ABSTRACT

Objectives: We aimed to estimate incremental productivity losses (sick leave and disability) of spirometry-defined chronic obstructive pulmonary disease (COPD) in a population-based sample and in hospital-recruited patients with COPD. Furthermore, we examined predictors of productivity losses by multivariate analyses.

Methods: We performed four quarterly telephone interviews of 53 and 107 population-based patients with COPD and controls, as well as 102 hospital-recruited patients with COPD below retirement age. Information was gathered regarding annual productivity loss, exacerbations of respiratory symptoms and comorbidities. Incremental productivity losses were estimated by multivariate quantile median regression according to the human capital approach, adjusting for sex, age, smoking habits, education and lung function. Main effect variables were COPD/control status, number of comorbidities and exacerbations of respiratory symptoms.

Results: Altogether 55%, 87% and 31% of population-based COPD cases, controls and hospital patients, respectively, had a paid job at baseline. The annual incremental productivity losses were 5.8 (95% CI 1.4 to 10.1) and 330.6 (95% CI 327.8 to 333.3) days, comparing population-recruited and hospital-recruited patients with COPD to controls, respectively. There were significantly higher productivity losses associated with female sex and less education. Additional adjustments for comorbidities, exacerbations and FEV1% predicted explained all productivity losses in the population-based sample, as well as nearly 40% of the productivity losses in hospital-recruited patients.

Conclusions: Annual incremental productivity losses were more than 50 times higher in hospital-recruited patients with COPD than that of population-recruited patients with COPD. To ensure a precise estimation of societal burden, studies on patients with COPD should be population-based.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third most frequent illness causing death, and the WHO has estimated that it will keep this position in year 2030 as well. COPD is a chronic disease where the patients’ health status usually deteriorates over time and which imposes considerable treatment-related costs on healthcare systems worldwide. Having COPD affects the productivity of the diseased, often measured as short and long-term absenteeism.

Estimates of productivity losses can serve as input when creating disease models simulating future impact of a disease, and may add to economic evaluations of treatment options. Studies with control groups are able to estimate the incremental, or excessive productivity losses, associated with a disease. That is, the increase in productivity losses associated with adding the index disease to a baseline level of productivity losses.

The usefulness of economic evaluations and estimates of productivity losses depend on the correct identification of COPD cases in a representative population. However, the first economic evaluations of new treatment options are often ‘piggy-backed’ on randomised controlled studies, with rigorous recruitment criteria in selected populations (specialist practices, hospital outpatient clinics). However, in order to serve as a
decision-making aid, productivity losses of COPD should be investigated in population-based samples where COPD is diagnosed by screening with postbronchodilator spirometry.

A few studies have estimated productivity losses of COPD in a general population. Most of these studies did not verify COPD by spirometry or had scarce data on productivity losses. The PLATINO study compared employment rates in patients aged 40 years or older with postbronchodilator COPD to patients without COPD. They showed that 42% of the patients and 57% of the controls reported having a paid job during the past 12 months. No quantitative estimates of productivity loss were reported from the PLATINO study. One Swedish study calculated productivity losses in a general population screened by spirometry. However, this study did not include a control group and no information was available regarding comorbidities or respiratory exacerbations.

Thus, there is a paucity of studies on real productivity loss from COPD in a true population setting. To the best of our knowledge, no study has compared the productivity losses of population-derived COPD cases with patients recruited from a hospital clinic, which could serve to evaluate the usefulness of economic evaluations based on randomised controlled trials.

The study of COPD-related costs (EconCOPD) offers a unique opportunity to address these issues. EconCOPD was a prospective 12 months cost-of-illness study of population-based patients with and without COPD, where cases were detected by state-of-the-art postbronchodilator spirometry. The aim of the current paper was to estimate annual, incremental societal productivity losses due to COPD and examine predictors of these. The study also included a separate group of hospital-recruited patients with COPD, enabling a comparison of productivity losses in population-based and hospital-recruited individuals with COPD.

METHODS

EconCOPD was conducted between March 2005 and August 2006 at the Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway. The Regional Committee for Medical and Health Research Ethics in Western Norway approved the study (approval REK Vest nr. 252.04). Some of the results were presented in a preliminary report at the European Respiratory Society annual conference in 2011.

Study population

EconCOPD consisted of three groups of participants from two sources: COPD cases and controls were recruited from a population-based cohort study, and additional patients with COPD were gathered from a patient register at Haukeland University Hospital. Details regarding the EconCOPD study population can be found in the online appendix and in previous publications.

For the current analyses, all participants were between 40 and 67 years of age. They were current and ex-smokers that had consumed at least the equivalent of 20 cigarettes/day for 2.5 years. COPD was defined as a postbronchodilator ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) less than 0.7 and an FEV1 less than 80% of predicted value according to age, sex and height. Postbronchodilator spirometry was performed according to ATS standards. The control subjects had FEV1/FVC >0.7 and FEV1% predicted >80%.

Design

At inclusion, all participants went through a face-to-face baseline interview where information concerning smoking habits, employment status and comorbidities was gathered. At 12, 24, 36 and 52 weeks, participants were interviewed by telephone, providing information regarding productivity losses (sick leave, disability pension) as well as exacerbations of respiratory symptoms. The latter were defined by an increase in two major symptoms (dyspnoea, sputum volume or sputum colour) or one major and two minor symptoms (cough, sore throat, nasal secretion, wheezing or asthaenia) for at least two consecutive days (modified Anthonisen criteria). Comorbidities were evaluated by asking for the presence of conditions listed in the Charlson Comorbidity Index. Modifying the cost-of-illness questionnaire from a comparable Swedish study, we developed questions regarding healthcare utilisation.

Productivity losses

Participants reported number of days with sick leave (irrespective of cause) since the preceding interview; these were added up for all four follow-up interviews and classified as ‘sick leave days’. Number of days in disability pension was added from the baseline interview as well as the follow-up interviews (‘disability days’). For patients receiving either graded sick leave or graded disability pension, we multiplied the number of days with the relevant percentage share. Disability days and sick leave days were added, and the resulting variable was named productivity loss.

Statistics

Bivariate analyses were conducted using parametric (t tests, ANOVA) or non-parametric (χ², Kruskal Wallis, trend test, Spearman’s correlation) tests where appropriate after assessing normality.

Data on productivity losses were truncated, that is, there was a large number of zeros and 365 days of lost productivity. Thus, the incremental, or excessive, productivity losses were estimated by median quantile regression analyses. The principal models were one including population-recruited COPD cases and controls, and one with hospital-recruited patients with COPD and the population-recruited controls. The adjusted incremental productivity losses associated with
COPD were identified by a categorical variable indicating case/control status. The regression coefficients of this latter variable reflects the change in productivity losses when ‘adding’ COPD to the baseline productivity loss in control subjects. All models were adjusted for sex, age, smoking habits and education. Additional models explored the effect of adding FEV₁% predicted, number of comorbidities and number of exacerbations of respiratory symptoms.

All analyses were performed with Stata SE V.11 for Macintosh OSX (Stata Corp, College Station, Texas, USA).

RESULTS
Table 1 shows population characteristics and unadjusted productivity losses. In total, 53 COPD cases and 107 controls from the population-based sample completed 1 year of follow-up, as well as 102 hospital-recruited patients with COPD. There was no significant difference between the three groups with respect to gender, but both groups of COPD cases were older, and they had more exacerbations of respiratory symptoms and more comorbidities than the controls (p<0.01). An E-table 1 also shows the frequency of selected comorbid conditions and chronic respiratory symptoms. The controls had a larger percentage of university-educated people (p<0.01).

At baseline most population-recruited controls reported having a paid job (87%), compared to fewer population-recruited (55%) and hospital-recruited patients with COPD (31%). Disability pension was most prevalent in the hospital-recruited COPD cases, and least prevalent among the control subjects.

There was considerable truncation of our main outcome variables. In total 56%, 25% and 5% of hospital-recruited patients with COPD, population-based COPD cases and controls, respectively, reported 365 days of lost productivity. Conversely, 41% and 38% of the population-recruited controls and population-based COPD cases had no productivity loss for the entire year. Only 8% of the hospital-recruited COPD cases had no productivity loss during the follow-up period. There was a significant trend that hospital-recruited COPD cases had the highest, while controls had the smallest number of lost days (test for trend, p<0.001).

Bivariate analyses of productivity losses in the three participant groups (tables 2 and 3) showed that in all three groups women had higher productivity losses than men. In hospital-recruited patients with COPD, increased productivity losses were associated with lower education and lower FEV₁% predicted, and number of comorbid conditions.

Incremental analyses
Table 4 shows the results of the median quantile regression analyses with number of days of lost productivity as the outcome. The coefficients for the COPD status show the incremental productivity losses associated with COPD when controlling for gender, age, education and smoking habits. That is, when we compared population-based COPD cases to controls, the presence of postbronchodilator COPD was related to an additional 5.8 (95% CI 1.4 to 10.1) days of productivity loss. Hospital-recruited patients with COPD lost 330.6 (95% CI 327.8 to 333.3) days when comparing control subjects. There were significantly higher productivity losses associated with the female sex and less education. When we added FEV₁% predicted to these two models, the incremental productivity losses associated with COPD status became non-significant and 284.5 (95% CI 267.4 to 301.2) days, comparing population-recruited and hospital-recruited COPD cases to controls, respectively (E-table 2).

We also explored the effect of number of comorbid conditions and number of exacerbations of respiratory symptoms (table 5). This adjustment removed the effect of the COPD status for the comparison population-recruited COPD cases and controls, and reduced the productivity losses for the hospital-recruited COPD cases by 5.5% (from 330 to 312 days). Adding one comorbid condition increased productivity losses by 5.0 (95% CI 2.6 to 7.4) and 5.1 (95% CI 3.2 to 7.1) days in the models analysing population-recruited and hospital-recruited COPD cases, respectively. An increase of one exacerbation increased the productivity loss in the population-recruited sample, but to a lesser degree in the model including hospital-recruited patients with COPD. When we adjusted for FEV₁% predicted values in similar analyses (E-table 3), the effect of comorbidities increased to 14.8 (95% CI 8.1 to 21.5) days when comparing hospital-recruited patients with COPD to the controls. In this latter model, the annual productivity losses related to COPD were 204.5 (95% CI 165.9 to 243.1) days, a reduction of 38% compared to the baseline model in table 4.

DISCUSSION
The annual incremental productivity losses incurred by population-based patients with COPD were 5.8 days, and increased by a factor of more than 50 when we compared them with patients recruited from a university hospital register. Our findings highlight that studies with patients recruited from hospital clinics provide biased estimates of disease burden in COPD.

When we explored the effects of pulmonary function, comorbidities and respiratory symptom exacerbations, the difference between population-derived estimates and estimates based on hospital-recruited patients with COPD persisted. Nevertheless, these variables were able to fully explain the productivity losses in COPD in a general population, and almost 40% of the productivity loss in hospital-recruited patients with COPD.

To the best of our knowledge, no other study has compared estimates of productivity losses when patients with COPD are recruited from different sources. Other
### Table 1: Characteristics of hospital-recruited and population-recruited COPD cases and population-recruited control patients below 67 years of age in the EconCOPD study

| Characteristics                                      | Hospital-recruited COPD cases | Population-recruited COPD cases | Population-recruited controls | Statistic |
|-------------------------------------------------------|------------------------------|---------------------------------|-------------------------------|-----------|
| N                                                     | 102                          | 53                              | 107                           |           |
| Male, N (%)                                           | 57 (56)                      | 30 (57)                         | 54 (50)                       | $\chi^2$, p=0.662 |
| Age, mean years (SD)                                  | 59 (5.2)                     | 58 (6.2)                        | 53 (6.9)                      | ANOVA, p<0.001 |
| Smoking status                                         |                              |                                 |                               |           |
| Current smoker, N (%)                                 | 41 (40)                      | 31 (58)                         | 57 (53)                       |           |
| Former smoker, N (%)                                  | 61 (60)                      | 22 (42)                         | 50 (47)                       |           |
| Education, N (%)                                      |                              |                                 |                               |           |
| Primary                                               | 36 (35)                      | 22 (42)                         | 20 (19)                       |           |
| Secondary                                             | 54 (53)                      | 19 (36)                         | 48 (45)                       |           |
| University                                            | 12 (12)                      | 12 (23)                         | 39 (36)                       |           |
| FEV$_1$% predicted, N (%)                             |                              |                                 |                               |           |
| ≥80%                                                  | 107 (100)                    |                                 |                               |           |
| ≥50%, <80%                                            | 51 (50)                      | 47 (89)                         |                               |           |
| ≥30, <50%                                             | 28 (27)                      | 4 (8)                           |                               |           |
| <30%                                                  | 23 (23)                      | 2 (4)                           |                               |           |
| Mean FEV$_1$% predicted (SD)                          | 47.0 (12.6)                  | 65.5 (12.6)                     | 94.3 (8.33)                   | ANOVA, p<0.001 |
| Median FEV$_1$% predicted (IQR)                       | 50.7 (29.7)                  | 68.4 (13.3)                     | 93.1 (10.1)                   | Kruskal–Wallis with ties, p<0.001; trend test p<0.001 |
| Number of comorbid conditions                         |                              |                                 |                               |           |
| Mean (SD)                                             | 1.5 (1.7)                    | 1.0 (0.9)                       | 0.7 (1.0)                     | ANOVA, p<0.001 |
| Median (IQR)                                          | 1 (2)                        | 1 (1)                           | 0 (1)                         | Kruskal–Wallis with ties, p=0.003; trend test p=0.001 |
| Number of events of exacerbations of respiratory symptoms |                              |                                 |                               |           |
| Mean (SD)                                             | 6.8 (6.5)                    | 3.5 (7.3)                       | 0.8 (1.6)                     | ANOVA, p<0.001 |
| Median (IQR)                                          | 5.5 (10)                     | 1 (4)                           | 0 (1)                         | Kruskal–Wallis with ties, p<0.001; trend test p<0.001 |
| Employment status at baseline, N (%)                  |                              |                                 |                               |           |
| Paid job                                              | 32 (31)                      | 29 (55)                         | 93 (87)                       |           |
| Retired                                               | 1 (1)                        | 4 (8)                           | 4 (4)                         |           |
| Disability pension                                    | 66 (65)                      | 16 (30)                         | 8 (7)                         |           |
| Other*                                                | 3 (3)                        | 4 (8)                           | 2 (2)                         |           |
| Days in sick leave during 1 year                      |                              |                                 |                               |           |
| Total number                                          | 1287.7                       | 1023.5                          | 1676.5                        | ANOVA, p=0.59 |
| Mean (SD)                                             | 12.6 (30.0)                  | 19.3 (55.4)                     | 15.7 (36.4)                   | Kruskal–Wallis with ties, p=0.05; trend test p=0.03 |
| Median (IQR)                                          | 0 (5)                        | 0 (3)                           | 1 (14)                        |           |
| Days with disability pension during 1 year            |                              |                                 |                               |           |
| Any disability pension, N (%)                         | 69 (68)                      | 19 (36)                         | 9 (8)                         | $\chi^2$, p<0.001 |
| Total number                                          | 23 322                       | 5344.3                          | 2504                          | ANOVA, p<0.001 |
| Mean (SD)                                             | 228.6 (170.3)                | 100.8 (156.3)                   | 23.4 (83.1)                   | Kruskal–Wallis with ties, p<0.001; trend test p<0.001 |
| Median (IQR)                                          | 365 (365)                    | 0 (256)                         | 0 (0)                         |           |
studies have provided estimates of productivity losses. Darkow et al analysed a US database with claims from 550,000 employees. They compared matched controls to COPD and found that 23% of 1355 identified COPD cases made at least one disability claim, versus 7% of control subjects. These productivity losses seem low, but patients without a job were not included. Furthermore, COPD is underdiagnosed, particularly in less severe disease, even though they utilise a considerable amount of healthcare resources. Finally, by relying on diagnosis codes on claims, patients who did not utilise healthcare resources were ignored and the productivity loss per patient might be over-estimated.

The obstructive lung disease in Northern Sweden study (OLIN) has provided costs of productivity losses for patients with COPD from a general population. They found that the annual work absence was 22.6, 0, 0.71, and 1.14 days; and early retirement 15.2%, 6.9%, 4.1%, and 0.2% in GOLD stages IV, III, II and I, respectively. However, the OLIN study did not include a control group. The consequential inability to estimate incremental productivity losses raises the questions of which part of the costs were actually causally related to COPD, and whether all costs were captured. Neither the OLIN studies, nor the study by Darkow et al investigated the effect of comorbidities or exacerbations of respiratory symptoms.

Exacerbations of respiratory symptoms and comorbidities were able to explain most of the productivity losses in patients with COPD from our population-based sample. In the model with hospital-recruited COPD cases, the number of productivity loss days were reduced, but remained significant. Quite surprisingly, exacerbations of respiratory symptoms only contributed marginally to the latter model. This finding might reflect that in a severely diseased population with a large number of patients with 365 days of lost productivity, there are fewer days available to be lost to exacerbations than in the population-based sample. Comorbidities might be more likely to influence permanent disability than the more transient effect of exacerbations. Furthermore, the effects of exacerbations and comorbidities might indicate that the effect of reducing exacerbations is even stronger in population-based samples than

Table 1

| Days with productivity loss during 1 year | Hospital-recruited COPD cases | Population-recruited COPD cases | Population-recruited controls | Statistic |
|----------------------------------------|-------------------------------|--------------------------------|--------------------------------|-----------|
| Total number                            | 24,609.7                      | 6367.8                         | 4180.5                         | χ², p<0.001 |
| Zero days of productivity loss, N (%)   | 8 (8)                         | 20 (38)                        | 44 (41)                        | χ², p<0.001 |
| 365 days of productivity loss, N (%)    | 57 (56)                       | 13 (25)                        | 5 (5)                          | χ², p<0.001 |
| Mean (SD)                               | 241.3 (158.7)                 | 120.2 (158.5)                  | 39.1 (86.6)                    | ANOVA, p<0.001 |
| Median (IQR)                            | 365 (320)                     | 9 (329.3)                      | 5 (26)                         | Kruskal–Wallis with ties, p=0.0001; trend test p<0.001 |

Trend tests for hospital patients < population-based patients < control subjects.

ANOVA, analysis of variance; COPD, chronic obstructive pulmonary disease; EconCOPD, COPD-related costs; FEV₁, forced expiratory volume in 1 s.

Table 2

| Gender | Smoking status | Education |
|--------|----------------|-----------|
|        | Current | Ex     | Primary | Secondary | University |
| Hospital-recruited COPD cases, median (IQR) | 314 (355)* | 365 (140.5) | 318 (353) | 365 (278) | 365 (120)* | 365 (337) | 16.5 (362) |
| Population-recruited COPD cases, median (IQR) | 2.5 (28)* | 132.5 (365) | 7 (295) | 37 (365) | 4 (365) | 28 (332) | 4 (76) |
| Population-recruited controls, median (IQR) | 1.5 (8)* | 8 (32) | 5 (34) | 3.5 (14) | 29 (202.5) | 5 (16.5) | 1 (14) |

COPD, here defined by FEV₁/FVC<0.7 postbronchodilation and FEV₁ <80% of predicted values.
*p<0.05, Kruskal-Wallis test, adjusted for ties.
COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.
in hospital-recruited samples. Consequently, economic evaluations based on hospital-recruited patients from randomised controlled trials might underestimate the effect of reducing exacerbations on productivity losses and give less favourable cost-effectiveness measures when examining societal costs.

The major strength of the current study was the ability to estimate incremental productivity losses in a sample of patients with COPD recruited by screening a general population of ex-smokers and current-smokers by post-bronchodilator spirometry. Instead of trying to identify the cause of each day of lost productivity, we estimated the effect on all-cause productivity loss by changing participant status from control to patient. Furthermore, the project was prospective and data were obtained by four interviews of trained staff during a full calendar year, at intervals minimising recall bias. Comprehensive data enabled us to include unique information regarding comorbidities as well as exacerbations of respiratory symptoms.

Certain potential limitations should be discussed. First, we excluded never-smoking patients and patients younger than 40 years of age. This was mainly to avoid confounding by patients with chronic asthma, and to ensure that smoking habits would not be the dominating difference between patients with COPD and controls. The COPD diagnosis was made primarily based on spirometry, but restricted to FEV1 less than 80% of predicted. Patients with overlap syndrome or chronic asthma were, as such, included. Second, we had a low number of population-recruited participants with severe and very severe airway obstruction. However, we found a significant association between increasing FEV1 and decreasing productivity losses. Third, participants in the

| Covariate                          | Population-recruited COPD cases and controls (N=160); (95% CI) | Hospital recruited COPD cases and population-recruited controls (N=209); (95% CI) |
|------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------------------------|
| COPD status                        | Ref (5.8 (1.4 to 10.1))                                         | Ref (330.6 (327.8 to 333.3))                                                    |
| COPD, FEV1 <80% of predicted       | Ref (9.5 (5.7 to 13.3))                                         | Ref (8.3 (5.9 to 10.6))                                                         |
| Sex                                | Male (0.06 (−0.24 to 0.37))                                    | Female (0.17 (−0.03 to 0.37))                                                   |
| Smoking habit                      | Current smoker (0.8 (−3.3 to 5.0))                             | Ex-smoker (1.0 (−1.5 to 3.4))                                                   |
| Education                          | University (4.23 (−0.3 to 8.8))                                | Secondary (5.0 (2.0 to 8.0))                                                    |
|                                    | Primary (6.2 (1.0 to 11.5))                                    | Constant (25.5 (22.1 to 28.9))                                                  |
|                                    | Constant (−4.22 (−20.7 to 12.2))                              | Constant (−10.0 (−20.7 to 0.6))                                                 |

Results from quantile median regression models.

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 3: Spearman’s r for correlations between days of lost productivity and age, FEV1% predicted values, comorbidities and exacerbations of respiratory symptoms in hospital-recruited COPD cases, population recruited-COPD cases and population-recruited control subjects

Table 4: Annual days of lost productivity in a general population and in a hospital population

6 Erdal M, Johannessen A, Askildsen JE, et al. BMJ Open Resp Res 2014;1:e000049. doi:10.1136/bmjresp-2014-000049.
current study were recruited from the city of Bergen, Western Norway and 11 surrounding municipalities, which is a rather small geographic area. However, a comparison between national Norwegian survey data for individuals older than 40 years of age with patients from the original cohort study that EconCOPD recruited from, was comparable. There might also be issues of selection bias, but the response rates were high, and non-response analyses have only shown that more elderly patients declined participation or were lost to follow-up, and that FEV1 was associated with mortality. The point of view and, furthermore, the FCM might be less suitable in Norway due to very low unemployment rates. Sixth, our data did not include information regarding occupation. However, we did adjust for education, which might convey some similar information. Finally, we did not have data on presenteeism, that is, diminished working capability due to disease, which inevitably made our estimates conservative.

Our aims with the current analyses included a comparison of incremental productivity losses in population-based COPD cases with those in hospital-recruited cases. A former analysis showed that the treatment-related costs of hospital-recruited patients with COPD were considerably higher than costs in population-based patients with COPD. That trend seemed to be even more evident when we estimated productivity losses. The initial economic evaluations that often guide implementation of new therapies are frequently based on phase 3 studies with rigid inclusion criteria, and patients who quite often are recruited from hospitals and private practices. Thus, the current study sheds light on the practicality loss of 5.8 days. In hospital-recruited patients, this
estimate was more than 50 times higher. The relative impact of adjustment for comorbid conditions and exacerbations of respiratory symptoms was larger in the former group. Our findings also emphasise the need to estimate disease burden in population-based surveys, and to base economic evaluations on population-based studies rather than evaluations piggybacked on randomised clinical trials.

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Correction

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The second sentence of the Design section of the article has been amended to read: The latter were defined by an increase in two major symptoms (dyspnoea, sputum volume or sputum colour) or one major and one minor symptom (cough, sore throat, nasal secretion, wheezing or asthaenia) for at least two consecutive days (modified Anthonisen criteria).

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