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Incremental costs of COPD exacerbations in GOLD stage 2+ COPD in ever-smokers of a general population

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ABSTRACT

Objectives: To estimate treatment- and productivity-related costs associated with COPD in two different samples, and to analyse the association between the costs and moderate and severe exacerbations.
Methods: We performed a baseline visit and four telephone-interviews during a one-year follow-up of 81 COPD cases and 132 controls recruited from a population-based sample, and of 205 hospital-recruited COPD patients. COPD was defined by post-bronchodilator spirometry. Total costs consisted of treatment related costs and costs of productivity losses. Exacerbation-related costs were estimated by multivariate median regression.
Results: The average annual disease-related costs for a COPD patient from the hospital sample was nearly twice as high as for a COPD case from the population sample (€26,518 vs €15,021), and nearly four times as high as for a control subject (€6740). For both sampling sources, the average annual costs of productivity losses were substantially higher than the treatment related costs (€17,014 vs €9,504, €11,192 vs €3,829, and €4494 vs €2,246, for the hospital COPD patients, the population-based COPD cases, and the controls, respectively). Severe exacerbations were an important cost driver for the treatment related costs in both COPD groups. Moderate exacerbations explained all the costs of productivity losses in the population-based COPD cases, but did not affect the costs of productivity losses in the hospital-recruited COPD patients.
Conclusion: We found that there were significant incremental costs associated with COPD, and the treatment related costs were significantly affected by exacerbations. The costs of productivity losses substantially exceeded the treatment related costs in both sampling sources.

1. Introduction

Chronic obstructive pulmonary disease (COPD) has become the third leading cause of death [1]. Many COPD patients experience acute exacerbations (AECOPD), often with infectious cause. Acute exacerbations of COPD are associated with increased mortality, increased lung function decline, and an increased use of healthcare resources [2–8].

The actual costs of AECOPD in general populations are difficult to obtain from the existing literature. This is partly due to differences in healthcare organization and different levels of costs across regions and countries, but methodological approaches also vary immensely. Most previous studies have been performed in selected populations [9,10], use self-reported or registry-based diagnosis rather than diagnosis based on post-bronchodilator spirometry [9,11], or leave out important costs like those induced by lower productivity [12–18]. In addition, costs may be estimated from a top-down [9], or a bottom-up [11] approach, they may be estimated by attributing costs or by adapting an incremental (also often called the excessive or marginal) cost approach, and costs can be registered prospectively or collected in retrospect. For a chronic, long-lasting disease such as COPD, with associated comorbidities, we would advocate that a prospective, population-based, bottom-up study that presents incremental treatment related costs and costs of productivity losses would provide decision makers with the most reliable and relevant cost estimates.

To our knowledge, the only such prospective, population-based bottom-up study so far is the OLIN (Obstructive Lung disease in Northern Sweden) study. However, they evaluated only the treatment related costs of exacerbations [12,19], and did not use an incremental cost

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approach.

The EconCOPD-study was a prospective, one-year study of healthcare utilisation including COPD patients from both a population-based sample and a hospital population, as well as in population-based control subjects without COPD. We have previously shown that the hospital-recruited COPD patients had threefold incremental treatment-related costs compared to the population-based COPD cases [20].

The main aim of the current analysis was to estimate the societal, treatment-related costs and costs related to productivity losses associated with COPD in a population-based sample compared to a hospital-recruited sample, and to analyse the association between costs and moderate and severe exacerbations. A secondary aim not studied previously, was to shed light on the effects of studying exacerbations in selected populations by comparing our population-based estimates to the costs in the hospital-recruited sample.

The current analysis thus adds costs of productivity losses to our previous work [20], and furthermore, it estimates the fraction of costs attributable to moderate and severe exacerbations.

2. Methods

The EconCOPD-study took place between March 2005 and August 2006 at Haukeland University Hospital, in Bergen, Norway. The Regional Committee for Medical and Health Research Ethics in Western Norway approved the study (REK Vest case number 252.04), and all participants provided written consent.

2.1. Study population and design

Details on sampling procedures and data collection have been published previously [21]. Briefly, the participants included in the EconCOPD-study were grouped in three subsamples based on sample source and COPD-status, i.e. *controls* without COPD and *COPD cases* from a follow-up of the population-based Hordaland Country Respiratory Health Survey [22], and thirdly *COPD patients* from Haukeland University Hospitals' patient register. The *controls* enabled us to estimate incremental costs of COPD, i.e. the excessive costs of an index disease by comparing to a group without the index disease, and, additionally, to adjust for the baseline risk of having exacerbation-like symptoms [23].

All participants were current or former smokers of $\geq$2.5 pack years, and at least 40 years old at time of inclusion. All participants were examined with post-bronchodilator spirometry abiding to ATS standards [24]. COPD was defined as a ratio of the forced expiratory volume in 1 s (FEV_1) to the forced vital capacity (FVC) < 0.70 and $FEV_1 < 80\%$ of predicted [25]. The control subjects had an FEV_1/FVC-ratio > 0.70 and $FEV_1 > 80\%$ of predicted.

During the baseline visit, participants were interviewed about their smoking habits, education, employment status, comorbidities, and medication use. Later, participants were interviewed by telephone after 12, 24, 36, and 52 weeks regarding respiratory symptoms, absence from work, medication use, and healthcare utilisation. A moderate exacerbation was defined as the use of antibiotics or corticosteroids due to respiratory symptoms, and a severe exacerbation as hospitalisation due to respiratory disease. Number of comorbid conditions were defined as the count of positive answers to a slightly modified Charlson Comorbidity Index [26]. The online supplement includes translations of the relevant interviewer questionnaires.

2.2. Costs

The total costs incurred by each participant was the sum of the treatment-related costs and costs of productivity losses from the perspective of the society. All treatment-related costs were estimated by multiplying rates of utilisation with relevant unit costs. The components of treatment-related costs were medication use, GP consultations, specialist consultations, emergency care, hospitalisations, physiotherapy, nursing services, home healthcare providers, home oxygen treatment, and rehabilitation. All unit costs are given in e-Table 1a and e-Table 1b, and details on how unit costs were estimated are given in the online supplement as well as in a previous publication [20]. The productivity losses were estimated by asking participants in detail concerning their absence from paid work [27], and divided in short-term and long-term disease-related absence. The cost of this productivity loss was estimated with a human capital approach, by multiplying the total number of lost days by the mean income per day according to sex, age, and education for 2006 given by SSB (Statistics Norway), and adding 20% to include all costs for employers [28]. Hence, as a proxy for the cost of lost productivity we have used the total employers' compensation per worker [29]. In Norway, the employers' costs approximate 20%, or even a bit more, making our estimates somewhat conservative [30]. All costs were transformed from 2006-NOK to Euros (€) using the mean exchange rate for year 2006 (8.05 NOK = 1 €).

2.3. Statistical analyses

To test the distribution of characteristics across participant groups we used parametric (*t*-test, ANOVA) or non-parametric (Chi2, Kruskal-Wallis) tests. P-values < 0.05 were considered statistically significant. Due to skewed distribution of the cost components, we chose Kruskal-Wallis tests with ties for the initial unadjusted analyses comparing costs across the three groups.

We performed multivariate regression analyses estimating costs attributed to exacerbations and other covariates. We chose quantile median regression [31] which is a non-parametric method providing coefficients in the same unit of measurement as the outcome variable. For the main multivariate analyses, we fitted two separate multiple median regression models; one comparing cases to controls, and one comparing patients to controls. We analysed the treatment related costs and the costs related to production losses separately for both of these comparisons. The regression analyses were performed two times in each comparison with differing adjustment variables in the two sub-models. The "basic" model adjusted for severity of COPD according to GOLD-stages II-IV (GOLD-stage II defined by FEV_1 50–80% of predicted, GOLD-stage III by FEV_1 30–50% of predicted, and GOLD-stage IV by $FEV_1 < 30\%$ of predicted), gender, age, comorbidity score, educational level, and pack years smoked. The "exacerbations" model adjusted for the basic variables and additionally for both moderate and severe exacerbations. In the comparison of cases to controls, we combined GOLD stage 3 and 4 due to few cases with severe airflow limitation.

All analyses were performed using Stata SE 15.1 (StataCorp, College Station, TX, USA).

3. Results

3.1. Characteristics

In total, 418 out of 471 included participants completed one year of follow-up, of which 132 were controls (97% completed follow-up), 81 COPD cases (90% completed follow-up), and 205 COPD patients (84% completed follow-up). Characteristics at baseline for each of the three study groups, including exacerbation rates during follow-up, are summarised in Table 1. Exclusion of participants above retirement age did not change the pattern of differences between the sampling sources (e-Table 2).

E-table 3 shows the annual utilisation of healthcare services and the annual productivity loss, which was multiplied by the unit costs to provide the unadjusted annual costs of healthcare utilisation and productivity loss (Table 2). The group of COPD patients incurred significantly higher costs than the other two groups. The total mean costs per person were € 26,518, €15,021, and € 6740 for the patients, cases, and controls respectively ($p < 0.001$). In the online supplement, we show the same analyses when retirees are excluded (e-tables 4 and 5).

Table 1
Characteristics of hospital- and population-recruited COPD cases and population-recruited control subjects in the EconCOPD-study.

Recruitment source (N)	Hospital-recruited COPD patients (205)	Population-recruited COPD cases (81)	Population-recruited controls (132)	p-value
Male, N (%)	123 (60%)	53 (65%)	69 (52%)	
Age, mean (SD)	67 (9.2)	63 (10.0)	57 (10.6)	**
Smoking status Current smoker, N (%)	68 (33%)	38 (47%)	63 (48%)	*
Former smoker, N (%)	137 (67%)	43 (53%)	69 (52%)	
Pack years, mean (SD)	32.7 (31.0)	32.3 (35.6)	15.6 (12.3)	**
Educational level Primary, N (%)	75 (37%)	32 (40%)	27 (20%)	**
Secondary, N (%)	100 (49%)	30 (37%)	63 (48%)	
University, N (%)	30 (15%)	19 (23%)	42 (32%)	
FEV1% predicted ≥80%, N (%)			132 (100%)	**
≥50%, <80%, N (%)	103 (50%)	69 (85%)		
≥30%, <50%, N (%)	68 (33%)	8 (10%)		
<30%, N (%)	34 (17%)	4 (5%)		
Comorbid conditions Mean (SD)	1.9 (1.8)	1.2 (1.5)	0.8 (1.0)	**
Resource-defined exacerbations Moderate, mean (SD)	0.7 (1.0)	0.4 (0.9)	0.1 (0.4)	**
Severe, mean (SD)	0.3 (0.6)	0.0 (0.1)	0.0 (0.1)	**
Total number of exacerbations in group	203	31	15	
Maintenance therapy, N (%)	164 (80%)	31 (38%)	2 (2%)	**
Vaccination, N (%) Influenza	146 (71%)	28 (35%)	15 (11%)	**
Pneumococcus	97 (47%)	4 (5%)	2 (2%)	**
Oxygen therapy, N (%)	19 (9%)	0	0	**
Employment status at baseline, N (%) Paid job	36 (17)	31 (38)	94 (71)	**
Retired	94 (46)	29 (36)	26 (20)	
Disability pension	71 (35)	17 (21)	10 (8)	
Other***	4 (2)	4 (5)	2 (1)	

COPD = chronic obstructive pulmonary disease. SD = standard deviation. FEV_1 = forced expiratory volume in 1 s. Iqr = interquartile range. BMI = body mass index.
Categorical variables tested by Chi^2 test, and continuous variables by test for trend across ordered groups where controls = rank 1, cases = rank 2, and patients = rank 3. * = $p < 0.05$. ** = $p < 0.01$. *** Students, unemployed, homemakers.

3.2. Incremental cost models

After estimating costs related to disease treatment and lost productivity, we wanted to evaluate the incremental or excessive costs of COPD. In regression models of costs including both subjects with and without COPD, the incremental costs of COPD are given by the coefficients for a categorical variable where control subjects constitute the reference category.

We first modelled the treatment-related costs, comparing cases and controls (Fig. 1a). Moderate and severe exacerbations were evaluated in separate models, and were added to a basic model, to be able to visualize how much of the incremental costs that were explained by

Table 2
Annual unadjusted costs per person by components of treatment related costs and costs related to productivity losses, according to participant status. All estimates in 2006 Euros. N = 418.

(N)	Hospital-recruited COPD patients	Population-recruited COPD cases	Population-recruited controls	Test for trend
Hospitalisation, mean, median (iqr)	5278, 0 (4861)	1812, 0 (0)	1304, 0 (0)	$p <$ 0.001
Medication costs, mean, median (iqr)	2098, 1975 (1432)	1056, 866 (1161)	515, 245 (787)	$p <$ 0.001
Contacts with healthcare professionals[a], mean, median (iqr)	1343, 667 (817)	759, 378 (864)	425, 172 (429)	$p <$ 0.001
Pulmonary rehabilitation, mean, median (iqr)	564, 0 (489)	202, 0 (0)	2, 0 (0)	$p <$ 0.001
Oxygen treatment, mean, median (iqr)	221, 0 (0)	0, 0 (0)	0, 0 (0)	$p <$ 0.001
Total treatment related costs, mean, median (iqr)	9504, 4595 (7059)	3829, 1478 (2143)	2246, 612 (1488)	$p <$ 0.001
Short time disease-related work absence, mean, median (iqr)	768, 0 (0)	1550, 0 (0)	1651, 0 (959)	$p <$ 0.001
Long term disease-related work absence, mean, median (iqr)	13411, 0 (36727)	7777, 0 (0)	2094, 0 (0)	$p <$ 0.001
Total costs of productivity losses[b], mean, median (iqr)	17014, 0 (44072)	11192, 0 (11078)	4494, 0 (2152)	$p =$ 0.033
Total costs (treatment-related + costs of productivity losses), mean, median (iqr)	26518, 11737 (45786)	15021, 2483 (18601)	6740, 1541 (5812)	$p <$ 0.001

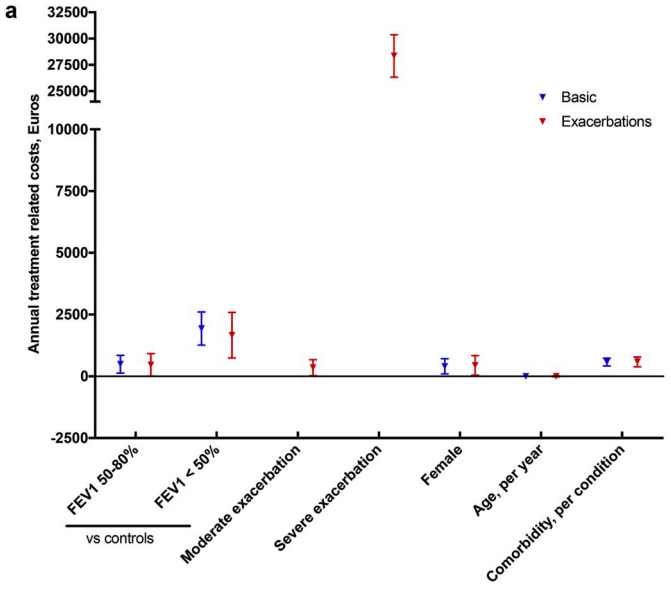

Fig. 1a. Cases and controls, multivariate median regression for treatment-related costs. "Basic" model adjusting for GOLD-stage, gender, age, per comorbid condition added, education, and packyears. "Exacerbations" model adjusting for all as in basic model + both moderate and severe exacerbations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

exacerbations. In the basic model, COPD cases with FEV1 50–80% (GOLD stage 2) had annual treatment related costs of €490 (95% confidence interval €132–849), whereas the corresponding number for cases with FEV1 less than 50% of predicted were €1938 (1266–2610). When we adjusted for moderate and severe exacerbations these numbers fell to €462 and €1,684, respectively – thus exacerbations explained 6% of treatment-related costs in GOLD stage 2 and 13% of treatment related costs in GOLD stage 3 and 4. Among the adjustment variables both comorbidities and sex were significant drivers of costs in all models.

Next, we looked into costs incurred by productivity losses in cases and controls (Fig. 1b), and found that there were no significant costs of productivity losses in GOLD stage 2, whereas the annual costs of productivity losses in GOLD stage 3 and 4 were €46,215 (30,190–62,240). When we adjusted for exacerbations, this cost was reduced and lost significance, showing that moderate exacerbations explained all costs related to productivity losses.

When patients and controls were compared, treatment related costs in the basic models rose to €2252 (947–3557), €3221 (1773–4669) and €5684 (3955–7412) in GOLD stage 2, 3 and 4, respectively (Fig. 1c). When we added moderate and severe exacerbations to the model, costs were reduced by 27%, 40% and 48%, respectively. In the basic model with productivity losses the costs were €28,845 (19,383–38,307), €29,570 (18,759–40,382) and €48,338 (36,548–60,128) in GOLD stage 2, 3 and 4, respectively (Fig. 1d). The addition of exacerbations did not add significantly to these models. All regression models are shown in the online supplement, e-Tables 6 and 7.

* Kruskal-Wallis with ties. ** ANOVA. Test for trend; non-parametric trend test for hospital patients > population-based cases > control subjects. NA – not applicable. Iqr - interquartile range. [a] Healthcare professionals includes: general practitioners, specialist physicians in private practice, hospital physicians at outpatient clinics, emergency room visits, physiotherapists, home nursing services and house maid from the local healthcare authorities. [b] Includes a 20% increase to cover for employers' costs.

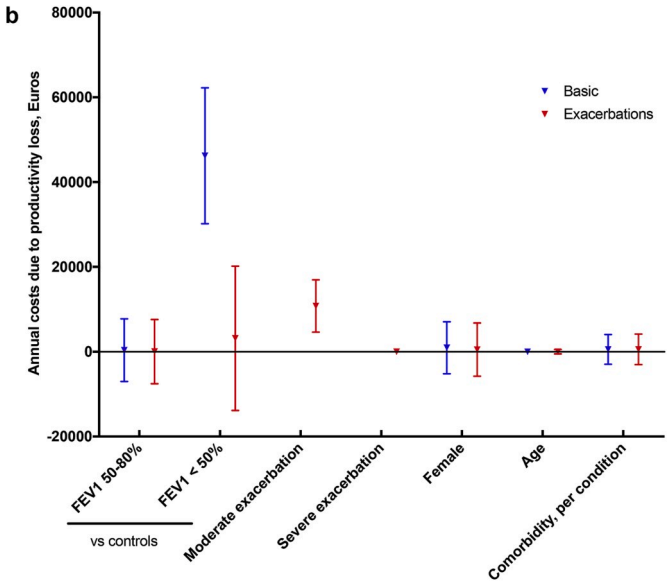

Fig. 1b. Cases and controls, multivariate median regression for productivity losses. "Basic" model adjusting for GOLD-stage, gender, age, per comorbid condition added, education, and packyears. "Exacerbations" model adjusting for all as in basic model + both moderate and severe exacerbations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

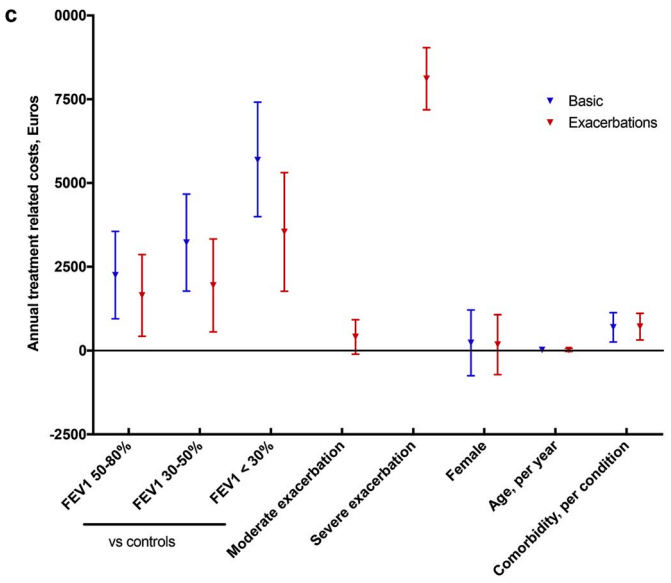

Fig. 1c. Patients and controls, multivariate median regression for treatment-related costs. "Basic" model adjusting for GOLD-stage, gender, age, per comorbid condition added, education, and packyears. "Exacerbations" model adjusting for all as in basic model + both moderate and severe exacerbations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

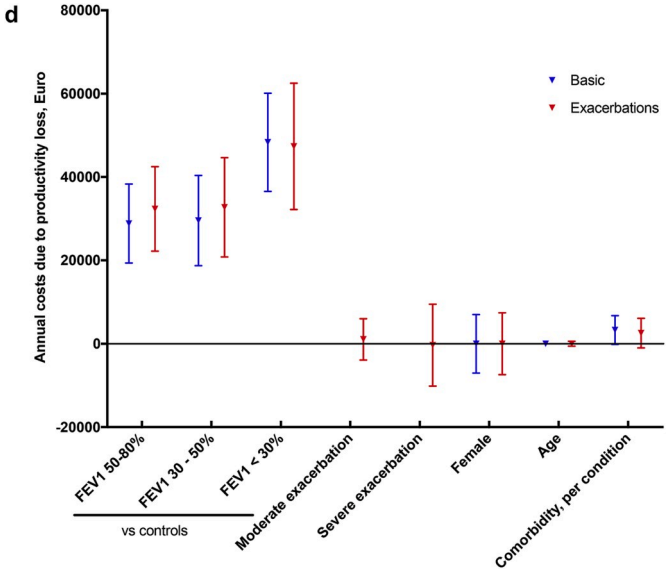

Fig. 1d. Patients and controls, multivariate median regression for productivity losses. "Basic" model adjusting for GOLD-stage, gender, age, per comorbid condition added, education, and packyears. "Exacerbations" model adjusting for all as in basic model + both moderate and severe exacerbations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

In a general population, we found that acute exacerbations of COPD explained 6% of annual treatment-related costs in GOLD stage 2 COPD, and 13% in the combined stage 3–4 COPD. For costs related to productivity losses, there were no predictors associated with significantly higher costs for patients with FEV1 over 50% of predicted, whereas moderate exacerbations actually explained all costs associated with COPD in subjects with FEV1 less than 50% of predicted.

The average annual disease-related costs for a COPD patient recruited from a hospital register was nearly twice as high as for a COPD case recruited from the general population (€26,518 vs €15,021), and nearly four times as high as for a control subject (€6740). Moderate exacerbations had no impact on costs related to productivity losses in hospital-recruited COPD patients, where increasing severity of airflow obstruction was the only significant cost driver. Sampling source is of great importance when evaluating cost-of-illness studies, and one should use estimates from both general populations and hospital populations to retrieve information relevant for both decision makers and for more severely ill patients.

It is challenging to compare our results to previous studies as different methods have been used. None of the previous studies evaluating costs of COPD have estimated the incremental costs of exacerbations or other explanatory variables in multivariate regression analyses, making our study a small but important contribution to a comprehensive understanding of the topic. The cost-of-illness study performed by Jansson et al. in the OLIN-study [32] adjusted for several explanatory variables to evaluate the relationship between costs and lung function, but did not adjust for exacerbations. Further analyses on the same material from the OLIN-study was performed by Andersson et al. [12], and found that the average treatment related costs per moderate exacerbation was SEK211, and per severe exacerbation SEK21,852. Additionally, they found that exacerbations were responsible for 35–45% of the total per capita treatment related costs, whereas in our study moderate exacerbations were responsible for approximately 7% of the treatment related costs associated with both GOLD-stage 2 and with GOLD-stage 3/4. Further on, in our study, severe exacerbations were responsible for very little (2%) of the treatment related costs associated with GOLD-stage 2, but also responsible for as much as 18% of the treatment related costs associated with GOLD-stage 3/4. This latter publication from the OLIN-study did not consider the costs of subjects without COPD, and hence, was not able to incorporate costs that were more difficult to attribute to a specific disease, and are therefore difficult to compare to our results.

A study by Abudagga et al. [9] did not distinguish between treatment related and costs of productivity losses, but evaluated per-patient exacerbations costs and looked upon predictors of exacerbations in a generalized linear model. They found that moderate exacerbations were responsible for a cost of $124 per patient per year, and severe exacerbations for $6260 per patient per year. Though not directly comparable to our method of estimating incremental costs, the relationship between the costs of the two types of exacerbations was the same -the severe exacerbations were 50 times more expensive than the moderate, both in Abudaggas' study and for the attributable costs of exacerbations on treatment related costs for the cases in our study.

We found that there were significantly increased treatment related costs associated with being female in the population-based sample of COPD cases, and this association was not altered when adjusting for moderate and/or severe exacerbations. This was not the case for the hospital-recruited COPD-patients. The explanation behind this is not certain, but several previous studies have seen the same pattern of increased health care utilisation and costs amongst women [33–35]. Postulated possible reasons for this have been that in post-menopausal women the quality of care is sub-optimal, and hence drives the costs [33]. More specifically for COPD, there has been seen a gender dimorphism [36], which could render the females more symptomatic at equal or even lower levels of smoking exposure. This is also supported by Watson et al. who found women to report a more severe dyspnoea score than men [37]. Some early studies also highlight this, stating that women are more likely to detect dyspnoea due to more attention to, and a higher awareness of, somatic sensations [38]. Kilic et al. found that women had more moderate exacerbations, and when experiencing severe exacerbations, the time from onset of symptoms till admission was longer than for men, and their hospitalisation length was increased [39], all of which can contribute to more costly exacerbations for women.

When the costs of severe exacerbations outnumber those of moderate exacerbations by a factor of 50, prevention of severity transition can save considerable costs in addition to having positive effects on the patients' health. Several points where intervention can prevent an exacerbation going from moderate to severe have been studied [40]. Preventing further decline in lung function, vaccination, early detection of infections, and pulmonary rehabilitation are all important factors when trying to avoid severe exacerbations [41–46].

Although there has been debate around the usefulness of cost-of-illness studies [47], they provide help to decision-makers by giving an order of monetary magnitude for each disease studied [48]. If complying with recommendations for methods and interpretation, such as keeping to the bottom-up approach, cost-of-illness studies can be reliable and comparable, and hence a helpful tool in health economic decisions [28]. The main strength of our study, is that it included both general population-recruited COPD cases and controls, *and* COPD patients from a hospital register, making us able to clearly point out the excessive or incremental costs of COPD, as well as demonstrating the importance of study population. We have performed a comprehensive collection of cost items, and to our knowledge, no similar studies to date investigate both treatment related costs and costs of productivity losses in COPD. Additionally, our study was performed prospectively in a bottom-up manner, and recall bias was minimized due to telephone interviews being done every three months. The overall response rate was high (79%), and hence, we would argue that our results are applicable at the population level.

Certain limitations need to be mentioned. First, the number of population-recruited cases was low, and few of these cases experienced severe exacerbations. Hence, the attributable costs of severe exacerbations in the regression analyses for the cases are difficult to interpret. Yet, even in this group, there was significantly increased exacerbation risk with increasing severity of COPD, suggesting sufficient power [49]. Second, the participants in our study were recruited from Bergen and 11 surrounding municipalities in Western Norway, and not from Norway in general. Nonetheless, a comparison between national Norwegian survey data for individuals in the same age range and the original cohort from which our participants were recruited from, showed no discrepancies [50]. Third, some would argue that the friction cost method (FCM) is favourable to the human capital approach (HCA) that we used, and that the HCA overstates the costs related to productivity loss. In the FCM, productivity loss is discounted based on the assumption that co-workers or unemployed persons cover swiftly for absenteeism [51]. However, in an attempt to capture alternative costs, there will nevertheless be a loss of productivity to the society when an individual is incapacitated. Additionally, the FCM might not suit the low Norwegian unemployment rates [52], making the supply of labour less flexible than elsewhere where unemployment rates are higher. Further, the FCM requires data that we did not possess, and hence, we cannot state for sure in which direction our results would have been altered if changing method to the FCM compared to the chosen HCA. Though, in general, it is accepted that the FCM generates lower total costs [28,29]. When we estimated costs due to lost productivity, one might argue that sick leave and disability pension represents transfers and not actual costs. This is a matter of cost perspective. The monetary value of sick leave payments and disability pensions are not actual costs, but the non-productivity caused by the disease (in this case COPD) is a cost. Measuring non-productivity by counting the days in sick leave and disability pension is in our opinion a valid approach that has been used by other authors [53]. Finally, we have neither included GOLD stage I participants nor never smokers. Most likely, this has given a higher cost average than if they had been included, but our clinical experience is that individuals in this group have few respiratory symptoms, and there is considerable overlap with asthma. Furthermore, the fixed criterion that we used for detecting chronic airway obstruction tends to overestimate disease prevalence compared to the alterative lower-limit of normal, and excluding individuals with FEV1 >80% brings the estimates

from these to criterions, closer [54].

Adding moderate exacerbations to our multiple-stage regression cost models changed the treatment related costs associated with COPD in the general population with about 7%. Adding severe exacerbations changed the treatment related costs associated with severe COPD in the general population with about 18%, implying that the costs in this group are partially explained by the occurrence of severe exacerbations. This result was expected since severe exacerbations were defined as hospitalisation due to respiratory disease, and hospitalisations were one of the components used to calculate the treatment related costs.

More severe disease was associated with increased costs of productivity losses. The significance of this disappeared when taking moderate exacerbations into consideration, indicating that moderate exacerbations are the main cost driver for costs related to productivity loss in COPD in the society. The population-based COPD cases were relatively young, there were few cases with severe airflow obstruction and the workforce participation rate was high. Thus, *a priori* one would expect a low occurrence and low impact of severe exacerbations on productivity losses. For the COPD patients, moderate exacerbations made no impact on the treatment related costs of COPD. Although exacerbations are frequent in this group [49], the level of treatment is probably so high that the "minor events" that moderate exacerbations represent do not lead to significantly increased treatment costs. On the other hand, approximately a third of the treatment related costs associated with severe COPD were explained by severe exacerbations. The cost of productivity losses for the patients were not much affected by exacerbations which is reasonable when taking into account that 65% of the possible total working force in this group were receiving a disability pension, and hence not "available" for rendering any extra productivity loss.

The annual costs of productivity losses dominated the total costs, and amounted to 2 to 3 times that of the treatment related costs, depending on which sampling source we used. For the costs of productivity losses, the exacerbations had less impact than what we saw for the treatment related costs which were more affected by exacerbations. Prevention of exacerbations is not only essential for the prognosis and wellbeing of the patients, but should also be a key target to reduce the treatment related costs associated with COPD. On the other hand, to reduce the costs of productivity losses in COPD, prevention of exacerbations would most likely have a modest effect in the costly individuals handled by the hospital clinics. Our study implicates that the costs of productivity losses need to be prevented at an early stage, before the COPD patients become disable or sick to a degree that affects their ability to work. To achieve this, we think it is essential to improve the diagnosis of COPD, reduce tobacco smoking even further, and make use of rehabilitation programmes more frequently and at earlier disease stages.

In conclusion, we have found that there are significant incremental costs associated with having COPD, and that the treatment related costs are substantially affected by exacerbations. The costs of productivity losses significantly exceed the treatment related costs. To reduce the total costs of COPD, it is important both to avoid exacerbations, and to halter the development of more severe disease to sustain the working capacity of the patients as long as possible.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Marta Erdal: Formal analysis, Writing - original draft, Writing - review & editing. **Ane Johannessen:** Formal analysis, Writing - original draft, Writing - review & editing. **Per Bakke:** Writing - review & editing. **Amund Gulsvik:** Writing - original draft, Writing - review & editing. **Tomas Mikal Eagan:** Formal analysis, Writing - original draft, Writing - review & editing. **Rune Nielsen:** Formal analysis, Writing - original draft, Writing - review & editing.

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Appendix A. Supplementary data

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