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FACTORS AFFECTING COPD-RELATED COSTS: A MULTIVARIATE ANALYSIS OF A SWEDISH COPD COHORT

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ABSTRACT

Aim: Chronic Obstructive Pulmonary Disease (COPD) is an increasing public health problem, generating considerable costs. The objective of this study was to identify the factors affecting COPD-related costs.

Methods: A cohort of 179 subjects with COPD was interviewed over the telephone on four occasions about their annual use of COPD-related resources. The data set and the explanatory variables were analysed by means of multivariate regression techniques for six different types of cost: societal (or total), direct (health care) and indirect (productivity), and three subcomponents of direct costs – hospitalisation, outpatient, and medication.

Results: Poor lung function, dyspnoea and asthma were independently associated with higher costs. Poor lung function (severity of COPD) significantly increased all six examined cost types. Dyspnoea (breathing problems) also did this, though to a varying extent. The presence of reported asthma increased total, direct, outpatient and medication costs.

Conclusions: Poor lung function and, to a lesser extent, extent of dyspnoea and concomitant asthma, were all strongly associated with higher COPD-related costs. Strong efforts should be made to prevent the progression of COPD and its symptoms.

Word count: 178

Key words: COPD, costs, cost drivers, multivariate explanatory model

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major public health problem. In 1990 it was ranked as the twelfth leading cause of disability-adjusted life-years (DALYs) lost and, according to projections, it will become the fifth such cause in 2020.(1) COPD is also a costly disease, generating considerable health-care costs as well as indirect costs in terms of lost productivity from days off work, early retirement and death caused by disease.(2-6)

Earlier research has identified several risk factors that affect the costs of COPD. For example, Crocket et al. showed a dependency between co-morbidity and length of stay in hospital.(7) Poor self-reported health status and health-related quality of life have been shown to increase resource utilisation.(6,8) In addition, poor lung function affects health-care utilisation.(3,9-11) However, few studies have been carried out which are detailed multivariate analysis of COPD costs.(12) As COPD is a complex disease with multiple facets it is essential to take into account the effect on costs from a number of potentially influencing factors and not to focus on one individual background factor at a time, as has been done in previous research.

The objective of this study was to identify factors influencing COPD costs in the Swedish society by means of multivariate analysis. From a policy standpoint, it is important to identify different risk factors and cost drivers in the society and to work proactively to influence these, if possible. We have also corrected for other confounding factors (e.g. age, gender). We analysed the factors potentially influencing societal (total), direct (health care) and indirect (productivity loss) costs, and the direct costs were further subdivided into hospitalisation, outpatient care (specialist, GP, nurse and home visits) and medication costs, as different factors may influence different types of costs and may be important to different payers and thus relevant from different perspectives.

MATERIALS AND METHODS

Study sample

The study sample was derived from the Obstructive Lung Disease in Northern Sweden (OLIN) studies, i.e. large-scale studies on the epidemiology of COPD, asthma and type-1 allergy in Northern Sweden which started in 1985.(13,14) Today, longitudinal studies of a number of cohorts are under way, including a total of approximately 40,000 children, adults, and elderly persons. The first survey of the second cohort of the OLIN studies included pulmonary function tests performed from 1993 to 1995 on 1,900 subjects born in 1925-26, 1940-41, 1955-56 and 1970-71. The third survey of the first cohort of the OLIN studies was performed in 1996-98 and included lung function tests performed on 2,600 subjects in three age cohorts: persons born in 1919-20, 1934-35 and 1949-50. The study cohort in the current study was derived from these two surveys and comprised subjects classified as having COPD.

COPD was defined according to the British Thoracic Society's criteria (15), which divide COPD into mild, moderate and severe disease. In addition, persons with an post-bronchodilator FEV_1/VC ratio<70% (Ratio of Forced Expiratory Volume in 1 second and Vital capacity) and $FEV_1 \geq 80\%$ of the predicted value, which corresponds to the GOLD criteria for mild COPD (16), were included in the study. These individuals are most commonly not diagnosed in clinical practice and are thus generally low-cost patients, but because of a high prevalence they account for a substantial proportion of the total societal costs of COPD.(3) Subjects with chronic airway obstruction who referred to themselves as asthmatics were also included in the OLIN studies, which is supported by the BTS guidelines.(15) Subjects with other diseases that explained their impaired pulmonary function were excluded. The study sample and methods have been described in detail previously.(3,11)

Of 261 selected subjects, 212 individuals did agree to be interviewed about resource utilisation on four occasions in the course of a year. A structured telephone interview, using a specially designed and pilot-tested questionnaire, was conducted by one of the authors (SAJ). To minimise potential recall bias, the patients kept daily diaries of resource use. The trained interviewer did on each occasion discuss these in detail with the interviewee. We verified the costly hospitalisations through hospital records. The 49 persons in the original study sample who did not take part in the study did not differ from the 212 participating subjects in terms of age, gender, smoking habits, area of residence or FEV_1.(3,11)

Costs

Societal COPD-related costs were divided into direct and indirect costs, 2004 values (exchange rate in May 2008: SEK 1 = USD 0.168, EUR 0.108). The direct costs included costs for hospitalisation, medication, health-care visits and contacts, oxygen therapy, equipment aids, moving to new quarters, home adaptations, and education or an occupational change. The indirect costs included absence from work, either short or long-term. The sample was considered too small to include costs due to mortality. For a more detailed description on how the unit costs were estimated, please see Jansson et al (3) and Andersson et al (11).

Regression analysis

Univariate and multiple linear regression analysis were performed to investigate the effects of different factors on COPD costs. These effects were analysed by the following definitions of costs: total costs (Equation, Eq. 1), direct costs (Eq. 2), indirect costs (Eq. 3), hospitalisation costs (Eq. 4), outpatient care costs (Eq. 5) and medication costs (Eq. 6). All tests of statistical significance were carried out at the 5% level, with 95% confidence intervals (CI) in the multiple analyses.

A test battery was applied to check for key properties of the regression models: White's test for homoscedasticity in the error distribution, the Jarque-Bera asymptotic test for normality and the Ramsey regression specification error test (RESET) for omitted variables.(17-19) We also calculated the variance inflation factors (VIFs) to look for problems of multicolinearity of the right-hand-side variables.

The sensitivity analysis employed: (i) estimation techniques, (ii) samples in which outliers defined by standardised residuals whose absolute values were higher than 1.96 were excluded, and also (iii) model specification.

The regression model was pre-defined as follows:

$\ln(C_{ji}+1)$= f(gender, age, population density, asthma, other co-morbidity, employment, disability pension, smoking, dyspnoea, disease severity),

where *C* represents *j* dependent variables, i.e. total, direct, indirect, hospitalisation, outpatient care and medication costs, and where 1 was added to avoid numerical problems. Since the distribution was skewed towards higher costs, we used a logarithmic transformation (natural logarithm) for the dependent variable. The coefficients, and hence the effect on costs, are the log of the ratio of the costs for the groups. For instance, a coefficient of 0.517 (Male, Eq. 1) means that the ratio is $e^{0.517}$, i.e. approximately 68% higher costs for males (coded to 1) compared to women (coded to 0). Costs and effects should always be interpreted in relation to the chosen baseline.

The definition of and hypotheses behind these variables are as follows (more information and references are presented in Discussion and Table 1):

- Gender: male is coded as 1; men are expected to generate higher costs

- Age: divided into 4 categories (≤ 63 yrs, 64-69, 70-75 and 76 and above); older patients are expected to accrue more costs
- Population density: divided into 4 categories of village size (less than 200 inhabitants, 200-2000 inhabitants, 2000-10,000 inhabitants, more than 10,000 inhabitants); people living in more populated areas are expected to consume more health care because of the closeness to health care providers
- Asthma: presence of asthma (coded as 1); asthma is fairly common co-morbidity with COPD and expected to add resource use on top of COPD-related use
- Other co-morbidity: presence of other co-morbidities (coded as 1); co-morbidities, h the most common ones being different types of cardiovascular disease (myocardial infarction, heart failure, hypertension, hyperlipidemia, etc), are expected to increase resource use even further
- Employment: unemployment (coded as 1); unemployment are expected to drive costs upwards
- Disability pension: early retirement (coded as 1); an indicator of patient's general health status and expected to generate higher costs
- Smoking: measured by number of pack-years; smoking is the main risk factor of COPD and heavy smokers are expected to have higher costs
- Dyspnoea: dyspnoea categorised into one of six categories, where category 0 (base category in analysis) are denoted for patients who do not present with any dyspnoea problems and category 5 are for the patients who are too breathless to leave the house; a positive linear relationship is expected with costs. The Medical Research Council (MRC) dyspnoea scale was used for this purpose (20).
- Disease severity: severity is based on lung function measured by FEV_1 (Forced Expiratory Volume in 1 second) where the base category in the analysis is the mild

patients (FEV_1>80); previous research has shown that costs are very much correlated with disease severity.

All potential factors were expected to affect to some extent each of the six studied cost types, hence all ten were included in all analyses.

The initial data set included 212 persons with COPD. Complete data were obtained for 179 observations as some observations were missing for population density, employment and smoking. In Table I, summary statistics are given for each of the variables used in the regression. There were no significant differences between the discarded observations and the final sample of 179.

< Table I here >

RESULTS

Table II presents the univariate analysis of all explanatory variables in relation to the six dependent variables. The variables with most significant correlations with the six cost types were severe COPD (FEV_1 <40%), presence of asthma and dyspnoea score 5.

< Table II here >

Tables III-IV present the 6 multivariate analyses. Results were slightly different compared to the univariate analysis. Severe COPD (FEV_1<40% of predicted) significantly increased all six cost types (Eq. 1–6). Individuals with severe COPD in all cases had much higher total costs than those with very mild COPD (p values ranging from <0.001 to <0.05). Moderate COPD (FEV_1 40-59%) increased total, indirect and medication costs, while mild COPD (FEV_1 60-79%) only had a significant effect on medication costs, compared to subjects with very mild COPD (baseline category).

< Tables III-IV here >

Individuals with a higher degree of dyspnoea symptoms generally presented with higher costs, except for indirect costs (Eq. 3). The presence of asthma raised total costs through direct, outpatient and medication costs (Eq. 1–2, 5–6). The increase in direct costs for those with disability pension reflected mainly higher medication costs (Eq. 2, 6). Patients in the age group 64–69 had lower medication consumption (Eq. 6), whereas people living in areas with the highest population density consumed more medication (Eq. 6). The very elderly and unemployed had lower indirect costs, as expected (Eq. 3).

Gender, other co-morbidity and pack-years had no significant effect on any of the cost types. This will be further elaborated on in the Discussion below.

Health-related quality of life and its relation to costs was analysed via EQ-VAS and SGRQ (St George's Respiratory Questionnaire).(21,22) The generic instrument EQ-VAS was in no case significant. The disease-specific instrument SGRQ was strongly significant ($p<0.001$ for total costs), indicating that poor quality of life was correlated with higher costs (data not shown). Quality of life was also strongly correlated with the dyspnoea variables. Because of missing values these two QoL variables reduced the sample size by a further 25% and they were therefore excluded from further analysis.

Methodological considerations and sensitivity analysis

The null hypothesis of normality in the error terms and the RESET test of no functional form misspecification were rejected in some of the equations (see bottom of table 3 and 4). This may be attributable to the exclusion of relevant variables or the use of an inappropriate functional form. However, it may also be attributable to the fact that the linear regression assumes that the dependent variable was unlimited and continuous, whereas our cost variables had a lower limit of zero. If a massive weight is located at zero, then this characteristic may destroy the linearity assumption and the estimates will be biased. VIF and tolerance statistics were also calculated. These statistics provide measures of multicolinearity for the right-hand-side variables in the models. A general rule of thumb is that a VIF in excess of 20 (or a tolerance of less than 0.05) may merit further investigation. In our case the mean VIF was 2.16 and in no case higher than 5.53 (the tolerance statistic is 0.18), so we assumed that multicolinearity is not a serious problem.

The results reported in Tables III-IV are remarkably robust to changes in the model specification and data. We excluded observations with standardised residuals whose absolute values were higher than 1.96 in the total cost model. By this criterion, seven observations (3.9% of the sample) were deleted. The total cost equation was then re-analysed and the results were about the same as in Table III.

As smoking is the main cause of COPD we also tested a number of smoking-related variables in addition to pack-years (age when started smoking, current or ex-smoker, a proxy for the 9^{th} deciles of high smokers), but none changed the overall results.

DISCUSSION

COPD is a complex disease. From a policy standpoint, it is important to identify different risk factors and cost drivers and to work proactively to influence these, if possible. The objective of this study was to analyse the factors driving COPD costs in Sweden by means of multivariate techniques. The analysis was based on a data set consisting of 179 subjects, a representative cohort of subjects with COPD in Sweden.(3,11)

Poor lung function (measured by FEV_1) significantly increased all six cost types. Disease severity, most commonly diagnosed by clinical FEV_1 measurements but also self-reported, has previously been reported as having strong links with resource use and costs.(3,23) Hence, the results were very much expected. What stands out is the fact that two additional variables contribute even further and thus we arrive at an even better prediction of patient costs.

Perhaps the most interesting finding in this study is the fact that severe dyspnoea leads to even higher costs, taking into account the already strong influence of disease severity measured by FEV_1. Dyspnoea was also highly correlated with quality of life and when the disease-specific instrument SGRQ was included, the dyspnoea variables turned out to be non-significant.

The positive correlation between self-reported asthma and high total costs of COPD appears to arise through outpatient care and medication costs. Patients with COPD may also have an asthma component. Others with COPD prefer to label themselves as asthmatics, or may even have been incorrectly classified as having asthma by the health-care system, as many persons with COPD are diagnosed as having asthma. Several medications are used for both diseases, such as inhaled glucocorticosteroids and bronchodilators. This might be the reason why persons with COPD, who also reported that they had asthma, use more medication.(3) The

fact that hospitalisation costs do not increase could be a sign that a possible asthma component is well controlled.

There were also interesting results for the variables disability pension and population density. Individuals with disability pension tend to consume more health-care resources and hence cost more. There may be a three-way link with age and co-morbidity, which drives costs. Medication costs were increased by population density. It is, however, well known that closeness to health care drives costs.(24,25) The medication model is also the one with the best explanatory power.

Three variables; other co-morbidity, gender and pack-years had no significant effect on any of the cost types. About 62% of the sample presented with concomitant disease(s). Recent studies point to the close relationship of cardiovascular disease and COPD.(26) Wouters (23) found in a survey of seven countries that patients with co-morbidity generated up to double the COPD-related costs compared to COPD patients without co-morbidity. We lack in our sample, however, exact information as to what the concomitant diseases were (except asthma) and how many they were. These other diagnoses (except asthma) are also self-reported and hence not clinically validated. For males, expenditure in other disease areas has been shown to be higher, although this could not be confirmed here. Wouters did not find a consistent pattern for gender in COPD.(23) Strassels reported that women consumed more COPD resources than men.(6) Finally, one would expect higher costs for those who have consumed more tobacco over their life span. It is well known that smoking is related to COPD itself and also to COPD severity.(13) As many as 83% of our sample was either current or ex-smokers. However, Strassels did not find a relationship between tobacco exposure and resource consumption either.(6) The explanation may be that there is a selection bias in that those high

consumers of tobacco that remain alive are the "healthy" ones (a so-called survival effect). It appears that FEV_1 and dyspnoea are in the causal pathway between smoking and costs.

To the best of our knowledge, there is no previous study that has studied the same research question as in this study: factors influencing total COPD costs, split by various cost components. The few related studies have used varying models, methods, focus, patient samples, settings, cost components and endpoints. In consequence, the results have been rather mixed as can bee seen in Table 5.

< Table 5 here >

In the univariate analyses QoL, lung function and co-morbidity seem to influence admissions and resource use in COPD.(3,6-11) As for the multivariate analyses, Mapel et al (27) tried to identify the clinical factors that were most predictive of increased direct medical costs in a COPD population consisting of 2116 subjects. Severity of airflow obstruction as a significant but weak predictor. Prior hospitalisation, home oxygen use, the presence of comorbid conditions and symptoms of dyspnoea were better predictors of direct medical costs. Garcia-Aymerich et al. studied potential risk factors of exacerbations and admissions for COPD exacerbations in 86 subjects.(28) Three or more COPD admissions in the previous year, FEV_1, under prescription of long-term oxygen therapy and current smoking were all significant risk factors for COPD hospitalisation. Decramer et al. examined the utilisation of healthcare resources in 57 patients with moderate to severe COPD.(29) They concluded that utilisation of health-care resources in patients with COPD was related to ventilatory and peripheral muscle strength. Kessler et al. looked at the predictive factors of hospitalisation for acute exacerbation in 64 patients with moderate to severe COPD.(30) The significant risk factors identified were low body mass index (BMI), limited ability to walk, and a few clinical

measurements (increased gas exchange impairment, pulmonary haemodynamic worsening and mean pulmonary artery pressure). Finally, Oostenbrink & Rutten-van Mölken sought to identify risk factors for hospitalisation in 519 COPD patients.(31) Underweight (BMI <18.5), history of concomitant diseases and increased dyspnoea were the risk factors identified. As can be seen, some of the identified risk factors for hospitalisation and health-care resource use overlap with the risk factors in the present study. Furthermore, some or all the studies above have found no or mixed relationships to hospitalisation and health-care resource use for variables like age, gender, co-morbidity and smoking habits – variables which were also found to be non-significant in this study.

Some preliminary policy conclusions may be drawn from our analysis. First, the three most important cost drivers are all health-related. Thus, early detection through screening and prevention initiatives in high-risk individuals has a potential to be very cost-effective. Patients with COPD who have severe dyspnoea symptoms and poor lung function have several times higher costs than those with COPD who have milder dyspnoea symptoms and better lung function. Early diagnosis followed by active interventions aimed at delaying disease progression (e.g. preventive measures such as quitting smoking, early initiation of glucocorticosteroids in suspected asthmatics, etc.) may reduce resource use in the long run, such as for hospitalisation and outpatient care and medication.(32) Second, people living in more populated areas tend to use more medication, although hospitalisation costs and/or the costs of outpatient care in these areas are not lower. The concept of supplier-induced demand (also known as Roemer's Law) was established back in the early 1960s.(24,25) Given the argumentation above, high medication use might actually be a sound investment. Third, unlike some previous research, we find no relationship either between level of smoking and costs, gender and costs, or co-morbidity (except asthma) and costs. It seems that lung function and dyspnoea are such strong predictors of costs that they largely eliminate the influence of

other factors. This leads us to the final, and most interesting finding of this study – dyspnoea is a very strong cost driver. Earlier research has shown that the severity of COPD increases costs.(3,9-11,23) However, what has not been established in the previous literature is that suffering from severe dyspnoea adds even more costs to patients with severe COPD. Treatments that prevent severe dyspnoea thus have a large potential to be cost-effective in addition to improving QoL. More studies are required to confirm this.

The present paper also contributes to the methodological literature of COPD costs in several respects. Earlier research has identified a number of factors that may affect the costs of COPD. However, no multivariate analysis of COPD costs has been carried out.(12) We have added a few more potential explanatory factors to the current literature and have applied state-of-the-art econometrics to examine this research question. In an extensive sensitivity analysis we also explored a number of measurement and specification issues. On a methodological note, it is interesting to see the differences between the univariate regression analysis in Table II and the multiple regression analyses in Tables III-IV. Our multivariate method eliminated a number of variables previously considered to affect COPD costs when analysed in a univariate way. This study has also shown that different types of costs are affected by slightly different factors.

While we believe our analysis and data offer advantages compared to previous studies, there are also important limitations. By optimal selection of the study sample, we have been able to show clear effects of various variables on COPD costs, although the sample size admittedly is relatively small. Furthermore, there is a large preponderance of costs located at zero. We corrected for the latter problem by also using alternative estimation techniques, although the results remained the same. With more data our analysis could be further expanded by alternative methods of analysis, including taking better account of the large number of zero

costs. Other limitations concern the fact that some variables may have been omitted, which affect the COPD costs. This could be indicated by the explanatory power, ranging from 24 to 58%, for the six equations. Furthermore, the collected resource use data can be considered out of date. While this may be true, no real breakthrough treatment for COPD has been launched since these data were recorded. So, while it is likely that the **level** of resource use is different compared to today, we do not anticipate that the **relationships** between the variables have changed over time. Finally, the present analysis does not reflect disease progression as the study period was 12 months, although to some extent this is taken into account by including patients with severity ranging from very mild to severe.

In conclusion, the three dominant factors affecting the costs of COPD are poor lung function (FEV_1), asthma co-morbidity and severe dyspnoea. These factors significantly increased all or most of the different components of costs. Strong efforts should be made to prevent the progression of COPD and its symptoms.

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Table I: Descriptive statistics of the variables used in the regression analysis. Number of observations = 179.

Variable	**Mean**	**SD**
Dependent variables (SEK)¤:		
Total costs	30 369 (3310)	86 257
Direct costs	11 263 (1228)	37 207
Indirect costs	19 106 (2083)	64 512
Hospitalisation costs	5022 (547)	30 520
Outpatient care costs	1199 (131)	2388
Medication costs	4409 (481)	7821
Independent variables (as % of the sample except where otherwise stated):		
Male*	58	50
Age: ≤ 63*	34	
Age: 64 – 69	25	
Age: 70 – 75	20	
Age: ≥ 76	21	
Popdensity1: ≤200 inhabitants*	5	
Popdensity2: 200 – 2000 inhabitants	7	
Popdensity3: 2000 – 10 000 inhabitants	25	
Popdensity4: ≥ 10 000 inhabitants	64	
Asthma presence*	46	
Other co-morbidity*	61	
Unemployed*	2	
Disability pension*	28	
Pack-years (yrs)	21.6	17.7
Dyspnea0 (None of these)*	37	
Dyspnea1 (Only get breathless after strenuous exercise)	25	
Dyspnea2 (Get breathless when hurrying on level ground or walking on slight exercise)	20	
Dyspnea3 (Have to stop even when walking at my own pace or walk slower than most people of my age)	4	
Dyspnea4 (Have to stop for breath every five minutes when walking, even on level ground)	2	
Dyspnea5 (Too breathless to leave the house)	12	
FEV_1class1: > 80% (Very mild)*	14	
FEV_1class2: 60–79% (Mild)	39	
FEV_1class3: 40–59% (Moderate)	36	
FEV_1class4: < 40% (Severe)	11	

¤ Costs in EURO within brackets.

* Baseline category in the regression analyses.

† Adapted from the MRC Dyspnoea Scale.(20)

Table II: Relationship between six different types of costs and functional variables in single regression analysis – Pearson correlations.

	Total costs (Eq. 1)	**Direct costs (Eq. 2)**	**Indirect costs (Eq. 3)**	**Hospitalisation costs (Eq. 4)**	**Outpatient costs (Eq. 5)**	**Medication costs (Eq. 6)**
Male	NS	NS	NS	NS	NS	NS
Age: 64-69	NS	NS	0.29*	NS	NS	NS
Age: 70-75	NS	NS	-0.21#	NS	NS	NS
Age: ≥76	NS	NS	-0.22#	NS	NS	NS
Popdensity2	NS	NS	NS	NS	NS	NS
Popdensity3	NS	NS	NS	NS	NS	NS
Popdensity4	NS	NS	NS	NS	NS	NS
Asthma presence	0.49*	0.52*	0.15¤	NS	0.32*	0.62*
Other co-morbidity	NS	NS	NS	NS	NS	NS
Unemployed	NS	NS	NS	NS	NS	NS
Disability pension	0.21#	NS	0.30*	NS	NS	NS
Pack-years	NS	NS	NS	0.18¤	NS	NS
Dyspea1	NS	NS	NS	NS	NS	NS
Dyspea2	NS	0.16¤	NS	NS	NS	0.18¤
Dyspea3	NS	0.15¤	NS	NS	0.20#	0.15¤
Dyspea4	NS	NS	NS	0.25*	NS	NS
Dyspea5	0.20#	0.19¤	NS	0.37*	NS	0.15¤
FEV_1 class2: 60-79%	-0.16¤	NS	NS	NS	NS	-0.22#
FEV_1 class3: 40-59%	0.18¤	NS	NS	NS	NS	0.19¤
FEV_1 class4: <40%	0.28*	0.30*	0.22#	0.34*	0.27*	0.33*

*P<0.001 #P<0.01 ¤P<0.05 NS: not significant

Note: For definitions and baseline categories of the variables, please see Table I and Methodology section.

Table III: Results from the regression analyses on total, direct and indirect costs. Number of observations = 179.

Covariate/Dependent variable	Total costs (Equation 1)		Direct costs (Equation 2)		Indirect costs (Equation 3)	
	Coefficients (95% CI)	p-value†	Coefficients (95% CI)	p-value	Coefficients (95% CI)	p-value
Male	0.517 (-0.65:1.68)	0.38	0.332 (-0.76:1.42)	0.55	0.533 (-0.68:1.75)	0.39
Age: 64 – 69	-0.985 (-2.94:0.97)	0.32	-1.730 (-3.49:0.03)	0.05	0.311 (-2.06:2.68)	0.80
Age: 70 – 75	-0.712 (-2.53:1.11)	0.44	0.148 (-1.55:1.85)	0.86	-2.990 (-4.52:-1.46)	0.00
Age: ≥ 76	-0.173 (-1.74:1.39)	0.83	0.518 (-1.01:2.05)	0.50	-2.687 (-4.10:-1.28)	0.00
Popdensity2: 200 – 2000 inhabitants	0.478 (-2.40:3.36)	0.74	1.128 (-1.78:4.03)	0.44	-0.143 (-3.11:2.82)	0.92
Popdensity3: 2000 – 10 000 inhabitants	1.327 (-1.05:3.70)	0.27	1.223 (-1.04:3.49)	0.29	-0.351 (-2.94:2.24)	0.79
Popdensity4: ≥ 10 000 inhabitants	1.994 (-0.34:4.33)	0.09	1.835 (-0.39:4.05)	0.10	-0.108 (-2.60:2.38)	0.93
Asthma presence	3.496 (2.38:4.61)	0.00	3.680 (2.62:4.74)	0.00	0.813 (-0.34:1.97)	0.17
Other co-morbidity	-0.393 (-1.67:0.88)	0.54	0.029 (-1.24:1.30)	0.96	-0.847 (-2.14:0.45)	0.20
Unemployed	-2.698 (-8.33:2.93)	0.35	-2.183 (-7.58:3.22)	0.43	-2.932 (-5.36:-0.51)	0.02
Disability pension	1.828 (-0.15:3.81)	0.07	1.823 (0.17:3.47)	0.03	0.453 (-1.95:2.86)	0.71
Pack-years	-0.014 (-0.05:0.02)	0.43	-0.017 (-0.05:0.01)	0.29	-0.011 (-0.04:0.02)	0.46
Dyspnea1	1.804 (0.24:3.36)	0.02	1.696 (0.27:3.12)	0.02	0.963 (-0.55:2.48)	0.21
Dyspnea2	0.867 (-0.76:2.49)	0.29	1.324 (-0.14:2.78)	0.08	0.221 (-1.55:1.99)	0.80
Dyspnea3	2.503 (0.33:4.67)	0.02	3.243 (1.19:5.30)	0.00	-1.481 (-3.35:0.38)	0.12
Dyspnea4	3.844 (1.83:5.86)	0.00	3.801 (2.05:5.56)	0.00	1.761 (-1.56:5.08)	0.30
Dyspnea5	2.359 (0.26:4.46)	0.03	2.193 (-0.05:4.44)	0.06	-0.146 (-2.23:1.93)	0.89
FEV_1class2: 60–79%	1.589 (-0.01:3.19)	0.05	1.177 (-0.36:2.71)	0.13	1.129 (-0.03:2.29)	0.06
FEV_1class3: 40–59%	2.561 (0.68:4.44)	0.01	1.286 (-0.47:3.04)	0.15	2.797 (1.18:4.41)	0.00
FEV_1class4: < 40%	4.882 (2.87:6.89)	0.00	4.430 (2.48:6.38)	0.00	4.533 (1.76:7.30)	0.00
Constant	0.133 (-2.55:2.81)	0.92	-0.054 (-2.60:2.49)	0.97	0.770 (-2.13:3.67)	0.60
R^2	0.439		0.457		0.293	
Homoscedasticity Test‡ - χ^2_{141}	137.77		142.87		146.16	
Normality Test§ - χ^2_1	3.76		1.50		28.94¤	
RESET Misspecification Testll – $F_{3,154}$	1.45		2.22		9.92¤	

Notes: For interpretation of coefficients, please see Methods section. ¤. $P < 0.05$. †. P-values reported are based on heteroscedastic-consistent standard error estimate.
‡. The homoscedasticity test is the White's test, which uses all regressors, cross products and square of regressors as auxiliary variables.(17) §. The normality test is the Jarque-Bera asymptotic test.(18) ll. The RESET test uses as auxiliary variables the predicted values of the regression estimates raised to polynomials of the third order.(19)

Table IV: Results from the regression analysis of three subcomponents of directs costs – hospitalisation, outpatient and medication costs. Number of observations = 179.

Covariate/Dependent variable	Hospitalisation costs (Equation 4)		Outpatient costs (Equation 5)		Medication costs (Equation 6)	
	Coefficients (95% CI)	p-value†	Coefficients (95% CI)	p-value	Coefficients (95% CI)	p-value
Male	0.433 (-0.38:1.24)	0.29	0.359 (-0.83:1.55)	0.55	0.404 (-0.57:1.38)	0.42
Age: 64 – 69	-0.162 (-1.50:1.17)	0.81	-0.957 (-2.93:1.01)	0.34	-1.793 (-3.17:-0.42)	0.01
Age: 70 – 75	-1.050 (-2.38:0.28)	0.12	0.085 (-1.82:1.99)	0.93	0.618 (-0.79:2.02)	0.39
Age: ≥ 76	-0.193 (-1.44:1.06)	0.76	0.441 (-1.21:2.10)	0.60	0.486 (-0.78:1.76)	0.45
Popdensity2: 200 – 2000 inhabitants	1.846 (-0.58:4.27)	0.13	-1.333 (-4.15:1.49)	0.35	0.696 (-1.55:2.94)	0.54
Popdensity3: 2000 – 10 000 inhabitants	1.615 (-0.16:3.39)	0.08	-0.751 (-2.98:1.47)	0.51	1.348 (-0.41:3.10)	0.13
Popdensity4: ≥ 10 000 inhabitants	1.131 (-0.46:2.72)	0.16	-0.152 (-2.20:1.89)	0.88	1.914 (0.17:3.66)	0.03
Asthma presence	-0.346 (-1.22:0.53)	0.44	2.188 (1.02:3.35)	0.00	4.583 (3.65:5.51)	0.00
Other co-morbidity	0.332 (-0.55:1.21)	0.46	0.156 (-1.10:1.42)	0.81	-0.702 (-1.81:0.40)	0.21
Unemployed	-1.163 (-3.58:0.31)	0.10	-0.459 (-5.61:4.69)	0.86	-1.081 (-4.98:2.82)	0.58
Disability pension	-0.385 (-1.65:0.88)	0.55	1.467 (-0.38:3.32)	0.12	2.163 (0.86:3.46)	0.00
Pack-years	0.002 (-0.03:0.03)	0.88	-0.002 (-0.04:0.03)	0.91	-0.009 (-0.04:0.02)	0.54
Dyspnea1	0.854 (0.01:1.70)	0.05	1.128 (-0.31:2.56)	0.12	1.123 (-0.13:2.38)	0.08
Dyspnea2	0.807 (-0.02:1.64)	0.06	0.268 (-1.41:1.95)	0.75	0.505 (-0.79:1.80)	0.44
Dyspnea3	1.376 (-1.29:4.05)	0.31	3.684 (1.06:6.30)	0.01	1.890 (-0.43:4.21)	0.11
Dyspnea4	4.723 (-0.37:9.82)	0.07	-0.173 (-4.86:4.52)	0.94	0.840 (-1.20:2.88)	0.42
Dyspnea5	3.607 (1.36:5.85)	0.00	0.765 (-1.28:2.80)	0.46	0.657 (-1.25:2.57)	0.50
FEV_1class2: 60–79%	-0.148 (-0.62:0.33)	0.54	0.395 (-1.18:1.97)	0.62	1.205 (0.12:2.29)	0.03
FEV_1class3: 40–59%	0.205 (-0.92:1.33)	0.72	-0.035 (-1.89:1.82)	0.97	2.178 (0.81:3.54)	0.00
FEV_1class4: < 40%	2.429 (0.23:4.62)	0.03	3.199 (0.96:5.44)	0.00	5.489 (3.90:7.08)	0.00
Constant	-1.477 (-3.19:0.23)	0.09	1.312 (-1.24:3.87)	0.31	-1.271 (-3.24:0.70)	0.20
R^2	0.304		0.240		0.574	
Homoscedasticity Test‡ - χ^2_{141}	125.47		159.89		140.25	
Normality Test§ - χ^2_{22}	239.9¤		11.46¤		1.31	
RESET Misspecification Test‖ – $F_{3,154}$	9.13¤		0.41¤		3.89¤	

Notes: For interpretation of coefficents, please see Methods section. ¤. P<0.05. †. P-values reported are based on heteroscedastic consistent standard error estimate.
‡. The homoscedasticity test is the White's test, which uses all regressors, cross products and square of regressors as auxiliary variables.(17) §. The normality test is the Jarque-Bera asymptotic test.(18)
‖. The RESET test uses as auxiliary variables the predicted values of the regression estimated raised to polynomials of the third order.(19)

Table V: Summary of previous studies on factors influencing COPD-related healthcare resource use.

Study	Description	Results – predictive factors of higher utilisation
Various univariate analyses (3,6-11)	Univariate analysis on admissions and resource use	• Quality of Life (QoL) • Lung function • Co-morbidity
Mapel et al (27)	Multiple analysis of factors most predictive of future direct medical costs in COPD, 2116 subjects	• FEV_1% predicted • Prior hospitalisation • Home oxygen use • Comorbidity • Symptoms of dyspnoea
Garcia-Aymerich et al (28)	Risk factors of admissions for COPD exacerbations, 86 subjects	• Three or more COPD admissions in the previous year • FEV_1 • Under-prescription of long-term oxygen therapy • Current smoking
Decramer et al (29)	Utilisation of healthcare resources for moderate to severe COPD, 57 subjects	• Ventilatory muscle strength • Peripheral muscle strength
Kessler et al (30)	Predictive factors of hospitalisation for acute exacerbations in moderate to severe COPD, 64 subjects	• Low body mass index (BMI) • Limited ability to walk • Increased gas exchange impairment • Pulmonary haemodynamic worsening • Mean pulmonary artery pressure
Oostenbrink & Rutten-van Mölken (31)	Risk factors for hospitalisation, 519 subjects	• Underweight (BMI<18.5) • History of concomitant diseases • Increased dyspnoea