results. Segú *et al.* (34) studied a sample of 2414 Spanish patients with chronic bronchitis who sought medical attention from their primary care physician. The mean cost of antibiotic treatment was $30. About 21% of patients (*n*=507) required a new medical visit, defined as treatment failure. Of these, 154 patients were seen in A&E departments and 78 were admitted to hospital. The mean cost associated with these treatment failures was $404. Pechevis *et al.* (35) estimated the costs associated with recurrent respiratory infections in 244 French subjects with chronic obstructive bronchitis. The direct health-care costs per acute exacerbation were estimated to be FRF 3289 (about SEK 4600), of which 60% were hospital-related. Tiri and Grossi (36) put the costs of diagnostics and medical services and of medication (i.e. excluding hospitalisation) at about ITL 638 000 (about SEK 3000) in 54 Italian COPD subjects with exacerbations. About 50% of the overall figure was due to anti-infective treatment.

From a more global perspective, McGuire *et al.* (10) estimated for England and Wales the annual excess costs of acute exacerbations in patients with chronic bronchitis to be £45 million in 1994–1995. This figure represents between 0.1 and 0.2% of the National Health Service budget. Similarly, Niederman *et al.* (37) estimated the US costs of acute exacerbations in patients with chronic bronchitis to be $1.2 billion for patients above the age of 65 and $419 million for patients below this age. It is difficult to relate these exacerbation costs to the overall burden of COPD in these countries as the cost-of-illness studies employ a different methodology than the exacerbation studies.

The key cost driver in our study was hospitalisation, which accounted for 67% of the weighted costs of SEK 3136 per exacerbation. The weighted cost per exacerbation could be translated into a national estimate of SEK 1.7 billion per year. To put these numbers into perspective, a previous study on the same sample and with similar methodology has estimated that the annual Swedish health-care costs of COPD are about SEK 3.8 billion (6). In addition to the cost of exacerbations, this amount includes the cost of regular medication use, scheduled physician visits, etc. The annual value of SEK 1.7 billion should,

however, be interpreted with caution in that we have not taken into account the likelihood of seasonal variations in the frequency of exacerbations. For instance, Niederman *et al.* (37) found that for exacerbations in chronic bronchitis, the rates of hospital discharges were highest (about one-third of the total) in the first quarter of the year. If, for example, we make the conservative assumption that because of a higher prevalence the costs of exacerbations are 50% higher during our study period (winter), compared to the other 7½ months of the year, the annual Swedish costs of exacerbations fall to SEK 1.3 billion.

The *a priori* definitions of different types of exacerbations are clear, based on the intensity of resource use and not on clinical criteria. An exacerbation was classified according to the highest level of resource use, and this is bound to affect the level of costs. However, at present no generally accepted definition of exacerbations exists, nor can the individual be fully trusted in this regard. With this limitation in mind, it is comforting to note the similar distribution of different types of exacerbations in the clinical study by Paggiaro *et al.* (38).

The duration of an acute exacerbation is difficult to measure, given the day-to-day variation in symptoms. In a study on the effects of exacerbations on quality of life, Seemungal *et al.* (12) found that 50% of exacerbations were not reported by subjects. Recovery of lung function to baseline occurred after about 11 days. Our study attempted to find out from the subjects the duration of the reported exacerbation; however, it was found that the duration reported was closely related to the duration of a given prescription, e.g. a 7-day course of antibiotics or a 10-day course of systemic corticosteroids. Subjects, who were often elderly, were generally not able to recall or establish the starting and stopping dates, as they constantly experienced symptoms of varying severity. We did not measure day-to-day lung function as did Seemungal *et al.*

The potential for recall bias (39) could affect the results in two ways. Firstly, subjects were sent a letter in March 2000 in which they were asked about the incidence of respiratory problems during the winter season (November–March in the north of Sweden). The subjects, most of whom were elderly, could have forgotten early incidents of respiratory problems. However, we did exclude eight exacerbations reported by five subjects because reliable data were missing, resulting in a slight underestimate of the frequency. Secondly, if the actual incident was recalled, some resource use in connection with the exacerbation/incident could have been omitted, such as telephone calls. The latter is likely to be a minor problem for the moderate and severe exacerbations because all major resource use was verified by the patient records (visits and hospital admissions, which accounted for more than 85% of total costs). The subjects were also asked to bring their medication to the phone at the start

of the interview, which increased the validity of medicine use.

We also chose to include very mild COPD patients. There is a risk that we may also have included some asthmatic patients in our sample, especially since Table 3 shows that between 13 and 18% are non-smokers. However, in this particular area of Sweden a high proportion of the inhabitants may be at a serious risk of occupational exposures as many work in the steel industry and in mining, which are also well-known risk factors of lung disease. About 10% of our sample work or have worked in these two sectors. Furthermore, Miratvitlles *et al*. (40) reported that, in fact, 22% of a Spanish primary care COPD sample were non-smokers.

This study presents the first comprehensive information on the resource use and costs of COPD exacerbations, based on clinical practice. The limited earlier data on exacerbations are to a large extent based on samples from randomised clinical trials, samples that were selected on the basis of a number of inclusion and exclusion criteria. We used very few such criteria. Our data should be particularly valid in that they reflect a real-life setting and the subjects were guided by an experienced nurse during the telephone interview. The most expensive resource use, visits and hospital admissions, which accounted for about 85% of total costs, were verified by a review of patient journals. As for pulmonary rehabilitation, this is still uncommon in Sweden, and from the perspective of COPD in the general population, the costs for COPD rehabilitation are limited. That is also true for costs of surgery for emphysema, which indeed are high for the small number of cases that exist, but very limited from the perspective of the general population. We did not find any evidence of either in our sample. A second unique aspect of this study is that we have attempted to address the costs of mild, moderate and severe COPD exacerbations and have compared the costs. Most previous studies in which costs have been reported have involved only exacerbations admitted to hospital rather than outpatients as in this study. A third strength is the high response rate of 95%.

These cost estimates are only relevant for Sweden in that they reflect local treatment patterns, the organisation of health-care and welfare, and relative prices. However, we have seen that both the absolute and relative levels are in line with the limited existing data. The present sample and the geographical area (Norrbotten) studied are probably representative of the rest of Sweden in the way COPD is currently treated (6). Future prospective studies should verify and expand on our results. Further, our follow-up period covered $4\frac{1}{2}$ months, i.e. the winter period. During the winter, exacerbations occur more frequently, which is why our study focused on that period. Measuring annual costs of exacerbations requires a 12-month prospective follow-up period.

The size of the sample may in future studies need to be larger than our 61 individuals with 75 exacerbations. Alternatively, individuals may need to be followed for considerable periods of time to accumulate enough exacerbations to analyse. The numbers of exacerbations studied, once division is made in the severity of exacerbations or COPD, become even smaller. At the time of the study was planned (the autumn of 1999), however, we had very limited *a priori* information regarding the frequency of exacerbations, especially those of different grades of severity. Anthonisen *et al*. (18) had pointed out that COPD exacerbations occur at a rate of approximately one per year. In contrast, Seemungal *et al*. (12) had reported a total annual rate of exacerbations of 2.7 per patient in a sample of moderate-to-severe patients. An annual average of 2 exacerbations was later reported by Miravitlles *et al*. (40) in a survey of Spanish health centres. Our data show a much lower value, which in part may be due to differences in definitions and samples. The fact that only one-third of the individuals experienced an exacerbation is in line with the 6-month results of Paggiaro *et al*. (38). We did, however, try to include all available individuals with moderate and severe COPD in order to generate as many exacerbations as possible. We also give the 95% confidence intervals to enable the reader to assess the reliability of our results.

Exacerbations are the key drivers in the costs of COPD (8). These costs are likely to increase, given the increasing elderly population (25). Also, frequent exacerbations have been demonstrated to affect the quality of life (12). Furthermore, Seemungal *et al*. (41) recently presented data which indicate that exacerbations for some patients may also increase the general decline in lung function. Preventing or reducing the severity of exacerbations is potentially very cost-effective and will also enhance the quality of life of subjects. There are a number of promising drugs under development with the potential to improve the well-being of individuals with COPD.

In conclusion, exacerbations are costly, the costs varying considerably with the severity of the exacerbation. Furthermore, because of a higher frequency of more severe exacerbations, subjects with a more severe disease have significantly higher costs for exacerbations. The prevention of exacerbations, in particular those that are moderate/severe, is potentially cost-effective.

Acknowledgements

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