Chronic obstructive pulmonary disease (COPD): exacerbations and costs.

Marta Erdal, MD

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2021

UNIVERSITY OF BERGEN

Chronic obstructive pulmonary disease (COPD): exacerbations and costs.

Marta Erdal, MD

Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 27.10.2021

Year: 2021

Title: Chronic obstructive pulmonary disease (COPD): exacerbations and costs.

Name: Marta Erdal, MD

Print: Skipnes Kommunikasjon / University of Bergen

Contents

Scientific environment

The following work for the degree of philosophiae doctor (PhD) was conducted between 2013 and 2021 under the supervision of Rune Nielsen, Ane Johannessen, and Tomas Mikal Eagan. Some of it while partially having clinical work, and some as a fulltime PhD-candidate. During the whole period, I have been enrolled at the PhD-programme at the Faculty of Medicine, University of Bergen, Bergen, Norway. I have been employed both at the Department of Thoracic Medicine, Haukeland University Hospital, and at the Department for Clinical Science, University of Bergen, both in Bergen, Norway.

For the paper concerning unemployment, I collaborated with the coordinating centre for the BOLD study situated at the National Heart & Lung Institute at Imperial College, London, UK. Additionally, I had the privilege of working with a writing group consisting of researchers from study centres from several continents.

Acknowledgements

The road ending up in this thesis has been long and winding. And especially during the first years I felt quite lost pretending to do what they called research. They, my supervisors, on the other hand, have seemed quite optimistic and convinced that we were moving in the correct direction. I am not sure if they were pretending too, initially, or if it was their experience that told them it would not all be in vain.

First and foremost, I have to thank my main supervisor Rune Nielsen for patiently guiding me through these years. Even though I failed at the most basic chores, and had an inherent opposition to learning the language of statistical commands, he didn`t appear to be bothered. Rune has been a very competent, keen and flexible supervisor whom with I have had many interesting conversations, both on scientific topics and on the ups and downs of everyday life. All very appreciated!

My co-supervisors, Tomas Eagan and Ane Johannessen, made an excellent trio together with Rune. Tomas seems to have no limit to his capacity for work, and has always answered all my doubts, manuscript outlines, and other enquiries I may have had, meticulously, and with an undisputable professionality. Ane has her background from social sciences, and has been a very appreciated counterbalance in our work. With her experience from large international cohorts, she has a special talent for seeing the big picture. Her touch has lifted our sight to a higher level of understanding.

I would also like to thank Professor emeritus Amund Gulsvik, Professor Per Bakke, and professor Jan Erik Askildsen for valuable insight and discussion of all papers. Thanks to the University of Bergen and the Department of Clinical Science at the Faculty of Medicine for my 4-year scholarship making this thesis feasible.

Life works in mysterious ways. Or at least by chance. Had it not been for a fantastic wedding on the outskirts of Madrid back in 2012, I suspect I would not have gotten a hold on a working position at the Department of Thoracic Medicine (Lungeavdelinga), and this thesis would not have existed. I owe a big thanks to

Siri ❤ Audun, and to Marianne, who somehow got a nice impression of me in that same wedding and had me employed a few months later! Or maybe it was thanks to my eldest son, Eirik, who was a 6 months old ball of loveliness at that stage.

Lungeavdelinga received me with open arms, and I have always felt in safe surroundings there. Firstly, under the determined guidance of Kahtan Al-Azawy, and lately under Sverre Lehmanns patient and attentive leadership. Thank you! I appreciate all my colleagues there, and think the environment is truly encouraging. Special thanks are owed to hardworking and smiling dr Aamelfot, fair dr Fløtten, and joyful dr Thelle for helping me through my first daunting years of treating cancer patients, and to invincible dr Sharma and the expert nurses at ROE (respiratorisk overvåkingsenhet) who rescued me several times in the middle of the night when death was lurking around the corner.

Taking on the work for this PhD degree, has also involved many trips to international congresses where my dear friends Solveig and Bahareh have made it worthwhile to leave the kids behind, for a while. Sharing hotels, meals, presentation nerves and evening cheers were important factors that made the road fun walking. I would also like to thank Louise, Gunnar, Kristel, Jon, Elise, Einar Marius, Bernt, Christine, Christina, Anders x2, Margrethe, Trygve, Frode, Øistein, for all the fun both in and out of office. Special thanks go to Eli, whom I have been so lucky to work with in the data collection for the BOLD2 project. Thank you for being so kind and so dedicated, and for always having control of what we are supposed to do!

The data used in this PhD was collected many years prior to my entrance in the project, and I am also indebted to all study co-workers making this thesis realizable.

I have not been very present socially the last decade, but still my friends are there whenever I need them. Marta Elise, Arnhild, Randi, Eli, Laila, Monica, Marita, Ragnhild, Marte, Siri, Elisabeth, Sigrun, Maria, and Kristin –you are the best!

Last but not least, I would like to thank my family. Thanks to Mamma for being my feminist ideal, and the most caring grandmother. To Pappa for loving science whilst

believing in reincarnation, and for teaching me that life is hard, and then you die. Thanks to my dear brother Skjalg whom with I grew up in the forests of Stord amongst grizzly bears, wolfs, and silver foxes.

To my family-in-law, in Uruguay, thanks for all the great moments we have had -so far!

To Andrés, la alegría de la casa, you make me laugh every day. Thanks for being here with me, no es poca cosa! Along with Eirik, Francisco, and Ask, you are my sunshine.

Terms and Abbreviations

AECOPD	Acute exacerbation of COPD
ANOVA	Analysis of variance
ATS	American Thoracic Society
BMI	Body mass index
BODE	Body mass index, airflow Obstruction, Dyspnoea, and Exercise index
BOLD	Burden of Obstructive Lung Disease collaboration
CAO	Chronic airflow obstruction
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
Chi squared test	A statistical hypothesis test that compares two categorical variables in a contingency table to see if they are related.
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CUA	Cost-utility analysis
ECRHS	European Community Respiratory Health Survey
The EconCOPD study	The Economics of COPD Study
ERS	European Respiratory Society
€	Euro (European currency)
FCM	Friction cost method

FEV_1	Forced expiratory volume in 1 second
Forest plot	A graphical display of the estimated results of several studies addressing the same topic, along with the overall result, or summary measure, of all the studies together. Also known as a blobbogram.
FVC	Forced vital capacity
GLI	Global Lung function Initiative
GLM	Generalised linear model. A statistical model that is a flexible generalisation of ordinary linear regression allowing for other distributions than the normal distribution for its response variables.
GNIPC	Gross national income per capita
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
HCA	Human capital approach
HCRHS	Hordaland County Respiratory Health Survey
HUH	Haukeland University Hospital
ICD-10	International Classification of Diseases, version 10
IQR	Interquartile range
IRR	Incidence rate ratio
I^2 statistic	The fraction of variance in meta-analysis that is due to heterogeneity rather than chance. An intuitive expression of the inconsistency of study results.

LLN	Lower limit of normal
LMIC	Low-to-middle income countries
Kruskal-Wallis test	A non-parametric statistical test that evaluates differences on a continuous dependent variable (outcome) by a categorical independent variable (exposure).
Median quantile regression	A regression method that estimates the median of the dependent outcome conditional on the values of the independent variables, that does not assume normal distribution, and that can handle outliers in the data.
Meta-analysis	A statistical analysis that combines and compiles the results of various studies that address the same question.
mMRC	modified Medical Research Council Dyspnoea Scale
NA	Not applicable
Negative binomial regression	A regression method based on Poisson regression, particularly suited for over-dispersed count outcome variables.
NHANES	National Health and Nutrition Examination Survey
Non-parametric tests	Statistical tests that do not assume anything about the underlying distribution of the data, usually meaning that the data is not normally distributed. Also called distribution free tests.
NOK	Norske kroner (Norwegian currency)
OLIN study	Obstructive Lung Disease in Norrbotten study
OR	Odds ratio

OTC	Over-the-counter
PLATINO	Proyecto Latinoamericano de Investigacion en Obstruccion Pulmonar
REK	Regional Committee for Medical and Health Research Ethics
RR	Relative risk, or risk ratio
SD	Standard deviation
SE	Standard error (of the mean)
SEK	Svenska kronor (Swedish currency)
Spearman`s rank correlation	A non-parametric statistical test used to measure the degree of association between two variables.
SSB	Statistisk Sentralbyrå (Statistics Norway)
t-test	A statistical hypothesis test for the comparison of the means of two samples in which the distribution is normal.
TORCH	Towards a Revolution in COPD Health study
UK	United Kingdom
USA	United States of America
USD	United States Dollar (currency of the USA)
WHO	World Health Organisation
Wilcoxon rank-sum test	A statistical test used to test if two samples likely derives from the same population, or that the two populations have the same shape. It is a non-parametric test that use

	the rank of the observed data instead of the actual observations themselves.
WTP	Willingness-to-pay

List of publications

I. Grønseth R, **Erdal M**, Tan WC, Obaseki DO, Amaral AFS, Gislason T, Juvekar SK, Koul PA, Studnicka M, Salvi S, Burney P, Buist AS, Vollmer WM, Johannessen A. ***Unemployment in chronic airflow obstruction around the world: results from the BOLD study.*** European Respiratory Journal Sep 2017, 50(3) 1700499.

II. **Erdal M**, Johannessen A, Askildsen JE, Eagan T, Gulsvik A, Grønseth R. ***Productivity losses in chronic obstructive pulmonary disease: a population-based survey.*** BMJ Open Resp Res 2014;1:e000049.

III. **Erdal M**, Johannessen A, Eagan T, Bakke P, Gulsvik A, Grønseth R. ***Incidence of utilization- and symptom-defined COPD exacerbations in hospital- and population-recruites patients.*** Int J Chron Obstruct Pulmon Dis. 2016;11(1):2099-2108.

IV. **Erdal M**, Johannessen A, Bakke P, Gulsvik A, Eagan TM, Nielsen R. ***Incremental costs of COPD exacerbations in GOLD stage 2+ COPD in ever-smokers of a general population.*** Respiratory Medicine: X. Volume 2, November 2020, 100014, ISSN 2590-1435, doi.org/10.1016/j.yrmex.2020.100014.

Abstract / summary

Background: Chronic obstructive pulmonary disease (COPD) is a major contributor to morbidity and mortality worldwide. Being a preventable disease in most cases, the burden on both patients and society may be reduced substantially. Previous research on COPD burden has focused on symptoms and treatment costs, while studies on working capacity and total societal costs are scarce. Additionally, burden has mainly been studied in selective samples from outpatient wards or hospitals, and is not representative for a general population.

The objectives of this PhD thesis were to estimate the worldwide burden of unemployment due to COPD, to estimate the incidence and predictors of COPD exacerbations, to calculate the costs associated with COPD and its exacerbations, and estimate of the productivity loss in Norway. A secondary aim, was to compare our estimates in a selected hospital sample to those in a general population sample.

Methods: For the paper on worldwide unemployment, we used cross-sectional data from 18710 participants in 26 sites in the Burden of Obstructive Lung Disease (BOLD) study. Odds ratios (ORs) for unemployment associated with chronic airflow obstruction (CAO) was estimated with a multilevel mixed-effects generalized linear model. For the three other papers, we used the EconCOPD dataset which is a one-year prospective, observational study including 132 controls and 81 COPD cases from a general population, and 205 COPD patients from a hospital-register. Multivariable regression models were fitted to find potential adjusted associations between predictors and outcome.

Results: The adjusted odds ratio (95% confidence interval) for unemployment in the BOLD study was 1.43 (1.14 – 1.79) for CAO subjects. Age, per 10-year increment, and lower education were important risk factors for unemployment in high-income sites ((4.02 (3.53–4.57) and 3.86 (2.80–5.30), respectively), while female sex was important in low- to middle-income sites (3.23 (2.66–3.91)). In the EconCOPD study, the annual incremental productivity losses were 5.8 (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. Further, COPD patients from the population- and hospital-based samples experienced on average 0.4 utilization-defined and 2.9 symptom-defined versus 1.0 and 5.9 annual exacerbations, respectively. The incidence rate ratios for utilization-defined AECOPD were 2.45 (95% CI 1.22–4.95), 3.43 (95% CI 1.59–7.38), and 5.67 (95% CI 2.58–12.48) with Global Initiative on Obstructive Lung Disease spirometric stages II, III, and IV, respectively. 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). The productivity losses were substantially higher than the treatment related costs.

Conclusion: Globally, CAO was associated with significantly increased levels of unemployment. In Norway, COPD was associated with a significantly higher productivity loss, and higher costs, compared to control subjects. Further on, the COPD patients from the hospital sample had a significantly higher burden of exacerbations, and higher costs than the COPD cases from the general population. Sampling from a general population gives more externally valid results when studying the burden of COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD), is characterised by impaired lung function and respiratory symptoms, and overlaps with lung conditions such as destructive emphysema and chronic bronchitis. Early observations of emphysema and chronic bronchitis can be found from the 18th and 19th century, e.g. by Bonet, Morgagni, and Laënnec [1]. This was before tobacco smoking became widespread, but after the industrialization had introduced harmful fumes especially exposing working class men. Not until the 1950s and -60s, along with an increasing attention to the disorder, an attempt was made to define COPD [1].

COPD is now the third leading cause of death worldwide [2]. Though preventable, there is no cure for this chronic disease that affects up to one out of every ten adults [3, 4]. In industrialized countries, cigarette smoking is the main cause behind COPD. In developing countries, biomass fuel and indoor cooking are additional risk factors [5]. Symptoms that are common in COPD include shortness of breath, cough, and sputum production [3, 5, 6]. The natural course of COPD varies from patient to patient, however in many cases it involves periods of worsening of symptoms, or so called exacerbations, with the requirement of additional treatment [3]. These exacerbations give rise to higher mortality, reduced quality of life, and increased need for health care services, and are a major burden for the patients and to society [7-10]. Measuring disease burden can be done with various methods depending on the point of view of the researcher. Having the patients in mind, mortality and morbidity, and also grading the disability related to the disease, are important aspects. Additionally, disease burden can be examined from an economic point of view, making it possible to rank the relative economic burden to society of various diseases [11].

The purpose of this PhD thesis, was to evaluate the burden of COPD to society, and to estimate the incidence of COPD exacerbations from various perspectives. COPD affects a substantial proportion of the population, and we wanted to investigate the costs of the disease through possible reduced working capacity, both in Norway and worldwide. Additionally, we wished to quantify the burden caused by acute

exacerbations, and to study potential differences between a general population sample and a selected hospital sample.

1.1.1 Chronic obstructive pulmonary disease - definition

There are several ways to define, or understand, COPD. The most widely used definition, is that by The Global Initiative for Chronic Obstructive Lung Disease (GOLD), an international collaboration consisting of scientists and clinicians from all over the world [12]. In the GOLD "Global Strategy for Prevention, Diagnosis, and Management of COPD", COPD is defined as a chronic, inflammatory disease of the airways and/or the lung parenchyma where airways are narrowed, the parenchyma may be destructed, and alterations in the pulmonary vasculature may occur [3]. It is characterised by irreversible airflow limitation, giving rise to a persistently reduced lung function measured by spirometry. Many patients experience dyspnoea, cough, and/or overproduction of phlegm, and in most cases the disease is progressive [3, 5]. Thus, according to GOLD, performing spirometry is mandatory to diagnose COPD. The irreversible expiratory airflow limitation – or chronic airflow *obstruction* – seen in COPD should be reproducible over time, and not reversible upon medication –as can be seen in most asthmatic patients (for more details see *1.1.6 COPD – diagnosis,* and under the Methods section, part *3.3 Spirometry*).

1.1.2 COPD – epidemiology

An early study from 1985 to 1988 found the prevalence of COPD to be around 5% [13]. There has been debate around which diagnostic method to use as the estimates of prevalence vary substantially according to which definition of obstruction is applied [14]. Applying a fixed ratio between the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC), has been advocated by GOLD [15], and has been used worldwide to diagnose obstructive lung diseases. Alternatively, an age-adjusted cut-off value for the FEV_1/FVC-ratio, where a value

below the 5th percentile is considered abnormal, can be utilized, and is referred to as the lower limit of normal (LLN). In general, using a fixed ratio for the FEV_1/FVC, results in higher prevalence estimates than if applying the LLN. It seems that using the LLN for diagnosing COPD per spirometry results in more correctly diagnosed individuals as there are fewer falsely negative among the younger individuals, and fewer falsely positive among the elderly [16-19].

More recent and larger population studies have found the prevalence of COPD to be around 10-11% on an overall, global basis [3, 4], and in Norway it might be as high as 14% using the fixed ratio to define COPD [20]. In the general population investigated in the Obstructive Lung Disease in Norbotten (OLIN) study, 50% of elderly smokers, aged 76 to 77 years old, had developed COPD [21].

Traditionally, more men have had the diagnosis of COPD, but the last couple of decades the sex differences have diminished. Partially, this can be explained by increasing consumption of tobacco amongst women, but the association is more complex than that, involving different susceptibilities between the genders, and furthermore, hormonal and genetic factors may play a role [22-24]. Apart from the South-East Asian region, the prevalence of smoking in many low-to-middle-income countries (LMIC) is lower than in high income countries, though the gap is narrowing [25]. As the health consequences of smoking have become evident, and tobacco policies have become more restrictive, most countries see a reduction in tobacco use [26]. For instance, in Norway, a reduction in COPD morbidity was seen between 2001 and 2017 along with decreasing smoking rates [27]. Recent evidence, though, show that despite of this, some LMIC experience a rising prevalence of smoking, such as the Eastern Mediterranean region and the African region [25]. Scarce epidemiological data and less use of spirometry may have led to lower estimates of COPD for these regions, and it is expected that the COPD prevalence will rise in LMIC the coming years [26, 28].

Worldwide, COPD has become the third most important cause of mortality, claiming 3.0 million lives in 2016 [2].

1.1.3 COPD – aetiology

The aetiology behind COPD is normally an exposure to noxious gases or particles over a long period of time. Historically, cigarette smoking has been the main cause, but also exposure to biomass fuels, e.g. indoor cooking over open fire, is considered an important aetiologic factor [5], as well as workplace exposures [29, 30]. A minor group of patients suffer from alpha-1-antitrypsin deficiency that can lead to emphysema at young age [31], and additionally, air pollution has been proven to increase the prevalence of COPD [32, 33].

Though several important risk factors have been identified, not all exposed to these risk factors end up having COPD [34]. Moreover, some patients seem to suffer from a more severe COPD at lower levels of exposure to risk factors. Some proof of a genetic predisposition, or host factors, to developing the disease has emerged, suggesting there is an interaction between genes and environment behind severe cases of COPD [35-37], but the extent or importance of these mechanisms in everyday clinical practice is still not clear [38].

1.1.4 COPD – pathophysiology

The pathologic changes in the respiratory system leading to COPD after years of exposure to harmful substances, can mainly be divided into three distinct processes. Many patients have alterations in *the airways*, where chronic inflammation due to infiltration of immune cells into the tissue results in hyperplasia of the mucus glands, and smooth muscle hypertrophy. Remodelling/fibrosis can also be found. Further on, this gives rise to thickening of the airway walls, with limitation of airflow (obstruction) and overproduction of sputum [39-41]. A second pathologic change in COPD, is the *destruction of lung parenchyma*, or emphysema. In emphysema, the airway walls in the alveoli, beyond the terminal bronchioles, are destructed, and

hence, the distal airspace is enlarged, see Figure 1. The elastic recoil force driving air out of the lung, is therefore decreased, giving a reduced maximal expiratory airflow [42]. Thirdly, *the pulmonary vasculature* might undergo changes including enlargement of the intima and hypertrophy of smooth muscles [39, 43]. Hence, gas exchange is impaired, and some patients develop pulmonary hypertension [44].

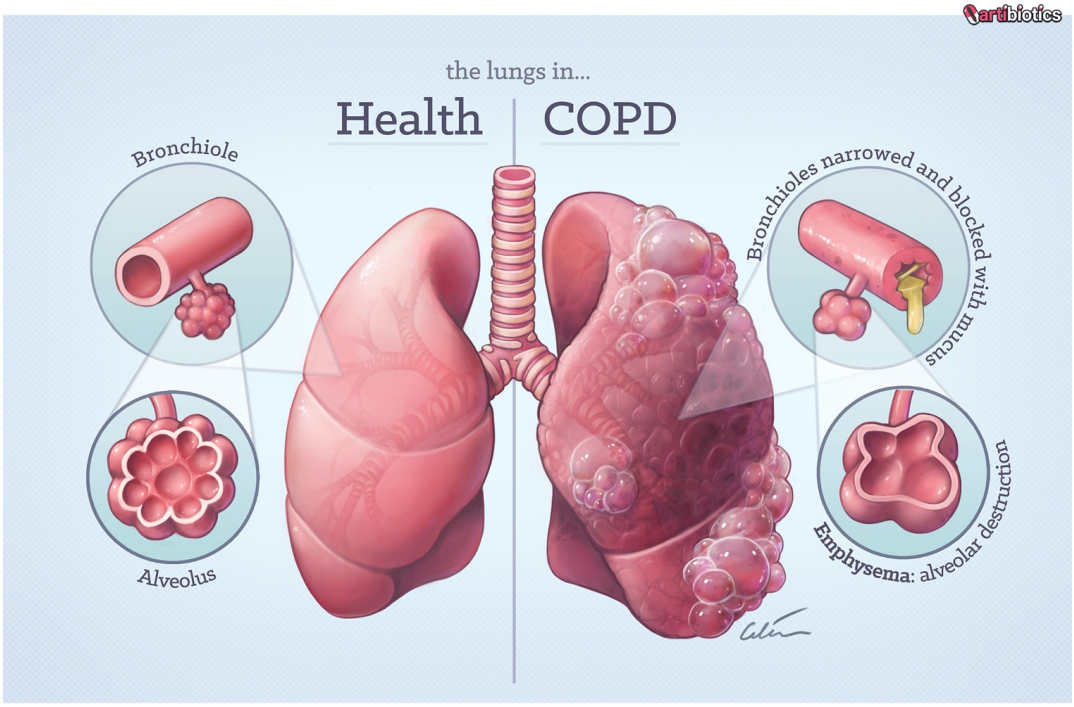


Figure 1: Features of healthy vs COPD lungs. Medical illustration by Dr Ciléin Kearns (Artibiotics). Reprinted with permission.

1.1.5 COPD – symptoms and comorbidities

With knowledge of the pathogenesis behind COPD, one can understand the characteristic presentation of the patients. Most experience some degree of dyspnoea, cough, and/or sputum production on a daily basis [3].

One important feature of COPD is the presence of comorbid conditions [45]. The most severe and frequent comorbidities in COPD are, amongst others, cardiovascular disease, lung cancer, anxiety and depression, osteoporosis, diabetes, obesity, and gastroesophageal reflux disease (GERD) [46]. Comorbidities have been shown to decrease the quality of life, to have an association with increased rates of exacerbations, and to increase the mortality in COPD [45, 47, 48].

There is significant overlap of the symptoms and of how COPD patients present, but to some extent one can distinguish certain phenotypes of COPD. A *phenotype* can be defined as the observable traits or characteristics of an organism. The two traditional COPD phenotypes included the emphysematous patient suffering from dyspnoea. Often underweight, with barrel chest, tachypnoea, and a slightly reddened face, this phenotype became known as the pink puffer. The second traditional phenotype was the blue bloater, an overweight, hypoxaemic patient with symptoms of chronic bronchitis such as cough and overproduction of sputum [49]. Both brilliantly portrayed by Frank Netter (Figure 2a and Figure 2b). As the appreciation of the complexity and heterogeneity of COPD has grown, so has the perception of phenotypes. In clinical work, you might meet the occasional “pink puffer” or “blue bloater”. But more often, the patients do not fit into either of these two described phenotypes. It is now widely acknowledged that one size do not fit all when it comes to chronic airway diseases, and that we need to move towards a more multidisciplinary approach. The term treatable traits, has been put forward, where the search for specific biological pathways, or endotypes, that can explain the observable phenotype, is important. Emphasising such individual patient presentation, and offering a multidimensional management, has been shown to improve the patients` quality of life [50].

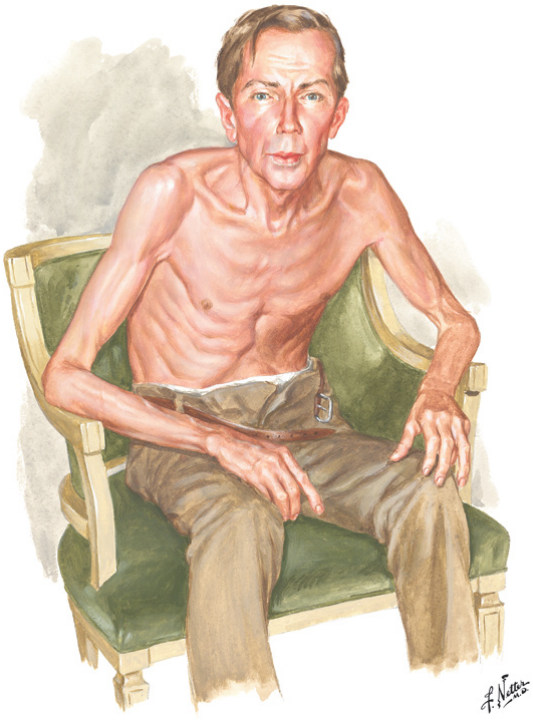


Figure 2a:

The Pink Puffer, by Frank Netter. Characterized by a slim, barrel-chested appearance, often suffering from dyspnoea.

Figure 2b:

The Blue Bloater, by Frank Netter. Characterized by a cyanotic, overweight patient suffering from cough and overproduction of sputum.

1.1.6 COPD - diagnosis

The diagnosis of COPD should be made on the basis of symptoms suggestive of the disease combined with proof of airflow obstruction per spirometry that is not reversible after administration of a bronchodilator, and that is reproducible over time [3, 6]. A reduced FEV_1/FVC-ratio indicates airflow obstruction, either defined by a fixed value of 0.7, or by the lower limit of normal.

GOLD has during the years advocated various tools to grade disease severity of COPD. Reduction in FEV_1 is used to grade COPD either as mild (FEV_1 > 80% of predicted), moderate (FEV_1 50-80% of predicted), severe (FEV_1 30-50% of predicted), or very severe (FEV_1 < 30% of predicted), also known as GOLD-stages 1-4 respectively [51]. More recently, the GOLD group suggested a more complex system of grading the disease using both dyspnoea score, and exacerbation history, in an attempt to make more personalised decisions on treatment. This is known as the ABCD assessment tool [52].

In most cases, there is an anamnestic history of significant exposure to pneumotoxic substances (normally cigarette smoking, or exposure to occupational dust), or a family history of chronic pulmonary disease. The clinical presentation can include dyspnoea, wheezing, cough or repeated bronchitis, and/or overproduction of sputum, though some present with the incidence of a comorbid condition [3, 6, 39].

Previous studies have also shown that COPD is massively underdiagnosed. In the Burden of Obstructive Lund Disease (BOLD) study, more than 80% of subjects with chronic airway obstruction were not aware of this [53]. This might of course be related to variation in the access to healthcare services, but also to systematic underreporting of airway symptoms. A failure to report symptoms of COPD has been associated both with a stigma related to having COPD, and with the sedentary lifestyle many affected individuals adopt [54, 55]. On this background, it is recommended that anyone above 40 years of age who present with symptoms suggestive of COPD should undergo spirometry, especially if they have a history of smoking or other relevant exposures [3, 5, 6].

1.1.7 COPD – exacerbations

The course of COPD involves periods of exacerbation of symptoms in between more stable periods [3, 6]. Such exacerbations are responsible for a temporarily increased need for treatment or even hospitalisation of the patients. Some patients experience frequent exacerbations, whilst others seem to avoid such exacerbations completely [56]. These acute exacerbations of COPD (AECOPD) often have an infectious cause and are associated with a more rapid decline in lung function, increased use of healthcare resources, and increased mortality compared to COPD patients without frequent exacerbations [7-10, 57-59]. Previous literature has shown a varying rate of exacerbations amongst COPD patients. Some studies have provided an estimate of less than one exacerbation per patient per year [60, 61], whilst other studies have shown the exacerbation rate to be between two and three per patient per year [7, 62]. These previous studies used different sample sources, and they differed in how they defined an AECOPD. In general, population-based studies found lower rates of exacerbations [60, 61, 63] than those targeting more selected populations, i.e. outpatient clinics or hospital registers [7, 62, 64]. In addition, more permissive definitions of an exacerbation resulted in higher exacerbation rates than more strict definitions. E.g., in the Hokkaido sample studied by Suzuki et al., the rate of exacerbations was 0.78 per patient per year when defining an exacerbation as a subjective complaint of symptoms, whilst only 0.06 per patient per year when defining an exacerbation as the need of hospitalisation due to respiratory symptoms [65].

Predictors of exacerbations have been examined in various studies [56, 60, 64-71], and it has repeatedly been seen that both higher age [64, 66, 67], increasing airflow obstruction [56, 60, 68], a history of previous exacerbations [56, 64, 68], inflammatory biomarkers [69, 70], gastroesophageal reflux disease [71], and reduced quality of life [65, 67, 68] all increase the risk of exacerbation. But again, the results from these studies are difficult to compare due to differing sampling sources and design.

All in all, previous studies vary substantially in their methodology, and are difficult to compare. Very few have samples from general populations [60, 68]. When undertaking this PhD project, the effect of sampling source and exacerbation definitions on the results had not been studied in adequate circumstances. We wanted to investigate how the exacerbation rate potentially could differ between a general and a selected population, and how the definition of an exacerbation could affect the results.

Table 1; selected previous studies on incidence of acute exacerbations of COPD.

1st author / journal / year published	Study aim(s)	Design / population / follow-up	Definition of COPD	Spirometry	Definition of exacerbation	Statistical methods	Main results	Comments
Seemungal / Am J of Respir and Crit Care Medicine/ 1998	AECOPD effect on HRQoL. Evaluate predictors of AECOPD.	Outpatient clinics. No AECOPD 4 weeks prior to study. N=70 (52 male, 18 female). 1 year follow-up. Diary cards (symptoms, fever, treatment). PEF. SGRQ measured HRQoL.	FEV_1 < 70% of predicted. ß2-agonist reversibility < 15% or 200 mL.	Yes. Pre- and post-BD.	Anthonisen criteria. Unreported AECOPD: no revision by physician.	Categorical variables: Chi^2 test and Mann-Whitney U test. Continuous variables: *t* test. Univariate and backward multiple regression. No. of exacerbations grouped: 0-2 and >2 / yr.	Mean 2.7 exacerbations per person per year (1.5 reported. Range 1 to 8). Past AECOPD and daily cough or wheeze predicted AECOPD. AECOPDs strongly correlated to SGRQ.	Low power. Population selected from outpatient clinics. The majority of participants were men. No control group.
Donaldson / Thorax / 2002	1) Identify exacerbations. 2) Evaluate relationship between lung function decline and AECOPD.	Outpatient clinics. N=109 (median 74 men) fulfilled 365 days of diary information. Only 32 participants (29 men) with FEV_1. 4 years of prospective follow-up.	FEV_1<70% of predicted, and negative reversibility. Absence of asthma/other significant respiratory disease.	Yes.	Anthonisen criteria. Hospital admission for AECOPD.	Cross sectional random effects models to evaluate the effect of exacerbation frequency on lung function decline.	100 participants (moderate to severe COPD). 757 AECOPD in 3 years. Median 2.53 AECOPD/yr. Significantly faster decline in lung function amongst frequent exacerbators.	Participants selected from outpatient clinic. All had an FEV_1< 70 % of predicted. Majority of participants were men. No control group.
Montes de Oca / Chest / 2009.	1) Evaluate AECOPD frequency. 2) Explore predictors of	Cluster-sampling from households of general populations in 5 Latin-American cities.	Post-BD FEV_1/FVC ratio < 0.70	Yes.	Self-reported and symptom-defined (deterioration of breathing	Wald test for differences between GOLD stages. Multivariate	759 of 5314 subjects had COPD. 7.9% AECOPD the past year.	Sampling from a general population. Did not compare

PLATINO study.	exacerbation frequency.	All adults ≥ 40 years invited. 5314 subjects completed interviews and spirometry. 12 months of follow-up.			symptoms that affected daily activities or caused missed work).	logistic regression to examine predictors of AECOPD.	Increasing exacerbation frequency with increasing severity of COPD. Mean exacerbation rate per year was 0.58.	results to controls.
Han / Radiology / 2011. **COPDGene study**	To investigate the relationship between AECOPD and quantitative measures of emphysema and airway disease.	21 centres, cross-sectional. Participants from local communities and outpatient clinics. Age 45 – 80 yrs. ≥10 packyears. Spirometry and CT thorax. Questionnaires 4 times a year for 5 years.	Post-BD FEV_1/FVC-ratio < 0.7.	Yes.	A flare-up of chest trouble last 12 months AND increased healthcare utilisation. A maximum of 6 episodes accepted for the last 12 months.	Multivariate analysis with a zero-inflated Poisson distribution. Adjustment for age, sex, smoking status, and FEV_1 percent of predicted.	1002 participants. Mean AECOPD freq: 0.68/pers/year. ≥2 AECOPD/yr: younger, more women, less current smokers, lower FEV_1, higher total lung emphysema percentage.	Participants both from general population and from selected outpatient clinics. Possible annual exacerbation rate restricted to 6/pers. Resource-based definition of exacerbations.
Suzuki / ERJ / 2014	To investigate determinants of COPD exacerbations.	5 yrs cohort. Physician-diagnosed COPD recruited from 10 hospitals. Age ≥ 40 yrs. ≥ 10 packyears. Asthma excluded. Median follow-up time 5 yrs. Monthly/bimonthly visits. Every 6 months, data on any change gathered.	Post-BD FEV_1/FVC < 0.70. All GOLD stages included.	Yes.	1) subjective 2) Anthonisen 3) symptom + prescription change, 4) symptom + AB or 5) symptom + hospital admission	Poisson regression. Significant variables in univariate models included in multivariate regression.	Decreasing AECOPD from definition 1 to 5 (0.78, 0.24, 0.20, 0.13, and 0.06 AECOPD/pers/yr). Higher AECOPD frequency with severe airflow obstruction, with more dyspnoea, and with lower HRQoL.	Selected sample from hospital/outpatient clinics, and no control group.
Husebø / PlosOne / 2014	To examine predictors AECOPD	Prospective cohort study. GOLD stage II-IV.	FEV_1/FVC < 0.7 15 min post-BD, FEV_1 < 80% of predicted	Yes.	Anthonisen criteria. Severity according to	Random effects negative binomial	350 of 403 had ≥1 exacerbation. Median duration 14 days.	Selected participants from outpatient clinics and

	frequency and duration.	3 yr follow-up. Age 44-76 years. ≥10 packyears. Peripheral blood: biomarkers.	according to Norwegian reference values.		healthcare utilisation.	regression for the incidence rate ratios (IRR) for each potential predictor.	Mean annual exacerbation rate/pers 1.40. Predictors: higher age, female sex, frequent AECOPD, higher GOLD stage, chronic cough, use of ICS.	specialist practices. No control group.

Abbreviations: AB; antibiotics. AECOPD; acute exacerbation of COPD. BD; bronchodilator. COPD; chronic obstructive pulmonary disease. FEV_1; forced expiratory volume in 1 second. FVC; forced vital capacity. GOLD; Global initiative for chronic Obstructive Lung Disease. HRQoL; health-related quality of life. ICS; inhaled corticosteroids. PEF; peak expiratory flow. SGRQ; St. George`s Respiratory Questionnaire.

1.1.8 COPD – treatment and prevention

As with love [72], "there ain`t no cure" for COPD. First and foremost, the best way to preserve lung health and avoid COPD is to avoid smoking. Restrictive tobacco policies are one of the most effective measures to maintain a good public (lung) health [73]. Both increased smoking cessation rates and reduced smoking initiation have been attributed to tobacco-control programmes [74, 75]. Increased taxes on tobacco have been identified as the most effective intervention against non-communicable diseases and the expected millions of premature deaths attributed to tobacco-use in the decades to come [76, 77].

All COPD patients should be recommended to quit if still smoking [3, 5, 6]. In sustained quitters, the Lung Health Study showed a slower decline in lung function, less need of hospitalisation, and a lower all-cause mortality rate [78]. Secondly, pulmonary rehabilitation has been proven effective in improving health-related quality of life, tolerance to exercise, and reducing the need for health care services [79]. A study by Maddocks et al showed that even fragile COPD patients could have great benefit from pulmonary rehabilitation, improving both dyspnoea, physical activity, and overall health status [80]. The third most important intervention is vaccination, both against seasonal influenza, and pneumococcal disease. In two separate Cochrane reviews, it was found that influenza vaccination was significantly associated with a reduced exacerbation rate [81], and that pneumococcal vaccination protected against community-acquired pneumonia [82]. Further on, there has been seen an additive effect of receiving these two vaccines together [83].

The medication available consists mainly of inhalation drugs that can alleviate symptoms, and to some degree reduce the exacerbation rate and need for hospitalisation [84, 85]. It is recommended that all COPD patients that are symptomatic try out either rescue medication (if intermittent symptoms) or maintenance therapy (if persistent symptoms). The effect of rescue medication is rapid, but short-lasting. The most widely used drug for rescue medication is the ß-agonist salbutamol with nearly 300.000 users in Norway [86], but also the short-

acting anticholinergic drug ipratropiumbromid has quite a wide use. Maintenance therapy should include some form of long-acting medication, either a LABA (long-acting ß-agonist), or a LAMA (long-acting muscarinic antagonist) [3, 5, 6], or a combination of the two. ICS (inhaled corticosteroids) have been used widely, but have an association with increased rates of pneumonia. Hence, ICS should be preserved for those experiencing frequent exacerbations where a somewhat reduced rate of serious events has been seen [84], or for patients with eosinophilia where recent evidence suggests a benefit [87]. Additionally, there can be a slight positive effect on inflammation adding the systematic PD4-inhibitor roflumilast in severe cases of COPD [88]. End-stage COPD may result in respiratory failure with hypoxaemia and/or hypercapnia, and some patients may profit from long-term oxygen treatment (LTOT). When exacerbating, patients often need systemic corticosteroids, and in many cases antibiotics. Patient education should enable patients to increase the rescue medication as appropriate when experiencing a worsening. If severe, exacerbations may lead to hospitalisation, and in some cases even intubation and treatment in intensive care units [3, 5, 6].

1.1.9 COPD – burden and prognosis

In the 1990s, there was a lack of comparable studies on burden of disease, and the World Health Organisation (WHO) together with the World Bank pushed forward an initiative resulting in the Global Burden of Disease (GBD) Study [89]. This study used comprehensive and consistent methods to achieve comparable information on causes of disease and how global health changes over time. From the GBD, Murray et al found that COPD ranged second on the list of causes of disability-adjusted life-years (DALYs) [90], confirming how debilitating the disease is. Additionally, it was found that the burden attributable to tobacco smoking remained constant from 1990 to 2010 at 6.3% of all the DALYs in the world [90]. Whilst utmost descriptive, the GBD Study does not give an economic evaluation of the societal costs associated with each disease in monetary units, nor does it examine what drives the costs.

The individual burden of COPD is influenced by many factors. For instance, the mental and physical capability to face daily symptoms, and personal economy to pay for treatment or to be able to be absent from work, can all affect how the patients experience their disease. In general, COPD symptoms are associated with a reduced quality of life, but also with higher incidence of comorbid depression and anxiety, reduced sleep quality, and with worse disease prognosis [91]. In some cases, be it a genetical predisposition or in those who cannot manage to stop smoking in time, the condition can become very severe and give a heavy burden on the individual promptly [92, 93]. In most cases though, the disease progresses slowly [94], and can be delayed with effective means such as smoking cessation and pulmonary rehabilitation [73, 78, 95]. In smokers at 65 years of age with GOLD-stage 3 to 4 COPD, it has been estimated that nearly 10 years of life expectancy is lost due to COPD and continued smoking. On the other hand, COPD in never-smokers is associated with a reduction in life expectancy of 1.3 years in GOLD-stage 3 to 4 [96].

1.2.1 Health economics

The science of economy, or economics, concerns the production, distribution, and consumption of activities that aid in determining how scarce resources should be allocated to fulfil the needs of those living within each economy [97].

As a part of the larger area socioeconomics, health economics deals with how the resources of the society can be best used to gain most health in a population. The available resources are not infinite, and hence, what can be spent on health in any society, has a limit. It is stated that the aims of the Norwegian health politics, are to "gain more life years of good health in the entire population", that "every citizen should have equal access to help for equal needs", and to "reduce the social inequality in health" [98]. To obtain these aims with limited resources, one is obliged to prioritise. How to prioritise fairly is inevitably a question where personal opinion, or political conviction, may play a role, but some help can be found in moral theory that guide decision making and evaluate the morality of actions and public policies

[99]. Further on, prioritising fairly can more easily be done when real cost estimates for the different conditions exist, facilitating the evaluation of each condition relative to one and another.

Costs in health economy can include many items, for instance patient expenditures on medication, the cost of an appointment with a GP or at an outpatient clinic, the time spent by relatives on care of a patient, or the costs to society associated with sick leave or disability to work. The definition of a cost in economics is the value of opportunity forgone as a result of spending resources in an activity, also known as the opportunity cost [100]. In other words, regarding health, a cost is the forgone opportunity to spend that amount of money in a different manner had it not been spent on the disease in question.

Many studies use attributable costs to give estimates of how much costs a disease is responsible for. With this approach, the costs explicitly related to the treatment of the index disease are estimated and can allow us to calculate the percentage of the total medical costs that are attributable to the index disease. In contrast, the excessive costs (also called the incremental costs or marginal costs), are the costs in a sample with the index disease compared to the costs in a population without the index disease, a control group. With good matching of the controls for confounding factors, such as age, gender and education, the incremental cost approach can give more accurate results than the attributable cost approach [101].

1.2.2 Health economics - cost-of-illness studies

Cost-of-illness (COI) is defined as the value of the resources that are expended or forgone as the result of a health problem. It encompasses costs related to health care utilization (direct costs), costs due to absenteeism from work or lost productivity (indirect costs), and costs related to suffering and pain (intangible costs) [102, 103]. There are several methods of how to undertake COI studies, but the common underlying assumption has traditionally been that such an economic study represents

the potential benefits of a health care programme (or treatment, or intervention) had it eradicated the illness [104].

The direct costs, or treatment-related costs, consist of healthcare costs and non-healthcare costs. The healthcare costs are those that arise from use of medication, treatment sessions or consultations with any health care personnel, admission to hospital, or any cost related to the diagnosis, treatment, rehabilitation, or terminal care of a disease. The non-healthcare costs are those incurred by transportation to and from providers of care, informal care e.g. by family members, or costs due to relocation or legal help [103].

The direct costs can be estimated in a bottom-up, or a top-down manner. In the bottom-up manner, each expenditure, or unit, has its related cost, the unit cost. Each unit cost is multiplied by how many times the unit was used, for example how many GP consultations a patient had per year. Finally, all unit costs are summed up to give the total direct costs, for instance per patient per year. On the other hand, the top-down approach starts in the other end, taking the total national health care expenditure and dividing this total sum on each disease category in the ICD-10 system.

Apart from the top-down or bottom-up approach to estimate the direct costs, COI studies can be described depending on the epidemiological data used, i.e. an approach based on either prevalence or incidence. With a prevalence based method, the economic burden of a disease is calculated for a specific time period, most often a year. Using an incidence based approach, patients are included when they get the disease (or when the disease is diagnosed), and can give rise to costs as long as they have the disease, *i.e.* the lifetime costs of the disease in interest are estimated. [104]. For long-lasting diseases, the incidence based approach might not be feasible due to the follow-up time being too far into the future, and the prevalence based method might be the only way to perform such studies. In general, incidence based COI studies result in higher costs than the prevalence based studies due to the fact that future costs are summed up with the incidence based method, while with the

prevalence based method the costs are assigned to the year when the disease appears and future expenditure is discounted. Especially for chronic and long-lasting diseases, the differences in cost results between using a prevalence and an incidence based method could be substantial [103]. Finally, COI studies can be performed either collecting data prospectively, or retrospectively. Briefly, a retrospective study design is less expensive and less time consuming to perform compared to a prospective design. Though, with a prospective design assigning costs can be more accurately done, e.g. using diaries during the study period.

The productivity losses, or *indirect costs*, are the costs related to absenteeism from work or to the disability to participate in the workforce and can be estimated mainly in 3 different ways. So far, there is no consensus on which method is the best. The human capital approach (HCA) forms the theoretical background for estimating productivity losses due to morbidity and mortality [103]. In the 1950s and `60s, economists began having interest for human resources as a neglected part of the economy, and hence, good health was also seen as an investment to society [105]. The HCA was further developed from its origin to express the value of human labour. It states that the future earnings of an individual are equal to its potential value to the economy. Average wages are used to put monetary value on each individual´s contribution, using the assumption that the wage of a worker is equal to his/her marginal product. The marginal product being defined as the change in total output as one additional unit of input is added to production [11]. The HCA fits best in societies with full employment, or at least with a low unemployment rate, which has led to an alternative method to perform COI studies – the friction cost method (FCM).

In the FCM, it is argued that if a person is sick or dies prematurely, and therefore cannot work or only work partially, he/she is eventually replaced from the pool of unemployed individuals [103]. In contrast to the HCA, in the FCM there is only a period of reduced or lost productivity, the friction period, until the sick/deceased is replaced, and normal productivity is achieved again. I.e., it is the friction period that needs to be calculated to put a value on the lost productivity [103]. The length of this

period depends upon the availability of qualified personnel, and upon unemployment rates.

Both the HCA and the FCM have been criticised by economists saying that wages have nothing to do with how much should be spent on saving someone`s life. It has been argued that a third approach should be used, namely the willingness-to-pay (WTP) approach. With the WTP method, each individual is asked to put a monetary value on how much they would spend to reduce the risk of disease, and this value is considered the real cost of disease. It seems that doing so, those asked imagine all kinds of effects a reduction in health risk may have on their lives, and even intangible costs may be covered for with the WTP method [106]. However, the WTP method does not consider that people have different fortunes and salaries, so that the willingness to pay does not necessarily reflect the *ability* to pay.

Macroeconomic issues, or the economy as a whole in each country, will inevitably affect which method for performing COI studies that is most appropriate in each case. Some countries have in majority a public health care system, others have a majority of private health care, and many economies offer a combined health care system to its inhabitants. Hence, the amount paid by the authorities and by the patients themselves, vary hugely from country to country. Based on such differences, each researcher must choose what is most suitable for his/her circumstances, and this makes the field of health economy even more difficult to unite and compare. Elucidating methodological details is the minimum requirement to facilitate the comprehension of what perspective research has been conducted under, and to evaluate if separate studies are comparable or not.

Cost-of-illness studies have been criticised for squandering with research resources, and that the monetary costs of disease are irrelevant if not reported together with a potential benefit of preventing or treating the disease in question. It has been argued that there is already meaningful information available to describe the cost of illness, i.e. data on mortality or hospital admissions, and that no further estimation of the costs is necessary as these data already quantifies the problem in an adequate manner [107]. On the other hand, when there is a known prevention strategy available that can prevent the occurrence of an illness, cost-of-illness studies are useful. For a preventable disease such as COPD, COI studies can be used as an estimate of the opportunity cost forgone if prevention is not accomplished. Additionally, preventing smoking would not only affect rates of COPD, but also many other diseases with a high burden, such as cancer and cardiovascular disease. Hence, COI studies on COPD give a very conservative estimate of possible savings in the health budgets. In other words, COI studies should not be used to say which of a set of illnesses is worst, but to give an order of magnitude to the opportunity cost that is forgone if the disease is not prevented [102, 103, 107].

1.2.3 Health economics - costs of COPD

Being defined as a preventable disease [3, 5, 6], great reduction of both personal and socioeconomic burden from COPD is within reach. The actual monetary cost of COPD and AECOPD to society has been investigated in a few studies [108-112]. In the OLIN study, Jansson et al found the average annual direct costs to range from € 269 to € 5,351 for mild and very severe cases, respectively [112]. In the same study, the indirect costs ranged from € 327 to € 12,004 for mild to very severe disease, respectively. Using the same population sample, Andersson et al found that severe exacerbations were 10 times more costly than moderate exacerbations, and that hospitalisation costs accounted for two thirds of the total exacerbation cost [110]. A study by Dalal et al, found that per simple COPD admission to hospital the cost was USD 7,242, and per complex admission due to COPD the cost was USD 20,757

[111]. In a study by AbuDagga et al, the mean cost per moderate exacerbation was USD 269, whilst the cost per severe exacerbation was USD 18,120 [108]. Each additional exacerbation was associated with 9.1% higher exacerbation costs in the follow-up year. Miravitlles et al found a mean cost per exacerbation of € 345, of which costs related to hospital care constituted 73% [109].

It is clear that COPD is a costly disease. Investigating both treatment-related costs and productivity losses in a general population using a prospective approach has to our knowledge only been done on the OLIN sample, and neither did they have a control sample enabling estimation of the incremental costs, nor did they evaluate the productivity losses due to exacerbations. For a fairer distribution of resources, having a population-based estimate on total costs of disease, and knowing what the main cost drivers are, is essential. To give such an estimate for the long-lasting and chronic disease COPD, we argue that not only should the study sample be from a general population, the design also ought to be prospective with a bottom-up approach including a control group to provide incremental costs.

Table 2; selected previous publications on costs of COPD and COPD exacerbations until 2013.

1st author / journal / year published	Study aim(s)	Design / population / follow-up	Definition of COPD	Costs examined	Statistical method	Main results	Comments
AbuDagga / Int J Chron Obstruct Disease / 2013	Annual exacerbation rates, related costs, and predictors of exacerbations in chronic bronchitis.	Retrospective, top-down. Patients with chronic bronchitis aged 40 years or older. N = 17,282.	Hospitalisation/ER-visits; ICD-9 J491.xx, pharmacy fills for COPD medication during follow-up.	Total annual exacerbation-related direct costs for moderate and severe exacerbations.	Multivariable GLM with gamma distribution to estimate total per-patient exacerbation costs.	42.6% had ≥1 exacerbation. Mean 0.7/year. Mean cost per moderate exacerbation $269 for moderate exacerbations, for severe exacerbations $18,120.	No spirometry Only CB. Only exacerbation costs evaluated.
Miravitlles / Lung / 2013	To investigate outcomes and related costs of moderate and severe AECOPD in outpatients.	An observational, multicentre cohort study. Participants ≥ 40 years. COPD confirmed by spirometry. Cost analysis included utilisation of health care resources. N=260.	Post-BD FEV_1/FVC < 0.70 and FEV_1 <80% of predicted.	Treatment-related costs during exacerbation (medication, medical visits, laboratory tests, hospital admissions).	Student *t*-test or Mann-Whitney *U* test for continuous variables. Chi^2 test for categorical variables. No multivariate analyses.	80% had an AECOPD the previous year, of which 13.8% were admitted to hospital. Mean cost per exacerbation €345, €251 of which were attributed to hospitalisation.	Selected outpatient sample. No control group. No multivariate regression.

Jansson / Res Med / 2013	To estimate societal costs, and relationship between costs and disease severity. Changes in costs over 10-year period.	COPD subjects from general population. Lung function tests, questionnaires. Interviewed per telephone four times a year. Diary. N=244.	Post-BD spirometry $FEV_1/FVC < 0.70$, and classification of disease severity according to GOLD criteria.	Unit costs multiplied with resource use = mean annual direct costs per subject for each stage of COPD severity. Indirect costs calculated according to the HCA.	Non-parametric tests for differences in costs. Mean annual costs by bootstrapping with 10,000 replicates. Sensitivity analysis for the total societal costs.	Mild COPD: 269 €/pers/yr. Very severe COPD: 5351 € /pers/yr. Direct costs driven by drugs and hospitalisation (very severe COPD). Early retirement more costly than sick-leave. Indirect costs higher than direct costs.	Costs not analysed with multivariate regression. No control group.
Dalal / Res Med / 2011	To describe and characterize hospital costs of COPD care.	Retrospective, cross-sectional study. Primary outcomes: LOS, mortality, and readmission rates. Follow-up time 30 to 60 days.	ICD-9 code J49.xx	Medical and pharmacy costs related to hospital admissions, and ER visits were calculated and described.	Counts and percentages calculated for categorical variables. Means and SD calculated for continuous variables. No statistical testing.	71,493 events included. Mean LOS twice as long for complex admission. Costs associated with complex admission nearly three times as high as for simple admissions ($20,757 versus $7987).	No statistical comparison was made, only a description of costs.

Abbreviations: AECOPD; acute exacerbation of COPD. BD; bronchodilator. CB; chronic bronchitis. COPD; chronic obstructive pulmonary disease. ER; emergency room. FEV_1; forced expiratory volume in 1 second. FVC; forced vital capacity. GLM; generalised linear model. GOLD; Global initiative for chronic Obstructive Lung Disease. HCA; human capital approach. ICD-9; International Classification of Diseases, version 9. LOS; length of stay. SD; standard deviation.

2 Objectives of the thesis

1) To estimate and compare the employment status in BOLD-participants with and without chronic airway obstruction across the world.

2) To estimate the productivity losses associated with COPD in Norway, to compare the results from a general population to that of a hospital sample, and to investigate possible predictors of productivity losses in COPD.

3) To estimate the incidence and examine potential predictors of acute exacerbations of COPD in a general population, and to compare the results to a hospital sample. Do the results differ if an exacerbation is defined by symptom-worsening compared to a definition based on resource use?

4) To estimate the annual socioeconomic costs related to COPD and COPD exacerbations, evaluate predictors of increased costs, and to compare the results between a general population and a hospital sample.

3 Material and methods

This thesis builds upon two distinct datasets, one from the Burden of Obstructive Lung Disease (BOLD) study, and one from the Economics of COPD (EconCOPD) study. The Norwegian site in the BOLD study, and the EconCOPD study, both recruited from the 2003-2005 follow-up of the Hordaland County Respiratory Health Survey (HCRHS). Details on sampling and design of the HCRHS are previously published [13]. Shortly, the HCRHS is a cohort study based on a random sample of the adult population between 15 and 70 years of age in Hordaland County in 1985, with three follow-ups (in 1987-88, 1996-97, and in 2003-05), see Figure 3. In 2005, there were a total of 1717 responders who were eligible for invitation to the EconCOPD study. For the BOLD study, the same 1717 were eligible for inclusion, together with 755 HCRHS non-responders. Figures 4 and 5 show the flow charts for these two studies, respectively.

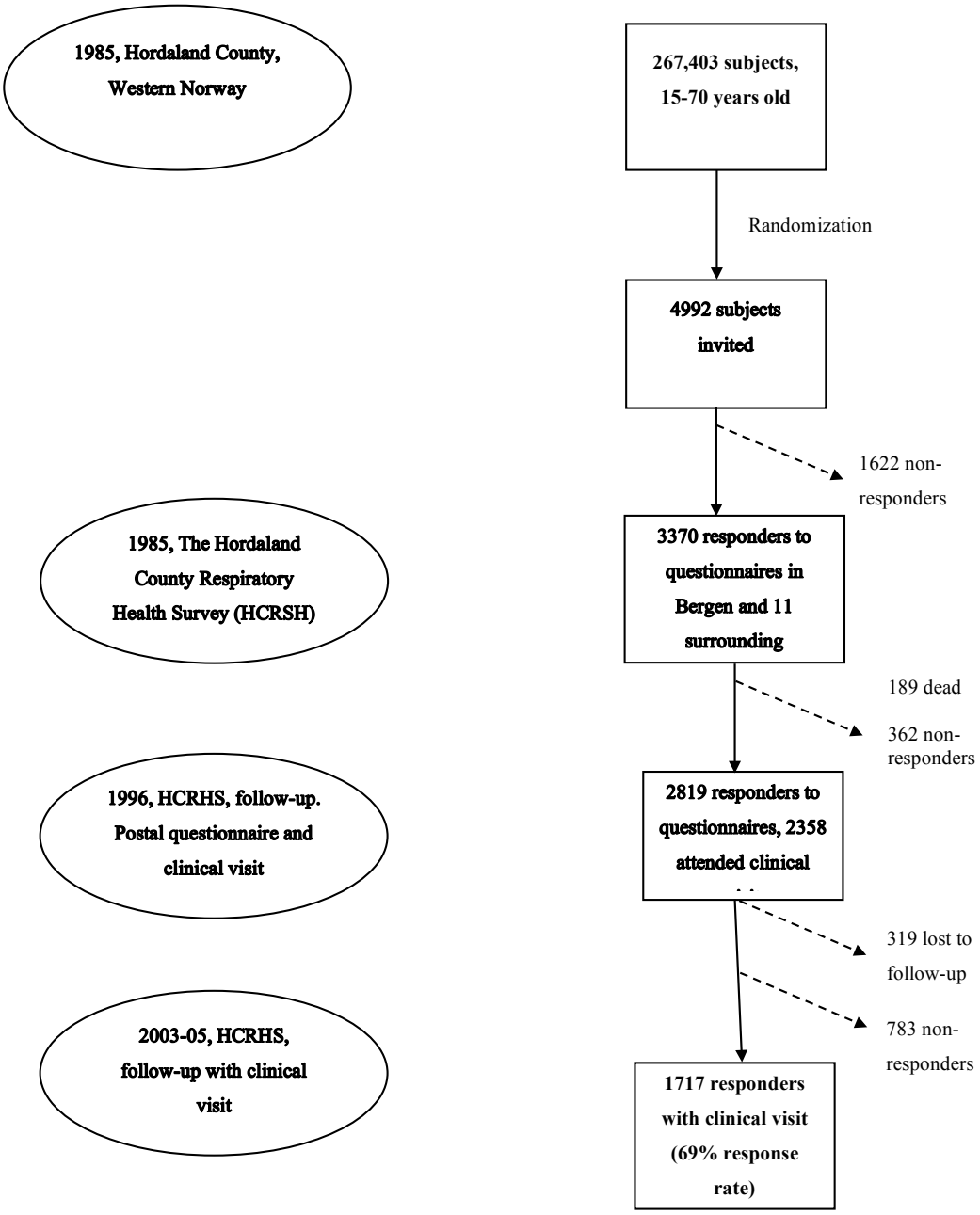


Figure 3: Flow chart for the HCRHS until third follow-up in 2003-05.

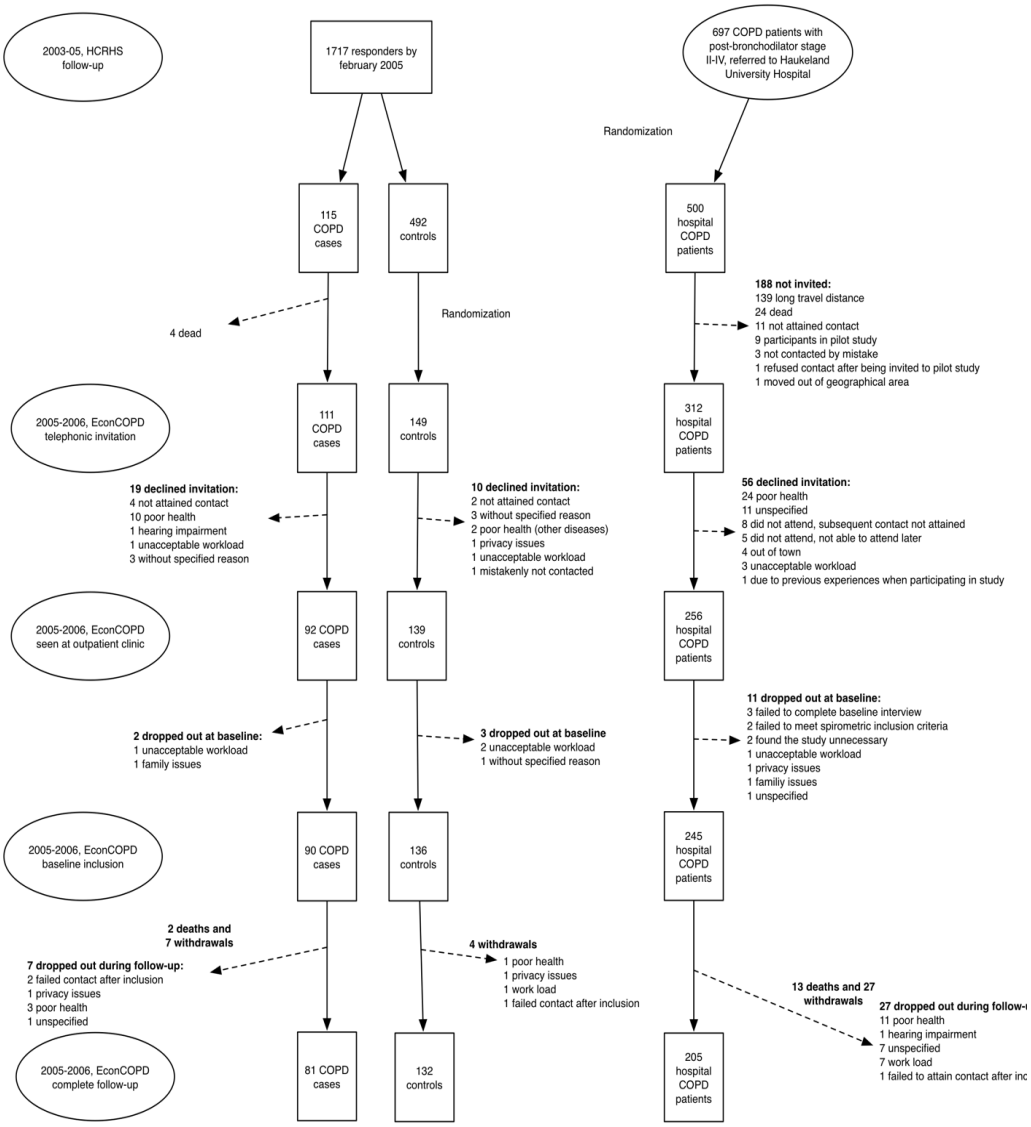


Figure 4; *Flow chart for the EconCOPD survey. Cases and patients had COPD defined as FEV_1/FVC <0.7 and FEV_1 <80% of predicted. Controls had FEV_1/FVC >0.7 and FEV_1 >80% of predicted. All participants were ≥ 40 yrs and had at least smoked the equivalent of 2.5 packyears. Figure reprinted with permission from Rune Nielsen`s dissertation [113].*

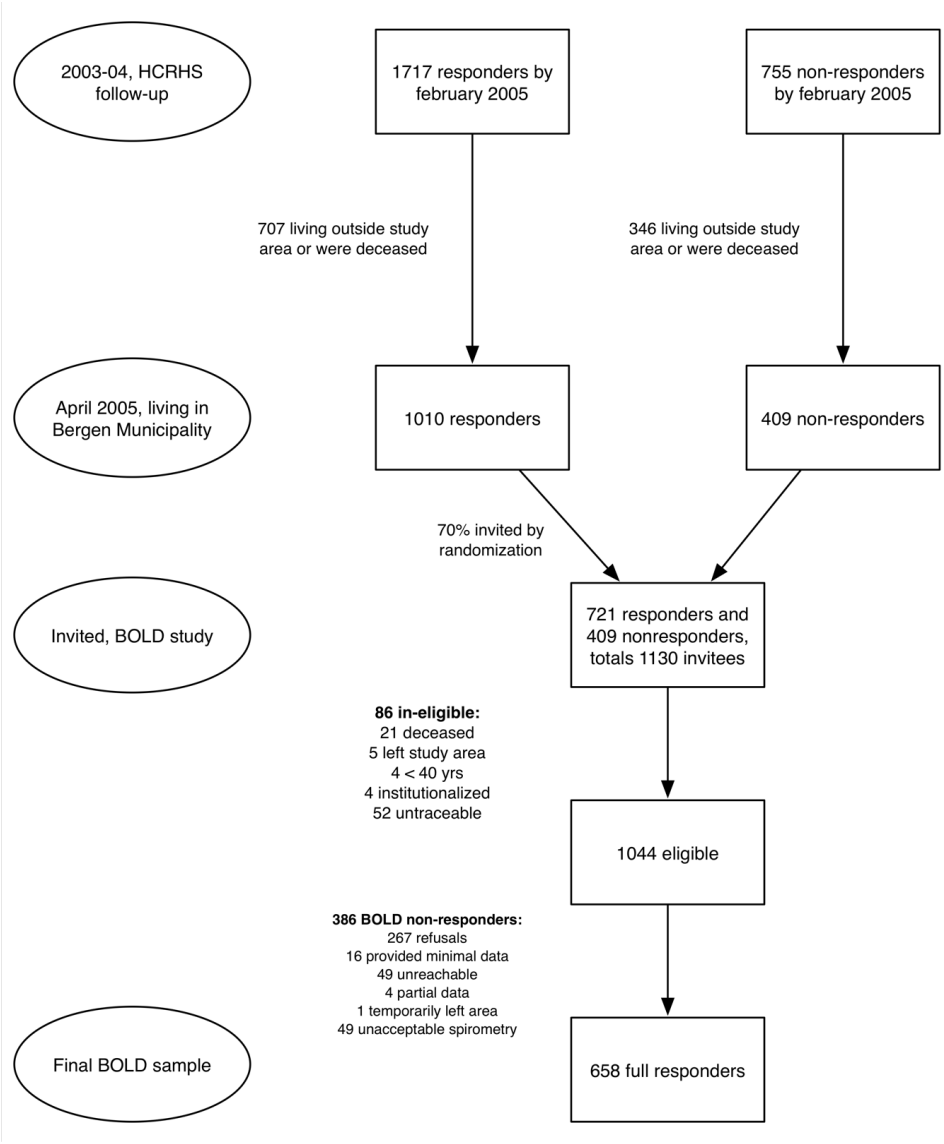


Figure 5: Flow chart for the Norwegian site of the BOLD survey. Figure reprinted with permission from Rune Nielsen`s dissertation [113].

3.1 Study population and design

3.1.1 The BOLD Study

The BOLD study is an international, multicentre, cross-sectional study that collected data for over 30.000 persons in 42 sites when completed. The BOLD protocol has previously been published [114]. Briefly, the BOLD study was designed as a prevalence study of COPD amongst non-institutionalised adults of 40 years or more. The primary aims of the BOLD initiative is to 1) measure the prevalence of COPD and its risk factors in various areas of the world; 2) estimate the burden of COPD in terms of impact on quality of life, activity limitation, respiratory symptoms, and use of health care services; and 3) develop a model to project future burden of disease for COPD.

In Norway, Bergen was the only participating site. Haukeland University Hospital (HUH), and the Institute of Medicine, University of Bergen, cooperated in the study, and recruited responders and non-responders from the follow-up of the HCRHS, see Figure 4. At the time of invitation, the eligible invitees had an age-range of 35 to 90 years old, but only those 40 years or older were invited. All non-responders (N=409) from the third follow-up of the HCRHS in 2003-05 who had not moved or died (N=346) were invited. A random 70% of 1010 responders 40 years or older were also invited. Of these 1130 possible participants, 1044 were eligible for full participation. 386 of these ended up as non-responders (see Figure 5), and 658 were full responders forming the final BOLD sample for Bergen. All participants were either seen at the outpatient clinic, or in their homes by an investigator. Questionnaires were answered, and a post-bronchodilator spirometry was performed. The study co-workers were all trained and certified by BOLD coordinating centres to obtain the highest quality possible for the gathered data and for the performance of spirometry.

When undertaking the analysis for paper I, the BOLD study had completed the data collection in 26 sites around the world (Figure 6). In total, 22118 participants had provided interview data, of which 18710 performed a satisfactory post-bronchodilator

spirometry and were included in the analysis. However, when analysing the outcome, risk of unemployment, all participants above 65 years of age (defined as retirees) and homemakers/caregivers were excluded. After this exclusion, there were no cases with chronic airflow obstruction (CAO) left in Tirana, Albania, hence this site was not included in the analyses of the effect of CAO on unemployment risk. Sampling strategy and response rates for all sites are given in the Appendix.

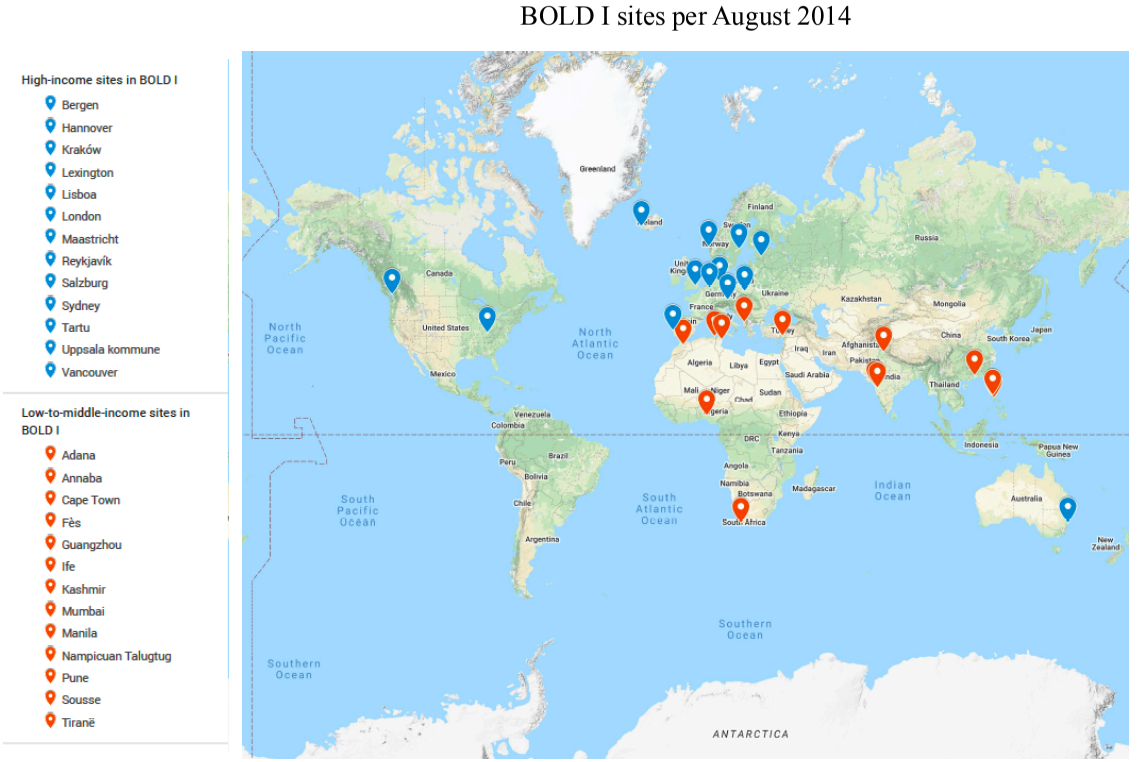


Figure 6; Participating sites in the BOLD study for Paper I, stratified by income status.

3.1.2 The EconCOPD study

The EconCOPD study was a prospective COI-study of a Norwegian general population with one year of follow-up. It was conducted between March 2005 and August 2006 at the Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway. The study sample was made up of three different groups of participants; COPD cases from the general population, control subjects from the same general population, and hospital recruited COPD patients. All participants were at least 40 years old when invited, and had smoked a minimum of 2.5 pack years of cigarettes – 1 pack year being defined as smoking 20 cigarettes daily for one year.

Both the population-based controls and COPD cases were recruited based on age, smoking habits, and spirometry from the 2003-05 follow-up of the HCRHS. The hospital-based COPD patients were recruited from the COPD register of HUH between September 1997 and December 2004. ICD-10 codes J41-J44 (emphysema, chronic bronchitis, and COPD) and J96 (respiratory failure) were used to identify potential subjects for inclusion in the study. A few subjects were present both in the HCRHS and in the hospital register. To avoid including them in both samples, they were kept in the HCRHS-population, and deleted from the hospital register.

Both the population-based COPD cases and the hospital-recruited COPD patients had spirometry defined COPD of GOLD-stage II–IV with a post-bronchodilator FEV_1/FVC-ratio of less than 0.7, and an FEV_1 of less than 80% of predicted. The control subjects had an FEV_1/FVC-ratio above 0.7, and FEV_1 of at least 80% of predicted.

Initially, an invitation letter was sent out to all eligible participants who were contacted by telephone after receiving the letter. Those interested in participating were given an appointment at the outpatient clinic at the Department of Thoracic Medicine, HUH. During this appointment, they first

received study information, and then signed the informed consent form, before they went on with a face-to-face interview. This baseline interview gathered information on demographic variables including educational level, smoking habits, diagnoses, comorbidities and drug utilization. After inclusion, the participants were followed for one year with telephone interviews at 12 weeks, 24 weeks, 36 weeks, and 52 weeks after the baseline interview. The follow-up interviews by telephone covered information regarding utilization of health care services and respiratory symptoms since last interview, and also if there had been any change in working life participation due to sick leave or disability pension. All questionnaires and the consent form are attached in the Appendix. Figure 4 shows the details of the inclusion and causes of non-response for the whole study period.

3.1.3 Ethics

Both the BOLD study and the EconCOPD study included only volunteers that had provided written consent to participate. The BOLD protocol was written in accordance with the Helsinki declaration, and was approved by ethics committees at all local sites. In the Norwegian site, the Regional Committee for Medical and Health Research Ethics in Western Norway (REK Vest) approved the study (approval REK Vest case no. 098.05). The EconCOPD study was also approved by REK Vest before study start (REK Vest case no. 252.04).

3.2 Questionnaires and exposures

All questionnaires used in this thesis, both for the BOLD study and the EconCOPD study, are presented in the Appendix.

3.2.1 The BOLD study (Paper I – Unemployment in chronic airflow obstruction)

The BOLD core questionnaire was asked to all participants by study co-workers, in a structured face-to-face interview in each site. The questionnaire gathered information on smoking habits, education, living standards, job status, self-reported comorbidities (hypertension, heart disease, diabetes, stroke, and lung cancer), respiratory symptoms (dyspnoea, wheezing, and chronic bronchitis), and exacerbations of respiratory symptoms. Previously validated instruments, as the 1978 ATS/DLD Respiratory Symptom Questionnaire [115], the European Community Respiratory Health Study screening questionnaire [116], and the US Lung Health Study questionnaire [117], were used when possible. Smoking status was divided into never-smokers (subjects who had smoked < 20 packs of cigarettes in their lifetime), ex-smokers (subjects who reported an age at which they had stopped smoking), and current smokers. The highest level of completed schooling defined the participant`s educational level (either no schooling, primary school, middle school, high school, some college, or completed college/university education). Dyspnoea was defined according to the modified Medical Research Council (mMRC) questions, and graded from 0 to 4 [118]. Wheezing was defined as attacks of wheezing associated with dyspnoea in the last 12 months, while chronic bronchitis was defined as productive cough on most days at least three months per year for at least two consecutive years.

3.2.2 The EconCOPD study (Papers II, III, and IV)

Before the main EconCOPD study, a pilot survey was performed [119]. Based on this pilot survey, the questionnaires for the main study were developed and named “the Norwegian Cost of COPD baseline Questionnaire (NCCQ-b)”, and “the Norwegian Cost of COPD follow-up Questionnaire (NCCQ-f)”. The most important change from the pilot survey, was that instead of asking for costs specifically due to respiratory disease (for calculating attributable costs), the final questionnaire asked for all health care utilization independent of disease. This enabled the calculation of excessive costs, in which you need access to

health care utilization irrespective of which condition triggers the requirement of health care services.

All papers from the EconCOPD study used the same definition of smoking status and educational level. Smoking status was divided into current smoking, or former smoking if the participant gave a date or year for having quit smoking. In some statistical models, we examined smoking exposure using the number of packyears smoked (one packyear being equivalent of smoking 20 cigarettes per day during one year). Educational level was divided into three levels: primary school, secondary school, and university. Further, the Charlson Comorbidity Index was used to gather information of comorbidities [120]. For questions regarding health care utilization, we modified a questionnaire from a Swedish study on the burden of COPD, the OLIN study [121]. Severity of COPD was defined using the GOLD stages II, III, and IV. All stages had an obstructive post-bronchodilator FEV_1/FVC-ratio of less than 0.7. GOLD stage II had in addition an FEV_1 between 50 and 80% of predicted, stage III between 30 and 50% of predicted, and stage IV < 30% of predicted.

3.2.3 Paper II – Productivity losses in chronic obstructive pulmonary disease

In the paper on productivity losses in COPD, both the baseline and the follow-up questionnaires were used. An exacerbation of respiratory symptoms was defined according to the modified Anthonisen criteria [122] as 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 asthenia) for at least two consecutive days. Both the hospital-recruited COPD patients, the population-dwelling COPD cases, and the population controls were asked about symptoms of respiratory exacerbation. With this approach, we were able to quantify the occurrence of exacerbation-like events in the control group, and to estimate the difference in its occurrence between all groups.

3.2.4 Paper III – Incidence of COPD exacerbations

In this paper, only the four follow-up questionnaires were used to calculate the annual cumulative incidence of acute exacerbations of COPD (AECOPD). To evaluate the potential differences in the incidence of utilization-defined and symptom-defined exacerbations, we used two distinct definitions of an AECOPD in this paper, see Section 3.5 Outcome variables. Adjustment was made for several demographic variables (sex, age, education, and smoking habits), and further adjustment for other potential predictors (comorbidities, severity of COPD, maintenance therapy, and BMI) was made. Maintenance therapy was defined as regular use of long-acting muscarinic antagonists, long-acting beta-2 agonists, inhaled corticosteroids, or theophylline. BMI was defined as the weight of the participant in kilograms divided by their squared height measured in meters. Smoking status was divided into current or ex-smokers.

3.2.5 Paper IV – Incremental costs of COPD and COPD exacerbations

In this paper, we evaluated the annual costs associated with COPD, both in the hospital-recruited COPD patients, and in the population-dwelling COPD cases. We used the four follow-up questionnaires to cover for a whole year. We used the utilization-based definition of an exacerbation, and the exacerbations were divided into moderate or severe. The moderate exacerbations were those requiring antibiotics or corticosteroids, whilst the severe exacerbations were those requiring hospitalization. COPD severity was defined 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).

3.3 Spirometry

Spirometry is a pulmonary function test (PFT) that measures the volumes of air a person inhales and exhales as a function of time [123]. It is valuable as a screening test for general respiratory health, and if used together with

information on symptoms or exposures to lung toxic agents, it can be used diagnostic in many circumstances. Performing a spirometry involves maximum inhalation followed by a forceful exhalation where the subjects are asked to exhale as rapidly and forcefully as possible until the airflow stops. The spirometer registers the volume of air exhaled as time passes. The most important measurements are the forced vital capacity (FVC), the forced expiratory volume in one second (FEV_1), and their ratio (FEV_1/FVC).

3.3.1 The BOLD study

In the BOLD study, a portable ndd EasyOne® Spirometer (ndd Medizintechnik AG, Zürich, Switzerland) was used. All BOLD technicians went through certification, and all spirometer manoeuvres were evaluated at the BOLD study pulmonary function reading centre [114]. The spirometry was performed before and after bronchodilation with 200 µg salbutamol through a large-volume spacer. Spirometry was performed according to American Thoracic Society standards [124]. Equations for Caucasians from the third National Health and Nutrition Examination Survey (NHANES-III) were used to estimate predicted values for FEV_1, FVC, and the FEV_1/FVC-ratio according to the subjects` age, height, and sex. Spirometric CAO was defined as a post-bronchodilator FEV_1/FVC-ratio below lower limit of normal (LLN).

3.3.2 The EconCOPD study

In the EconCOPD study, the spirometry results from the 2003-05 follow-up in the HCRHS and from the 2003-05 investigation of the HUH COPD patients were used. Spirometry was performed 30 minutes after inhalation of 400 µg salbutamol through a large-volume spacer, and all measurements were done according to ATS standards [124]. A Vitalograph 2160 spirometer (Vitalograpgh Ltd, Maids Moreton, UK) was applied. Predicted values were calculated using a pre-bronchodilator reference equation based on the HCRHS population [125]. COPD was defined by a fixed ratio of $FEV_1/FVC < 0.7$, post-

bronchodilator. Grade of airflow obstruction, i.e. disease severity, was classified according to the GOLD-stages by FEV_1 in % of predicted [3].

3.4 Data management and quality control

The data management and quality control for both the HCRHS and the BOLD study have been published previously [4, 113, 114, 126] and is briefly described hereunder.

3.4.1 The BOLD study

The BOLD Operations Centre (OC) provided overall administration and supervision of the whole study initiative. Initially, the OC was situated at the Kaiser Permanente Center for Health Research in Portland, Oregon. The OC had the responsibility of supervising all aspects of the protocols for each site. The study incorporated meticulous quality control into the methods to secure reproducibility. All spirograms were reviewed by the pulmonary function reading centre, initially located in Salt Lake City, Utah. Only spirometry results that fully met the ATS acceptability criteria and were reproducible to within 200 mL were included in the study. Both the OC and the pulmonary function reading centre were later joint in the coordinating centre at the National Heart and Lung Institute, Imperial College London, UK. Data collection and transferring of data from questionnaires was standardised, and once completed for any given site, the OC provided the site with an electronic copy of its own cleaned and edited data set. The OC retained a copy of the data sets for all sites for pooled, cross-site analyses.

Before data collection, all study staff was trained and certified in study procedures. There are formal written procedures for all aspects of the study, including the questionnaire, lung function testing, data management, and study sample collection. The questionnaires were both translated into the local

language at each site, and back-translated into English by the OC to check for incongruences between the original and the back-translated version [4, 114].

3.4.2 The EconCOPD study

Four medical students, one project nurse, and the project physician performed the baseline visits. All interviewers performing the baseline interview had attended a seminar presenting the protocol and a lecture on COPD. They practiced interviewing technique by participating in role play, and by interviewing symptomatic COPD patients admitted to the Department of Thoracic Medicine, HUH. The project physician, Rune Nielsen, observed the interviews at the inward. Additionally, all interviewers watched one complete baseline visit held by the project physician. All questionnaires were checked and corrected for errors, inconsistencies, and missing values by the project physician or the project nurse. Using SPSS Data Entry version 4.0, all the data were transferred to a database [113].

For the follow-up interviews, three more medical students worked part-time in the study. They were trained through reading the written guidelines and questionnaires, and observed one interview conducted by the project physician. Additionally, their first interview was supervised by the project physician. Regular observations of the interviewers were conducted during the 12 months of follow-up, including feedback on interview performance. All questionnaires were controlled in the same manner as the baseline interview, and data were entered into the database likewise after checking for errors [113].

3.5 Outcome variables

3.5.1 Paper I - Unemployment in chronic airflow obstruction in the BOLD study

The main outcome in this paper was employment status. Participants were asked if they had worked for income at any time the year prior to the study, or

if they were fulltime homemakers/care givers. All participants ≥ 65 years of age were defined as retirees. All others that had not worked for income or were not homemakers or care givers, were defined as unemployed. Retirees and caregivers/homemakers were excluded from the analysis, leaving a dichotomous outcome variable (unemployed yes/no). The variable spirometric CAO was analysed as the main predictor of employment status, and both unadjusted and adjusted comparisons between individuals with and without spirometric CAO were made. See section on statistical analyses, *3.7*, for more details.

3.5.2 Paper II - Productivity losses in chronic obstructive pulmonary disease

In this paper, the main outcome was productivity loss. Number of days in disability pension was added from the baseline interview and the four follow-up interviews to give total days in disability pension. For participants who were in paid employment, sick leave, irrespective of cause, was added for the four follow-up interviews to give total sick leave days. For those reporting a graded sick leave or disability pension, the percentage was multiplied by number of days absent from work. Days in sick leave and disability pension were summed up to give the main outcome productivity loss.

3.5.3 Paper III - Incidence of COPD exacerbations

The aim of this paper was to estimate the incidence and potential predictors of AECOPD. We used two definitions of an AECOPD to analyse the main outcome of exacerbation rates. The symptom-based definition was the same as in paper II (see section 3.2.3). The utilization-based exacerbations were defined by the use of antibiotics or corticosteroids due to respiratory disease, or by hospitalization due to respiratory disease. All exacerbations recorded in the four follow-up interviews were summed to give the number of annual exacerbations per participant.

3.5.4 Paper IV - Incremental costs of COPD and COPD exacerbations

The main outcome in the last paper of this PhD project, was the excessive costs for COPD patients and COPD cases compared to control subjects. We both investigated the treatment-related costs, the productivity losses, and the total costs (treatment-related costs plus productivity losses). The treatment-related costs were direct costs, and included both the societal cost related to e.g. hospital admission, rehabilitation, or refunds of treatment, as well as the individual cost from for instance drug expenses, transportation and the like. The productivity losses, or the indirect costs, were the costs to society due to absenteeism from work. The treatment-related costs were calculated by multiplying the rates of utilization with the corresponding unit costs, see section *3.6 Unit costs.* The productivity losses were calculated using a human-capital approach where average wages per day based on sex, age, and education were multiplied by the total days of lost productivity in a year [103]. The mean income per day according to sex, age, and education was given for the year 2006 by Statistics Norway (SSB). We added 20% to the average income to cover for the total employers` compensation per worker [127]. All costs were transformed from 2006-NOK to Euros using the mean exchange rate for that year (8.05 NOK = 1 €).

3.6 Unit costs

For paper IV, *Incremental costs of COPD exacerbations in GOLD stage 2+ COPD in ever-smokers of a general population,* both the treatment-related entities and the days of lost productivity required denomination in a monetary unit.

3.6.1 Unit costs of treatment-related items

The annual unadjusted costs covering treatment-related items, were calculated by multiplying the rate of utilization per year of each item with the corresponding unit cost. The items we included were intended to cover total treatment costs, i.e. both costs payed for by the individual and by national

health insurance, attached under section Supplementary material. For extensive details, see the project physicians` dissertation [113].

For hospitalisation costs, we used the Samdata report from SINTEF (The Foundation for Scientific and Industrial Research at the Norwegian Institute of Technology) [128]. The report from SINTEF used information both from public and private hospitals of the Diagnosis Related Group-activity (DRG) to estimate the average costs per day of admission to Norwegian hospitals, excluding capital costs (i.e. fixed, one-time expenses due to purchase of for instance land, buildings, or equipment).

The costs related to visits to health care providers were collected from The Norwegian Labour and Welfare Organisation and The Norwegian Directorate of Labour and Welfare [129]. All claims for the national health insurance are administered by them, and they provided us with estimates based on all claims from 2005-2006. Costs for GP-, ER-, and specialist-visits irrespective of cause were gathered, and the price for home visits was differentiated from office visits. The costs of visits to outpatient clinics were acquired from The Norwegian Directorate for Health and Social Affairs [130]. The estimates were based on data from 14 hospitals in 2007, not including capital costs.
National estimates for the costs of home nursing services were not available, but The Municipality of Bergen City, Western Norway, brought forth the costs per hour of home nursing services as of January 1st 2008 [131]. Included in these costs were hourly costs, fixed costs per visit, and monthly costs. Maid services provided by local health authorities were paid for by the patients themselves, and we used self-reported expenditures for this item.

To calculate drug costs, all regular medication and reliever medication was counted in terms of how many follow-up days they had been used. The dose was then set to one defined daily dose (DDD) according to the ATC/DDD-system [132]. Additionally, intermittent medication use, and over-the-counter

(OTC) medication were counted and transferred to DDD. The cost per DDD was supplied by the Norwegian Pharmacy Association [133], and was used to calculate unit costs for prescription medication. For OTC medication, sales numbers from the pharmaceutical industry was used to calculate unit costs, based on information from Farmastat AS [134].

Some individuals participated at the pulmonary rehabilitation programme at the Department of Thoracic Medicine, HUH. The programme lasted for 16 days, and involved both group training and education given by physicians, physiotherapists, nurses, and pharmacologists. Costs for individual participation were provided by the Pulmonary Rehabilitation unit at the Department of Thoracic Medicine, HUH, for year 2007 [135]. DRG-based costs per day were € 140 (NOK 1,120). In addition, the participants had a physician consultation that was billed (adding co-payment and hospital claims to the national health insurance) at € 155 (NOK 1,239). To calculate the prices in 2005- and 2006-valuta, we used the consumer price index [136]. Physiotherapy, either individual or in groups, was priced according to official costs set by the Ministry of Health and Care Services for year 2005-2006 [137].

For the few participants in the EconCOPD study that used long term oxygen treatment at home, the costs per year were supplied by the Department of Thoracic Medicine, HUH. These costs included the expenses of the equipment, and the personnel costs [135].

3.6.2 Unit costs of productivity losses

Absence from work was quantified in days in paper II. In paper IV, the days of absenteeism, or lost productivity, were transformed to a monetary unit to give the costs associated with sick leave and disability pension. We used the human capital approach, and each day of lost productivity was valued according to the mean income per day by sex, age, and education provided by Statistics

Norway, see Appendix. An additional 20% was added to cover for employer`s costs [103].

3.7 Statistical analyses

3.7.1 Unadjusted analyses

Initial unadjusted analyses in all papers were executed to compare the characteristics between the groups of participants. Categorical variables were analysed with chi squared tests. For continuous variables, we first made histograms to evaluate their distribution. When the assumption of a normal distribution was met, we used parametric tests such as the *t*-test, and Analysis of variance (ANOVA). For continuous variables with a skewed distribution, we used non-parametric tests such as chi squared, Kruskal-Wallis, and Spearman´s correlation test. Some additional tests for trend were made in the Econ COPD study to assess the utilisation across the three participant groups, and for this purpose we used the Stata nptrend command which is a modified Wilcoxon rank-sum test. In the paper on unemployment across the world in the BOLD study, additional unadjusted, but stratified analyses were performed to assess the proportions who reported having a current paid job. Participants were stratified into high- or low-to-middle income sites and according to sex to visualise possible differences in job status between the sites and genders. The cut-off point between high- and low-to-middle income sites was set at USD 10000 in Gross National Income Per Capita (GNIPC) of the country [138]. Risk ratios were estimated as the unemployment prevalence in persons with CAO divided by the unemployment prevalence in persons without CAO.

3.7.2 Adjusted analyses

3.7.2.1 Choice of adjustment variables

In the analyses for paper I from the BOLD study, we investigated the association of the main exposure, spirometric CAO, on the outcome unemployment. There are several factors known to affect the unemployment

risk, such as higher age, female sex, cigarette smoking, and lower education [139, 140]. To be defined as a confounder, and hence, to be included in our analyses as adjustment variables, these factors also need to be associated with the exposure, spirometric CAO, and precede both exposure and outcome in time. CAO increases both with age, female sex, smoking, and lower education [5, 141, 142], and these are all potential confounders for our association of interest. The comorbidities we asked for, were heart disease, hypertension, diabetes mellitus, stroke, and lung cancer. It has been seen that most of these diseases increase the risk of unemployment [143-146], and they are known comorbidities in COPD [3]. Even if we cannot always be certain that these comorbidities precede spirometric CAO (sometimes the CAO may precede the comorbidities), we included also these as confounding factors in our analyses. Apart from these possible confounders, we furthermore included FVC in our analyses as a particular variable of interest. It has previously been seen that FVC is low in poor countries, though the aetiology behind this is not fully understood [147]. The proof of FVC being racially determined is weak [148], and it has been postulated that environmental factors may be the cause behind the link between poverty and low FVC (factors affecting in utero, or in early childhood to adolescence). As we had many participating sites from LMIC, we wanted to elucidate on how much of the possible association between CAO and unemployment that could be explained by the FVC. Finally, in our last model, we included respiratory symptoms to evaluate their possible association to and effect on the unemployment.

In the three papers from the EconCOPD dataset, we included many of the same possible confounders as in the BOLD paper. Age, gender, smoking status, educational level, and comorbidities were all included based on a priori knowledge of the association both to the exposures and the outcomes. In paper II, where productivity loss was the outcome, and COPD (vs no COPD) was the main exposure of interest, we included exacerbations of respiratory symptoms as a possible predictor of productivity loss. It seems that exacerbations increase

the time spent off work [149], and we included it as a variable in our model to be able to separate the effect of this aspect from our disease of interest. In paper III, we included only those variables that proved significant from bivariate analyses with a p-value < 0.10 in the final multivariate regression model. This choice was made to maximize the precision of the adjustment estimates [150], which might be of particular importance in datasets with limited power. Further on, in paper III, we included maintenance therapy as a predictor of the outcome AECOPD. It has been seen that maintenance therapy reduces the risk of exacerbations[151]. Finally, in paper IV, we also included sample origin and vaccination status as variables of interest in the multivariate model of the association between COPD and costs. Both in paper II, and IV, we wished to investigate what would happen to the magnitude of association with differing levels of adjustment [150], and presented the results from several models with increasing subsets of adjustment variables.

3.7.2.2 Paper I - Unemployment in chronic airflow obstruction in the BOLD study

The main outcome in this paper was a dichotomous employment status. Using log-binomial generalised linear models specified as glm with fam(bin) and link(log), we fitted 5 models with increasing adjustment. All models adjusted for site as a cluster-level variable. Model 1 compared the odds ratio (OR) for being unemployed in subjects with CAO versus subjects without CAO, with no other explanatory variables included. Demographic variables; age, sex, education, and smoking habits were added in Model 2. Model 3 added comorbidities to the variables included in Model 2. In Model 4, FVC was added as an adjustment variable. And in the most adjusted model, Model 5, respiratory symptoms were added.

Further on, models 2-5 were repeated for high-income and low-to-middle-income sites separately. To evaluate site-specific and overall odds ratios for CAO on unemployment, we performed individual participant data meta-

analyses with Forest plots corresponding to the models 1-5 (except the site adjustment). The total variation across sites due to true site-by-site heterogeneity (rather than what could be expected by chance alone) was explained by the I^2 statistic.

3.7.2.3 Paper II - Productivity losses in chronic obstructive pulmonary disease

For the data on productivity losses, there were many participants with either zero or 365 days of lost productivity in the year of follow-up. Due to this skewed distribution of the outcome, we used a median quantile regression model to assess the incremental productivity losses in cases and patients with COPD versus controls. We had two main models in which the first one included population-based COPD cases and controls, and the second included hospital-recruited COPD patients and population-based controls. In all models, we adjusted for sex, age, education, and smoking habits. Supplemental models adjusted for FEV_1 % predicted, number of comorbidities, and exacerbations of respiratory symptoms. The incremental productivity loss associated with having COPD was obtained by including a categorical variable indicating the case/control status of the participant. I.e., the change in the regression coefficient for this variable, equals the incremental productivity loss when adding COPD to the baseline productivity loss of the control subjects.

3.7.2.4 Paper III - Incidence of utilization- and symptom-defined exacerbations

As the outcome in the second paper, the distribution of the exacerbation rate in our third paper, was likewise skewed, with a majority of participants with 0 exacerbations. Hence, we chose a negative binomial regression model for the multivariate analyses. Initially, we performed bivariate analyses of each potential predictor using a Kruskal-Wallis test with ties. The predictors that were statistically significant with a *p*-value of < 0.10 were included in the final multivariate regression model.

We pooled the hospital-recruited COPD patients with the population-based COPD cases, and adjusted for participant group to estimate the effect of sample population on the exacerbation rate (with the general population as the reference group). Models for both symptom- and utilisation-defined exacerbations were estimated. Adjustment variables apart from participant sample group included sex, age, educational level, smoking habits, pack-years, FEV_1 % predicted, number of comorbidities, maintenance therapy, influenza vaccination, pneumococcal vaccination, oxygen therapy, and BMI. The results were given in incidence rate ratio (IRR) for each predictor, showing their associated relative risk of exacerbation adjusted for the other variables.

3.7.2.5 Paper IV - Incremental costs of COPD exacerbations

Also, the cost components had a skewed distribution, and we used quantile median regression to estimate costs attributed to exacerbations and other variables. With quantile median regression, the regression coefficients provided are in the same unit of measurement as the outcome, i.e. in monetary units in this case. We fitted two separate regression models, the first one comparing population-based COPD cases to controls, and the second comparing hospital-recruited COPD patients to controls. For both of these comparisons we calculated the treatment-related costs and the productivity loss-related costs separately. We made two regression models in which the "basic" model included adjustment for COPD severity according to GOLD-stages II-IV, sex, age, comorbidity score, educational level, and pack-years smoked. The second model called "the exacerbations model", adjusted for the same predictors as in the basic model, and additionally for both moderate and severe exacerbations. In the population sample of COPD cases there were few participants with severe airflow limitation (GOLD-stages III and IV). We therefore pooled these two groups of airflow limitation in the multivariate regression analyses.

3.7.3 Sample size and power calculations

The rationale for the chosen sample size and power calculations for the EconCOPD study have been published previously [113].

Briefly, in research, a null hypothesis should be put forward before undertaking the analyses needed to verify or reject this null hypothesis. The sample collected to evaluate if the null hypothesis is true or false, needs to be of a certain size to be able to detect any potential effect that is truly present. There are mainly two errors one can commit when evaluating the null hypothesis – rejecting the null hypothesis in favour of a false alternative hypothesis, also called a Type I error. The opposite is failing to reject the null hypothesis in favour of a true alternative hypothesis, also called a Type II error. The probability of committing a Type I error is known as α, and the probability of committing a Type II error is known as β [152]. The power of a sample is the probability of not making a Type II error, or with other words, the probability that a statistical test will pick up an effect that is truly present. Mathematically, power = $1 - \beta$, and usually β is set to be 0.2. The principal factors affecting power are the significance level (α), the sample size, and the variance in the measured outcome variable. The probability of committing a type I error, α, is the significance level one decides to be considered as statistically significant, normally 0.05. With the desire of a low probability of making both a Type I and a Type II error, power should be as close to 1 as possible, and the significance level as close to 0 as possible [152]. In the EconCOPD study, calculations from the pilot study showed that a sample size of 85 individuals in each group was necessary to be able to detect a difference in costs of 150NOK [113] (with the aim of a β-value of 20%, and a significance level of 5%).

3.7.4 Statistical software

For all our papers, we used Stata SE for Macintosh OSX (Stata Corp, College Station, Texas, USA). In paper I, the version 14 was utilised, in paper II version 11, in paper III version 13.1, and in paper IV version 15.1.

4 Results

4.1 Paper I - Unemployment in chronic airflow obstruction in the BOLD study

With the aim of recruiting subjects who were representative of each local population in 26 sites, interview data for 22,118 participants was gathered, and complete data including an acceptable post-bronchodilator spirometry for 18,710 participants was obtained.

Of these 18,710 participants, 2123 (11.3%) had CAO. All unadjusted comparisons between subjects with CAO and subjects without CAO were significant except for the comorbidity of self-reported diabetes. Subjects with CAO were more often men, older, had smoked more, had a lower education, lower lung function, more comorbidities, higher grade of dyspnoea, more attacks of wheezing, and more chronic bronchitis compared to the subjects without CAO.

For the analyses on employment status, all participants aged ≥ 65 years were excluded, leaving 11,675 participants for remaining analyses. In total, 36.7% (95% CI 34.7 – 38.8) of the subjects with CAO reported having a paid job the past 12 months. The corresponding number for the subjects without CAO was 53.2% (52.4 – 53.9). The unemployment rates varied substantially between the sites, but there was a quite consistent pattern of higher unemployment amongst subjects with CAO than amongst subjects without CAO, especially in high-income sites. In LMIC, CAO was not significantly associated with unemployment in all sites. For instance, the unemployment rates (crude OR (95% CI)) in Guangzhou, China, and in Manila, Philippines, were 35.7% versus 49.9% (0.7 (0.4 – 1.5)), and 10.3% versus 19.5% (0.5 (0.2 – 1.4)) for the CAO subjects versus the non-CAO subjects, respectively. On the other hand, in Annaba, Algeria, and in Cape Town, South Africa, the unemployment rates were 50.0% versus 24.6% (2.0 (1.2 – 3.3)), and 52.2% versus 33.5% (1.6 (1.2 – 2.0) for the CAO subjects versus the non-CAO subjects, respectively.

More men than women reported having a paid job both in high-income and in low-to-middle-income countries. This difference between the genders was more pronounced in LMIC, and seemed to be explained by a higher proportion of females reporting a status as unpaid homemakers/caregivers in these sites.

Evaluating the adjusted odds ratio of being unemployed according to CAO status, we used log-binomial generalised linear models with an increasing number of predictors. The first model, adjusting for site, gave an OR (95% CI) for being unemployed of 1.79 (1.41 – 2.27) for the participants with CAO. Further adjustment with the demographic factors sex, age, smoking habits, and education (model 2), reduced the OR to 1.44 (1.15 – 1.81), though it remained statistically significant. In model 3, we added adjustment for comorbidities, and in model 4 additional adjustment for FVC in % of predicted was made, but none of these variables significantly changed the OR of unemployment amongst subjects with CAO which remained at 1.43 (1.14 – 1.79) in model 4. Further adjustment with respiratory symptoms in model 5, did reduce the OR for unemployment to 1.26 (1.00 – 1.57), but the association between unemployment and CAO was still statistically significant.

All the multivariate regression models were repeated with stratification between high- and low-to-middle-income countries. In these stratified and adjusted models, CAO was a significant risk factor for unemployment in all high-income countries. Female sex and increasing age were the most important risk factors of unemployment in LMIC with overall ORs 3.23 (2.66 – 3.91) and 2.20 (1.96 – 2.47), respectively, in model 4. In high-income countries, increasing age and lower education were important risk factors of being unemployed. A 10-year increment in age was associated with an OR of being unemployed of 4.02 (3.53 – 4.57), and the OR of unemployment for primary school education compared to university education, was 3.86 (2.80 – 5.30), with adjustments as in model 4.

Examining the heterogeneity between the sites, we performed individual participant data meta-analyses with Forest plots of odds ratios and overall I^2 statistics. As an equivalent to the model 4 mentioned above, though without site-adjustment, the overall adjusted OR for unemployment amongst CAO subjects was 1.41 (1.18 – 1.69), with an I^2 statistic of 12.9% (as a quantification of the site-by-site heterogeneity).

4.2 Paper II - Productivity losses in chronic obstructive pulmonary disease

For the analysis of productivity losses in the prospective observational study EconCOPD, we focused on the data of the 102 hospital-recruited COPD patients, 53 population-based COPD cases, and 107 control subjects who were below the Norwegian retirement age of 67 years.

Unadjusted comparisons between the groups showed that there were no sex differences between them. The hospital-recruited COPD patients were significantly older, had a lower educational level, lower lung function, more comorbid conditions, and experienced more events of exacerbations of respiratory symptoms, both when using ANOVA, chi squared, or Kruskal-Wallis as appropriate. Also tests for trend using nptrend confirmed significant differences between the sample groups (hospital patients > population-based patients > controls).

At baseline, the proportions reporting having a paid job amongst the hospital-recruited COPD patients, the population-based COPD cases, and the controls were 31%, 55%, and 87%, respectively. On the other hand, the proportions reporting receiving a disability pension at baseline were 65%, 30%, and 7%, among the respective groups.

During one year of follow-up, the mean days (SD) in sick leave were 12.6 (30), 19.3 (55.4), and 15.7 (36.4), for the patients, the cases, and the controls, respectively. The mean number of days (SD) with a disability pension during the year of follow-up was 228.6 (170.3), 100.8 (156.3), and 23.4 (83.1), respectively. The median number of days (IQR) with a disability pension during follow-up, was 365 (365), 0 (256), and 0 (0), respectively.

The days in sick leave and days with a disability pension were summed in our main outcome -days of productivity loss. This outcome was quite asymmetrically distributed, with 56% of hospital-recruited COPD patients having 365 days of lost productivity, and only 8% of this subsample having 0 days of lost productivity. Meanwhile, 38% of the population-based COPD cases had 0 days of lost productivity. Anyhow, there was a consistent and significant trend that the hospital-recruited COPD patients had the highest and the controls had the lowest number of days lost (test for trend, $p<0.001$).

In our adjusted analyses, median quantile regression gave the incremental productivity losses associated with having COPD. Adjustment variables were sex, age, educational level, and smoking habits. Comparing population-based COPD cases to controls, the presence of post-bronchodilator COPD was associated with an increase in productivity losses of 5.8 days (95% CI 1.4 – 10.1). Comparing hospital-recruited COPD patients to controls, having COPD was associated with an increase in productivity losses of 330.6 days (327.8 – 333.3). In both comparisons, female sex and lower education were also associated with a significantly increased productivity loss after adjustment for the other variables.

Examining the effect of comorbid conditions and events of exacerbations of respiratory symptoms on the association between COPD and productivity losses in the initial analyses, we found that amongst the population-based COPD cases the association was no longer statistically significant. Amongst the hospital-recruited COPD patients, the association was reduced to 312 days from the original 330 days, a reduction of 5.5%. Per added comorbid condition, the incremental days of lost productivity were increased by 5.0 (2.6 – 7.4), and 5.1 (3.2 – 7.1) amongst the population-based COPD cases and the hospital-recruited COPD patients, respectively.

4.3 Paper III – Incidence of utilization- and symptom-defined COPD exacerbations

In this prospective observational study with one year of follow-up, including participants from three sample groups, we gathered questionnaire information and spirometry data for a total of 205 COPD patients from a hospital register, 81 COPD cases from a general population, and 132 control subjects from the same general population.

Unadjusted comparisons between the groups showed that there were no sex differences between them. The hospital-recruited COPD patients were significantly older, had smoked more packyears but were more frequently former smokers, had a lower educational level, lower lung function, more comorbid conditions, experienced both more resource-defined and more symptom-defined exacerbations, used more maintenance therapy, had more frequently undergone vaccination, and were more often underweight, when compared to population-based COPD cases and to controls.

Incidence rates of exacerbations per person per year for the population-based COPD cases and for the hospital-recruited COPD patients, were 0.4 and 1.0 for the utilization-defined exacerbations, and 2.9 and 5.9 for the symptom-defined exacerbations, respectively (all p-values for the comparisons between the sample groups were < 0.001). The control subjects also met the criteria for having an exacerbation at a rate of 0.1 per person per year, and 0.7 per person per year for the two respective definitions of an exacerbation.

A majority of participants experienced zero exacerbations during the follow-up period. Using the utilization-based definition 349 participants (83%) had zero exacerbations, and with the symptom-based definition 264 participants (63%) had zero exacerbations.

Due to the skewness of the data, we applied a negative binomial regression model for the multivariate analyses. COPD patients from the hospital register and COPD cases from the population sample were pooled together, and adjustment was made for recruitment source in addition to the other adjustment variables (sex, age, smoking status, GOLD-stage, comorbidities, maintenance therapy, influenza vaccination, and pneumococcal vaccination). Packyears, educational level, and BMI were omitted from the multivariate regression models due to insignificant results in the prior bivariate analysis.

The results were given in incidence rate ratios (IRRs) for experiencing an acute exacerbation of COPD (AECOPD) for each variable compared to its reference. With the resource-based exacerbation definition, the IRR (95% CI) was 1.59 (1.00 – 2.52) for experiencing an AECOPD amongst the hospital-recruited COPD patients compared to the population-based COPD, whilst using the symptom-based definition gave an IRR of 1.78 (1.20 – 2.64) for the same comparison.

For both exacerbation definitions, the variables GOLD-stage, and receiving maintenance therapy were significantly associated with an increased IRR of AECOPD. With the resource-based definition, GOLD-stage II was associated with an IRR of 2.45 (1.22 – 4.95), GOLD-stage III 3.43 (1.59 – 7.38), and GOLD-stage IV 5.67 (2.58 – 12.48). The same pattern of increasing risk of experiencing an exacerbation with increasing airflow limitation was seen with the symptom-based definition, with IRRs of 3.08 (1.96 – 4.84), 3.45 (1.92 – 6.18), and 4.00 (2.09 – 7.66) for GOLD-stages II, III, and IV, respectively.

With the resource-based definition, female sex was significantly associated with an elevated risk of having an AECOPD, IRR 1.57 (1.15 – 2.14). This was not the case when employing the symptom-based definition, but instead, increasing age and having taken the influenza vaccine were negatively associated with the risk of AECOPD with IRRs of 0.71 (0.60 – 0.83), and 0.71 (0.50 – 1.00), respectively.

4.4 Paper IV - Incremental costs of COPD exacerbations

In the final paper, we sought to estimate the costs of COPD exacerbations in the 205 COPD patients from a hospital register, and 81 COPD cases in the EconCOPD study. The comparison to the 132 controls provided the opportunity to estimate incremental costs.

The annual unadjusted costs per person were significantly higher among the hospital-recruited COPD patients compared to the population-based COPD cases, and to the control subjects. For instance, mean hospitalisation costs per person per year were 5278 € for a hospital-recruited COPD patient, while it was 1812 € for a population-based COPD case. The total mean annual treatment-related costs summed up to 9504 € per hospital-recruited COPD patient, 3829 € per population-based COPD case, and 2246 € per control subject. The annual long-term disease-related productivity losses amounted to 13,411 € per hospital-recruited COPD patient, 7777 € per population-based COPD case, and 2094 € per control subject. The total mean annual costs of productivity losses were 17,014 € per hospital-recruited COPD patient, 11,192 € per population-based COPD case, and 4494 € per control subject. The total mean costs per person, i.e. the sum of the treatment-related costs and the productivity losses, were 26,518 € for the hospital patients, 15,021 € for the population cases, and 6740 € for the controls, respectively ($p<0.001$).

In the multivariable analyses, we used median regression to model the incremental costs of COPD. We made 4 main models, each of which had two versions, one with basic adjustments (FEV_1, sex, age, comorbidities, education, and packyears), called the *basic* model, and the second version with additional adjustment for moderate and severe exacerbations, called *the exacerbation* model.

In the first main model, we estimated the adjusted incremental treatment-related costs comparing population-based cases to controls. The basic model gave an incremental cost of 490 € (95% CI 132 – 849 €) associated with GOLD-stage II, and 1938 € (1266 – 2610) associated with GOLD stages III/IV. Adjusting for moderate and severe exacerbations, these numbers fell to 462 € and 1684 €, respectively. In other words, exacerbations explained 6% of the treatment-related costs in GOLD-stage II, and 13% of the treatment-related costs in GOLD-stages III and IV. Female sex and comorbidities were also significant cost drivers in the first model.

The next main model, estimated the incremental productivity losses comparing population-based COPD cases to controls. In the basic model, no significant incremental productivity costs were associated with GOLD-stage II. But for participants in GOLD-stage III and IV, the incremental costs of the annual productivity losses were 46,215 € (30,190 – 62,240). When adjusting for moderate exacerbations, this cost lost its` significance, demonstrating that moderate exacerbations explained all productivity-related costs for the COPD cases.

In the third main model, the treatment-related costs for hospital-recruited COPD patients were compared to that of the controls. In these analyses, we did not need to pool GOLD-stage III and IV participants together, as we did for the population cases. In the basic model, there was a significant incremental cost associated with GOLD-stages II, III, and IV at 2252 € (947 – 3557), 3221 € (1773 – 4669), and 5684 € (3955 – 7412), respectively. Adjusting for exacerbations, these costs were reduced to 1646 € (428 – 2863), 1943 € (557 – 3329), and 3539 € (1771 – 5308), respectively. In other words, the treatment-related costs associated with the GOLD-stages remained statistically significant, but were reduced with 27%, 40%, and 48% when adjusting for exacerbations, for the respective grades of airflow limitation. Comorbidities were an additional significant cost driver in this comparison, both in the basic and in the exacerbations model. The corresponding incremental costs were 694 € (254 – 1134) per comorbid condition added in the basic model, and 714 € (317 – 1111) per comorbid condition added in the exacerbations model.

The fourth and last main model, estimated the incremental costs of productivity losses for the hospital patients compared to the controls. Again, increasing airflow limitation resulted in increasing costs. For GOLD-stage II, III, and IV, the incremental costs of productivity losses were 28,845 € (19,383 – 38,307), 29,570 € (18,759 – 40,382), and 48,338 € (36,548 – 60,128), respectively. Further adjustment for exacerbations did not significantly change these results.

5 Discussion

In this section, the methodological issues will be discussed firstly. This will include study design, possible errors that can be made in epidemiology, and statistical and health economic considerations. Secondly, the main results will be discussed. This includes a discussion of the association between COPD and disease burden in the form of unemployment and productivity losses, the measures of incidence of AECOPD, and the cost estimates and cost drivers. Finally, the effect of sample size will be discussed.

5.1 Methodological considerations

5.1.1 Study design

In this thesis, we have utilised two datasets that both included participants from a general population. The BOLD study was a cross-sectional study including non-institutionalised persons from multiple study centres around the world. Cross-sectional studies are like snap shots of reality reflecting a situation in that specific moment. As such, cross-sectional studies cannot prove if the connection between an assumed predictor and an outcome is causative, or which of them arose first in time. Our research objective in paper I, was to describe the rates of unemployment in subjects without CAO and in subjects with CAO, and to analyse if there was an association between the assumed predictor CAO and the outcome of unemployment. As a descriptive study of associations, the cross-sectional design is adequate and serves to answer the aims of the study.

The rate of unemployment we found was significantly different between the healthy subjects and the CAO subjects, but we cannot prove that having CAO predicts a higher risk of unemployment. There is a possibility of unemployment arising beforehand and being the cause of CAO. There is some evidence that economic hardship leads to health-endangering personal behaviour, like increased smoking [153]. Yet, lacking the proof of temporality, we would like to argue that a condition like CAO, that takes decades to develop and that inflicts daily symptoms of heavy burden, is more likely to be the cause of unemployment, and not vice versa.

The second dataset we utilised, was the EconCOPD study. This was an observational, prospective cohort study that followed the participants for one year, i.e. with a longitudinal design. The participants were recruited from two distinct sources, COPD patients from a hospital register, and both COPD cases and control subjects from a general population, and comparisons between these samples were made. Cohort studies are in general more time-consuming and expensive than case-control studies and may be presented as of inferior quality compared to randomized controlled trials. But when there is no intervention to be evaluated, cohort studies are considered to give the most reliable outcomes in observational epidemiology. During the follow-up time, cross-sections can be made at certain time intervals in which information of interest is collected and used to calculate the longitudinal occurrence of the disease in question.

The aims we sought to illuminate using the EconCOPD study, were firstly to estimate the incremental productivity losses of COPD and its predictors. Secondly, we aimed to estimate the impact of recruitment source and outcome definition on the incidence of acute exacerbations of COPD and possible predictors of AECOPD. Thirdly, we wanted to estimate the treatment- and productivity-related costs associated with COPD in two different samples, and to evaluate the association between the costs and moderate and severe exacerbations. A cohort study with two sampling sources enabled us to reach these aims in an adequate manner. All COPD cases and a random sample of control subjects from the HCRHS follow-up in 2003-2005 were invited. Additionally, a random sample of COPD patients from the hospital registry was also invited. The participant characteristics that differed between the groups were adjusted for in multiple regression models reducing the risk of confounding. To reduce the risk of recall bias, interviews were made at an interval of three months. An alternative approach would have been a matched case-control study. With a matched case-control design, 2-4 controls are normally recommended per case, and would have made such a design more expensive, and would have required a larger number of controls than in the longitudinal cohort design we chose. Another alternative would have been to investigate these issues in a retrospective manner, e.g. by collecting data from registries. Retrospective studies have the advantage of being cheaper, and less time-consuming than prospective studies. Prospective studies, on the other hand, have fewer possible sources of bias and confounding, less missing data, and give, in general more accurate results than retrospective studies [154].

5.1.2 Errors in epidemiology

Errors can occur when performing research in epidemiology, by chance, so called random errors, or systematically. Errors may disturb the results of the research, and researchers might as a consequence see associations that are non-causal.

5.1.2.1 Random error and precision

Precision in epidemiology refers to how close repeated measurements of the same object are to each other [155], and is also known as reliability. Human beings and equipment can give rise to imprecise measurements, and it is crucial to minimize these errors. With low precision, there is a greater spread of the results of each measurement. But the mean value of measurements will inevitably deviate less from the true value when the number of measurements increases.

Random errors are those that occur by chance. As such, they do not recur, and if truly random, they are distributed in both directions compared to the truth (the reason why they are also called non-differential errors/misclassification) [155, 156]. With large samples of high power, random errors should not cause erroneous associations. Though, with small samples, or outcomes that are rare, random errors may be a source of concern.

Most variables are subject to random error which may arise at different stages of the data collection. Demographic information such as sex, age, and educational level should not be substantially prone to random errors. Other variables, such as packyears smoked, exact number of days in sick leave, lung function measurements, or BMI, might be affected by random errors. Still, with the sample size we had both in the BOLD study and in the EconCOPD study, it is hard to believe that the results should be affected in only one or the other direction by these unpredictable errors.

5.1.2.2 Systematic error and validity

The validity of epidemiologic research can be divided in two. External validity deals with how representative the results of a study are for the reference population. In other words, how generalizable the results are. In the planning and design of studies, choices should be made to enhance the future external validity of the findings. Internal validity, however, concerns how representative the results are for the participants of the study.

The high internal validity of randomized controlled trials is ensured by the random allocation of participants into study arms (e.g. active treatment vs placebo). Thus, even unmeasured variables are in principle evenly distributed over these arms, and with participants behaving obediently there will be no trouble with the internal validity.

In epidemiological, real world data, however, there will always be some amount of systematic error due to comparison between non-random groups. The validity in such studies is based on knowing how these groups differ, but these differences are prone to both random and systematic measurement error, of which the latter may disturb the internal validity. These systematic errors are often referred to as *biases*.

If the systematic errors are sufficiently substantial, type-I or type-II errors can occur. A type-I error is defined as falsely rejecting a true null hypothesis of no association, and a type-II error as accepting a false null hypothesis.

5.1.2.3 External validity

In the BOLD study, the reference, or target, population was adults over 40 years in a wide range of low, middle, and high income countries across the world. Each site used an approved method to recruit participants that were not institutionalised and 40 years or older. Additionally, the participants should have an equal distribution of demographic variables compared to the general population at each site to secure that the study have high external validity.

In Norway, the BOLD participants were recruited from the 2003-2005 follow-up of the HCRHS. The participants in the HCRHS study, were initially recruited back in 1985. In 2003-2005, the third follow-up of these participants was accomplished. One can put questions to how representative this study sample was in the early 2000s, after two decades of follow-up. Those not lost to follow-up, or who had not died, and chose to continue participating, might possess particular characteristics differentiating them from those who did not, or could not, keep on participating. To minimize this risk, a great effort was put down to maintain high response rates. Additionally, it was ensured that the sample had sufficient similarity in the distribution of age, sex, and smoking habits to that of the Norwegian population[4].

The EconCOPD study involved three subsamples of participants. The population-based control subjects and COPD cases had the ever-smoking population above the age of 40 years in Hordaland county as its reference population. Ever-smoking subjects above the age of 40, and treated for COPD at a university hospital, were represented by the third subsample of hospital-based COPD patients. The EconCOPD study also recruited its participants from the third follow-up of the HCRHS, and the same reflections about the representativeness of the study participants in the BOLD study, are valid here. Table 3 shows the comparison of age, sex, and educational level between the 2003-2005 HCRHS follow-up and Norwegian national survey data [113]. Though there were some small differences, it seems quite impartial to say that the 2003-2005 HCRHS follow-up was relatively representative of the Norwegian adult population as a whole.

5.1.2.4 Internal validity

Systematic errors, or bias, might cancel, reduce, or amplify the associations or effects studied. Hence, minimizing these errors, improves the internal validity of a study. Systematic errors can be divided in three main types –information bias, selection bias, and confounding [156].

5.1.2.5 Information bias

Information bias appears when there are systematic errors in the measurement of the variables in a study. The result of information bias would be that the associations are wrongfully displaced in one or the other direction [156]. Demographic variables are less prone to systematic errors compared to other variables that involve some kind of measurement, using either machines or estimated by humans.

In this PhD project, a potentially consequential measurement error would be if the spirometric values were systematically incorrect. To minimize this risk, all spirometers were calibrated daily, or before each manoeuvre. All measurements were performed according to strict standards following the ATS criteria [157], and personnel were trained to obtain acceptable and reproducible results. In the BOLD study, there was additional quality control of every manoeuvre at a pulmonary function reading centre. In addition to the actual physical measurements, the values accomplished by spirometry are also made relative by comparing them to a reference population, generating values of FEV_1 and FVC in "percent of predicted". The reference population chosen might not be correct for all participants, and can be a source of misclassification of participants into the COPD-group or the healthy group. We think such misclassification can be of greater importance in international studies where ethnicity varies more for the participants than in studies like the EconCOPD where most participants were of Norwegian ethnicity.

Furthermore, interpretation of the spirometric values for diagnostic purposes implies methodological choices that might differ between studies (i.e. how to define obstruction). Choosing the fixed ratio to define obstruction, compared to the LLN, might affect the results in the direction of having increased false positive results amongst elderly people, and more young people being classified as false negative [18, 19]. In clinical practice, many now advocate the use of LLN [158], and it is recommended to be included in the new Norwegian guideline on COPD treatment that is currently under preparation [159]. The average ages in the EconCOPD, were 57, 63, and 67 years for the controls, COPD cases, and COPD patients. Thus, one might argue that at least for the controls and cases, there should not be many false positives. The COPD patients, though, that were recruited from the hospital register, were somewhat older. The fact that 50% of these patients had an $FEV_1 < 50\%$ of predicted, make the group of participants "available" to misclassification much smaller, as it is very unlikely to misclassify someone who already has severe or very severe airflow limitation to not having any limitation at all.

In the EconCOPD study, the results from spirometries performed in the 2003-05 HCRHS follow-up were used. During the short time-span between the two studies, spirometry results might have changed. It is known that individual variation can be substantial when performing spirometry as it depends much upon technique and execution. Hence, there might be some misclassification of lung function for the participants in the EconCOPD study. Most likely, such errors will occur randomly. Subjects with mild disease would probably have been more prone to these errors than the participants in the EconCOPD study, where all COPD cases and patients had an $FEV_1 < 80\%$ of predicted. Comparing the general population sample to the hospital sample, we think that the population sample is more vulnerable to measuring errors in spirometry since values in a less severely sick population will come closer to the threshold for FEV_1/FVC. If a greater proportion from the general population sample was misclassified as sick than in the hospital sample, these individuals would probably consume very little health care services and give rise to an underestimation of the costs associated with COPD. All in all, we believe that possible misclassification of participants has not been substantial enough to alter our results significantly.

If some variables were prone to be either overreported or underreported, our results could have been pulled in one direction compared to the truth. In the BOLD paper, the question identifying the study population asked for “any paid work” the last year, not differentiating between full-time and part-time work, and, hence, if some participants needed to reduce their work participation due to CAO, they were still registered as employed in our dataset. This can have led to an underestimation of the association between CAO and unemployment.

For the paper on incidence of AECOPD, we did the analyses both with a symptom-based definition, and a resource-based definition. Symptoms are subjective, and only a proportion of patients will seek help based on them. By necessity, there will be fewer exacerbations with a resource-based definition of AECOPD compared to a symptom-based definition. One could argue that the difference seen is the difference made up of an information bias that lies incorporated in a symptom-based definition. Personal behaviour, though, might also be an important explanatory factor to the difference seen in exacerbation rate between the two definitions applied. Some are prone to seek medical advice earlier than others, or for differing grades of symptoms. Such behavioural variability has been seen between the genders [160], and between varying age groups [161].

Some kind of self-reported information was used in all four papers. Such information is dependent on the participant´s memory, and is, hence, exposed to being not perfectly correct. This is called recall bias.

In the prospective EconCOPD study, we contacted the participants at relatively short intervals (every three months) to minimize the risk of recall bias. A comprehensive review of previous studies on patient self-reports to quantify health care utilisation, was performed by Evans et al [162]. Looking upon the length of the recollection period and the validity of the results, a three-month interval was considered fair for utilisation data. In addition, results from the EconCOPD pilot study indicated that the recall interval was sufficient [119]. Finally, the Hawthorne effect might have made the participants report differently due to the fact that they were aware of being observed [163]. Little is known about the magnitude of this effect, and it is difficult to eliminate in real life studies. Only blinded randomised controlled trials are free of its influence.

Further on, it is known that the more serious an event is, the more likely it is remembered [162]. We found that the participants with lower lung function had more severe exacerbation events. This could have skewed the results toward more events being recalled in those with more severe COPD, eventually resulting in more accurate utilisation of health care services for these participants compared to those with a higher FEV_1 and less severe events that could more easily be forgotten, or underreported. Opposed to this, it has also been seen that as the utilisation of health care increases, so does the underreporting, i.e. the more health care services the patients use, the higher the tendency to forget or underreport these events [164]. The net effect of better memory for more severe events and increased underreporting the more events one experience, is not easily detangled.

5.1.2.6 Selection bias

If selecting participants, or groups of individuals, for research is performed in such a way that the sample obtained is not representative of the target population, bias is introduced to the research [155, 156]. This type of bias is referred to as selection bias.

Intending to avoid selection bias, one can use randomisation in selecting subgroups from the population one wishes to study. If these subgroups are equivalent to the population they are supposed to represent when it comes to major characteristics, selection bias is less probable to affect the results. When performing cohort studies over time, it is inevitable to lose some participants along the way. It is essential to investigate who is lost and who complete the follow-up to be able to evaluate if the results can have been affected by the loss of participants. If there is a differential loss of participants between the exposed group and the non-exposed group, the results are affected. Usually, though, the relationship between exposure and outcome in non-responders is not known, and hence, selection bias cannot be accurately calculated.

Another aspect of selection bias, is self-selection or volunteer bias that can threat the validity of research if self-selection is related to the exposure or the outcome that is being studied [155]. It is known that individuals volunteering to participate in research are more often women, younger, healthier, and with a higher education [165-167].

EconCOPD recruited its participants from the third follow-up of the HCRHS, and from the patient register at HUH. Originally, the HCRHS study invited a simple randomised sample of 1.9% of the adult population aged 15 to 70 years residing in Hordaland County in 1985 (n=4992). In the second follow-up, 3370 subjects from the original sample whom resided in Bergen and immediate vicinity were invited. Among the survivors, 2819 (89%) responded. The third follow-up invited the responders from the second follow-up, and 69% of the invited subjects participated. Approximately 20 years had passed from the beginning of the HCRHS study until the initiation of the EconCOPD study, and it is likely that some survivor bias affected who could continue to participate in the study. Previous studies have found that more healthy individuals with a better prognosis are overrepresented in longitudinal cohorts [168, 169]. If the EconCOPD study included more healthy individuals than what would be seen in the general population of Hordaland County, the prevalence of COPD and the health care utilisation in this sample would be underestimated resulting in weaker associations than what truly may be present in the target population, and possibly exaggerating the differences between hospital recruited COPD patients and population-based COPD cases.

In the EconCOPD study, recruitment was made by telephone and invitation letters, and only a low proportion of participants was not reached. Non-response analyses comparing age, sex, and lung function between responders and non-responders for the three subsamples of the EconCOPD are shown in Table 4 (reprinted with permission [113]). Amongst the hospital-recruited COPD patients, both non-response, withdrawal during follow-up, and death during follow-up, were associated with a significantly higher age ($p<0.05$). In addition, in those that died during follow-up, FEV_1 % of predicted was lower than in survivors. Subjects that died during the year of follow-up were not included in our analyses.

For the population-based subsamples, comparing death during follow-up to complete follow-up, death was significantly associated with higher age in the group of COPD cases. Neither non-response nor withdrawal in either population-based subsample was associated with age. In both of the two population-based subsamples, non-response, withdrawal, and death, were unassociated with sex, lung function, or smoking habits (Table 4). All in all, there was no consistent pattern of differences between non-responders and participants suggesting selection bias in our results, though the extent of a potential survivor bias is not known.

In the BOLD study, each site carried out a sampling design ensuring selection of a sample representative of the local general population. Some sites used simple randomisation, some stratified random sampling, others cluster sampling, or random digit dialling (see Appendix for details). The Norwegian site in Bergen, used a stratified random sample of responders and non-responders to the third follow-up of the HCRHS, and had a response rate with complete spirometry and questionnaire data for 68%. A study by Eagan et al. on the original HCRHS cohort, found that unemployed individuals tended to respond later to participation in research compared to employed individuals [170]. If employment status affected the response rates in the BOLD study, our results on unemployment across the world could have been affected by selection bias. Inclusion of fewer unemployed participants could result in an underestimation of the association to CAO. Further on, we chose a cut-off for the retirement age at 65 years. This cut-off was broadly discussed in the author group, as there was no standard age of retirement across the sites. In Norway, the normal retirement age is 67 years, whilst some sites in the BOLD study reported that their participants nearly never would retire due to the lack of government social support, whilst others again had a lower retirement age than Norway. The cut-off at 65 years was chosen as a pragmatic compromise. The net effect of this cut-off age on the results is not known, but if any effect on the results, there must be a differing relationship between CAO and unemployment according to these age groups. CAO and unemployment increases with age, and if the cut-off was set too low, we might have included fewer participants with CAO, resulting in an underestimation of the association.

Table 3: Comparison of demographic variables in responders ≥ 40 years in the 2003-05 HCRHS follow-up and in national survey data.

	HCRHS ≥ 40 yrs	Norway ≥ 40 yrs
Age, yrs		
40-49, N (%)	453 (32)	639,053 (30)
50-59, N (%)	447 (32)	595,423 (28)
60-69, N (%)	267 (19)	374,975 (18)
70-79, N (%)	180 (13)	299,162 (14)
	66 (5)	209,186 (10)
Mean age, yrs	57 (57-58)	
Male gender, %	725 (51)	1,014,299 (48)
Education		
Primary, N (%)	379 (27)	712,771 (33)
High-School, N (%)	651 (46)	976,149 (45)
University, N (%)	382 (27)	468,429 (22)
Smoking habits		
Current, N (%)	407 (29)	(26)
Ex-smoker, N (%)	484 (34)	
Never-smoker, N (%)	505 (36)	

Smoking habits not available in national survey data except for current smoking.

Table 4: Non-response analyses in EconCOPD by participation status.

	Hospital-recruited COPD patients	Population-based COPD cases	Population-based controls
Declined vs accepted invitation, N	81 vs 245	21 vs 90	13 vs 136
Age	p=0.009	NS	NS
Sex	NS	NS	NS
FEV_1 % pred	NS	NS	NS
Lung function group	NS	NS	NS
Withdrew/deceased vs complete follow-up, N	40 vs 205	9 vs 81	4 vs 132
Age	p=0.0002	NS	NS
Sex	NS	NS	NS
Smoking habits	NS	NS	NS
Pack years	NS	NS	NS
FEV_1 % pred	NS	NS	NS
Lung function group	NS	NS	NS
Deceased vs complete follow-up, N	13 vs 205	2 vs 81	No deceased
Age	p=0.02	p=0.02	NA
Sex	NS	NS	NA
Smoking habits	NS	NS	NA
Pack years	NS	NS	NA
FEV_1 % pred	0.009	NS	NA
Lung function group	0.008	NS	NA

NS; non-significant (p>0.05). NA; not applicable. FEV_1; forced expiratory volume in one second. 1 pack year = 20 cigarettes/day during 1 year. [113].

5.1.2.7 Confounding

Confounding is the phenomenon observed when a variable complies with three criteria: 1) It is an independent risk factor for the outcome, 2) it is associated with the exposure in the source population, and 3) it is not affected by the exposure or the outcome. Confounders may bias or blur the results. For example, hypertension is a known cause of cardiovascular disease, and so is smoking. But smoking is also a cause of hypertension, so when investigating the effect of hypertension on cardiovascular disease, one must have information on smoking too, as it is a possible confounder in this example.

Both in the stage of design and the stage of analysis, it is important to control for confounding to minimize bias. Only in contrafactual thinking, which is impossible per se, confounding and biases can be completely removed. At the time of designing a study, one can choose to use randomisation, restriction or matching, to reduce confounding. Randomisation refers to assigning the study subjects randomly into groups of exposure and non-exposure, and hence creating groups that have comparable distribution of key characteristics. By restriction, participants are chosen so that confounding by known confounders are eliminated. E.g., if age or sex is known confounders for an association, only participants of one sex or of a specific age interval are chosen to participate. Finally, by matching, a control group that is similar in confounding variables to the exposed group, is included for comparison.

At the stage of analysis, confounding can be controlled for by stratification, standardisation, or adjustment in multiple regression. With stratification, one can create two groups that differ in the occurrence of a known confounder. For instance, if smoking is a confounder of the association between hypertension and cardiovascular disease, one can analyse the results stratified by smoking, and look for differences.

In some occasions, one would like to compare results across countries, or across any groups of individuals. For instance, one could be interested in comparing the mortality rates due to road accidents in two countries. But the two populations are normally not immediately comparable, and this is where standardisation can come in handy. By using a standard population, two populations that are not necessarily comparable can be compared via the standard population.

Last but not least, statistical methods of multiple regression analysis can control for confounding. Especially when there are multiple confounders to adjust for, stratification is less suitable. With multiple regression analysis, several confounders or covariates can be adjusted for at the same time to elucidate the effect of each one of them on the outcome of interest. Information about the confounding factors must have been collected during the study. Depending on the outcome, be it a continuous, categorical or time-to-event outcome, one need to choose a regression method that is suitable for every occasion. Attention must be paid to the risk of overadjusting and the possibility of introducing bias when doing multiple adjustments. Additionally, the statistical power is reduced when adjusting for multiple covariates, and the sample size must be large enough to be able to handle this [171].

In the BOLD study, several techniques were used to control for confounding. In our multiple regression model, we adjusted for an increasing number of covariates in a total of five models. These possible confounders were site, CAO, age, sex, education, smoking habits, comorbidities, FVC, and respiratory symptoms. Our main predictor of interest was CAO. Further, previous research has seen that educational level, age, sex, and social class is related to the risk of unemployment, and hence were confounders that needed to be adjusted for in our multiple regression models. We did not have information on social class, however it has been argued that education is the most important precondition to social class, and hence that education at least partially explains the association between social class and unemployment [172]. Comorbidities, FVC, and respiratory symptoms were added to evaluate their effect on the result. Apart from adjustment, we performed stratified analysis for the association between CAO and unemployment in different parts of the world according to income status. There was an overall association between CAO and unemployment after adjusting for sex, age, education, smoking habits, comorbidities, and FVC. When stratifying on income status of the site, this association was less clear. The association was statistically significant in all high-income sites, but not in all LMIC. One could argue that the sites in the BOLD study are so fundamentally different when it comes to traditions and culture, economy, welfare schemes, and sociodemographic factors, that a comparison is futile. Evaluating the results from each site, we were made aware of some basic differences between the sites, and thus, we performed analyses both with a stratification on income, and on sex, to further describe the situation in the various sites. Using the strata high- and low-to-middle income, the confounding effect of income on unemployment was reduced, though we only had information on income as an ecological variable (per capita per country), not per participant. Additional site-heterogeneity was elucidated using individual participant data meta-analysis displaying OR for CAO on unemployment in Forest plots. And finally, to evaluate if age could be an effect modifier rather than a confounder, we introduced an interaction term for age

rather than adjusting for age in the regression equations. An effect modifier is a factor that is associated with the outcome, but not with the exposure, and if present, the magnitude of the effect of the exposure on the outcome will vary depending on the level this third factor/effect modifier [156]. The results showed no differences for the effect of age, and it was kept as a confounding variable.

In the EconCOPD study, possible predictors of productivity losses, AECOPD incidence, and costs, were included in the multiple regression models. It has previously been demonstrated that lower education, female gender, and higher age are associated with higher productivity losses and costs [173-175], and we adjusted for these covariates in our multivariate equations.

In the paper on incidence of AECOPD, initial bivariate analyses were performed for each possible predictor, and those significant at a level of $p<0.10$ were included in the final multivariate model. With this approach, precision of adjustment estimates is maximised [150]. Additionally, the magnitude of associations was evaluated by presenting the results from several models with differing combinations of adjustment variables. Some variables that were not available, and hence not adjusted for, come to mind while wrapping up this thesis during the pandemic. Factors such as hygiene or frequency of hand washing, social contacts or having children around exposing the participants to a variety of viruses, would be interesting to investigate in relation to AECOPD. Additionally, one could imagine that other factors such as physical activity or participating in pulmonary rehabilitation, nutrition, or seasonality also could affect the rate of exacerbations.

In both data sets, there might have been some unidentified factors that confounded the results. Even so, we are quite certain that we have included the most important possible confounders, and that further adjustment would not alter the results significantly. Further adjustment would also increase the risk of overadjustment and bias toward the null [176].

5.1.3 Statistical considerations

Paper I on unemployment in the BOLD study, had a dichotomous outcome. Traditionally such outcomes have been studied with logistic regression. Lately, though, sophisticated statistical methods have made it possible to use other regression equations even for categorical outcomes. We used a generalized linear model (GLM) with multilevel mixed-effects. In more traditional, simpler models, interactions between variables and nested structure in the data would be ignored. Multilevel models allow for a more complex construction of regression equations in such a manner that the reciprocal influence between individuals and society is recognized, and the analyses of the phenomena become more correct [177]. Alternatively, we could have used a fixed-effect model. In a fixed-effect model, the sites included would have been treated more exclusively, whereas in the mixed-effect model we used, the sites are treated as a random sample of all possible sites. We believe that the sites in the BOLD study can represent a random sample of many sites across the world, and that it is better to treat them as such.

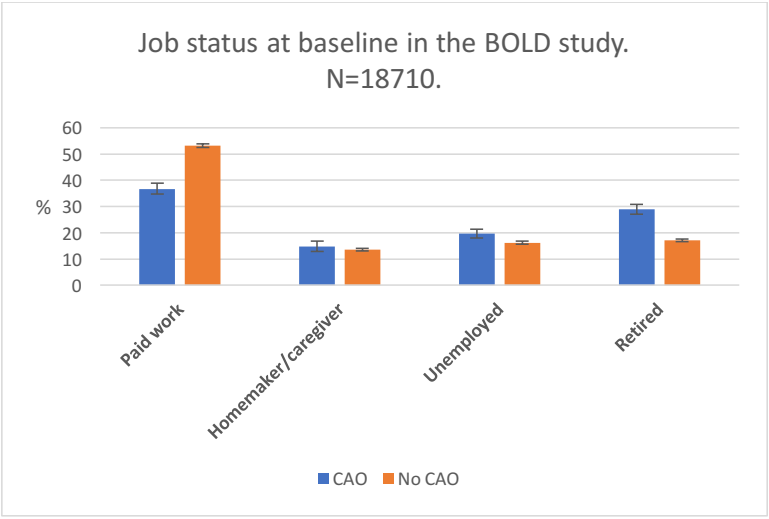


Figure 6: Distribution of job status at baseline in the BOLD study. Whiskers show 95% CI.

In the EconCOPD study, we investigated three outcomes -productivity losses, incidence of AECOPD, and costs related to COPD and exacerbations. The distribution of all these outcomes was skewed. For the initial unadjusted analyses, we thus used Kruskal-Wallis test with ties. Additionally, in the paper on productivity losses we did a Spearman`s rho test for the correlations between days of lost productivity and age, FEV_1 % of predicted, comorbidities, and exacerbations of respiratory symptoms. For the multivariate regression analyses, we performed median quantile regression that does not rely on the assumption of normality nor homoscedasticity, and hence suited our skewed outcomes [178]. A further advantage, is that the coefficients of median quantile regression are given in the same units as the outcome, facilitating interpretation.

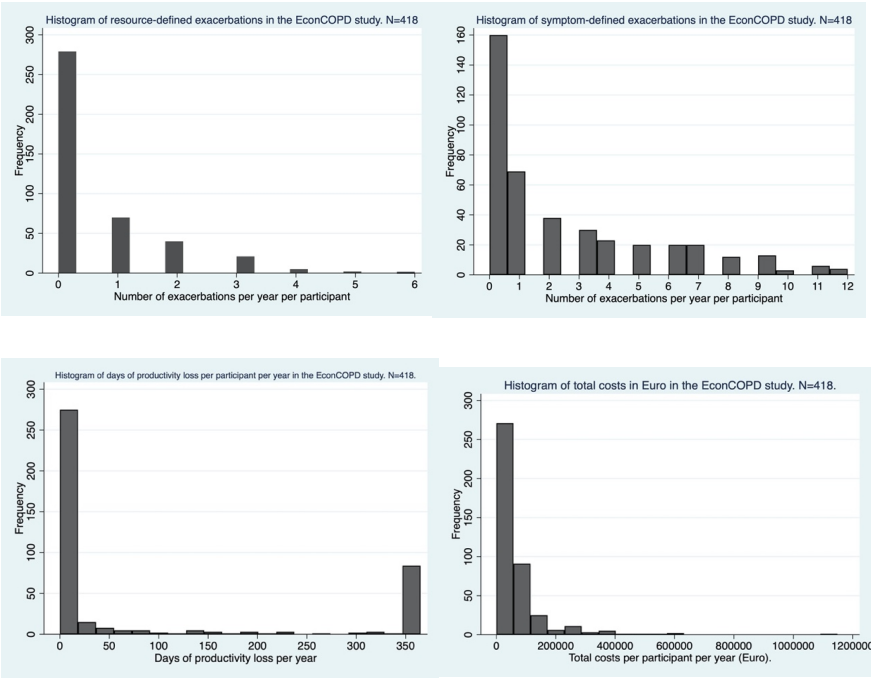


Figure 7: Distribution of outcomes (incidence of exacerbations, productivity losses, and costs) in the EconCOPD study. Patients, cases, and controls included, N=418.

5.1.4 Health economic considerations

The burden of disease, and how to measure this, is still a topic of debate. There are many aspects to include in a comprehensive appraisal of disease burden, and this complexity might be the origin of why there is no consensus on how to do this. Using descriptive cohorts, with no intervention and the availability of a control group, we chose to calculate the incremental costs. As an option, attributable costs can be calculated, but it has been seen that incremental, or so called excessive costs, are more accurate than attributable costs [101].

As the criticism of COI studies arose, some alternative approaches were developed to deal with the possible shortcomings of COI studies [179]. These include more sophisticated measures of change in health related to disease, like quality-adjusted life-years (QALYs), and the previously mentioned DALYs. Such measures both consider the change in quality of life *and* the change in quantity, i.e. the lower life expectancy associated with disease [97]. A further criticism has been that burden of disease studies, are of no value if not reported together with some kind of benefit or efficiency measurement [11]. I.e., there is a need of comparing the burden in a group with a given health care programme to the burden in a group without such a programme, or intervention, to enable decision makers to take informed choices. There are three main study types that consider the costs in relationship to a beneficiary outcome (or an aggravated outcome), namely cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA).

Cost-effectiveness analyses, are mostly used to estimate the effects of a limited range of treatment options to illustrate for decision makers the possible choices they can make within their budget [11]. The effectiveness measures can for instance be cases detected of a certain disease, exacerbation-free intervals of asthma or COPD, or years of life gained. Decision makers then have to make trade-offs when they decide upon which effect/intervention/treatment/screening to spend their limited resources on. Lately, cost-utility analyses have become more popular as the outcome often is measured in QALYs or DALYs that incorporate weighting of the various disease states that are investigated, enhancing comparability. In CUA, several different outcomes can be investigated together with a final combined outcome stating the costs per e.g. QALY gained, allowing for comparisons across any different health care programme [11].

In contrast to CEA and CUA, CBA value the programme consequences in monetary units. With this approach, both the costs of a programme and the outcome of the programme, is given in the same monetary unit, making direct comparison of the expenditures to the gains possible. The difference between these two, is the net social benefit, be it negative or positive, clarifying if the programme is worthwhile or not [11]. All in all, comparing health care programmes, be it preventive programmes, or treatment alternatives, data on QALYs or DALYs combined with the effectiveness or benefit of the programme, give a comprehensive evaluation of the burden of disease and possible advantages that can be obtained from different choices in health care.

Both the BOLD study and the EconCOPD study were descriptive observational studies with no intervention. We did not have information in our data sets to make evaluations of the consequences of COPD on reduced quality of life or disability-adjustments. Such analyses could have provided valuable additional insight. From the EconCOPD dataset, we performed a comprehensive cost-of-illness analysis on the data available in our descriptive cohort study, including both direct and indirect incremental costs of COPD in two different samples. The burden is given in monetary units, and can as such, be compared to similar COI studies on COPD, or on other diseases.

We chose the human capital approach when assigning a monetary value to the lost productivity. The most used alternative way of assigning money value to reduced working capacity, is the friction cost method. As explained in the introduction, this method implies finding the time period when absenteeism from work leads to reduced productivity until someone from the pool of unemployed people start doing the chores of the one absent. In Norway, there has not been a high unemployment rate for many decades [180], and hence, if someone is sick or disabled to work, it can be viewed as a permanent loss of productivity. Additionally, the HCA value human beings independently of their capacity to participate in the work force. I would like to argue that this viewpoint is more ethical than a perspective where people have no value if not working for an income.

With the intention of accomplishing a COI study that includes total costs to society, we have performed a detailed gathering of data. Albeit, there might be some costs missing to make it complete. Intangible costs are the costs related to pain and suffering both among patients and relatives, and are the ones most difficult to measure. We did not include intangible costs as we did not have the information in our dataset to do so, and this make our results on the burden of COPD even more conservative.

5.2 Discussion of the main results

The paper from the BOLD study presented the burden of unemployment associated with CAO. The papers from the EconCOPD study, addressed the burden inflicted by COPD by productivity losses, acute exacerbations, and societal costs. Additionally, all three papers from the EconCOPD study examined the differences between a selected hospital sample and a general population sample.

5.2.1 Unemployment and productivity losses

At baseline in the BOLD study, the CAO subjects reported being unemployed in 19.6% (95% CI 18.0 – 21.4) of the cases, and having paid work in 36.7% (34.7 – 38-8) of the cases. The corresponding numbers for the non-CAO subjects was 16.2% (15.6 – 16.8) and 53.2% (52.4 – 53.9) for unemployment and paid work, respectively. There was no overlap of the confidence intervals, indicating significant differences, though unadjusted. After extensive adjustment and excluding participants above 65 years of age, we found a 43% overall increased risk of being unemployed for the CAO subjects compared with the non-CAO subjects (OR 1.43 (95% CI 1.14 – 1.79)).

In the EconCOPD study, 87% of the control subjects reported having a paid job, whilst 55% and 31% of the COPD cases and –patients had a paid job. The controls, cases and patients reported receiving a disability pension in 7%, 30% and 65% of the cases, respectively. In adjusted analyses, the COPD cases from the general population had an annual incremental productivity loss of 5.8 days (95% CI 1.4 – 10.1) compared to the controls, and the hospital recruited COPD patients had an annual incremental productivity loss of 330.6 days (327.8 – 333.3) compared to controls. The rates of unemployment and paid work differ slightly in the BOLD Study and the EconCOPD Study. The rates given from the BOLD Study, include all participants at all sites, not only the participants from Bergen. Further, the wording of the question was not identical in the two studies. In the BOLD Study, the question read: “At any time in the past 12 months, did you work for an income?”, with “yes” or “no” as possible alternatives. In the EconCOPD Study, the question was worded as follows: “What is your current work situation?”, with the options of ticking “paid work” (full time or part time), “disability pension”, “early retirement”, “student”, “age pension”, or “unemployed”.

Few prior studies have investigated employment rates and productivity losses for COPD patients in general populations [112, 181-183], and even fewer have included spirometry for diagnosing airflow obstruction [112, 183]. Montes de Oca et al found the mean work life participation to be 41.8% amongst COPD patients versus 57.1% amongst controls in five Latin-American cities [183]. The proportion of employed participants in the global BOLD study was quite similar, though slightly lower. A possible explanation could be that the five sites included in the PLATINO study (Montevideo, São Paulo, Santiago, Caracas, and Mexico City) reflects a more homogeneous society than all the sites included in the BOLD study. In their adjusted analyses, COPD was not significantly associated with employment status in the developing countries included in the PLATINO study. When stratifying on income status of the participating sites in the BOLD study, we found a similar pattern. In most of the LMIC in the BOLD study (apart from Annaba, Cape Town, and Kashmir), having CAO was not significantly associated with unemployment. In the high-income sites, though, there was a more persistent pattern of higher unemployment amongst CAO participants compared to non-CAO subjects. By stratifying on income status, we clearly see that a comparison across sites that differ to such an extent in economy, and by acquaintance also in culture and social welfare, is very intricate. An important source of origin to this pattern, might be the differing welfare systems in the BOLD sites. If disease does not entitle the inhabitants in a society to receive social security, one might suspect that many still have to force themselves to keep on working even when they feel disabled to do so. In high-income sites, however, the inhabitants have the privilege of counting on economic support when disease and disability reduce their working capacity, and may therefore be inclined to quitting work sooner.

In the OLIN study, Jansson et al found more sick leave amongst COPD patients with mild airflow obstruction, whilst all other GOLD-stages had more early retirement [112]. They did not report employment rates, and did not use a control group to estimate incremental productivity loss. But apart from these methodological issues, their approach was similar to ours. They had a population-based sample, used the HCA to calculate the costs of reduced productivity, and they calculated the direct costs in a bottom-up manner. 0.2% vs 15.2% were classified as early retirees amongst the mild vs very severe cases of COPD in Jansson`s study, and average annual number of days in sick-leave ranged from 1.1 to 22.6 for the respective disease severities. Not surprisingly, we saw the same pattern of less sick leave with increasing COPD severity along with increasing use of disability pensions.

Days of productivity losses for COPD patients were reported by Lou et al in a study from rural China [182]. They found a mean annual productivity loss of 150 days per COPD patient, and that family members lost 59 days of work annually. The study was performed in a rural area with more than 50% illiteracy amongst the participants. All participants had COPD, but 96% had never heard about the diagnosis, and a third did not know that smoking was a risk factor. It is evident that these conditions make comparison to Norway difficult.

There has been a repeated debate in Norwegian society about the welfare schemes and the ability to participate in the workforce during short- and long-time sickness. In the 1970s, people with physical labour were not covered by the same schemes of full salary from the first day of sick leave as people with clerk jobs [184]. Parties on both the right and left wing of politics agreed that these schemes should be valid for all sorts of labour, it was "ideologically indisputable", as Jo Benkow from the Norwegian Conservative Party ("Høyre") stated it [184]. Even so, there has been repeated worries about work ethics amongst employees, and some argue that the welfare schemes are too permissive and easy to cash in on. Amongst adults aged 18-66 years, an increase in long-term sick leave from 2.5% to 3.0% was found for the years 2005 to 2009 [185]. This was along with an increase in employment rates where Norway had an employment rate approximately 7% higher than in the European Union [184]. It has been thought that more people with sub-optimal health are employed when there are more jobs available, and hence, the likelihood of sick leave increases. Additionally, people who need long-time sick leave or disability pensions seem to be a group of severely ill people who *in reality* are not able to work due to their illness [185].

A pattern of overuse of sick leave or disability pensions amongst COPD cases with low grade of symptoms is not evident in our data. The COPD patients from the hospital register, are, as a group, severely ill and have more comorbidities than the COPD cases from the general population. 31% of the hospital COPD patients and 55% of the population COPD cases were still working at baseline. We found that COPD cases from the general population had an incremental productivity loss of 5.8 days per year compared to controls. For COPD patients from the hospital register, on the other hand, the corresponding number was 330.6 days per year. Not only does this show that people with a modest COPD intend to stay in the workforce. With such a massive difference, it is also obvious that the heavier the burden on the patients gets, the higher the need for sick leave and disability pension. It is of maximum importance, both with a patient perspective and with a socioeconomic perspective, to avoid the progression of the disease from mild stage to more grievous stages.

There has been a paucity of data on productivity losses and unemployment associated with COPD, and especially from general populations. Our results show that COPD is associated with a higher risk of reduced working capacity, both when it comes to sick leave and permanent disability/unemployment. It is not immediately straightforward to compare results across countries with differing economies, cultures, and welfare systems, and the differing methods used in the scarce studies available, make it even more complicated to compare our results to previous literature. Comparison to other disease groups is challenging using our results as the previous literature on productivity losses is scarce, but an interesting study by JM Kinge et al investigated both the economic losses and burden of several medical conditions in Norway [186]. They found diseases of the respiratory system to rank 7th amongst all medical conditions considered, both when measured in DALYs lost, and when using the HCA to calculate the productivity losses. Large disease groups like neoplasms, mental disorders, diseases of the circulatory system, and musculoskeletal system ranked higher. The economic loss due to respiratory diseases was 17.2 billion NOK, more than 5% of the total economic loss due to all diseases in 2013.

5.2.1.1 Risk factors for unemployment and productivity losses

Overall in the BOLD study, we found several factors increasing the risk of unemployment apart from CAO. Decreasing FVC, female sex, increasing age, lower education, and comorbidities were all significant risk factors for unemployment. When stratifying on income, some variation became apparent between the sites. The strongest predictors of unemployment in high-income sites were age, and lower education. In LMIC, the strongest predictors were female sex, and age.

In the OLIN study, predictors of reduced working capacity were not examined. Our results are in line with the findings in the PLATINO study where age, female sex, lower education, comorbidities, and also dyspnoea were associated with a higher risk of unemployment [183]. They adjusted for both dyspnoea and spirometric COPD in their main model, whilst we had no additional adjustment for severity of airflow obstruction, or respiratory symptoms in our main model. When we added respiratory symptoms, the association between CAO and unemployment was reduced (1.26 (1.00 – 1.57)). We believe that the respiratory symptoms that accompanies COPD are important when it comes to quality of life and ability to work, as seen by the reduction of the association. But there are probably other variables involved in this complex interaction, as the association continues to be statistically significant even after additional adjustment for respiratory symptoms. One can speculate on what these variables might be, though it was not further tested in our material. Other symptoms associated with COPD, like asthenia, might explain some of the association. A stratification on exacerbation frequency might also have elucidated further on this issue.

5.2.2 Measures of incidence of acute exacerbations of COPD

Table 5 shows the mean annual exacerbation rate per COPD patient from selected studies. Methodological differences and varying definitions of AECOPD make comparison across studies difficult. All studies listed in Table 5 presented the mean annual exacerbation rate per COPD patient except the study by Wallace et al that gave the mean exacerbation rate per 100-person years. This was transformed to mean annual exacerbation rate per person by dividing by 100.

Table 5: An overview of studies on incidence of AECOPD. Incidence given as annual exacerbation rate per person.

		Author, year	Definition of AECOPD	Age span, and/or mean	AECOPD (no./pers/ year)	Remark
PROSPECTIVE	Cohort studies from general populations	Montes de Oca, 2009.	Symptom-defined.	≥40 years, mean 64.	0.58	*
		Han, 2011.	Resource-defined.	45 -80, mean 63.	0.68	Mixed popul.
		Erdal, 2016**	Symptom / resource.	≥40 years, mean 63.	1.0 / 0.4	
	Cohort studies from selected populations	Seemungal, 1998.	Symptom-defined.	Mean 67.8.	2.7	
		Donaldson, 2002.	Symptom-defined.	Mean 66.8.	2.53	
		Husebø, 2012.	Symptom-defined.	44-76, mean 63.	1.40	
		Suzuki, 2014.	Multiple definitions.	≥40 years, mean 70.	0.78 (sympt.)/ 0.13 (res.)	
		Erdal, 2016 **	Symptom / resource.	≥40 years, mean 67.	5.9 / 1.0	
RETROSPECTIVE	Register-based studies	Schermer, 2006.	Not stated.	35-75, mean 59.2.	0.88	
		AbuDagga, 2013.	Resource-defined.	≥40 years, mean 67.	0.7	
		Wallace, 2019.	Resource-defined.	≥40 years, mean 69.	0.55	

* "Best study"; prospective cohort study with a large sample from several general populations.

** Paper III of this thesis.

With the objective of studying the distribution and frequency of AECOPD in a general population, and to optimise the external validity of study results, we consider prospective cohort studies with a large sample from a general population to provide the most reliable and valid results. In Table 5 these are marked with an asterisk (*), and only one study other than ours, satisfied these criteria [60]. Again, this study is from the PLATINO project, and sampled from general populations in five Latin-American countries. They used a symptom-based definition of AECOPD, and exacerbations were self-reported for the year preceding the study. The mean annual exacerbation rate per COPD participant was 0.58, and when adding the need of visiting a doctor due to the worsening symptoms, the rate fell to 0.36/person/year.

Our results are quite on par with the results from the much alike PLATINO study, though in 2009 they had not begun their follow-up, and the study by Montes de Oca might be best classified as cross-sectional (not prospective). The subsample of COPD cases from our general population had a mean annual exacerbation rate of 1.0 when defining AECOPD by symptoms. Crossing over to a resource-based definition, the same subsample had an average annual exacerbation rate of 0.4. Our study was prospective, and collected information from participants every 12 weeks minimising recall bias. Some studies have seen that events requiring medical assistance or hospitalisation, i.e. more severe events, are better remembered than smaller symptom alterations [162, 187]. This can be interpreted as a higher accuracy for the information gathered on resource use than symptoms, favouring utilisation over self-reported symptoms for studies on exacerbations.

Elucidating further on rate of exacerbations, we analysed the hospital sample with both exacerbation definitions as well. Not surprisingly, the mean annual exacerbation rate was 5.9 and 1.0 per person with the symptom- and resource-based definitions, respectively, in this subsample. Seemungal et al, followed a small sample of 70 COPD patients attending an outpatient ward for 12 months [62]. With a symptom-based definition, they reported a mean annual exacerbation rate of 2.7 per participant, less than half of what we found. Donaldson et al also followed the same outpatient sample of COPD patients for a year as Seemungal et al, and defined exacerbations by symptoms [7]. The median exacerbation rate per COPD patient per year was 2.53. The average age in the sample used by Seemungal and Donaldson was close to the average of the participants in our hospital subsample. In the two mentioned studies though, only participants with an $FEV_1 < 70\%$ of predicted were included, whilst we included participants with an $FEV_1 < 80\%$ of predicted. One would expect the higher severity of airflow obstruction to result in higher exacerbation rates, not lower [60, 66, 68]. A possible explanation could be that in the studies by Seemungal and Donaldson, both utilising the same small sample, exacerbations were reported differently than in our study. They depended on the participants calling by telephone to study staff when experiencing a deterioration in symptoms, or noting their symptoms in diary cards. An aspect arising from these considerations, is whether AECOPD is adequately studied over one year, or if the low incidence suggests that the follow-up time should be longer for a more correct estimate.

5.2.2.1 Risk factors for the incidence of AECOPD

Increasing airflow limitation was associated with higher exacerbation risk in both subsamples, and with both exacerbation definitions. Progression of COPD is often reflected in a decline in lung function. With lower lung function, patients are more vulnerable for fluctuations, and minor changes in symptom burden may lead patients to change medication or to be admitted to hospital, hence fulfilling the definition of having an exacerbation. The finding is in accordance with previous literature [7, 60, 64, 66], and indicates that avoiding disease progression is essential both for patient wellbeing, and for the economic burden.

Further, for both exacerbation definitions, receiving maintenance therapy for COPD was positively associated with higher exacerbation risk in both subsamples. The previous mentioned PLATINO study had the same finding for "any respiratory drug" [60], and Husebø et al found that the use of ICS was associated with a higher exacerbation risk [64]. Other studies have found a protective effect of respiratory maintenance therapy on the risk of experiencing an exacerbation [151, 188, 189], and this is the main reason for recommending maintenance therapy in stable COPD [3]. We interpret our finding as an expression of disease severity, where patients with more frequent exacerbations have received ICS therapy, which is only partially effective in reducing these incidents.

For the resource-based definition, female sex was associated with increased risk of AECOPD (IRR 1.57 (95% CI 1.15 – 2.14), but this was not the case for the symptom-based definition where gender was not significantly associated with the outcome. Montes de Oca et al found an association between female sex and exacerbation risk in bivariate analyses, but this association became insignificant in multivariate analyses [60]. In the multivariate analyses by Husebø et al, female sex was, equally to our results, associated with increased risk of exacerbating [64].

Some observations indicate that women report more symptoms and utilise the health care system more frequently than men [190], but the explanation behind this seems very complex. It has been seen in several earlier studies that women experience more symptoms from COPD [191-193], and might seek medical advice earlier or more often as a consequence. Though it is not clear whether the explanation to the gender differences is biological, or cultural, a female phenotype has been proposed. Increased inflammatory response in females, higher susceptibility to tobacco, and the protective effect of oestrogens premenopause are postulated mechanisms that might be responsible for the gender differences in COPD [194-197]. Some have seen that physician`s responses to a patient complaint differs if the patient is male or female, resulting in less use of spirometry amongst women, more underdiagnosis in women, and less referral of women to specialists [142, 198, 199], constituting a cultural or societal explanation to the phenomenon. A possible interpretation of our result is that women have more severe exacerbations needing medical aid, as female sex only was associated with the risk of resource-defined exacerbations, not symptom-defined ones. Kilic et al found proof of this in their study performed in Ankara [200]. On the other hand, it was found by de Torres et al that men had significantly higher all-cause and respiratory mortality compared to BODE- and FEV_1-matched women [201]. A perception might be that how women seek medical aid is more appropriate than the tendency among men, reflected by these lower mortality rates. Comparison between different cultures and countries is also complicated, as gender differences vary immensely.

With the symptom-based definition of AECOPD, both age and receiving influenza vaccination were associated with a significantly reduced risk of exacerbation. Other studies have shown that increasing age is associated with a higher exacerbation risk [64, 66], but our finding was the opposite. One could speculate that elderly people do not like to complaint, and are taught to tolerate quite a lot from their childhood during the second world war or during economic hardship which was more normal in Norway before the petroleum era. The reduced risk of exacerbation associated with the influenza vaccine is in accordance with previous studies [202], supporting continuous use.

5.2.2.2 Effect of exacerbation definition

In both subsamples of COPD participants, the risk of AECOPD was higher with the symptom-based definition compared to the resource-based definition. In Table 5, in line with our findings, the studies listed with a symptom definition are the ones with the highest exacerbation rate [7, 62, 64]. There is one exception though: the general population cohort study by Montes de Oca et al [60] that used a symptom-based definition of AECOPD but giving a low annual exacerbation rate at 0.58/COPD patient. The most likely explanation is that this study was performed in a general population, and not on selected hospital or outpatient samples. Additionally, the study participants were asked for worsening of respiratory symptoms during the year prior to the study, which might have introduced some degree of recall bias.

The basis for the difference seen between the two exacerbation definitions is most likely that symptoms are actually the reason for contact with the health care system. And only a fraction of symptom events will be perceived by the patients as “important enough” to elicit health care utilisation. Furthermore, symptoms are of subjective origin, whilst resource-use is a more objective decision made by persons apart from the COPD patient. It takes more to get to the point of resource-use, than it takes to make a subjective complaint.

Suzuki et al carried out an interesting study in Sapporo, Japan, where they implemented several different exacerbation definitions [65]. They found a decreasing exacerbation rate with increasing criteria added to a symptom-based definition (criteria added were prescription change, antibiotic treatment, and hospital admission). Our results combined with previous knowledge endorse the realisation of studies on AECOPD with a resource-based definition for more accurate estimates. If other definitions are used, the researchers should specify the differences expected in the results due to the chosen definition.

5.2.3 Cost estimates for COPD and acute exacerbations of COPD

It is difficult to compare our results to earlier studies due to differing methodology. To the best of our knowledge, no other study has estimated the incremental costs of COPD exacerbations with multivariate regression analysis in a general population.

Table 6 summarises some important, previous studies on COPD costs and exacerbation costs. Cost estimates form the OLIN study in Northern Sweden have reported mean annual COPD costs according to GOLD-stage (Jansson et al) [112], and exacerbation costs of prior exacerbations in a top-down manner (Andersson et al) [110].

Table 6: An overview of studies on costs of COPD and costs of AECOPD as of April 2021. Costs given in Euros for comparability.

		Author, year	Age, mean	Direct costs	Indirect costs	Remark
PROSPECTIVE	Cohort studies from general populations	Andersson, 2002*	64	€ 14 - 247 - 2552.	Not included.	Mean cost per mild - moderate - severe exacerbation.
		Jansson, 2013§	68	€269 - 5351.	€327 - 12004.	Mean annual cost/COPD patient; GOLD I - IV.
		Erdal, 2020*§^	63	**€3829** *(€351 - 28349)*	**€11192** *(€10796 - 0).*	**Mean annual cost/COPD case** *(cost assoc.with moderate - severe AECOPD)*
	Cohort studies from selected populations	Miravitlles, 2013*	68	€345	Not included.	Mean cost per exacerbation.
		Erdal, 2020 *^	67	**€9504** *(NS - €8113)* .	**€17014** *(NS - NS)*	**Mean annual cost/COPD patient** *(cost assoc. with moderate - severe AECOPD)*
RETROSPECTIVE	Register-based studies	AbuDagga, 2013*	67	€196 / €13170	Not included.	Mean cost per moderate / severe exacerbation.
		Lisspers, 2018	65	€13179 (€532 - 8320)	€28000	Mean annual cost per COPD patient (direct costs per moderate - severe AECOPD).
	Systematic review	Rehmann, 2020	Not stated	€1715 - 10701.	*€998 - 5735* €3695 - 19031	Mean annual cost/COPD patient; Spain - Norway direct costs, *Greece - Germany for the costs of sick leave,* Sweden - Germany for the costs of early retirement

Costs calculated into Euros based on the exchange rate for the year of publication (applies to the studies by Andersson and AbuDagga).

*Studies that present costs per exacerbation

§ "Best studies": Randomly sampled, prospective cohort studies from a general population.

^Paper IV of this thesis. NS: non-significant.

Both direct and indirect costs of COPD were reported by Jansson et al [112]. As visualised in Table 6, our mean costs (for all GOLD-stages together) lie in the interval of costs reported for the separate GOLD-stages in Janssons study, though in the higher end of the interval both for the direct and indirect costs. We have reported mean costs per COPD participant, whilst in the OLIN study they stratified on GOLD-stage. In total, we speculate that our average resembles the expected mean from the OLIN study, though the total mean was not given by Jansson et al.

Jansson et al used a bottom-up approach to calculate the mean annual costs per COPD patient according to GOLD-stage. They had a general population sample that was prospectively followed and interviewed four times quarterly by telephone, the study design that EconCOPD was based on. The unit costs they used for calculation of the direct costs, included visits to GPs, primary care personnel, specialists, other hospital personnel, and emergency rooms. Further on, they also included costs per radiology exam, per day spent admitted to hospital (both to "regular" wards, and to intensive care units), costs for drugs, and oxygen therapy. Our direct costs were calculated using the same units apart from radiology exams, though we additionally had information on physiotherapy costs, home nursing, and rehabilitation programmes. For the indirect costs in the OLIN-study, they used the same HCA as we did, and calculated the days of lost productivity according to each participant`s average monthly salary. We calculated the productivity losses according to the average salary by sex, age, and education given by Statistics Norway. We did not have information on each individual`s salary. Overall, the final study design was very much alike that of the OLIN study, though we did include some additional unit costs. In OLIN, they reported the cost per GOLD-stage, whilst we estimated the mean cost per COPD patient/case independent of GOLD-stage. As speculated, if they were to give a general mean cost for all GOLD-stages, it seems that this mean would have been not so far from our estimated mean, though maybe a bit lower. We did include several cost items more, which may explain the speculated difference.

Other studies on COPD costs include those by Lisspers et al [203], and Rehman et al [204]. Lisspers et al used data registries from primary care centres across Sweden to retrospectively study direct and indirect costs associated with COPD and both moderate and severe AECOPD. Costs were compared to age- and sex-matched controls. It is difficult to compare our results to those of the study by Lisspers et al as they report costs per age-group, and stratified by frequent and non-frequent exacerbator phenotypes. They do present the total direct costs per COPD patient per year (€13,179 vs €2,716 per matched control). This is higher than what we found for the mean annual direct cost per population-based COPD case and per hospital-recruited COPD patient (€3,829 and €9,504, respectively). We could convert our results to 2018-€ by using the consumer price index-calculator of Statistics Norway to give our results in 2018-NOK. Then, with the exchange rate of 2018 (1€ = 9.94NOK), our results convert to €3,992 and €9,909 for the cases and the patients, respectively. There are some essential differences in design and data collection between our study at that of Lisspers et al that might explain the differences seen, i.e. prospective vs retrospective design, general population vs primary care, and they did not include home nursing services, physiotherapy, ER visits, oxygen therapy or rehabilitation programmes.

The systematic review performed by Rehman et al [204] included several European countries, and found substantial differences in the direct and indirect costs between the countries. The article they included from Norway [205] had the highest direct costs per patient per year (€10,701), but it seems the authors misinterpreted this article. They have not given the incremental direct costs for Norway, but presented the total health-related cost when having COPD. Spain had the lowest direct costs (€1,715). This review was published before our fourth paper, and they had no Norwegian study on indirect costs included. The indirect costs were divided into sick leave and early retirement. The costs associated with sick leave varied from €998 in Greece, to €5,735 in Germany. The costs of early retirement ranged from €3,695 in Sweden, to €19,031 in Germany. The indirect costs exceeded the direct costs in all countries who reported on both costs. In accordance with our arguments, Rehman et al consider the social security policies to be the main cause behind the differences in indirect costs. Additionally, they included studies with both HCA and FCM, and applying both bottom-up or top-down methods in their calculations of costs, which makes comparison difficult. The indirect costs presented from our fourth paper in Table 6, includes both sick leave and early retirement/disability pension. Our results lie in the interval found by Rehman et al for the separate European countries.

When it comes to the costs associated with exacerbations of COPD, there are no previous studies that have investigated this in a manner similar to ours. Unfortunately, no multivariate analysis was made to evaluate the exacerbation costs neither in the OLIN study[110], nor in the studies by Miravitlles et al [109], AbuDagga et al [108], nor Lisspers et al [203]. Further on, we have not found any published study concerning indirect costs of exacerbations. Anyhow, there is one observation that seems clear from the results of these studies –the costs of exacerbations increase with severity of the event, and also by severity of COPD. Both in our study and in AbuDagga`s study, the severe exacerbations were approximately 50 times more expensive than the moderate exacerbations.

5.2.3.1 Cost drivers

The total societal health-related costs *when having COPD*, were €26,518 and €15,021 per person per year, for the hospital-recruited and population-based COPD participants respectively. The corresponding annual cost per control subject, was €6,740. *The incremental* direct cost for the population COPD cases was €490 in GOLD-stage II, and €1,938 in GOLD-stage III-IV. For the hospital-recruited COPD patients, the incremental direct cost was €2,252, €3,221, and €5,684 for GOLD-stages II, III, and IV, respectively. The incremental indirect cost was non-significant for the population cases in GOLD-stage II, and €46,215 in GOLD-stages III-IV. For the hospital-recruited COPD patients, the incremental indirect cost was €28,845, €29,570, and €48,338 for GOLD-stages II, III, and IV, respectively.

For the population-based COPD cases, increasing GOLD-stage, exacerbations, comorbidities, and female sex, were all associated with higher direct costs. Some previous studies have shown a similar pattern of increased healthcare utilisation amongst women [174, 175], gender differences at equal or lower levels of smoking exposure [206], and as mentioned earlier in this thesis –a higher level of dyspnoea [193]. Kilic et al found that when women experienced severe exacerbations, the time till admission was longer than for men [200]. These are all possible mechanisms for higher costs amongst women. Both avoiding exacerbations and treating comorbidities have the potential of minimizing the direct costs in populations-based COPD cases. The indirect costs were significantly driven by GOLD-stage III and IV, but when adding adjustment for exacerbations this association lost its significance completely. GOLD-stage II was not significantly associated with increased indirect costs in the sample of population-based COPD cases. These findings might indicate that when FEV_1 has fallen below 50%, workforce participation is difficult in the stable state of the disease, and the contribution by exacerbations on top of this is modest. Decision makers could learn from this finding. Treatment and initiatives that prevent the progression of COPD into more severe disease stages could be proven economically beneficial.

Amongst the hospital-recruited COPD patients, exacerbations explained 27%, 40%, and 48% of the direct costs associated with GOLD-stage II, III, and IV, respectively. Comorbidities were also significant drivers of direct costs in this subgroup. The only significant driver of indirect costs in this subgroup of hospital-recruited patients, was increasing GOLD-stage. This implies that exacerbations are of great importance when it comes to treatment-related costs in this subgroup. But for the costs of productivity losses, exacerbations do not play an important role. The interpretation of this finding is interesting, and we think that the prevention of reaching this stage of severity is crucial both when it comes to reducing indirect costs, and for the patient`s wellbeing. At this point of the disease, many are receiving long-term disability pensions, and will not be able to return to work in the future. In other words, avoiding exacerbations will undoubtedly reduce the treatment-related costs in this subgroup, but the indirect costs they inflict on society are permanent at this stage of the disease. Guideline treatment and awareness of the comorbidities associated with COPD has the potential of further reducing the costs.

Dwelling a bit more on the costs associated with exacerbations, there seems to be a profound difference between the population-based and the hospital-recruited participants. The exacerbations explained a substantial part of the direct costs, but none of the indirect costs, of the hospital patients. On the contrary, for the population-based COPD cases, moderate exacerbations explained all the indirect costs associated with GOLD-stage III-IV, but only 6-13% of the direct costs. Nevertheless, the key finding is that in both groups, prevention of exacerbations could lead to reduced costs. These effects, though, will be visible in different parts of the national budgets. For the hospital patients, exacerbations are important to avoid to reduce the direct costs. But for the population cases, the exacerbations are more important to avoid if one wishes to reduce the costs associated with productivity loss.

5.2.4 Effect of sample source

In paper II, III, and IV, we compared the results for the population-based COPD cases to that of the hospital-recruited COPD patients. In all comparisons, the hospital-recruited COPD patients had a higher burden and inflicted higher costs than the population-based cases. This is not a surprising finding, but the actual difference between the two samples was surprising. The productivity losses, the rate of AECOPD, and the total costs for the hospital COPD patients were, respectively, 57 times, 2-2.5 times, and 2 times higher than for the population-based cases. For instance, belonging to the hospital sample was associated with 59% - 78% increased risk of exacerbation compared to the population sample. With such tremendous differences, it is obvious that sample source is of great importance when designing studies on COPD. In epidemiology, the ability to generalize results with high external validity, is of essential value. The source of sampling should be general populations as far as possible, and if using selected outpatient or hospital samples, the expected deviations in results should be pointed out by the authors. In addition, we would like to argue that pharmaceutical companies who frequently visit GPs to present the effects of various inhalation drugs, should specify that the majority of their studies are based on selected samples. Hence, the GPs should be informed that the expected effect are not valid for most of the patients consulting in primary care.

6 Main conclusions

1. 36.7% of individuals with chronic airflow obstruction had paid work the preceding year, whilst individuals without CAO had paid work in 53.2% of the cases. Chronic airflow obstruction was associated with a 43% higher risk of unemployment across the world in adjusted analyses. The association was strongest in high income countries. In low-to-middle income countries, female sex and increasing age were the strongest predictors of unemployment.

2. COPD cases from a general population had a mean annual incremental productivity loss of 5.8 days compared to controls. COPD patients recruited from a hospital register had a corresponding incremental productivity loss of 330.6 days compared to controls. Female sex and lower education were predictors of a higher productivity loss in both subsamples.

3. COPD cases from a general population experienced 0.4 mean annual resource-defined exacerbations of COPD, and 2.9 mean annual symptom-defined exacerbations of COPD. COPD patients from the hospital register experienced 1.0 mean annual resource-defined exacerbations of COPD, and 5.9 mean annual symptom-defined exacerbations of COPD. Increasing GOLD-stage was associated with an increasing rate of AECOPD in both subsamples.

4. Belonging to the hospital sample was associated with a significantly increased risk of experiencing an AECOPD compared to the general population sample. The risk was 59% increased with the resource-based definition of an AECOPD, and 78% increased with the symptom-based definition.

5. The average annual total costs for a COPD patient from the hospital sample was almost twice as high as for a COPD case from a general population (€26,518 vs €15,021). Compared to control subjects, COPD patients from the hospital register incurred nearly four times the costs. The costs related to reduced productivity were significantly higher than the treatment-related costs in both sampling sources.

6. Severe exacerbations were significant cost drivers of treatment-related incremental costs in both hospital-recruited patients and population-based cases. Moderate exacerbations explained all the incremental costs associated with the productivity losses in the population-based COPD cases, but none of the incremental costs associated with the productivity losses amongst the hospital COPD patients.

7. Increasing GOLD-stage, female sex, and comorbidities were significantly associated with incremental treatment-related COPD costs in the population-based sample. For the costs associated with productivity losses in this group, GOLD-stage II did not drive the costs. GOLD-stage III-IV was a significant cost driver before adjusting for exacerbations, but lost its significance after adjusting for moderate exacerbations. Amongst the hospital-recruited COPD patients, increasing GOLD-stage, severe exacerbations, and comorbidities were cost drivers of the treatment-related incremental costs. The costs of productivity losses in this group was driven by increasing GOLD-stage. Exacerbations did not affect the costs of productivity losses at this stage of the disease.

8. All three papers originating from the EconCOPD Study demonstrated significantly higher burden of COPD in the hospital-recruited sample compared to the population-based sample. Days of lost productivity per year was 57 times higher, the rate of AECOPD was 2-2.5 times higher (depending on exacerbation definition), and the costs were nearly 2 times higher in the hospital sample compared to the population sample.

7 Implications and future perspectives

This thesis describes the burden of COPD in unemployment and loss of working capacity, rate and risk of experiencing exacerbations, and societal costs. Further, we have detected the most important predictors of the burden measured in these outcomes. As stated by Chapman et al in the European Respiratory Journal: "Estimates of the components of the overall healthcare costs of a disease can help decision makers target interventions where they may have the most impact on overall disease-related healthcare costs because the component is a driver of the overall burden of the disease" [207]. We agree with this statement, and would like to append that sample source is of vital importance when performing cost-of-illness studies on COPD. Our papers show that not all populations are comparable, and not all choices made in the design of studies serve for comparison between studies. We argue that general populations should be the gold standard for cost-of-illness studies with the aims of achieving high external validity and to be of informative assistance for decision-makers. If a general population sample is not achievable, the authors should inform on the expected increased burden found in selected populations. Further, we recommend a bottom-up approach for the direct cost calculations, and in countries with low unemployment rates and mainly public health care, we recommend the HCA over the FCM or WTP.

The rate of exacerbations has been studied to quite an extent so far, and further studies on this topic might not be necessary. The findings of consistent increased burden in the hospital sample compared to the population sample though, have not been investigated previously. There is little doubt that these findings are reproducible, however it would be informative to examine this in other samples or other countries.

While exacerbation rate, and predictors of AECOPD, seem to have been fairly well studied, the approach we used to investigate incremental costs of AECOPD has not been applied previously. Fitting several multivariate regression models to elucidate on cost drivers, including moderate and severe exacerbations, revealed information not seen before. With this approach, we have given detailed estimates of which costs for which subgroups of COPD patients that are affected by exacerbations, and which are not. These findings need to be confirmed in future research.

Our findings in the BOLD study became even more interesting when stratifying the sites into high and low-to-middle income sites. CAO was consistently associated with higher risk of unemployment in the high-income sites, while it was not significantly associated with risk of unemployment in many LMIC. Rather, in these countries, female sex was the strongest predictor of unemployment. In high-income countries, lower education was, along with increasing age, a strong predictor of unemployment. This demonstrates where change is needed and where authorities should put their emphasis when aiming for minimizing inequity in working participation.

The role of female sex, or maybe one should say female gender as more of a cultural entity, might deserve some further investigation. Our findings associate female sex to higher productivity loss, higher rate of AECOPD, and higher costs. Some of these associations have been seen previously, especially the association to dyspnoea and exacerbation risk have been described in various studies [193, 195, 200]. The explanation behind this, however, is not completely understood. It seems to be of complex aetiology where both biology, genetics, and cultural or societal factors may play a role. While intervention based on sex is neither desirable nor ethical, further comprehension of the aetiology behind these issues may display some components to which change may serve as a relief on female burden of the disease. Perhaps, a longitudinal study incorporating early life events, childhood, and adulthood, with comprehensive data on heredity, demographic variables, lifestyle, occupational and leisure exposures, symptoms and extensive lung function testing could give further insight into this complex issue.

The studies used in this thesis were of observational origin, with no intervention. When it comes to productivity losses and costs, there seems to be a cut-off around GOLD-stage III. Before this stage, there is less permanent disability, and haltering the progression of the disease at GOLD-stage II could prevent people from falling out of the workforce. When less than approximately 50% of lung function is left, there is more use of permanent disability pensions, and people do not easily recover the ability to work. Prevention of disease progression is essential to maintain working capability.

It would be interesting to explore possible benefits of an intervention not yet sufficiently investigated –i.e. pulmonary rehabilitation. In a cost-benefit-analysis, pulmonary rehabilitation could be examined in two randomized groups of participants to explore possible effects upon quality of life, costs, exacerbations, and mortality. One study arm could supply regular treatment, and the other arm pulmonary rehabilitation in addition to regular treatment. Valuing the outcomes in a monetary unit, would enable the calculation of the net social benefit of such a programme. An approach like this could help decision makers target their interventions where they possibly would be of highest benefit, and would clarify if pulmonary rehabilitation could reduce the burden on the patients.

All in all, we have demonstrated some important disease-related features giving rise to higher burden and costs. Decision makers may take advantage of these findings to alleviate both patient and societal burden of COPD. Future research including cost-benefit-analyses may show where to target intervention to have the highest impact.

8 Errata

1. In paper I, the third sentence under Design (in the Methods section), should have said “The latter was 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 asthenia) for at least two consecutive days (modified Anthonisen criteria).

2. In paper III, Table 1 is correct, but in the text describing unadjusted comparisons between the groups, it should not say that smoking status (along with sex) had a similar distribution. Both pack years smoked and smoking status were significantly different in the three subgroups ($p<0.001$, and $p<0.012$ respectively).

3. The original manuscript sent to the committee, had wrong numbering of a figure in the plain text of the dissertation on page 51 (the actual figures had correct numbering). On page 51 it said: “Figure 3 shows the details of the inclusion and causes of non-response for the whole study period”. –corrected to “Figure 4 shows the details of the inclusion and causes of non-response for the whole study period”.

9 References

1. Petty, T.L., *The history of COPD.* Int J Chron Obstruct Pulmon Dis, 2006. **1**(1): p. 3-14.
2. World Health Organisation, *The top 10 causes of death.* 2018.
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD), *Global strategy for the diagnosis, management and prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018.*
4. Buist, A.S., et al., *International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study.* Lancet, 2007. **370**(9589): p. 741-50.
5. Celli, B.R., W. MacNee, and A.E.T. Force, *Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper.* Eur Respir J, 2004. **23**(6): p. 932-46.
6. Helsedirektoratet, N.D.o.H., *Kols. Nasjonal faglig retningslinje og veileder for forebygging, diagnostisering og oppfølging. National guideline for the prevention, diagnostication, and follow-up of COPD.* 2012.
7. Donaldson, G.C., et al., *Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease.* Thorax, 2002. **57**(10): p. 847-52.
8. Halpin, D.M., et al., *Exacerbation frequency and course of COPD.* Int J Chron Obstruct Pulmon Dis, 2012. **7**: p. 653-61.
9. Sullivan, S.D., S.D. Ramsey, and T.A. Lee, *The economic burden of COPD.* Chest, 2000. **117**(2 Suppl): p. 5S-9S.
10. Seemungal, T.A., J.R. Hurst, and J.A. Wedzicha, *Exacerbation rate, health status and mortality in COPD--a review of potential interventions.* Int J Chron Obstruct Pulmon Dis, 2009. **4**: p. 203-23.
11. Drummond MF, O.B.B., Stoddart GL, *et al*, *Methods for the economic evaluation of health care programmes. Third edition.* Oxford: Oxford University Press., 2005.
12. Global Initiative for Chronic Obstructive Lung Disease (GOLD), *GOLD webpage, about us.*
13. Bakke, P.S., et al., *Prevalence of obstructive lung disease in a general population: relation to occupational title and exposure to some airborne agents.* Thorax, 1991. **46**(12): p. 863-70.
14. Shirtcliffe, P., et al., *COPD prevalence in a random population survey: a matter of definition.* Eur Respir J, 2007. **30**(2): p. 232-9.
15. Rabe, K.F., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.* Am J Respir Crit Care Med, 2007. **176**(6): p. 532-55.
16. Cerveri, I., et al., *Underestimation of airflow obstruction among young adults using FEV1/FVC <70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes.* Thorax, 2008. **63**(12): p. 1040-5.

17. Swanney, M.P., et al., *Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction.* Thorax, 2008. **63**(12): p. 1046-51.
18. Smith, L.J., *The lower limit of normal versus a fixed ratio to assess airflow limitation: will the debate ever end?* Eur Respir J, 2018. **51**(3).
19. Vollmer, W.M., et al., *Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study.* Eur Respir J, 2009. **34**(3): p. 588-97.
20. Waatevik, M., et al., *Increased prevalence of chronic obstructive pulmonary disease in a general population.* Respir Med, 2013. **107**(7): p. 1037-45.
21. Lundback, B., et al., *Not 15 but 50% of smokers develop COPD?--Report from the Obstructive Lung Disease in Northern Sweden Studies.* Respir Med, 2003. **97**(2): p. 115-22.
22. Aryal, S., E. Diaz-Guzman, and D.M. Mannino, *Influence of sex on chronic obstructive pulmonary disease risk and treatment outcomes.* Int J Chron Obstruct Pulmon Dis, 2014. **9**: p. 1145-54.
23. Sorheim, I.C., et al., *Gender differences in COPD: are women more susceptible to smoking effects than men?* Thorax, 2010. **65**(6): p. 480-5.
24. Foreman, M.G., et al., *Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study.* Am J Respir Crit Care Med, 2011. **184**(4): p. 414-20.
25. World Health Organisation, *WHO global report on trends in tobacco smoking 2000-2025.*
26. Adeloye, D., et al., *Global and regional estimates of COPD prevalence: Systematic review and meta-analysis.* J Glob Health, 2015. **5**(2): p. 020415.
27. Melbye, H., et al., *Is the Disease Burden from COPD in Norway Falling off? A Study of Time Trends in Three Different Data Sources.* Int J Chron Obstruct Pulmon Dis, 2020. **15**: p. 323-334.
28. Woldeamanuel, G.G., A.B. Mingude, and T.G. Geta, *Prevalence of chronic obstructive pulmonary disease (COPD) and its associated factors among adults in Abeshge District, Ethiopia: a cross sectional study.* BMC Pulm Med, 2019. **19**(1): p. 181.
29. Hnizdo, E., et al., *Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey.* Am J Epidemiol, 2002. **156**(8): p. 738-46.
30. Balmes, J., et al., *American Thoracic Society Statement: Occupational contribution to the burden of airway disease.* Am J Respir Crit Care Med, 2003. **167**(5): p. 787-97.
31. Stoller, J.K. and L.S. Aboussouan, *Alpha1-antitrypsin deficiency.* Lancet, 2005. **365**(9478): p. 2225-36.

32. Doiron, D., et al., *Air pollution, lung function and COPD: results from the population-based UK Biobank study.* Eur Respir J, 2019. **54**(1).
33. Thurston, G.D., et al., *A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework.* Eur Respir J, 2017. **49**(1).
34. Lokke, A., et al., *Developing COPD: a 25 year follow up study of the general population.* Thorax, 2006. **61**(11): p. 935-9.
35. Sakornsakolpat, P., et al., *Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations.* Nat Genet, 2019. **51**(3): p. 494-505.
36. Silverman, E.K., et al., *Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease. Risk to relatives for airflow obstruction and chronic bronchitis.* Am J Respir Crit Care Med, 1998. **157**(6 Pt 1): p. 1770-8.
37. Barnes, P.J., *Chronic obstructive pulmonary disease.* N Engl J Med, 2000. **343**(4): p. 269-80.
38. Silverman, E.K., *Genetics of COPD.* Annu Rev Physiol, 2020. **82**: p. 413-431.
39. UpToDate.com, *Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging.* 2020.
40. Baraldo, S., et al., *Neutrophilic infiltration within the airway smooth muscle in patients with COPD.* Thorax, 2004. **59**(4): p. 308-12.
41. Cosio, M.G., M. Saetta, and A. Agusti, *Immunologic aspects of chronic obstructive pulmonary disease.* N Engl J Med, 2009. **360**(23): p. 2445-54.
42. Macnee, W., *Pathogenesis of chronic obstructive pulmonary disease.* Clin Chest Med, 2007. **28**(3): p. 479-513, v.
43. Santos, S., et al., *Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD.* Eur Respir J, 2002. **19**(4): p. 632-8.
44. Blanco, I., L. Piccari, and J.A. Barbera, *Pulmonary vasculature in COPD: The silent component.* Respirology, 2016. **21**(6): p. 984-94.
45. Miller, J., et al., *Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort.* Respir Med, 2013. **107**(9): p. 1376-84.
46. Smith, M.C. and J.P. Wrobel, *Epidemiology and clinical impact of major comorbidities in patients with COPD.* Int J Chron Obstruct Pulmon Dis, 2014. **9**: p. 871-88.
47. Divo, M., et al., *Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2012. **186**(2): p. 155-61.
48. Sin, D.D., et al., *Mortality in COPD: Role of comorbidities.* Eur Respir J, 2006. **28**(6): p. 1245-57.
49. Soriano, J.B. and P.R. Burgel, *On Don Quixote and pink puffers: multi-organ loss of tissue COPD.* Eur Respir J, 2018. **51**(2).
50. Agusti, A., et al., *Treatable traits: toward precision medicine of chronic airway diseases.* Eur Respir J, 2016. **47**(2): p. 410-9.

51. Global Initiative for Chronic Obstructive Lung Disease (GOLD), *Pocket guide to COPD diagnosis, management, and prevention. A guide for Health Care Professionals.* 2004.
52. Global Initiative for Chronic Obstructive Lung Disease (GOLD), *Pocket guide to COPD diagnosis, management, and prevention. A Guide for Health Care Professionals.* 2018.
53. Lamprecht, B., et al., *Determinants of underdiagnosis of COPD in national and international surveys.* Chest, 2015. **148**(4): p. 971-985.
54. Berger, B.E., M.C. Kapella, and J.L. Larson, *The experience of stigma in chronic obstructive pulmonary disease.* West J Nurs Res, 2011. **33**(7): p. 916-32.
55. Langsetmo, L., et al., *Underreporting exacerbation of chronic obstructive pulmonary disease in a longitudinal cohort.* Am J Respir Crit Care Med, 2008. **177**(4): p. 396-401.
56. Hurst, J.R., et al., *Susceptibility to exacerbation in chronic obstructive pulmonary disease.* N Engl J Med, 2010. **363**(12): p. 1128-38.
57. Perez-Padilla, R., et al., *Lung function decline in subjects with and without COPD in a population-based cohort in Latin-America.* PLoS One, 2017. **12**(5): p. e0177032.
58. Thomas, M., et al., *COPD exacerbation frequency, pharmacotherapy and resource use: an observational study in UK primary care.* COPD, 2014. **11**(3): p. 300-9.
59. Wedzicha, J.A., et al., *Mechanisms and impact of the frequent exacerbator phenotype in chronic obstructive pulmonary disease.* BMC Med, 2013. **11**: p. 181.
60. Montes de Oca, M., et al., *Frequency of self-reported COPD exacerbation and airflow obstruction in five Latin American cities: the Proyecto Latinoamericano de Investigacion en Obstruccion Pulmonar (PLATINO) study.* Chest, 2009. **136**(1): p. 71-78.
61. Han, M.K., et al., *Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes.* Radiology, 2011. **261**(1): p. 274-82.
62. Seemungal, T.A., et al., *Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1998. **157**(5 Pt 1): p. 1418-22.
63. Hoogendoorn, M., et al., *Prediction models for exacerbations in different COPD patient populations: comparing results of five large data sources.* Int J Chron Obstruct Pulmon Dis, 2017. **12**: p. 3183-3194.
64. Husebo, G.R., et al., *Predictors of exacerbations in chronic obstructive pulmonary disease--results from the Bergen COPD cohort study.* PLoS One, 2014. **9**(10): p. e109721.
65. Suzuki, M., et al., *Clinical features and determinants of COPD exacerbation in the Hokkaido COPD cohort study.* Eur Respir J, 2014. **43**(5): p. 1289-97.
66. Miravitlles, M., et al., *Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD*

patients: a multiple logistic regression analysis. The EOLO Study Group. Respiration, 2000. **67**(5): p. 495-501.
67. Mullerova, H., et al., *Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort.* Chest, 2015. **147**(4): p. 999-1007.
68. Bowler, R.P., et al., *Prediction of acute respiratory disease in current and former smokers with and without COPD.* Chest, 2014. **146**(4): p. 941-950.
69. Eagan, T.M., et al., *Systemic inflammatory markers in COPD: results from the Bergen COPD Cohort Study.* Eur Respir J, 2010. **35**(3): p. 540-8.
70. Thomsen, M., et al., *Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease.* JAMA, 2013. **309**(22): p. 2353-61.
71. Sakae, T.M., et al., *Exacerbations of COPD and symptoms of gastroesophageal reflux: a systematic review and meta-analysis.* J Bras Pneumol, 2013. **39**(3): p. 259-71.
72. Leonard Cohen, *Ain`t no cure for love.* https://www.youtube.com/watch?v=gM7vULqs31Q.
73. Anthonisen, N.R., et al., *Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study.* JAMA, 1994. **272**(19): p. 1497-505.
74. Abascal, W., et al., *Tobacco control campaign in Uruguay: a population-based trend analysis.* Lancet, 2012. **380**(9853): p. 1575-82.
75. Jha, P. and R. Peto, *Global effects of smoking, of quitting, and of taxing tobacco.* N Engl J Med, 2014. **370**(1): p. 60-8.
76. Jamison, D.T., et al., *Global health 2035: a world converging within a generation.* Lancet, 2013. **382**(9908): p. 1898-955.
77. Jha, P., *Avoidable global cancer deaths and total deaths from smoking.* Nat Rev Cancer, 2009. **9**(9): p. 655-64.
78. Wu, J. and D.D. Sin, *Improved patient outcome with smoking cessation: when is it too late?* Int J Chron Obstruct Pulmon Dis, 2011. **6**: p. 259-67.
79. Troosters, T., et al., *Pulmonary rehabilitation in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2005. **172**(1): p. 19-38.
80. Maddocks, M., et al., *Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study.* Thorax, 2016. **71**(11): p. 988-995.
81. Kopsaftis, Z., R. Wood-Baker, and P. Poole, *Influenza vaccine for chronic obstructive pulmonary disease (COPD).* Cochrane Database Syst Rev, 2018. **6**: p. CD002733.
82. Walters, J.A., et al., *Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2017. **1**: p. CD001390.
83. Froes, F., N. Roche, and F. Blasi, *Pneumococcal vaccination and chronic respiratory diseases.* Int J Chron Obstruct Pulmon Dis, 2017. **12**: p. 3457-3468.

84. Oba, Y., et al., *Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis.* Cochrane Database Syst Rev, 2018. **12**: p. CD012620.
85. Miravitlles, M. and A. Anzueto, *Insights into interventions in managing COPD patients: lessons from the TORCH and UPLIFT studies.* Int J Chron Obstruct Pulmon Dis, 2009. **4**: p. 185-201.
86. Reseptregisteret, F., *Tabell over antall brukere og omsetning i daglige doser; salbutamol, ipratropiumbromid.* 2019.
87. Harries, T.H., et al., *Blood eosinophil count, a marker of inhaled corticosteroid effectiveness in preventing COPD exacerbations in post-hoc RCT and observational studies: systematic review and meta-analysis.* Respir Res, 2020. **21**(1): p. 3.
88. Rabe, K.F., et al., *Roflumilast--an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial.* Lancet, 2005. **366**(9485): p. 563-71.
89. Murray, C.J., et al., *GBD 2010: design, definitions, and metrics.* Lancet, 2012. **380**(9859): p. 2063-6.
90. Murray, C.J. and A.D. Lopez, *Measuring the global burden of disease.* N Engl J Med, 2013. **369**(5): p. 448-57.
91. Miravitlles, M. and A. Ribera, *Understanding the impact of symptoms on the burden of COPD.* Respir Res, 2017. **18**(1): p. 67.
92. Kesten, S., et al., *Adverse health consequences in COPD patients with rapid decline in FEV1--evidence from the UPLIFT trial.* Respir Res, 2011. **12**: p. 129.
93. Molfino, N.A., *Genetic predisposition to accelerated decline of lung function in COPD.* Int J Chron Obstruct Pulmon Dis, 2007. **2**(2): p. 117-9.
94. Anto, J.M., et al., *Epidemiology of chronic obstructive pulmonary disease.* Eur Respir J, 2001. **17**(5): p. 982-94.
95. Corhay, J.L., et al., *Pulmonary rehabilitation and COPD: providing patients a good environment for optimizing therapy.* Int J Chron Obstruct Pulmon Dis, 2014. **9**: p. 27-39.
96. Shavelle, R.M., et al., *Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study.* Int J Chron Obstruct Pulmon Dis, 2009. **4**: p. 137-48.
97. Olsen, J.A., *Helseøkonomi -effektivitet og rettferdighet.* Cappelen akademisk forlag, 2006.
98. Det Kongelige Helsedepartement, *St.meld. nr.16 (2002-2003). Resept for et sunnere Norge. Folkehelsepolitikken.* 2002-2003.
99. Bellefleur, O., Keeling M., *Utilitarianism in public health.* Montreal, Quebec: National Collaborating Centre for Healthy Public Policy., 2016.
100. Practice, B.B., *A glossary of health economics terms.* 2020.
101. cdc.gov, *Part II: Economic Impact Analysis. Cost-of-illness.* https://www.cdc.gov/dhdsp/programs/spha/economic_evaluation/docs/podcast_ii.pdf.

102. Rice, D.P., *Cost of illness studies: what is good about them?* Inj Prev, 2000. **6**(3): p. 177-9.
103. Tarricone, R., *Cost-of-illness analysis. What room in health economics?* Health Policy, 2006. **77**(1): p. 51-63.
104. Jo, C., *Cost-of-illness studies: concepts, scopes, and methods.* Clin Mol Hepatol, 2014. **20**(4): p. 327-37.
105. Mushkin SJ, *Health as an investment.* Journal of Political Economy, 1962. **1962, vol.70, 129**.
106. Olsen, J.A. and R.D. Smith, *Theory versus practice: a review of 'willingness-to-pay' in health and health care.* Health Econ, 2001. **10**(1): p. 39-52.
107. Currie, G., et al., *Are cost of injury studies useful?* Inj Prev, 2000. **6**(3): p. 175-6.
108. Abudagga, A., et al., *Exacerbations among chronic bronchitis patients treated with maintenance medications from a US managed care population: an administrative claims data analysis.* Int J Chron Obstruct Pulmon Dis, 2013. **8**: p. 175-85.
109. Miravitlles, M., et al., *Clinical outcomes and cost analysis of exacerbations in chronic obstructive pulmonary disease.* Lung, 2013. **191**(5): p. 523-30.
110. Andersson, F., et al., *The costs of exacerbations in chronic obstructive pulmonary disease (COPD).* Respir Med, 2002. **96**(9): p. 700-8.
111. Dalal, A.A., et al., *Costs of COPD exacerbations in the emergency department and inpatient setting.* Respir Med, 2011. **105**(3): p. 454-60.
112. Jansson, S.A., et al., *Health economic costs of COPD in Sweden by disease severity--has it changed during a ten years period?* Respir Med, 2013. **107**(12): p. 1931-8.
113. Nielsen, R., *Costs of chronic obstructive pulmonary disease in a general population. Methodological aspects and longitudinal perspectives (dissertation)*. 2011.
114. Buist, A.S., et al., *The Burden of Obstructive Lung Disease Initiative (BOLD): rationale and design.* COPD, 2005. **2**(2): p. 277-83.
115. Ferris, B.G., *Epidemiology Standardization Project (American Thoracic Society).* Am Rev Respir Dis, 1978. **118**(6 Pt 2): p. 1-120.
116. ECRHS, *Protocol for the European Community Respiratory Health Survey II.* Department of Public Health Sciences, King`s College London, 2002.
117. Connett, J.E., et al., *Design of the Lung Health Study: a randomized clinical trial of early intervention for chronic obstructive pulmonary disease.* Control Clin Trials, 1993. **14**(2 Suppl): p. 3S-19S.
118. Bestall, J.C., et al., *Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease.* Thorax, 1999. **54**(7): p. 581-6.
119. Nielsen, R., et al., *Repeatability of health economic data in COPD.* Respir Med, 2008. **102**(11): p. 1556-62.

120. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.
121. Jansson, S.A., et al., *Costs of COPD in Sweden according to disease severity.* Chest, 2002. **122**(6): p. 1994-2002.
122. Anthonisen, N.R., et al., *Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease.* Ann Intern Med, 1987. **106**(2): p. 196-204.
123. Miller, M.R., et al., *Standardisation of spirometry.* Eur Respir J, 2005. **26**(2): p. 319-38.
124. Am J Respir Crit Care Med, *ATS. Standardization of Spirometry.* 1995. **1995;152:1107-1136.**
125. Gulsvik, A., et al., *Expiratory and inspiratory forced vital capacity and one-second forced volume in asymptomatic never-smokers in Norway.* Clin Physiol, 2001. **21**(6): p. 648-60.
126. TM., E., *Incidence and remission of asthma and respiratory symptoms in adults - The Hordaland County Cohort Study (dissertation).* Bergen: University of Bergen; 2004., 2004.
127. Pike, J. and S.D. Grosse, *Friction Cost Estimates of Productivity Costs in Cost-of-Illness Studies in Comparison with Human Capital Estimates: A Review.* Appl Health Econ Health Policy, 2018. **16**(6): p. 765-778.
128. The SINTEF Foundation, *SAMDATA 2006, Nøkkeltall for spesialisthelsetjenesten.* https://www.sintef.no/Projectweb/Startsiden/SAMDATA-pa-nett/SAMDATA-2006/Nokkeltall-for-spesialisthelsetjenesten-2006/. 2006.
129. The Norwegian Labour and Welfare Organisation and The Norwegian Directorate of Labour and Welfare. Personal communication from Senior consultants Jon P. Nossen and Vegard Håvik, 2007.
130. The Norwegian Directorate for Health and Social Affairs. Personal communication from Senior consultant Lars Rønningen, 2009.
131. The Municipality of Bergen City, N.P.c.f.S.c.B.S., 2008.
132. https://www.whocc.no/use_of_atc_ddd/, T.W.C.C.f.D.S.M.U.o.t.A.D.-s., 2008.
133. The Norwegian Pharmacy Association. Personal communication from consultant Julia Nemeth, 2009.
134. Farmastat AS. Personal communication from Senior Key Account Manager Stian Lekang, 2009.
135. The Department of Thoracic Medicine, H.U.H., Bergen, Norway. Personal communication from Margunn Gravdal, Alf H. Andreassen, and Else Marie Engelsen,, 2007.
136. Statistics Norway. The consumer price index. www.ssb.no/english/subjects/08/02/10/kpi_en, 2010.
137. The Norwegian Physiotherapist Association. Personal communication, 2009.

138. Gnatiuc, L., et al., *Gaps in using bronchodilators, inhaled corticosteroids and influenza vaccine among 23 high- and low-income sites.* Int J Tuberc Lung Dis, 2015. **19**(1): p. 21-30.
139. Axelrad, H., M. Malul, and I. Luski, *Unemployment among younger and older individuals: does conventional data about unemployment tell us the whole story?* J Labour Mark Res, 2018. **52**(1): p. 3.
140. Waldron, I. and D. Lye, *Employment, unemployment, occupation, and smoking.* Am J Prev Med, 1989. **5**(3): p. 142-9.
141. Kanervisto, M., et al., *Low socioeconomic status is associated with chronic obstructive airway diseases.* Respir Med, 2011. **105**(8): p. 1140-6.
142. Han, M.K., et al., *Gender and chronic obstructive pulmonary disease: why it matters.* Am J Respir Crit Care Med, 2007. **176**(12): p. 1179-84.
143. Johansen, H., *Living with heart disease--the working-age population.* Health Rep, 1999. **10**(4): p. 33-45(ENG); 31-45(FRE).
144. Kim, Y.A., et al., *Employment status and work-related difficulties in lung cancer survivors compared with the general population.* Ann Surg, 2014. **259**(3): p. 569-75.
145. Kraut, A., et al., *Impact of diabetes on employment and income in Manitoba, Canada.* Diabetes Care, 2001. **24**(1): p. 64-8.
146. Maaijwee, N.A., et al., *Long-term increased risk of unemployment after young stroke: a long-term follow-up study.* Neurology, 2014. **83**(13): p. 1132-8.
147. Burney, P., et al., *Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty--a BOLD analysis.* Thorax, 2014. **69**(5): p. 465-73.
148. Braun, L., M. Wolfgang, and K. Dickersin, *Defining race/ethnicity and explaining difference in research studies on lung function.* Eur Respir J, 2013. **41**(6): p. 1362-70.
149. Patel, J.G., et al., *COPD affects worker productivity and health care costs.* Int J Chron Obstruct Pulmon Dis, 2018. **13**: p. 2301-2311.
150. McGready, J., *Multiple Regression Analysis in Public Health.* Coursera, 2020. **Biostatistics in Public Health Specialization**.
151. Blanchette, C.M., N.J. Gross, and P. Altman, *Rising Costs of COPD and the Potential for Maintenance Therapy to Slow the Trend.* Am Health Drug Benefits, 2014. **7**(2): p. 98-106.
152. Statisticsteacher.org, *What is power?* 2017.
153. Wong, M.S., et al., *Spatially Analyzing the Inequity of the Hong Kong Urban Heat Island by Socio-Demographic Characteristics.* Int J Environ Res Public Health, 2016. **13**(3).
154. Song, J.W. and K.C. Chung, *Observational studies: cohort and case-control studies.* Plast Reconstr Surg, 2010. **126**(6): p. 2234-2242.
155. Tripepi, G., et al., *Selection bias and information bias in clinical research.* Nephron Clin Pract, 2010. **115**(2): p. c94-9.
156. Rothman KJ, *Epidemiology: An Introduction.* Oxford University Press., 2002.

157. *Standardization of Spirometry, 1994 Update. American Thoracic Society.* Am J Respir Crit Care Med, 1995. **152**(3): p. 1107-36.
158. Langhammer A, C.S., Humerfelt S, Melbye H, Nag T, Svanes Ø., *På tide med nye referanseverdier og grenseverdier for spirometri.* Tidsskr Nor Legeforen., 2018.
159. Nielsen, N., 2021.
160. UCL Institute of Health Equity, *Review of social determinants and the health divide in the WHO European Region: final report.* Copenhagen: World Health Organization, Regional Office for Europe; 2013. , 2013.
161. Mackenzie, C.S., et al., *Older adults' help-seeking attitudes and treatment beliefs concerning mental health problems.* Am J Geriatr Psychiatry, 2008. **16**(12): p. 1010-9.
162. Evans, C. and B. Crawford, *Patient self-reports in pharmacoeconomic studies. Their use and impact on study validity.* Pharmacoeconomics, 1999. **15**(3): p. 241-56.
163. McCambridge, J., J. Witton, and D.R. Elbourne, *Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects.* J Clin Epidemiol, 2014. **67**(3): p. 267-77.
164. Ritter, P.L., et al., *Self-reports of health care utilization compared to provider records.* J Clin Epidemiol, 2001. **54**(2): p. 136-41.
165. Jacobsen, B.K. and D.S. Thelle, *The Tromso Heart Study: responders and non-responders to a health questionnaire, do they differ?* Scand J Soc Med, 1988. **16**(2): p. 101-4.
166. Korkeila, K., et al., *Non-response and related factors in a nation-wide health survey.* Eur J Epidemiol, 2001. **17**(11): p. 991-9.
167. Van Loon, A.J., et al., *Survey non-response in the Netherlands: effects on prevalence estimates and associations.* Ann Epidemiol, 2003. **13**(2): p. 105-10.
168. Miller, D.P., M. Gomberg-Maitland, and M. Humbert, *Survivor bias and risk assessment.* Eur Respir J, 2012. **40**(3): p. 530-2.
169. Hu, Z.H., et al., *Role of survivor bias in pancreatic cancer case-control studies.* Ann Epidemiol, 2016. **26**(1): p. 50-6.
170. Eagan, T.M., et al., *Nonresponse in a community cohort study: predictors and consequences for exposure-disease associations.* J Clin Epidemiol, 2002. **55**(8): p. 775-81.
171. Jager, K.J., et al., *Confounding: what it is and how to deal with it.* Kidney Int, 2008. **73**(3): p. 256-60.
172. Lahtinen H, *Social class and the risk of unemployment: Trends, gender differences and the contribution of education.* Sage Journals, Acta Sociologica, 2018. **Vol 63, Issue 3, 2020**.
173. Puolakka, K., et al., *Predictors of productivity loss in early rheumatoid arthritis: a 5 year follow up study.* Ann Rheum Dis, 2005. **64**(1): p. 130-3.
174. Owens, G.M., *Gender differences in health care expenditures, resource utilization, and quality of care.* J Manag Care Pharm, 2008. **14**(3 Suppl): p. 2-6.

175. Nielsen, R., et al., *Aspects of healthcare utilisation in self-reported obstructive lung disease.* Clin Respir J, 2009. **3**(1): p. 34-41.
176. Rothman KJ, G.S., *Modern Epidemiology, 2nd edition.* Philadelphia: Lippincott, 1998.
177. Stata and FEAUSP, *Multilevel mixed-effects Generalized Linear Models in Stata.* Stata, 2017.
178. Marrie, R.A., N.V. Dawson, and A. Garland, *Quantile regression and restricted cubic splines are useful for exploring relationships between continuous variables.* J Clin Epidemiol, 2009. **62**(5): p. 511-7 e1.
179. Murray, C.J., Lopez A.D., World Health Organization, World Bank & Harvard School of Public Health., *The Global burden of disease : a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020 : summary / edited by Christopher J. L. Murray, Alan D. Lopez.* Harvard University Press, 1996.
180. Statistics Norway. *Labour force survey, seasonally-adjusted monthly figures.* (accessed 26 Feb 2014)]; Available from: https://www.ssb.no/en/arbeid-og-lonn/statistikker/akumnd.
181. Darkow, T., et al., *A retrospective analysis of disability and its related costs among employees with chronic obstructive pulmonary disease.* J Occup Environ Med, 2007. **49**(1): p. 22-30.
182. Lou, P., et al., *Vulnerability, beliefs, treatments and economic burden of chronic obstructive pulmonary disease in rural areas in China: a cross-sectional study.* BMC Public Health, 2012. **12**: p. 287.
183. Montes de Oca, M., et al., *Paid employment in subjects with and without chronic obstructive pulmonary disease in five Latin American cities: the PLATINO study.* Int J Tuberc Lung Dis, 2011. **15**(9): p. 1259-64, i-iii.
184. Fri Fagbevegelse, *I 1978 mente alle vi hadde råd.* Fri Fagbevegelse, LO-Aktuelt., 2013.
185. Statistisk Sentralbyrå, S.N., *Indikatorutvikling FD-trygd.* 2014.
186. Kinge, J.M., et al., *Economic losses and burden of disease by medical conditions in Norway.* Health Policy, 2017. **121**(6): p. 691-698.
187. Yaffe, R., et al., *Medical economics survey-methods study: cost-effectiveness of alternative survey strategies.* Med Care, 1978. **16**(8): p. 641-59.
188. Puhan, M.A., et al., *Inhaled drugs to reduce exacerbations in patients with chronic obstructive pulmonary disease: a network meta-analysis.* BMC Med, 2009. **7**: p. 2.
189. Dalal, A.A., et al., *Observational study of the outcomes and costs of initiating maintenance therapies in patients with moderate exacerbations of COPD.* Respir Res, 2012. **13**: p. 41.
190. Ladwig, K.H., et al., *Gender differences of symptom reporting and medical health care utilization in the German population.* Eur J Epidemiol, 2000. **16**(6): p. 511-8.
191. de Torres, J.P., et al., *Gender and COPD in patients attending a pulmonary clinic.* Chest, 2005. **128**(4): p. 2012-6.

192. Martinez, F.J., et al., *Sex differences in severe pulmonary emphysema.* Am J Respir Crit Care Med, 2007. **176**(3): p. 243-52.
193. de Torres, J.P., et al., *Gender associated differences in determinants of quality of life in patients with COPD: a case series study.* Health Qual Life Outcomes, 2006. **4**: p. 72.
194. de Torres, J.P., et al., *Gender differences in plasma biomarker levels in a cohort of COPD patients: a pilot study.* PLoS One, 2011. **6**(1): p. e16021.
195. Chen, Y., S.L. Horne, and J.A. Dosman, *Increased susceptibility to lung dysfunction in female smokers.* Am Rev Respir Dis, 1991. **143**(6): p. 1224-30.
196. de Torres, J.P., et al., *Gender and respiratory factors associated with dyspnea in chronic obstructive pulmonary disease.* Respir Res, 2007. **8**: p. 18.
197. Carlson, C.L., et al., *Hormone replacement therapy is associated with higher FEV1 in elderly women.* Am J Respir Crit Care Med, 2001. **163**(2): p. 423-8.
198. Miravitlles, M., et al., *[Attitudes toward the diagnosis of chronic obstructive pulmonary disease in primary care].* Arch Bronconeumol, 2006. **42**(1): p. 3-8.
199. Kesten, S. and K.R. Chapman, *Physician perceptions and management of COPD.* Chest, 1993. **104**(1): p. 254-8.
200. Kilic, H., et al., *Do females behave differently in COPD exacerbation?* Int J Chron Obstruct Pulmon Dis, 2015. **10**: p. 823-30.
201. de Torres, J.P., et al., *Sex differences in mortality in patients with COPD.* Eur Respir J, 2009. **33**(3): p. 528-35.
202. Varkey, J.B., A.B. Varkey, and B. Varkey, *Prophylactic vaccinations in chronic obstructive pulmonary disease: current status.* Curr Opin Pulm Med, 2009. **15**(2): p. 90-9.
203. Lisspers, K., et al., *Economic burden of COPD in a Swedish cohort: the ARCTIC study.* Int J Chron Obstruct Pulmon Dis, 2018. **13**: p. 275-285.
204. Rehman, A.U., et al., *The economic burden of chronic obstructive pulmonary disease (COPD) in Europe: results from a systematic review of the literature.* Eur J Health Econ, 2020. **21**(2): p. 181-194.
205. Nielsen, R., et al., *Excessive costs of COPD in ever-smokers. A longitudinal community study.* Respir Med, 2011. **105**(3): p. 485-93.
206. Burrows, B., et al., *The course and prognosis of different forms of chronic airways obstruction in a sample from the general population.* N Engl J Med, 1987. **317**(21): p. 1309-14.
207. Chapman, K.R., et al., *Epidemiology and costs of chronic obstructive pulmonary disease.* Eur Respir J, 2006. **27**(1): p. 188-207.

Papers

Paper I

ORIGINAL ARTICLE
COPD

Unemployment in chronic airflow obstruction around the world: results from the BOLD study

Rune Grønseth[1], Marta Erdal[1,2], Wan C. Tan[3], Daniel O. Obaseki[4], Andre F.S. Amaral[5], Thorarinn Gislason[6], Sanjay K. Juvekar[7], Parvaiz A. Koul[8], Michael Studnicka[9], Sundeep Salvi[10], Peter Burney[5], A. Sonia Buist[11], William M. Vollmer[12] and Ane Johannessen[13]

Affiliations: [1]Dept of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway. [2]Dept of Clinical Science, University of Bergen, Bergen, Norway. [3]UBC James Hogg Research Centre, St Paul's Hospital, Vancouver, BC, Canada. [4]Dept of Medicine, Obafemi Awolowo University, Ile-Ife, Nigeria. [5]National Heart and Lung Institute, Imperial College London, London, UK. [6]Dept of Respiratory Medicine and Sleep, Faculty of Medicine, University of Iceland, Landspitali University Hospital, Reykjavik, Iceland. [7]Vadu Health and Demographic Surveillance System, KEM Hospital Research Centre Pune, Pune, India. [8]Dept of Internal and Pulmonary Medicine, SheriKashmir Institute of Medical Sciences, Srinagar, India. [9]Dept of Pulmonary Medicine, Paracelsus Medical University, Salzburg, Austria. [10]Chest Research Foundation, Chest Research Foundation, Pune, India. [11]Pulmonary and Critical Care Medicine, UHN67, Oregon Health and Science University, Portland, OR, USA. [12]Kaiser Permanente Center for Health Research, Portland, OR, USA. [13]Centre for International Health, Dept of Global Public Health and Primary Care, University of Bergen, Bergen, Norway.

Correspondence: Marta Erdal, Dept of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway. E-mail: marta.erdal@k2.uib.no

@ERSpublications
Chronic airflow obstruction increases risk of unemployment, and is a burden to welfare systems worldwide http://ow.ly/cxzv30cQ17A

Cite this article as: Grønseth R, Erdal M, Tan WC, *et al*. Unemployment in chronic airflow obstruction around the world: results from the BOLD study. *Eur Respir J* 2017; 50: 1700499 [https://doi.org/10.1183/13993003.00499-2017].

ABSTRACT We aimed to examine associations between chronic airflow obstruction (CAO) and unemployment across the world.

Cross-sectional data from 26 sites in the Burden of Obstructive Lung Disease (BOLD) study were used to analyse effects of CAO on unemployment. Odds ratios for unemployment in subjects aged 40–65 years were estimated using a multilevel mixed-effects generalised linear model with study site as random effect. Site-by-site heterogeneity was assessed using individual participant data meta-analyses.

Out of 18 710 participants, 11.3% had CAO. The ratio of unemployed subjects with CAO divided by subjects without CAO showed large site discrepancies, although these were no longer significant after adjusting for age, sex, smoking and education. The site-adjusted odds ratio (95% CI) for unemployment was 1.79 (1.41–2.27) for CAO cases, decreasing to 1.43 (1.14–1.79) after adjusting for sociodemographic factors, comorbidities and forced vital capacity. Of other covariates that were associated with unemployment, age and education were important risk factors in high-income sites (4.02 (3.53–4.57) and 3.86 (2.80–5.30), respectively), while female sex was important in low- to middle-income sites (3.23 (2.66–3.91)).

In the global BOLD study, CAO was associated with increased levels of unemployment, even after adjusting for sociodemographic factors, comorbidities and lung function.

Introduction

Chronic airflow obstruction (CAO) is the primary characteristic of patients with chronic obstructive pulmonary disease (COPD) and affects up to one in five adults, depending on where they live, according to data from the Burden of Obstructive Lung Disease (BOLD) study [1]. COPD is expected to keep its position as the third most important cause of death worldwide [2], and imposes a substantial burden on quality of life [3] and healthcare utilisation [4]. So far, data on productivity-related burden of CAO or COPD have been scant [4].

Only three population-based studies have provided employment rates in CAO [5–7]. Erdal *et al.* [5] showed that 55% of individuals with CAO from a general Norwegian population were in a paid job, *versus* 87% of controls without CAO. However, controls were younger and had higher levels of education and the authors did not examine employment in multivariate analyses. Jansson *et al.* [6] examined CAO-specific disability in northern Sweden, but did not include a control group and did not report employment rates. In the PLATINO (Latin American Project for Research in Pulmonary Obstruction) study undertaken in five Latin-American countries, Montes de Oca *et al.* [7] showed that the workforce participation among subjects with CAO was lower than in healthy subjects (41.8% *versus* 57.1%). However, in multivariable analyses they found that higher age, dyspnoea, number of comorbid conditions, female sex and lower education were associated with unemployment, whereas CAO was only of borderline significance.

The BOLD study is a large international study providing population-based estimates of the prevalence and burden of CAO. One of the primary objectives of the BOLD study is to estimate disease burden in terms of activity limitation and economic impact [8]. In the current analysis, we have compared estimates of employment status in BOLD participants with and without CAO across the world.

Methods

The BOLD protocol has been published previously [8]. It was written in compliance with the Helsinki declaration and is approved by local ethics committees at all sites. All participants provided written consent.

Population

All participating sites were recruited from well-defined administrative areas with the goal of providing representative samples of the local population of ⩾600 non-institutionalised persons aged ⩾40 years. The current report includes participants from 26 sites (online supplementary material). Out of 22 118 participants providing interview data, 18 710 performed acceptable post-bronchodilator spirometry and were included in the descriptive part of the current analysis. However, when analysing risk for unemployment as outcome, all subjects aged ⩾65 years (defined here as retirees) and homemakers/caregivers were excluded. After excluding these subjects, there were no CAO cases left in Tirana (Albania), so this centre is not part of the analyses assessing the effect of CAO on unemployment. Online supplementary table S1 lists sampling strategy and response rates for all sites.

Data collection

The BOLD study is a cross-sectional study based on a structured, face-to-face interview using standardised questionnaires and pre-/post-bronchodilator spirometry. All study coworkers were trained and certified by BOLD coordinating centres.

The interviews gathered information on smoking habits, education, job status, self-reported comorbidities (hypertension, heart disease, diabetes, stroke and lung cancer) and respiratory symptoms (dyspnoea, wheezing and chronic bronchitis).

Participants indicated whether they had worked for income at any time in the preceding year or if they served as full-time homemakers/caregivers during that time frame. Since retirement was not formally captured under occupation, we excluded anyone aged ⩾65 years from analyses involving employment status. All other individuals not being categorised as working, homemakers/caregivers or retirees were defined as unemployed. The main outcome for the current study was a dichotomous employment status where retirees (⩾65 years) and homemakers/caregivers were excluded.

This article has supplementary material available erj.ersjournals.com

Received: March 10 2017 | Accepted after revision: June 20 2017

Support statement: This study was funded by the Wellcome Trust (grant number 085790/2/08/2). Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

Never-smokers were individuals who had smoked <20 packs of cigarettes during their lifetime, or less than one cigarette daily for a year. Ex-smokers were those who reported an age at which they had stopped smoking. Education was categorised according to the highest level of completed schooling and divided into no schooling, primary school, middle school, high school, some college and completed college/university.

Dyspnoea was defined using the modified Medical Research Council (mMRC) questions (grades 0–4, see online supplementary material for details) [9]. Subjects reporting being unable to walk for reasons other than breathing problems were excluded from the dyspnoea variable. Wheezing was defined as attacks of wheezing associated with dyspnoea in the past 12 months. Chronic bronchitis was defined as productive cough on most days in 3 months per year for at least two consecutive years.

Post-bronchodilator spirometry was performed using a hand-held spirometer (EasyOne; ndd Medizintechnik, Zürich, Switzerland) according to American Thoracic Society standards [10], before and ⩾15 min after inhalation of 200 µg salbutamol through a large-volume spacer. For quality control, all individual manoeuvers were reviewed by a pulmonary function reading centre.

Predicted values of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio were estimated from equations for caucasians from the third National Health and Nutrition Examination Survey (NHANES-III) [11]. Spirometric CAO was defined as post-bronchodilator FEV_1/FVC below lower limit of normal (LLN).

Analysis

The sample size of the BOLD study was set to be able to provide robust CAO prevalence estimates at the individual sites [8]. No power calculations were performed *a priori* for employment status.

For unadjusted comparisons of individuals with and without CAO, we used Pearson Chi-squared (categorical variables) and t-tests (continuous variables). To illustrate differences in unemployment and CAO in different parts of the world, we stratified descriptive analyses by high-income sites (Sydney (Australia), Salzburg (Austria), Vancouver (Canada), London (UK), Tartu (Estonia), Hannover (Germany), Reykjavik (Iceland), Maastricht (the Netherlands), Bergen (Norway), Krakow (Poland), Lisbon (Portugal), Uppsala (Sweden), Lexington (KY, USA)) and low- to middle-income sites (Guangzhou (China), Mumbai (India), Pune (India), Manila (Philippines), Nampicuan Talugtug (Philippines), Annaba (Algeria), Cape Town (South Africa), Adana (Turkey), Kashmir (India), Sousse (Tunisia), Ile-Ife (Nigeria) and Fes (Morocco)). Income categories were based on the gross national income per capita (GNIPC) of the country, with the cut point between low-to-middle income and high income being GNIPC 10 000 US$. [12]. We also calculated a risk ratio for unemployment associated with CAO as the prevalence of unemployment in CAO subjects divided by the prevalence of unemployment in non-CAO subjects, using a log-binomial generalised linear model (in Stata (StataCorp, College Station, TX, USA) specified as *glm* with *fam(bin)* and *link(log)*). A risk ratio >1 indicates higher risk of unemployment associated with CAO, while a ratio <1 indicates lower risk of unemployment associated with CAO. To illustrate sex differences in CAO status across sites, we tabulated study sites and CAO status, stratified by sex.

Multivariable analyses for the pooled dataset were conducted using a multilevel mixed-effects generalised linear model (online supplementary material). An alternative approach would be a fixed-effect model. The difference to the chosen mixed-effects approach would be that the latter treats the sites as a random sample of all possible sites, whereas the former would tend to focus more exclusively on the sites that were included in the study. The BOLD sites are in some sense a random sample of broader sites to which we wish to make an inference.

The main predictor variable was spirometric CAO. We fitted five mixed models, all adjusting for site as a cluster level variable. We first identified the total effect of CAO on unemployment in a model with no additional covariates included (model 1). Model 2 added demographic variables (age, sex and education) and smoking habits. Model 2 was extended into model 3 by adding comorbidities. Model 4 included FVC in addition to model 3 covariates. As our multivariable analyses include height, age and sex, which are the main components when using % predicted values, we thus chose to analyse lung function in terms of absolute values. In addition, a recent publication from the European Community Respiratory Health Survey III study has indicated that FVC in absolute values (lung size) is able to explain most of the difference in symptom burden between males and females [13]. FVC is a robust indicator of lung disease, especially when obstruction is already taken into account. In addition, we included model 5 with respiratory symptoms in addition to the model 4 covariates (online supplementary material). Details of comorbidities and symptoms are presented in the online supplementary material. Covariates added in each model were added not as independent risk factors for unemployment, but as potential confounding or mediating factors influencing the effect of CAO on unemployment. In addition, models 2–5 were performed separately for high-income sites and for low- to middle-income sites.

In individual participant data meta-analyses, we estimated site-specific and overall odds ratios for CAO on unemployment in forest plots, with increasing adjustment corresponding to models 1–5 (except for the site adjustment). The Stata command used was *ipdmetan* which performs a two-stage individual participant data meta-analysis using the inverse-variance method. Unlike traditional meta-analysis, the individual participant data meta-analysis in *ipdmetan* fits a specified model to the data of one site at a time, making use of all individual participants within the sites. The two-stage approach derives aggregate data in each site separately and then combines these in a traditional meta-analysis model. The I^2 statistic was reported to display the percentage of total variation across sites which was due to true site-by-site heterogeneity rather than what would be expected by chance alone (see the online supplementary material for more details) [14].

All analyses were performed using Stata SE version 14 for Macintosh OSX.

Results

Out of 18710 participants, 2123 (11.3%) had CAO. Compared to subjects without CAO, those with CAO were older, had lower education levels, more smoking exposure, more comorbidities, more respiratory symptoms and substantially lower FEV_1 (table 1). Overall, CAO was more common in males than in females. However, site-specific prevalence estimates stratified by sex showed that for some centres the sex ratio was reversed (online supplementary table S2). Excluding those aged ⩾65 years, 36.7% of participants with CAO reported paid work during the preceding year, whereas 53.2% of participants without CAO had undertaken paid work during the preceding year.

Figure 1 shows that more males than females reported current paid employment in both high- and low- to middle-income countries, but the difference was larger in low- to middle-income countries. This appeared to be explained by a substantial proportion of female unpaid homemakers/caregivers in low- to middle-income countries. More details on sex differences in employment status are given in online supplementary table S3.

Table 2 shows unemployment by CAO status in each study site, excluding homemakers, caregivers and retirees (subjects aged ⩾65 years). Despite a wide variation in unemployment rates by site, there was a fairly consistent pattern of higher unemployment among individuals with CAO in high-income sites. This pattern was less clear in the low- to middle-income sites.

In multivariable analyses, we assessed the odds ratio of being unemployed by CAO status and an increasing number of covariates (table 3). The first model showed that when we adjusted for site, the odds ratio (95% CI) of being unemployed was 1.79 (1.41–2.27) for participants with CAO. Adding the traditional confounders sex, age, smoking habits and education in model 2 decreased the odds ratio for unemployment in participants with CAO (OR reduction from 1.79 to 1.44), but the effect remained statistically significant. Further addition of comorbidities (model 3) and FVC (model 4) had little effect on the association between unemployment and CAO, even when these variables themselves were significantly associated with unemployment: the presence of comorbidities and declining FVC were all associated with increased odds of being unemployed. Table 3 shows that excess unemployment among those with CAO is partially explained by sex, age, smoking and education, but not explained additionally by comorbidities and FVC. When respiratory symptoms were added (online supplementary table S4), these were also significantly associated with unemployment and appeared to explain some of the effects of CAO. In this model, the odds ratio for CAO independent of reported symptoms fell to 1.26 (95% CI 1.00–1.57). Substituting self-reported COPD for LLN-defined CAO in our analyses increased the odds ratio of not being in paid work from 1.43 (95% CI 1.14–1.79) to 3.31 (95% CI 2.17–5.05) (additional analysis, data not shown). However, while the prevalence of spirometry-defined CAO was 11.3% in BOLD, the prevalence of self-reported COPD was only 1.2%, and while 36.7% of the spirometry-defined participants with CAO were in paid employment, the corresponding figure for the self-reported COPD cases was only 25% (results not shown).

To examine how the observed associations varied by country income, we performed multivariable analyses separately for high-income and low- to middle-income sites (table 4). CAO was a significant risk factor for unemployment in all models in high-income sites, but not in low- to middle-income sites. While age and lower education level were important risk factors for unemployment in high-income sites, female sex was the most pronounced risk factor for unemployment in low- to middle-income sites. To further depict the sex variation in job status, we created online supplementary table S3, which shows the prevalence of job status categories among males and females in each site. This table illustrates that almost no sites had more females than males in paid work (with Lexington, Lisbon and Ile-Ife as the only three exceptions). Further on, focusing on the low- to middle-income sites, this table demonstrates that the difference in "unemployed" job status between the sexes were very high in some sites, with the mean difference being

46.1% more unemployed females than males. There were some sites that had more unemployed males than females, but these were few (Annaba, Cape Town, Kashmir, Mumbai and Pune), and the mean difference was low (5.5%). In model 5, dyspnoea was an additional important risk factor for unemployment in high-income sites, together with age and education (online supplementary table S4).

To present the association between CAO and unemployment by site, and to examine site heterogeneity, we performed individual participant data meta-analyses with forest plots of odds ratios and overall I^2 statistics (figure 2 and online supplementary figures S1–S4). The overall odds ratio (95% CI) for unemployment among CAO subjects after adjusting for sex, age, smoking, education, comorbidities and FVC (*i.e.* the equivalent of model 4, but without site adjustment) was 1.41 (1.18–1.69) with site-by-site heterogeneity (I^2) of 12.9% (p=0.279). Meta-analyses with covariates corresponding to models 1, 2, 3

TABLE 1 Study participant characteristics in the Burden of Obstructive Lung Disease (BOLD) study by chronic airflow obstruction (CAO)

	Spirometric CAO	No spirometric CAO	Total
Subjects	2123	16587	18710
Female	46.4 (44.2–48.5)	51.9 (51.1–52.6)	51.3 (50.5–52.0)
Age years	60.7±11.9	55.2±11.0	55.8±11.3
Smoking			
Never-smoker	33.9 (32.0–36.0)	57.2 (56.4–58.0)	54.6 (53.8–55.3)
Ex-smoker	31.0 (29.1–33.0)	23.9 (23.2–24.5)	24.7 (24.1–25.3)
Current smoker	35.1 (33.1–37.1)	18.9 (18.4–19.5)	20.8 (20.2–21.4)
Education			
None	14.7 (13. 2–16.3)	12.1 (11.6–12.6)	12.4 (11.9–12.9)
Primary school	21.7 (20.0–23.5)	15.7 (15.2–16.3)	16.4 (15.9–16.9)
Middle school	17.0 (15.5–18.7)	16.0 (15.5–16.6)	16.1 (15.6–16.7)
High school	24.7 (22.9–26.6)	26.2 (25.5–26.8)	26.0 (25.4–26.6)
Some college	11.1 (9.8–12.5)	12.8 (12.3–13.4)	12.6 (12.2–13.1)
College/university	10.9 (9.6–12.3)	17.2 (16.6–17.8)	16.5 (15.9–17.0)
Job status			
Paid work	36.7 (34.7–38.8)	53.2 (52.4–53.9)	51.3 (50.6–52.0)
Homemaker/caregiver	14.8 (13.3–16.4)	13.5 (13.0–14.0)	13.7 (13.2–14.1)
Unemployed	19.6 (18.0–21.4)	16.2 (15.6–16.8)	16.6 (16.1–17.1)
Above retirement age	28.9 (27.0–30.8)	17.1 (16.6–17.7)	18.5 (17.9–19.0)
Lung function			
FVC % pred	89.2±21.8	90.3±16.1	90.2±16.9
FEV_1 % pred	69.2±21.4	92.0±16.7	89.4±18.7
Self-reported doctor's diagnosis			
COPD	15.3 (13.8–16.9)	2.4 (2.2–2.6)	3.9 (3.6–4.2)
Hypertension	32.9 (30.9–34.9)	26.2 (25.6–26.9)	27.0 (26.3–27.6)
Heart disease	14.3 (12.9–15.9)	10.0 (9.5–10.4)	10.5 (10.0–10.9)
Diabetes	7.2 (6.1–8.3)	7.5 (7.1–7.9)	7.5 (7.1–7.9)
Stroke	3.1 (2.4–3.9)	1.9 (1.7–2.1)	2.0 (1.8–2.2)
Lung cancer	0.7 (0.4– 1.1)	0.2 (0.1– 0.3)	0.3 (0.2– 0.3)
Dyspnoea			
mMRC 0	55.8 (53.5–58.0)	78.8 (78.1–79.4)	76.2 (75.6–76.9)
mMRC 1	17.1 (15.5–18.9)	12.1 (11.6–12.6)	12.7 (12.2–13.2)
mMRC 2	13.2 (11.7–14.8)	5.6 (5.2–5.9)	6.4 (6.1–6.8)
mMRC 3	8.5 (7.3–9.8)	2.7 (2.5–3.0)	3.3 (3.1–3.6)
mMRC 4	5.5 (4.5–6.6)	0.9 (0.7–1.0)	1.4 (1.2–1.6)
Attack of wheezing in past 12 months	22.3 (20.6–24.1)	6.3 (5.9–6.6)	8.1 (7.7–8.5)
Chronic bronchitis	15.4 (13.9–17.0)	5.1 (4.8–5.5)	6.3 (5.9–6.6)

Data are presented as n, % (95% CI) or mean±SD. n=18710 subjects from 26 study sites. All comparisons between CAO and non-CAO were significant (p<0.01, Pearson Chi-squared test for categorical variables, t-test for continuous variables) except for self-reported diabetes. Missing data: smoking habits n=11 (n=1 CAO, n=10 non-CAO); education n=25 (n=4 CAO, n=21 non-CAO); hypertension, diabetes, stroke, lung cancer and heart disease n=1 (n=1 CAO); dyspnoea n=1834 (n=258 CAO, n=1576 non-CAO), mostly because of other reasons for having trouble walking; wheezing n=11 (n=2 CAO, n=9 non-CAO); chronic bronchitis n=0. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; COPD: chronic obstructive pulmonary disease; mMRC: modified Medical Research Council scale.

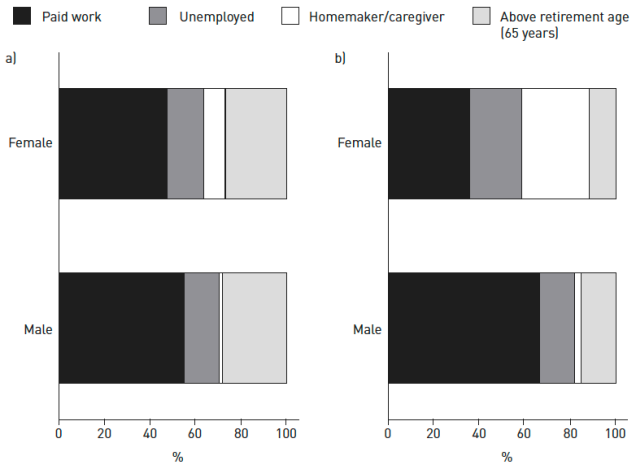


FIGURE 1 Distribution of job status by sex for participants in a) high-, and b) low- to middle-income countries. n=18 710.

and 5 are shown in online supplementary figures S1–S4, and show that there is no significant site heterogeneity in the association between airflow obstruction and unemployment when adjusting for the covariates in models 2, 3 and 5. However, in crude analysis (model 1), there is significant site heterogeneity (I^2 49.1%, p=0.003).

Discussion

The unweighted prevalence of spirometry-defined CAO was 11.3% in this sample of almost 19000 participants from the global BOLD study. The association between CAO and unemployment varied across sites in crude analyses, but the site heterogeneity lost significance after adjustment for relevant covariates: CAO was an overall important risk factor for unemployment after adjusting for sex, age, smoking, education, comorbidities and even FVC. When looking at high-income and low- to middle-income sites separately, this association was only statistically significant in high-income sites. Regarding other covariates, age and education were important risk factors for unemployment in high-income sites, while female sex was important for unemployment in low- to middle-income sites.

Comparable population-based studies have previously observed similar prevalence rates of COPD as the CAO rates found in the present study. The PLATINO (Latin-American Pulmonary Obstruction Investigation Project) study found the prevalence to be within the range of 7.8–19.7% [15], Hansen *et al.* [16] found the overall COPD prevalence in a Danish general population to be 12%, and the systematic review by Adeloye *et al.* [17] found the global prevalence of population-based spirometrically defined COPD to be 11.7%.

Only one multicentre study has previously provided population-based estimates of unemployment in CAO, identifying CAO using spirometry. In accordance with our findings, the PLATINO study, performed in five Latin-American countries, estimated that 41.8% of participants with CAO and 57.1% of those without CAO had a paid job the preceding year [7]. In the multivariable analysis of the PLATINO study they found a borderline lower probability of paid work (OR 0.83, 95% CI 0.69–1.00) for CAO patients, and, as in our study, they found significant effects of age, sex, education, dyspnoea and comorbidities. However, the PLATINO study researchers adjusted for dyspnoea in their main model, and this has probably reduced the effect of spirometry-defined CAO on the probability of having paid work. We observed the same pattern in our study; while CAO was significantly associated with unemployment in our main model with OR 1.43 (adjusting for sex, age, smoking, education, comorbidities and FVC), the odds ratio decreased to 1.26 (although still remaining significant, with 95% CI 1.00–1.57) after adding reported dyspnoea and

TABLE 2 Unemployment rates: prevalence of unemployment by site and spirometric chronic airflow obstruction (CAO) status

	Subjects[#] n	Unemployment %		Crude OR (95% CI)[¶]
		CAO	No CAO	
Total	11 675			
High-income				
Bergen, Norway	397	20.0	9.5	2.1 (1.0–4.2)
Hannover, Germany	361	25.0	20.8	1.2 (0.6–2.5)
Krakow, Poland	350	57.9	41.4	1.4 (1.0–1.9)
Lexington, USA	305	61.0	27.7	2.2 (1.6–3.0)
Lisbon, Portugal	320	53.9	39.8	1.4 (0.9–2.0)
London, UK	427	40.4	24.3	1.7 (1.1–2.4)
Maastricht, the Netherlands	396	31.3	20.4	1.5 (1.0–2.3)
Reykjavik, Iceland	557	14.0	3.3	4.2 (1.8–10.1)
Salzburg, Austria	860	35.2	25.4	1.4 (1.1–1.8)
Sydney, Australia	339	20.0	15.3	1.3 (0.6–3.0)
Tartu, Estonia	348	20.0	7.8	2.6 (0.9–7.5)
Uppsala, Sweden	371	23.8	6.0	4.0 (1.7–9.5)
Vancouver, Canada	594	21.8	11.5	1.9 (1.1–3.3)
Low- to middle-income				
Adana, Turkey	487	41.1	45.4	0.9 (0.7–1.2)
Annaba, Algeria	408	50.0	24.6	2.0 (1.2–3.3)
Cape Town, South Africa	510	52.2	33.5	1.6 (1.2–2.0)
Fes, Morocco	335	41.7	53.7	0.8 (0.5–1.3)
Guangzhou, China	359	35.7	49.9	0.7 (0.4–1.5)
Ile-Ife, Nigeria	667	5.1	7.6	0.7 (0.2–2.7)
Kashmir, India	366	7.6	1.3	5.8 (1.5–22.9)
Manila, Philippines	594	10.3	19.5	0.5 (0.2–1.4)
Mumbai, India	250	17.7	10.3	1.7 (0.6–5.1)
Nampicuan Talugtug, Philippines	493	23.2	14.7	1.6 (0.9–2.7)
Pune, India	671	6.5	4.1	1.6 (0.4–6.4)
Sousse, Tunisia	390	53.3	46.1	1.2 (0.7–1.9)
Tirana, Albania	520	0.0	5.0	

[#]: retirees (age limit defined as ⩾65 years) and homemakers/caregivers were excluded from the analysis.
[¶]: calculated based on prevalence of unemployment among subjects with CAO divided by prevalence of unemployment among subjects without CAO. A ratio >1 indicates higher unemployment prevalence among CAO subjects than among non-CAO subjects, while a ratio <1 indicates lower unemployment prevalence among CAO subjects.

other respiratory symptoms. In line with this, we speculate that symptoms and severity of CAO would probably explain the bulk of unemployment, and that it would be better to study these disease aspects than merely spirometry measurements. However, even after adjusting for mMRC, wheezing with dyspnoea and symptoms of chronic bronchitis in our study, the effect of spirometry-defined CAO on unemployment was still significant (model 5; online supplementary material). This suggests that there are properties other than the burden of current wheezing, dyspnoea and bronchitis that lead to unemployment, and adding objectively measured CAO identifies the magnitude of these. For instance, the patient might experience other symptoms (*e.g.* asthenia), be a frequent exacerbator or there might be some degree of reporting bias.

Other studies on workforce participation of CAO patients have been based on self-reported COPD diagnosis and not spirometry [18–22]. Studies of self-reported COPD observe stronger associations between the disease and participation in the workplace than the current study. This difference might be due to a bias towards more severely affected patients in studies based on self-reports [23]. Lamprecht *et al.* [24] showed that >80% of subjects with post-bronchodilator FEV1/FVC <LLN were undiagnosed, and that less severe airflow obstruction was an important predictor lack of diagnosis.

The inclusion of undiagnosed CAO patients by state-of-the-art spirometric case detection in representative population-based samples is the main strength of the current study. All epidemiological studies are subject to selection bias to some degree, and the use of representative samples and mostly high cooperation rates (over half >70%) reduce the likelihood of strong biases from selection. Furthermore, our main outcome is categorical and objective, and less prone to bias [25, 26] than reports of diagnoses, although some of the covariates may be more prone to recall bias. In addition, we have used post-bronchodilator measurements,

TABLE 3 OR (95% CI) for unemployment for lower limit of normal-defined chronic airflow obstruction (CAO) and other risk factors, with an increasing degree of adjustment (demographic characteristics, comorbidities and forced vital capacity (FVC))

	Model 1	Model 2	Model 3	Model 4
Spirometric CAO	1.79 (1.41–2.27)	1.44 (1.15–1.81)	1.45 (1.15–1.82)	1.43 (1.14–1.79)
FVC 10 percentage points decrease in % pred				1.08 (1.04–1.12)
Female		2.07 (1.85–2.32)	2.10 (1.87–2.36)	2.10 (1.87–2.35)
Age 10-year increment		3.09 (2.85–3.35)	2.91 (2.68–3.15)	2.90 (2.67–3.15)
Smoking status				
Current smoker		0.96 (0.83–1.10)	0.98 (0.85–1.13)	0.98 (0.85–1.13)
Ex-smoker		1.15 (1.01–1.32)	1.13 (0.99–1.30)	1.14 (0.99–1.30)
Education				
Some college		1.51 (1.23–1.85)	1.49 (1.22–1.84)	1.49 (1.21–1.83)
High school		2.03 (1.71–2.42)	2.02 (1.69–2.41)	2.01 (1.68–2.39)
Middle school		2.24 (1.83–2.73)	2.20 (1.80–2.69)	2.18 (1.79–2.67)
Primary school		2.78 (2.27–3.41)	2.76 (2.25–3.39)	2.72 (2.22–3.35)
No education		2.73 (2.09–3.57)	2.69 (2.05–3.51)	2.66 (2.03–3.49)
Comorbidities				
Hypertension			1.29 (1.13–1.46)	1.26 (1.10–1.43)
Heart disease			1.54 (1.27–1.86)	1.51 (1.25–1.83)
Diabetes			1.51 (1.23–1.85)	1.47 (1.19–1.80)
Stroke			1.82 (1.16–2.86)	1.80 (1.15–2.83)
Lung cancer			2.34 (0.81–6.76)	2.38 (0.82–6.93)

Adjustment variables: no fixed effects (model 1); age, sex, education and smoking (model 2); model 2 adjustment + comorbidities (model 3); model 3 adjustment + FVC (model 4). All five models were fit using a multilevel mixed-effects generalised linear model with study site included as random effect to account for within-site clustering. Reference values for categorical variables: no CAO, male, never-smoker, university education, no hypertension, no heart disease, no diabetes, no stroke and no lung cancer. n=11 675. Retirees (age limit defined as ⩾65 years) and homemakers/caregivers were excluded from the analysis.

in accordance with international guidelines, and we have a large sample size from a general global population with standardised data collection across sites. In addition, we have built regression models based on *a priori* hypotheses of associations, rather than including all variables that were significant in bivariable analyses or by an automated stepwise approach.

Some limitations deserve to be mentioned. First of all, the BOLD study is a cross-sectional study, and as such we cannot infer temporality and we have no direct evidence that the CAO was directly responsible for the unemployment. It is not unthinkable that some of the association between CAO and unemployment is a result of unemployed participants being more susceptible to the disease, even if we have adjusted for education, age and smoking habits. Economic hardship in the form of unemployment can worsen individual unhealthy behaviours including smoking [27]. Second, the employment question is based on any paid work in the past year, and does not differentiate between full-time and part-time work. In other words, subjects who have needed to reduce their work participation due to CAO from full-time to part-time will still be defined as in paid work in our analysis. This may lead to an underestimation of associations between CAO and employment. Being able to present absolute rates of disease-related unemployment standardised at the site population level would have been an advantage, but as our data did not include census information with age distribution details from each site this was not feasible. Future research should preferably include such data for this purpose. Furthermore, lack of a direct question on retirement means that we may have underestimated the problem of unemployment above 65 years of age. Our chosen cut-off of 65 years as retirement age may have affected results in both directions. Third, our spirometry-derived variables were calculated from the NHANES III reference equation for caucasians. This is relatively uncontroversial for measures of FEV_1/FVC in the age group 40–65 years, as normal values are not strongly associated with ethnicity. However, overall, the prevalence of spirometry-defined CAO (FEV_1/FVC <LLN) will be slightly lower with NHANES reference values than with the recently recommended Global Lung Function Initiative reference values [28]. The difference would not be large enough for us to expect substantial differences in the associations observed in the present study. If anything, a higher CAO prevalence would lead to larger effects of CAO on unemployment, including more individuals with less severe obstruction. The use of NHANES may be more controversial for the measures of FVC than for the ratio measures. In this case, we have used FVC as a continuous variable so that the "lower limit of normal" is not an issue, and, as we have allowed a separate baseline in each centre and as most centres are ethnically homogeneous, this should not present a problem [29, 30]. Since the main focus of the present study was on associations rather than prevalences,

TABLE 4 OR (95% CI) for unemployment for chronic airflow obstruction (CAO) and other risk factors, stratified by country income category, with increasing degree of adjustment (demographic characteristics, comorbidities and forced vital capacity (FVC))

	Model 2		Model 3		Model 4	
	High income	Low to middle income	High income	Low to middle income	High income	Low to middle income
Spirometric CAO	1.71 (1.17–2.49)	1.16 (0.78–1.73)	1.63 (1.16–2.28)	1.18 (0.79–1.76)	1.68 (1.16–2.45)	1.15 (0.77–1.71)
FVC 10 percentage points decrease in % pred					1.09 (1.03–1.15)	1.08 (1.02–1.14)
Female	1.36 (1.16–1.59)	3.34 (2.76–4.04)	1.43 (1.23–1.68)	3.25 (2.68–3.94)	1.44 (1.23–1.68)	3.23 (2.66–3.91)
Age 10-year increment	4.28 (3.77–4.86)	2.31 (2.06–2.59)	4.04 (3.55–4.59)	2.21 (1.96–2.48)	4.02 (3.53–4.57)	2.20 (1.96–2.47)
Smoking status						
Current smoker	1.34 (1.09–1.65)	0.88 (0.72–1.09)	1.36 (1.11–1.68)	0.89 (0.72–1.10)	1.36 (1.10–1.67)	0.89 (0.72–1.10)
Ex-smoker	1.31 (1.09–1.56)	1.15 (0.90–1.47)	1.28 (1.07–1.53)	1.13 (0.88–1.44)	1.29 (1.08–1.54)	1.12 (0.88–1.43)
Education						
Some college	1.85 (1.45–2.38)	0.96 (0.60–1.52)	1.83 (1.43–2.36)	0.95 (0.60–1.52)	1.83 (1.42–2.35)	0.97 (0.61–1.54)
High school	2.30 (1.84–2.88)	1.26 (0.92–1.73)	2.27 (1.81–2.84)	1.28 (0.93–1.76)	2.24 (1.79–2.81)	1.30 (0.94–1.78)
Middle school	3.65 (2.73–4.87)	1.23 (0.89–1.70)	3.54 (2.64–4.74)	1.26 (0.91–1.74)	3.49 (2.60–4.67)	1.26 (0.91–1.75)
Primary school	4.14 (3.02–5.66)	1.52 (1.10–2.10)	3.90 (2.84–5.37)	1.56 (1.13–2.16)	3.86 (2.80–5.30)	1.56 (1.13–2.16)
No education	1.96 (0.61–6.32)	1.61 (1.13–2.30)	2.01 (0.62–6.43)	1.64 (1.15–2.34)	1.98 (0.61–6.43)	1.65 (1.15–2.35)
Comorbidities						
Hypertension			1.25 (1.05–1.49)	1.25 (1.02–1.53)	1.22 (1.02–1.45)	1.22 (0.99–1.50)
Heart disease			1.56 (1.22–2.00)	1.20 (0.86–1.67)	1.53 (1.19–1.96)	1.18 (0.85–1.64)
Diabetes			1.53 (1.14–2.04)	1.39 (1.01–1.92)	1.46 (1.09–1.95)	1.38 (1.00–1.91)
Stroke			2.17 (1.14–4.13)	1.58 (0.83–3.02)	2.15 (1.13–4.10)	1.56 (0.82–2.99)
Lung cancer			2.87 (0.89–9.30)	1.01 (0.04–28.54)	2.86 (0.89–9.26)	1.03 (0.04–28.37)

Adjustment variables: no fixed effects (model 1); age, sex, education and smoking (model 2); model 2 adjustment + comorbidities (model 3); model 3 adjustment + FVC (model 4). All five models were fit using a multilevel mixed-effects generalised linear model with study site included as random effect to account for within-site clustering. Separate analyses were performed for high-income countries and low- to middle-income countries. Reference values for categorical variables: no CAO, male, never-smoker, university education, no hypertension, no heart disease, no diabetes, no stroke and no lung cancer. n=11 675. Retirees (age limit defined as ⩾65 years) and homemakers/caregivers were excluded from the analysis.

we chose to implement the same reference values for the whole study population. This may allow for possible factors that might have affected the lung function at a national level to become apparent, instead of being lost with the use of different reference equations at each site. Fourth, regarding study limitations, the registration of never-smokers may have been somewhat exaggerated if there were participants who started smoking recently before study inclusion, but who had not yet reached 20 lifetime packs of cigarettes. However, the risk of this would seem small given that the youngest participants included in the study are aged 40 years. Lastly, there might be a bias toward more females responding as unemployed in low- to middle-income sites due to cultural differences where females might not have formal employment, although they attend work and have an informal income. This information bias might make the sex difference in the risk of being unemployed somewhat higher than the actual risk in these sites, but unfortunately it is beyond the potential of our dataset to disentangle this possible female misclassification. Online supplementary table S3 shows that the differences between males and females applied to almost all sites.

The association between CAO and unemployment was significant in overall analyses, but in stratified analyses we observed that the association was probably driven by high-income sites. There may be several reasons for this. First, subjects in low- to middle-income countries may have more prevalent diseases than CAO that render them vulnerable to unemployment. Second, there may be more heterogeneity in low- to middle-income sites than in high-income sites. Our analyses showed consistent results across the high-income sites that seemed to be more homogeneous than the low- to middle-income sites, where CAO was a risk factor for unemployment in some sites and almost a protective factor against unemployment in other sites. The suspicion was further strengthened by crude meta-analysis, showing significant site heterogeneity in the univariate association between CAO and unemployment. However, when other covariates were accounted for, the site heterogeneity lost significance. Third, other factors may be more important than health factors for unemployment risk in low- to middle-income countries. We observed that female sex was an important risk factor for unemployment in these sites, while age and education

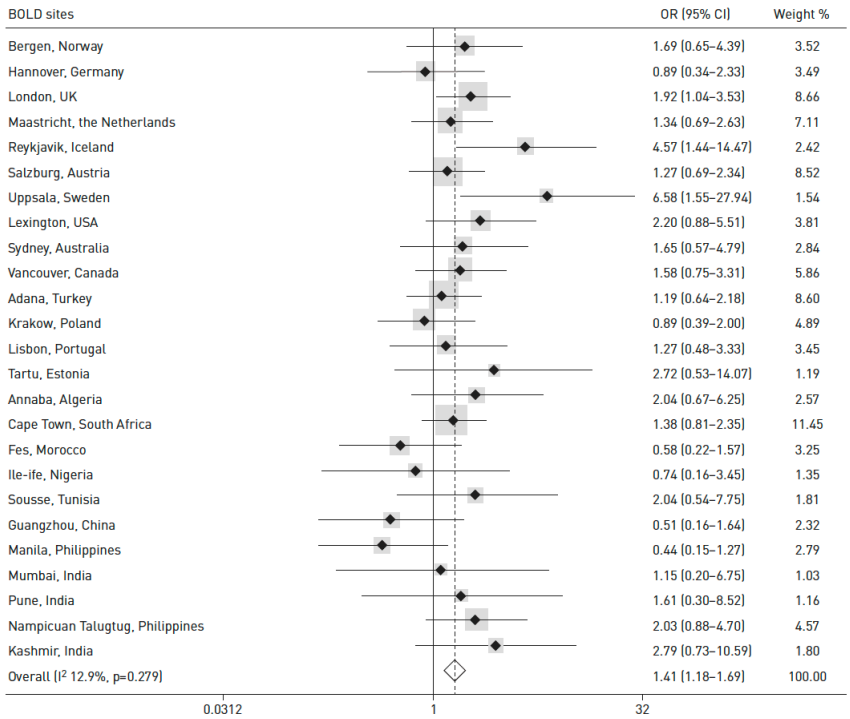


FIGURE 2 Odds ratios (95% CI) for unemployment for lower limit of normal-defined chronic airflow obstruction, adjusted for demographic characteristics, comorbidities and forced vital capacity (FVC). Adjustment variables: sex, age, smoking, education, hypertension, heart disease, diabetes, stroke, lung cancer and FVC. n=11 675, meta-analysis with results across sites and overall. Retirees (age limit defined as 65 years) and homemakers/caregivers excluded. BOLD: Burden of Obstructive Lung Disease study.

were important for the high-income sites. Traditional male/female roles in low- to middle-income countries may affect work-life participation to such a degree that they blur the association between health-related factors and unemployment. Such large sex differences in work participation were illustrated in online supplementary table S3 in the present study. And last, but not least, our results may be an indication of how disease burden act differently in high-*versus* low- to middle-income sites, due to a strictly economic component. In high-income sites those most severely affected are given the possibility to be economically sustained by the corresponding social security systems, while in low- to middle-income sites such alternatives are few or nonexistent. While in high-income sites, the welfare system bears the economic burden of disease, in low- to middle-income sites the people affected both bear the personal and the economic burden of disease.

In conclusion, we have found that work-life participation of subjects with CAO is overall lower than work-life participation of subjects without CAO, and that CAO is associated with unemployment after adjusting for sex, age, smoking, education, comorbidities and even FVC. There was no significant heterogeneity between sites, although stratified analyses showed that CAO may be of greater importance for unemployment in high-income sites. Our study shows the risk of unemployment among people with this prevalent respiratory disease, and illustrates how CAO considerably impacts productivity and social security systems worldwide.

Acknowledgements

We would like to thank all study participants and researchers at all sites for contributing to the successful execution of this study.

Collaborators: Research teams at centres: NanShan Zhong (principal investigator (PI)), Shengming Liu, Jiachun Lu, Pixin Ran, Dali Wang, Jingping Zheng and Yumin Zhou (Guangzhou Institute of Respiratory Diseases, Guangzhou Medical College, Guangzhou, China); Ali Kocabaş (PI), Attila Hancioglu, Ismail Hanta, Sedat Kuleci, Ahmet Sinan Turkyilmaz, Sema Umut and Turgay Unalan (Cukurova University School of Medicine, Department of Chest Diseases, Adana, Turkey); Michael Studnicka (PI), Torkil Dawes, Bernd Lamprecht and Lea Schirhofer (Paracelsus Medical University, Department of Pulmonary Medicine, Salzburg Austria); Eric Bateman (PI), Anamika Jithoo (PI), Desiree Adams, Edward Barnes, Jasper Freeman, Anton Hayes, Sipho Hlengwa, Christine Johannisen, Mariana Koopman, Innocentia Louw, Ina Ludick, Alta Olckers, Johanna Ryck and Janita Storbeck (University of Cape Town Lung Institute, Cape Town, South Africa); Thorarinn Gislason (PI), Bryndis Benedikdtsdottir, Kristin Jörundsdottir, Lovisa Gudmundsdottir, Sigrun Gudmundsdottir and Gunnar Gundmundsson (Landspitali University Hospital, Dept of Allergy, Respiratory Medicine and Sleep, Reykjavik, Iceland); Ewa Nizankowska-Mogilnicka (PI), Jakub Frey, Rafal Harat, Filip Mejza, Pawel Nastalek, Andrzej Pajak, Wojciech Skucha, Andrzej Szczeklik and Magda Twardowska (Division of Pulmonary Diseases, Department of Medicine, Jagiellonian University School of Medicine, Cracow, Poland); Tobias Welte (PI), Isabelle Bodemann, Henning Geldmacher and Alexandra Schweda-Linow (Hannover Medical School, Hannover, Germany); Amund Gulsvik (PI), Tina Endresen and Lene Svendsen (Department of Thoracic Medicine, Institute of Medicine, University of Bergen, Bergen, Norway); Wan C. Tan (PI) and Wen Wang (iCapture Center for Cardiovascular and Pulmonary Research, University of British Columbia, Vancouver, BC, Canada); David M. Mannino (PI), John Cain, Rebecca Copeland, Dana Hazen and Jennifer Methvin (University of Kentucky, Lexington, KY, USA); Renato B. Dantes (PI), Lourdes Amarillo, Lakan U. Berratio, Lenora C. Fernandez, Norberto A. Francisco, Gerard S. Garcia, Teresita S. de Guia, Luisito F. Idolor, Sullian S. Naval, Thessa Reyes, Camilo C. Roa Jr, Ma. Flordeliza Sanchez and Leander P. Simpao (Philippine College of Chest Physicians, Manila, Philippines); Christine Jenkins (PI), Guy Marks (PI), Tessa Bird, Paola Espinel, Kate Hardaker and Brett Toelle (Woolcock Institute of Medical Research, Sydney, Australia), Peter G.J. Burney (PI), Caron Amor, James Potts, Michael Tumilty and Fiona McLean (National Heart and Lung Institute, Imperial College, London, UK); E.F.M. Wouters and G.J. Wesseling (Maastricht University Medical Center, Maastricht, the Netherlands); Cristina Bárbara (PI), Fátima Rodrigues, Hermínia Dias, João Cardoso, João Almeida, Maria João Matos, Paula Simão, Moutinho Santos and Reis Ferreira (Portuguese Society of Pneumology, Lisbon, Portugal); Christer Janson (PI), Inga Sif Olafsdottir, Katarina Nisser, Ulrike Spetz-Nyström, Gunilla Hägg and Gun-Marie Lund (Department of Medical Sciences: Respiratory Medicine and Allergology, Uppsala University, Sweden); Rain Jõgi (PI), Hendrik Laja, Katrin Ulst, Vappu Zobel and Toomas-Julius Lill (Lung Clinic, Tartu University Hospital, Tartu, Estonia); Parvaiz A. Koul (PI), Sajjad Malik, Nissar A. Hakim and Umar Hafiz Khan (Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India); Rohini Chowgule (PI), Vasant Shetye, Jonelle Raphael, Rosel Almeda, Mahesh Tawde, Rafiq Tadvi, Sunil Katkar, Milind Kadam, Rupesh Dhanawade and Umesh Ghurup (Indian Institute of Environmental Medicine, Mumbai, India); Imed Harrabi (PI), Myriam Denguezli, Zouhair Tabka, Hager Daldoul, Zaki Boukheroufa, Firas Chouikha and Wahbi Belhaj Khalifa (Faculté de Médecine, Sousse, Tunisia); Luisito F. Idolor (PI), Teresita S. de Guia, Norberto A. Francisco, Camilo C. Roa, Fernando G. Ayuyao, Cecil Z. Tady, Daniel T. Tan, Sylvia Banal-Yang, Vincent M. Balanag Jr, Maria Teresita N. Reyes and Renato. B. Dantes (Lung Centre of the Philippines, Philippine General Hospital, Nampicuan and Talugtug, Philippines); Sanjay Juvekar (PI), Siddhi Hirve, Somnath Sambhudas, Bharat Chaidhary, Meera Tambe, Savita Pingale, Arati Umap, Archana Umap, Nitin Shelar, Sampada Devchakke, Sharda Chaudhary, Suvarna Bondre, Savita Walke, Ashleshsa Gawhane, Anil Sapkal, Rupali Argade and Vijay Gaikwad (Vadu HDSS, KEM Hospital Research Centre Pune, Pune, India); Sundeep Salvi (PI), Bill Brashier, Jyoti Londhe and Sapna Madas (Chest Research Foundation, Pune, India); Mohamed C. Benjelloun (PI), Chakib Nejjari, Mohamed Elbiaze and Karima El Rhazi (Laboratoire d'épidémiologie, Recherche Clinique et Santé Communautaire, Fès, Morroco); Daniel Obaseki (PI), Gregory Erhabor, Olayemi Awopeju and Olufemi Adewole (Obafemi Awolowo University, Ile-Ife, Nigeria); Mohamed Al Ghobain (PI), Hassan Alorainy (PI), Esam El-Hamad, Mohamed Al Hajjaj, Hashi Ayan, Rowena Dela, Rofel Fanuncio, Elizabeth Doloriel, Imelda Marciano and Lyla Safia Thoracic Society, Riyadh, Saudi Arabia); Talant M. Sooronbaev (PI), Bermet M. Estebesova, Meerim Akmatalieva, Saadat Usenbaeva, Jypara Kydyrova, Eliza Bostonova, Ulan Sheraliev, Nuridin Marajapov, Nurgul Toktogulova, Berik Emilov, Toktogul Azilova, Gulnara Beishekeeva, Nasyikat Dononbaeva and Aijamal Tabyshova (Pulmunology and Allergology Department, National Centre of Cardiology and Internal Medicine, Bishkek, Kyrgyzstan); Kevin Mortimer (PI), Wezzie Nyapigoti, Ernest Mwangoka, Mayamiko Kambwili, Martha Chipeta, Gloria Banda, Suzgo Mkandawire and Justice Banda (Malawi Liverpool Wellcome Trust, Blantyre, Malawi); Asma Elsony (PI), Hana A. Elsadig, Nada Bakery Osman, Bandar Salah Noory, Monjda Awad Mohamed, Hasab Alrasoul Akasha Ahmed Osman, Namarig Moham ed Elhassan, Abdel Muis El Zain, Marwa Mohamed Mohamaden, Suhaiba Khalifa, Mahmoud Elhadi, Mohand Hassan and Dalia Abdelmonam (Epidemiological Laboratory, Khartoum, Sudan); Hasan Hafizi (PI), Anila Aliko, Donika Bardhi, Holta Tafa, Natasha Thanasi, Arian Mezini, Alma Teferici, Dafina Todri, Jolanda Nikolla and Rezarta Kazasi (Tirana University Hospital, Shefqet Ndroqi, Albania); Hamid Hacene Cherkaski (PI), Amira Bengrait, Tabarek Haddad, Ibtissem Zgaoula, Maamar Ghit, Abdelhamid Roubhia, Soumaya Boudra, Feryal Atoui, Randa Yakoubi, Rachid Benali, Abdelghani Bencheikh and Nadia Ait-Khaled (Faculté de Médecine Annaba, SEMEP Elhadjar, Algeria); Akramul Islam (PI), Syed Masud Ahmed (co-PI), Shayla Islam, Qazi Shafayetul Islam, Mesbah-Ul-Haque, Tridib Roy Chowdhury, Sukantha Kumar Chatterjee, Dulal Mia, Shyamal Chandra Das, Mizanur Rahman, Nazrul Islam, Shahaz Uddin, Nurul Islam, Luiza Khatun, Monira Parvin, Abdul Awal Khan and Maidul Islam (James P. Grant School of Public Health, BIGH/BRAC University, Bangladesh); Li-Cher Loh (PI), Abdul Rashid and Siti Sholehah (Penang Medical College, Penang, Malaysia); Herve Lawin (PI), Arsene Kpangon, Karl Kpossou, Gildas Agodokpessi, Paul Ayelo and Benjamin Fayomi (Unit of Teaching and Research in Occupational and Environmental Health, Cotonou, Benin).

Author contributions are as follows. Design, planning and data collection: R. Grønseth, P. Burney and A. Johannessen. Data management and quality control: R. Grønseth, A. Johannessen, M. Erdal and W.M. Vollmer. Statistical analyses: R. Grønseth, A. Johannessen and W.M. Vollmer. Analysis plan: R. Grønseth, A. Johannessen, P. Burney, W.M. Vollmer and M. Erdal. Drafting: R. Grønseth, M. Erdal and A. Johannessen. Revision and approval of drafts: R. Grønseth, M. Erdal, W.C. Tan, D.O. Obaseki, A.F.S. Amaral, T. Gislason, S.K. Juvekar, P.A. Koul, M. Studnicka, S. Salvi, P. Burney,

A.S. Buist, W.M. Vollmer and A. Johannessen. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

References

1 Buist AS, McBurnie MA, Vollmer WM, *et al.* International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007; 370: 741–750.
2 The World Health Organization (WHO). Projections of Mortality and Causes of Death, 2015 and 2030. www.who.int/healthinfo/global_burden_disease/projections/en/ Date last accessed: June 16, 2017. Date last updated: 2013.
3 Janson C, Marks G, Buist S, *et al.* The impact of COPD on health status: findings from the BOLD study. *Eur Respir J* 2013; 42: 1472–1483.
4 Grønseth R, Jansson SA. The economic burden of respiratory diseases: COPD and asthma. *In*: Annesi-Maesano I, Lundbäck B, Viegi G, eds. Respiratory Epidemiology. Eur Respir Monogr 2014; 65: 116–124.
5 Erdal M, Johannessen A, Askildsen JE, *et al.* Productivity losses in chronic obstructive pulmonary disease: a population-based survey. *BMJ Open Respir Res* 2014; 1: e000049.
6 Jansson SA, Backman H, Stenling A, *et al.* Health economic costs of COPD in Sweden by disease severity – has it changed during a ten years period? *Respir Med*. 2013; 107: 1931–1938.
7 Montes de Oca M, Halbert RJ, Talamo C, *et al.* Paid employment in subjects with and without chronic obstructive pulmonary disease in five Latin American cities: the PLATINO study. *Int J Tuberc Lung Dis* 2011; 15: 1259–1264.
8 Buist AS, Vollmer WM, Sullivan SD, *et al.* The Burden of Obstructive Lung Disease Initiative (BOLD): rationale and design. *COPD* 2005; 2: 277–283.
9 Brooks SM. Task group on surveillance for respiratory hazards in the occupational setting. *ATS News* 1982; 8: 12–16.
10 American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152: 1107–1136.
11 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; 159: 179–187.
12 Gnatiuc L, Buist AS, Kato B, *et al.* Gaps in using bronchodilators, inhaled corticosteroids and influenza vaccine among 23 high- and low-income sites. *Int J Tuberc Lung Dis* 2015; 19: 21–30.
13 Ekström M, Schiöler L, Grønseth R, *et al.* Absolute values of lung function explain the sex difference in breathlessness in the general population. *Eur Respir J* 2017; 49: 1602047.
14 Higgins JP, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
15 Menezes AM, Perez-Padilla R, Jardim JR, *et al.* Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005; 366: 1875–1881.
16 Hansen JG, Pedersen L, Overvad K, *et al.* The prevalence of chronic obstructive pulmonary disease among Danes aged 45–84 years: population-based study. *COPD* 2008; 5: 347–352.
17 Adeloye D, Chua S, Lee C, *et al.* Global and regional estimates of COPD prevalence: systematic review and meta-analysis. *J Glob Health* 2015; 5: 020415.
18 Eisner MD, Yelin EH, Trupin L, *et al.* The influence of chronic respiratory conditions on health status and work disability. *Am J Public Health* 2002; 92: 1506–1513.
19 Sin DD, Stafinski T, Ng YC, *et al.* The impact of chronic obstructive pulmonary disease on work loss in the United States. *Am J Respir Crit Care Med* 2002; 165: 704–707.
20 Thornton Snider J, Romley JA, Wong KS, *et al.* The disability burden of COPD. *COPD* 2012; 9: 513–521.
21 Wouters EFM. Economic analysis of the Confronting COPD survey: an overview of results. *Respir Med* 2003; 97: S3–S14.
22 Yelin E, Katz P, Balmes J, *et al.* Work life of persons with asthma, rhinitis, and COPD: a study using a national, population-based sample. *J Occup Med Toxicol* 2006; 1: 2.
23 Lindberg A, Bjerg A, Rönmark E, *et al.* Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking report from the Obstructive Lung Disease in Northern Sweden Studies. *Respir Med* 2006; 100: 264–272.
24 Lamprecht B, Soriano JB, Studnicka M, *et al.* Determinants of underdiagnosis of COPD in national and international surveys. *Chest* 2015; 148: 971–985.
25 Evans C, Crawford B. Patient self-reports in pharmacoeconomic studies. Their use and impact on study validity. *Pharmacoeconomics* 1999; 15: 241–256.
26 Nielsen R, Johannessen A, Schnelle HM, *et al.* Repeatability of health economic data in COPD. *Respir Med* 2008; 102: 1556–1562.
27 Wong MS, Peng F, Zou B, *et al.* Spatially analyzing the inequity of the Hong Kong urban heat island by socio-demographic characteristics. *Int J Environ Res Public Health* 2016; 13: 317.
28 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
29 Burney PG, Hooper RL. The use of ethnically specific norms for ventilatory function in African-American and white populations. *Int J Epidemiol* 2012; 41: 782–790.
30 Hooper R, Burney P. Cross-sectional relation of ethnicity to ventilatory function in a West London population. *Int J Tuberc Lung Dis* 2013; 17: 400–405.

Paper II

Chronic obstructive pulmonary disease

BMJ Open Respiratory Research

Productivity losses in chronic obstructive pulmonary disease: a population-based survey

Marta Erdal,[1] Ane Johannessen,[2] Jan Erik Askildsen,[3] Tomas Eagan,[1,4] Amund Gulsvik,[4] Rune Grønseth[1,4]

To cite: Erdal M, Johannessen A, Askildsen JE, *et al*. Productivity losses in chronic obstructive pulmonary disease: a population-based survey. *BMJ Open Resp Res* 2014;**1**: e000049. doi:10.1136/bmjresp-2014-000049

► Additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjresp-2014-000049)

Received 21 May 2014
Revised 23 September 2014
Accepted 26 October 2014

[1]Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway
[2]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway
[3]Department of Economics, University of Bergen, Bergen, Norway
[4]Department of Clinical Science, University of Bergen, Norway

Correspondence to
Dr Rune (Nielsen) Grønseth; nielsenrune@me.com

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 FEV_1% 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.

KEY MESSAGES

- The societal burden of productivity losses in chronic obstructive pulmonary disease (COPD) is considerable and can, to a large degree, be explained by exacerbations and comorbid diseases.
- Patients with COPD recruited from hospital clinics have much higher productivity losses than Patients with COPD recruited from population-based samples.
- Economic evaluations should not be based on effectiveness studies recruiting patients from hospital or private practice as this will lead to biased results.

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.[1] 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.[2 3] Having COPD affects the productivity of the diseased, often measured as short and long-term absenteeism.[4]

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.[5] 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.[6]

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 postbronchodilation spirometry.

A few studies have estimated productivity losses of COPD in a general population.[4 7–13] Most of these studies did not verify COPD by spirometry[7 8 12 13] or had scarce data on productivity losses.[9–11] 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.[10] 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.[4]

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.[14 15] 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.[16] 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 (FEV_1) to forced vital capacity (FVC) less than 0.7 and an FEV_1 less than 80% of predicted value according to age, sex and height.[17] Postbronchodilator spirometry was performed according to ATS standards.[18] The control subjects had $FEV_1/FVC>0.7$ 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[19]). Comorbidities were evaluated by asking for the presence of conditions listed in the Charlson Comorbidity Index.[20] Modifying the cost-of-illness questionnaire from a comparable Swedish study,[21] 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 (χ^2, 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.[22] 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 coefficient 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 FEV_1% 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 FEV_1% 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 FEV_1% predicted to these two models, the incremental productivity losses associated with COPD status became non-significant and 284.3 (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 FEV_1% 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

	Hospital-recruited COPD cases	Population-recruited COPD cases	Population-recruited controls	Statistic
N	102	53	107	
Male, N (%)	57 (56)	30 (57)	54 (50)	χ^2, p=0.662
Age, mean years (SD)	59 (5.2)	58 (6.2)	53 (6.9)	ANOVA, p<0.001
Smoking status				χ^2, p=0.054
Current smoker, N (%)	41 (40)	31 (58)	57 (53)	
Former smoker, N (%)	61 (60)	22 (42)	50 (47)	
Education, N (%)				χ^2, p<0.001
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 (%)				χ^2, p<0.001
≥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 (%)				χ^2, p<0.001
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	
Mean (SD)	12.6 (30.0)	19.3 (55.4)	15.7 (36.4)	ANOVA, p=0.59
Median (IQR)	0 (5)	0 (3)	1 (14)	Kruskal–Wallis with ties, p=0.05; trend test p=0.03
Days with disability pension during 1 year				
Any disability pension, N (%)	69 (68)	19 (36)	9 (8)	χ^2, p<0.001
Total number	23 322	5344.3	2504	
Mean (SD)	228.6 (170.3)	100.8 (156.3)	23.4 (83.1)	ANOVA, p<0.001
Median (IQR)	365 (365)	0 (256)	0 (0)	Kruskal–Wallis with ties, p<0.001; trend test p<0.001

Continued

Table 1 Continued

	Hospital-recruited COPD cases	Population-recruited COPD cases	Population-recruited controls	Statistic
Days with productivity loss during 1 year				
Total number	24 609.7	6367.8	4180.5	
Zero days of productivity loss, N (%)	8 (8)	20 (38)	44 (41)	χ^2, p<0.001
365 days of productivity loss, N (%)	57 (56)	13 (25)	5 (5)	χ^2, 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.
*Students, unemployed, homemakers.
ANOVA, analysis of variance; COPD, chronic obstructive pulmonary disease; EconCOPD, COPD-related costs; FEV_1, forced expiratory volume in 1 s.

studies have provided estimates of productivity losses. Darkow *et al*[8] 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,[23 24] even though they utilise a considerable amount of healthcare resources.[25] 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.[4] 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*[8] investigated the effect of comorbidities or exacerbations of respiratory symptoms.[4]

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 2 Days of lost productivity in hospital-recruited COPD cases, population-recruited COPD cases and population-recruited control subjects by gender, smoking status and education

	Gender		Smoking status		Education		
	Men	Women	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 FEV_1/FVC<0.7 postbronchodilation and FEV_1 <80% of predicted values.
*p<0.05, Kruskal-Wallis test, adjusted for ties.
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 3 Spearman's r for correlations between days of lost productivity and age, FEV_1% predicted values, comorbidities and exacerbations of respiratory symptoms in hospital-recruited COPD cases, population recruited-COPD cases and population-recruited control subjects

	Age	FEV_1, % of predicted	Number of comorbid conditions	Number of events, exacerbations of respiratory symptoms
Hospital-recruited COPD cases, Spearman's r	r=0.154; p=0.12	**r=−0.390; p<0.001**	**r=0.341; p<0.001**	r=0.071; p=0.478
Population-recruited COPD cases, Spearman's r	r=0.035; p=0.80	r=−0.214; p=0.124	**r=0.28; p=0.039**	r=0.246; p=0.075
Population-recruited controls, Spearman's r	r=0.023; p=0.81	r=−0.136; p=0.163	r=0.156, p=0.108	**r=0.20, p=0.038**

The significance of bold is P<0.05.
COPD, here defined by FEV_1/FVC<0.7 postbronchodilation and FEV_1 <80% of predicted values.
COPD, chronic obstructive pulmonary disease; FEV_1, 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.[26] 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 FEV_1 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 FEV_1 and decreasing productivity losses. Third, participants in the

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

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		
No COPD	Ref	Ref
COPD, FEV_1 <80% of predicted	5.8 (1.4 to 10.1)	330.6 (327.8 to 333.3)
Sex		
Male	Ref	Ref
Female	9.5 (5.7 to 13.3)	8.3 (5.9 to 10.6)
Age, per year	0.06 (−0.24 to 0.37)	0.17 (−0.03 to 0.37)
Smoking habit		
Current smoker	Ref	Ref
Ex-smoker	0.8 (−3.3 to 5.0)	1.0 (−1.5 to 3.4)
Education		
University	Ref	Ref
Secondary	4.23 (−0.3 to 8.8)	5.0 (2.0 to 8.0)
Primary	6.2 (1.0 to 11.5)	25.5 (22.1 to 28.9)
Constant	−4.22 (−20.7 to 12.2)	−10.0 (−20.7 to 0.6)

Results from quantile median regression models.
COPD, here defined by FEV_1/FVC<0.7 postbronchodilation and FEV_1 <80% of predicted values.
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 5 Annual days of lost productivity in a general population and in a hospital population

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		
No COPD	Ref	Ref
COPD, FEV_1 <80% of predicted	0 (−5.2 to 5.2)	312.4 (305.4 to 319.5)
Per added comorbidity	5.0 (2.6 to 7.4)	5.1 (3.2 to 7.1)
Per added exacerbation of respiratory symptoms	6.50 (6.2 to 6.8)	0.7 (0.1 to 1.3)
Sex		
Male	Ref	Ref
Female	7.5 (3.0 to 12.0)	4.8 (−0.6 to 10.3)
Age, per year	0.0 (−0.4 to 0.4)	0.1 (−0.4 to 0.6)
Smoking habit		
Current smoker	Ref	Ref
Ex-smoker	0.0 (−4.7 to 4.7)	1.6 (−4.0 to 7.1)
Education		
University	Ref	Ref
Secondary	6.5 (1.3 to 11.7)	3.9 (−2.9 to 10.8)
Primary	8.5 (2.4 to 14.6)	27.6 (19.9 to 35.4)
Constant	−6.5 (−25.4 to 12.4)	−7.0 (−31.5 to 17.5)

Results from quantile median regression models showing effects of comorbid conditions and exacerbations of respiratory symptoms.
COPD, here defined by $FEV_1/FVC<0.7$ postbronchodilation and FEV_1 <80% of predicted values.
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

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.[27] There might also be issues of selection bias, but the response rates were high,[14] and non-response analyses have only shown that more elderly patients declined participation or were lost to follow-up, and that FEV_1 was associated with mortality.[27] Fourth, as in all studies based on self-reported data, there might be some degree of recall bias. To counter this, interviewers went through extensive training; there were comprehensive written interviewer guidelines and we chose a short recall period of 3 months combined with a prospective study design. Nevertheless, one might imagine that some degree of differential recollection of sick leave and comorbidities might exist, but what the effect would be on the results is more difficult to speculate on. Fifth, when we quantified productivity losses we used the human capital approach (HCA). There are alternative methods of estimating productivity losses, and some authors favour friction cost method (FCM) where the productivity losses are discounted based on the assumption that co-workers and un-employed, and structural changes to some degree compensate for absenteeism.[6] We chose the HCA primarily because we also want to elucidate the burden of disease from the patient's point of view and, furthermore, the FCM might be less suitable in Norway due to very low unemployment rates.[28] 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.[15] 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.[29] Thus, the current study sheds light on the validity of that approach, which approximates the incremental analysis with hospital-based patients with COPD and population-based controls. The considerable productivity loss in hospital-based COPD cases generates a larger potential for saving costs by reducing short-term or long-term disability, and serves as a bias. Thus, decision makers should be aware that this lack of external validity has implications for the credibility of cost-effectiveness analyses that aim to estimate societal costs.

We have shown that in a population-based sample, COPD was associated with an annual excessive productivity 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.

Acknowledgements The authors are indebted to Margrete Klemmetsby, Hege Marie Schnelle, Idunn Riisnes, Jan Egil Romestrand, Erik Helgeland, Jan Schille, Lene Svendsen, Tonje Lauvaasvaag, Heike Wiegmann and Lene Kvamsdal for their contribution in collecting the data for EconCOPD.

Contributors RG, AG, JEA and AJ were responsible for the design, planning and data collection. RG and ME contributed to the data management, quality control and drafting. RG, AJ, TE and ME performed the statistical analyses. All the authors contributed to the analysis plan and revision, and all gave approval of the drafts.

Competing interests RG reports grants from The Norwegian Association of Heart and Lung Patients and EXTRA funds from the Norwegian Foundation for Health and Rehabilitation, during the conduct of the study; grants and personal fees from Boehringer Ingelheim, personal fees from AstraZeneca and personal fees from GlaxoSmithKline, outside the submitted work.

Ethics approval The Regional Committee for Medical and Health Research Ethics in Western Norway (approval REK Vest nr. 252.04).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. The World Health Organization (WHO). *Projections of mortality and causes of death, 2015 and 2030*. http://www.who.int/healthinfo/global_burden_disease/projections/en/ (accessed 26 Feb 2014).
2. Miller JD, Foster T, Boulanger L, *et al*. Direct costs of COPD in the U.S.: an analysis of Medical Expenditure Panel Survey (MEPS) data. *COPD* 2005;2:311–18.
3. Nielsen R, Johannessen A, Benediktsdottir B, *et al*. Present and future costs of COPD in Iceland and Norway: results from the BOLD study. *Eur Respir J* 2009;34:850–7.
4. Jansson SA, Backman H, Stenling A, *et al*. Health economic costs of COPD in Sweden by disease severity—has it changed during a ten years period? *Respir Med* 2013;107:1931–8.
5. Drummond M. Cost-of-illness studies: a major headache? *Pharmacoeconomics* 1992;2:1–4.
6. Drummond MF, O'Brien BJ, Stoddart GL, *et al*. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press, 1997.
7. Allen H, Rogers W, Bunn WB III. Managing the burden of chronic obstructive pulmonary disease on workforce health and productivity: upping a leading employer's game. *J Occup Environ Med* 2012;54:1064–77.
8. Darkow T, Kadlubek PJ, Shah H, *et al*. A retrospective analysis of disability and its related costs among employees with chronic obstructive pulmonary disease. *J Occup Environ Med* 2007;49:22–30.
9. Lou P, Zhu Y, Chen P, *et al*. Vulnerability, beliefs, treatments and economic burden of chronic obstructive pulmonary disease in rural areas in China: a cross-sectional study. *BMC Public Health* 2012;12:287.
10. Montes de Oca M, Halbert RJ, Talamo C, *et al*. Paid employment in subjects with and without chronic obstructive pulmonary disease in five Latin American cities: the PLATINO study. *Int J Tuberc Lung Dis* 2011;15:1259–64, i–iii.
11. Nishimura S, Zaher C. Cost impact of COPD in Japan: opportunities and challenges? *Respirology* 2004;9:466–73.
12. Tinkelman D, Nordyke RJ, Isonaka S, *et al*. The impact of chronic obstructive pulmonary disease on long-term disability costs. *J Manag Care Pharm* 2005;11:25–32.
13. Wouters EF. Economic analysis of the Confronting COPD survey: an overview of results. *Respir Med* 2003;97(Suppl C):S3–14.
14. Nielsen R, Klemmetsby M, Gulsvik A. Economics of COPD: literature review and experiences from field work. *Clin Respir J* 2008;2(Suppl 1):104–10.
15. Nielsen R, Johannessen A, Omenaas ER, *et al*. Excessive costs of COPD in ever-smokers. A longitudinal community study. *Respir Med* 2011;105:485–93.
16. Sorheim IC, Johannessen A, Grydeland TB, *et al*. Case-control studies on risk factors for chronic obstructive pulmonary disease: how does the sampling of the cases and controls affect the results? *Clin Respir J* 2010;4:89–96.
17. Gulsvik A, Tosteson T, Bakke P, *et al*. Expiratory and inspiratory forced vital capacity and one-second forced volume in asymptomatic never-smokers in Norway. *Clin Physiol* 2001;21:648–60.
18. ATS. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995;152:1107–36.
19. Anthonisen NR, Manfreda J, Warren CP, *et al*. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196–204.
20. Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
21. Jansson SA, Andersson F, Borg S, *et al*. Costs of COPD in Sweden according to disease severity. *Chest* 2002;122:1994–2002.
22. Marrie RA, Dawson NV, Garland A. Quantile regression and restricted cubic splines are useful for exploring relationships between continuous variables. *J Clin Epidemiol* 2009;62:511–17.e1.
23. Lindberg A, Bjerg A, Ronmark E, *et al*. Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking report from the obstructive lung disease in Northern Sweden studies. *Respir Med* 2006;100:264–72.
24. Waatevik M, Skorge TD, Omenaas E, *et al*. Increased prevalence of chronic obstructive pulmonary disease in a general population. *Respir Med* 2013;107:1037–45.
25. Jansson SA, Lindberg A, Ericsson A, *et al*. Cost differences for COPD with and without physician-diagnosis. *COPD* 2005;2:427–34.
26. Evans C, Crawford B. Patient self-reports in pharmacoeconomic studies. Their use and impact on study validity. *Pharmacoeconomics* 1999;15:241–56.
27. Nielsen R. Costs of chronic obstructive pulmonary disease in a general population. Methodological aspects and longitudinal perspectives [dissertation]. Bergen: University of Bergen, 2011.
28. Statistics Norway. *Labour force survey, seasonally-adjusted monthly figures*. https://www.ssb.no/en/arbeid-og-lonn/statistikker/akumnd (accessed 26 Feb 2014).
29. Rutten-van Molken MP, Goossens LM. Cost effectiveness of pharmacological maintenance treatment for chronic obstructive pulmonary disease: a review of the evidence and methodological issues. *Pharmacoeconomics* 2012;30:271–302.

Miscellaneous

Correction

Erdal M, Johannessen A, Askildsen JE *et al*. Productivity losses in chronic obstructive pulmonary disease: a population-based survey. *BMJ Open Resp Res* 2014;1:e000049. doi:10.1136/bmjresp-2013-000049

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).

BMJ Open Resp Res 2016;3:e000049corr1. doi:10.1136/bmjresp-2014-000049corr1

Paper III

International Journal of COPD

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Incidence of utilization- and symptom-defined COPD exacerbations in hospital- and population-recruited patients

This article was published in the following Dove Press journal:
International Journal of COPD
2 September 2016
Number of times this article has been viewed

Marta Erdal[1,2]
Ane Johannessen[3]
Tomas Mikal Eagan[1,2]
Per Bakke[2]
Amund Gulsvik[2]
Rune Grønseth[1,2]

[1]Department of Thoracic Medicine, Haukeland University Hospital, [2]Department of Clinical Science, University of Bergen, [3]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

Objectives: The objectives of this study were to estimate the impact of recruitment source and outcome definition on the incidence of acute exacerbations of COPD (AECOPD) and explore possible predictors of AECOPD.

Patients and methods: During a 1-year follow-up, we performed a baseline visit and four telephone interviews of 81 COPD patients and 132 controls recruited from a population-based survey and 205 hospital-recruited COPD patients. Both a definition based on health care utilization and a symptom-based definition of AECOPD were applied. For multivariate analyses, we chose a negative binomial regression model.

Results: COPD patients from the population- and hospital-based samples experienced on average 0.4 utilization-defined and 2.9 symptom-defined versus 1.0 and 5.9 annual exacerbations, respectively. The incidence rate ratios for utilization-defined AECOPD were 2.45 (95% CI 1.22–4.95), 3.43 (95% CI 1.59–7.38), and 5.67 (95% CI 2.58–12.48) with Global Initiative on Obstructive Lung Disease spirometric stages II, III, and IV, respectively. The corresponding incidence rate ratios for the symptom-based definition were 3.08 (95% CI 1.96–4.84), 3.45 (95% CI 1.92–6.18), and 4.00 (95% CI 2.09–7.66). Maintenance therapy (regular long-acting muscarinic antagonists, long-acting beta-2 agonists, inhaled corticosteroids, or theophylline) also increased the risk of AECOPD with both exacerbation definitions (incidence rate ratios 1.65 and 1.73, respectively). The risk of AECOPD was 59%–78% higher in the hospital sample than in the population sample.

Conclusion: If externally valid conclusions are to be made regarding incidence and predictors of AECOPD, studies should be based on general population samples or adjustments should be made on account of a likely higher incidence in other samples. Likewise, the effect of different AECOPD definitions should be taken into consideration.

Keywords: COPD, exacerbations, general population, predictors

Introduction

Acute exacerbations of COPD (AECOPD) are associated with mortality and poorer quality of life, leading to higher consumption of health resources, and a more rapid decline in lung function compared to COPD patients without frequent exacerbations.[1–3] AECOPD pose a great burden to both patients and society.[4]

There is scarce knowledge on the incidence and predictors of COPD exacerbations in COPD patients from the general population. Estimates from previous studies have shown an AECOPD rate per person per year from 0.65 to 1.40.[5–7] These estimates vary by exacerbation definitions. A study comparing health care utilization and symptom-defined AECOPD observed higher incidence using the symptom-based definition.[8] The symptoms defining AECOPD are common, and even healthy individuals

Correspondence: Marta Erdal
Department of Clinical Science, University of Bergen, Postboks 7804, N-5020, Bergen, Norway
Tel +47 4112 6320
Email marta.erdal@uib.no

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/COPD.S108720

experience them at times.[5,9] Hence, if the symptom-based definition is to be used, inclusion of a control group is necessary for adjustment of the baseline burden of these symptoms in the healthy population.

Most previous studies are done on selected populations without a plausible control group.[1,3–6,8,10–13] Nevertheless, studies have indicated that exacerbation risk increases with higher age,[6,7,10–13] a history of previous exacerbations,[5–7,10,13,14] increasing airflow obstruction,[5,6,10–16] inflammatory biomarkers,[13,17–20] gastroesophageal reflux,[16,21,22] depression,[23,24] reduced quality of life,[5,8,13] low body mass index (BMI), or weight loss,[6,8,25] in addition to chronic respiratory symptoms.[7,11,15,26]

Only two previous studies have genuine population-based study samples. The PLATINO study used a symptom-based definition of AECOPD in a general population,[15] but it was retrospective, did not define a control group, and did not report utilization-based exacerbations. Based on the COPDGene sample, Bowler et al[5] reported utilization-defined exacerbations gathered by six-monthly telephone interviews, but they did not include a control group without airflow obstruction. Thus, to our knowledge, there is no study where two exacerbation definitions were applied to the same study population and where a control group was included.

Important treatment-related decisions are currently made based on studies using different definitions of AECOPD and based on samples that are not population based;[3,6,14] thus, the effect of these choices needs to be estimated and the impact on predictors of exacerbations needs to be examined. The aims of this study were to estimate the incidence of AECOPD in the general population with two different exacerbation definitions, compare the results to a hospital-based COPD study sample, and explore predictors of AECOPD in both COPD study samples. We hypothesized that the population sample exacerbated less often than the hospital sample and that the symptom-based exacerbation definition resulted in a higher exacerbation rate compared to the health care utilization-based definition.

Methods

Our data were from the EconCOPD study, a 1-year prospective observational study conducted between March 2005 and August 2006 at Haukeland University Hospital, Bergen, Norway. The study was approved by the Regional Committee for Medical and Health Research Ethics in Western Norway (REK Vest case number 252.04), and all participants provided written informed consent. Details on sampling procedures and data collection have previously been published.[27]

Study population and design

EconCOPD recruited three groups of participants who went through the same study during the same time frame: COPD patients from Haukeland University Hospital's COPD register and COPD cases and control subjects from a general population cohort. The population-based cases and controls were recruited from a follow-up examination of the Hordaland County Respiratory Health Survey in 2003–2004, a random and representative sample of the population in Hordaland County in 1985.[28] COPD patients from the general population sample who had received treatment at the University Hospital were only registered as participants in the population-based sample.

Participants were all current or former smokers of ≥2.5 pack-years and were at least 40 years old. The choice of using 2.5 pack-years as the lower limit for smoking exposure was made to exclude nontobacco-associated COPD cases.[29] COPD was defined as a post-bronchodilator ratio of the forced expiratory volume in 1 second (FEV_1) to the forced vital capacity <0.70 and FEV_1 <80% predicted according to age, sex, and height.[30] Postbronchodilator spirometry was performed according to American Thoracic Society standards.[31] The control subjects had an FEV_1/forced vital capacity ratio >0.70 and FEV_1 >80% predicted. The latter group was included to be able to adjust for a baseline risk of having exacerbation-like symptoms or events in a general population without respiratory disease.

All included participants were interviewed at baseline concerning smoking habits, education and employment status, and comorbidities. They were all clinically assessed by the project physician (RG). At 12 weeks, 24 weeks, 36 weeks, and 52 weeks, a follow-up interview was conducted by telephone, gathering information on productivity losses, health care utilization, and exacerbations of respiratory symptoms. Follow-up by telephone was considered satisfactory as no biological measurements were needed, the interval between interviews was short, and telephone coverage was reliable in the area.[32,33] Information on comorbidities was gathered by asking for conditions listed in the Charlson Comorbidity Index.[34]

Exacerbation definition

We defined a symptom-based AECOPD as an increase in two major symptoms (dyspnea, sputum volume, or sputum color) or one major and one minor symptom (cough, sore throat, nasal secretion, wheezing, or asthenia) for at least two consecutive days (modified Anthonisen criteria).[35,36] A health care utilization-defined exacerbation was defined by use of

antibiotics or corticosteroids due to respiratory disease or by hospitalization due to respiratory disease.

Statistical analyses

To test the distribution of characteristics across participant groups, we used parametric (*t*-test, analysis of variance) or nonparametric (χ^2, Kruskal–Wallis) tests.

The frequency of exacerbations was skewed. Thus, we chose Kruskal–Wallis tests with ties and negative binomial regression for bivariate and multivariate analyses, respectively.[37] For the latter, we first performed bivariate analyses of each possible predictor and included those that were significant with a *P*-value of <0.10 in the final multivariate model. To estimate the effect of sampled population, we pooled the population-based and hospital-recruited participants and adjusted for participant group as well as COPD severity (Global Initiative on Obstructive Lung Disease [GOLD]-defined FEV_1 categories). We estimated regression models both for symptom-defined exacerbations and exacerbations identified by health care utilization. The models included age, sex, smoking status, pack-years, educational level, FEV_1% predicted, number of comorbid conditions, maintenance therapy (defined as regular use of long-acting muscarinic antagonists, long-acting beta-2 agonists, inhaled corticosteroids, or theophylline), influenza vaccination, pneumococcal vaccination, oxygen therapy, and BMI. The incidence rate ratio for each predictor gives their associated relative risk of exacerbation, adjusting for the other predictors.

All analyses were performed using Stata SE 13.1 (StataCorp LP, College Station, TX, USA).

Results

Characteristics

The characteristics and unadjusted exacerbation rates of each study group are shown in Table 1. Sex and smoking status did not vary between the participant groups, but differences were found for age, education, lung function, comorbidities, and being underweight ($P<0.001$). Nearly all hospital-recruited COPD patients received maintenance therapy for their COPD (80%), whereas a significantly lower percentage used maintenance therapy in both the population-based COPD sample and the control group ($P<0.001$). A similar pattern applied to vaccination status.

A population-recruited COPD patient had an average of 0.4 utilization-defined exacerbations per year and 2.9 symptom-defined exacerbations per year. The respective numbers for COPD patients from the hospital register were 1.0 utilization-defined exacerbations per year and 5.9 symptom-defined exacerbations per year, while the participants in the control group had 0.1 and 0.7 exacerbations per year with the respective exacerbation definitions (Table 1). For all three groups, the resulting exacerbation rates were skewed, with a total of 349 (83%) and 264 (63%) participants having zero or one exacerbation per year with the utilization-based and the symptom-based definitions, respectively.

Bivariate analyses

In bivariate analyses, we found that receiving maintenance therapy was associated with a higher exacerbation rate. With the utilization-based definition, increased GOLD stage was related to increased exacerbation rate. We found no consistent pattern for age, sex, education, smoking status, BMI, or vaccination (Tables S1 and S2).

Multivariate analyses

Tables S3 and S4 show the results from the bivariate and multivariate negative binomial regression analyses, including all COPD patients defined by either of the two study samples, and the results are illustrated in Figure 1.

Applying the utilization-based exacerbation definition (Table S3), we found that the incidence rate ratio for COPD exacerbations was significantly higher in the hospital sample compared to the population sample, even after extensive adjustment for potential confounders. There were increasingly higher exacerbation risks with increasing severity of COPD. Female sex and receiving maintenance therapy were also significantly associated with higher risk of exacerbation in the multivariate model. Applying the symptom-based exacerbation definition (Table S4), we found, with three exceptions, the same main predictors as with the utilization-based definition. The exceptions were female sex that was not significantly associated with exacerbation risk, increasing age that was significantly associated with a lower exacerbation risk, and having undergone influenza vaccination that was significantly associated with a lower risk of exacerbation.

Discussion

We have shown that on average, a community-dwelling COPD patient had 0.4 utilization-based exacerbations per year, while COPD patients selected from a hospital register had one exacerbation per year (2.5 times more). The results for the symptom-based definition were 2.9 and 5.9 exacerbations per year (2.0 times more), respectively, for the two groups. In multivariate regression analysis, belonging to the hospital sample corresponded with a 59%–78%

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

Variable	Hospital-recruited COPD cases	Population-recruited COPD cases	Population-recruited controls	*P*-value
n	205	81	132	–
Male, n (%)	123 (60)	53 (65)	69 (52)	0.142
Age (yrs), mean (SD)	67 (9.2)	63 (10.0)	57 (10.6)	<0.001
Smoking status, n (%)				
Current smoker	68 (33)	38 (47)	63 (48)	0.012
Former smoker	137 (67)	43 (53)	69 (52)	–
Pack-years, mean (SD)	32.7 (31.0)	32.3 (35.6)	15.5 (12.3)	<0.001
Educational level, n (%)				
Primary	75 (37)	32 (40)	27 (20)	<0.001
Secondary	100 (49)	30 (37)	63 (48)	–
University	30 (15)	19 (23)	42 (32)	–
FEV_1% predicted, n (%)				
≥80	–	–	132 (100)	<0.001
≥50–<80	103 (50)	69 (85)	–	–
≥30–<50	68 (33)	8 (10)	–	–
<30	34 (17)	4 (5)	–	–
Mean FEV_1% predicted (SD)	47.7 (16.7)	64.9 (14.2)	95.4 (8.8)	<0.001
Median FEV_1% predicted (IQR)	50.4 (26.8)	68.7 (16.7)	94.2 (10.1)	<0.001
Comorbid conditions				
Mean (SD)	1.9 (1.8)	1.2 (1.5)	0.8 (1.0)	<0.001
Median (IQR)	1 (3)	1 (2)	0 (1.5)	<0.001
Resource-defined exacerbations				
Mean (SD)	1.0 (1.2)	0.4 (0.9)	0.1 (0.4)	<0.001
Median (IQR)	1 (2)	0 (0)	0 (0)	<0.001
Symptom-defined exacerbations				
Mean (SD)	5.9 (6.1)	2.9 (6.2)	0.7 (1.5)	<0.001
Median (IQR)	4 (8)	1 (3)	0 (1)	<0.001
Maintenance therapy, n (%)	164 (80)	31 (38)	2 (2)	<0.001
Undergone vaccination, n (%)				
Influenza	146 (71)	28 (35)	15 (11)	<0.001
Pneumococcus	97 (47)	4 (5)	2 (2)	<0.001
Oxygen therapy, n (%)	19 (9)	0	0	<0.001
BMI (m/kg^2), n (%)				
Underweight	14 (7)	3 (4)	1 (1)	0.026
Normal range	80 (39)	30 (37)	58 (44)	0.543
Overweight	111 (54)	48 (59)	73 (55)	0.734

Abbreviations: yrs, years; SD, standard deviation; FEV_1, forced expiratory volume in 1 second; IQR, interquartile range; BMI, body mass index.

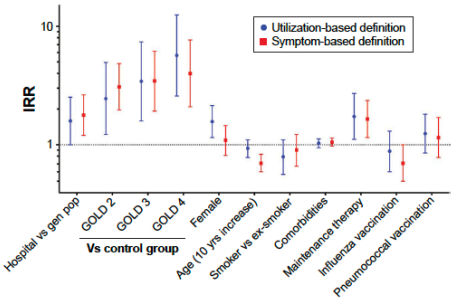


Figure 1 IRRs for COPD exacerbations when using a utilization-based and symptom-based definition.
Note: Results from multivariate negative binomial regression models.
Abbreviations: IRR, incidence rate ratio; gen pop, general population; GOLD, Global Initiative on Obstructive Lung Disease; yrs, years.

increased relative risk of experiencing an exacerbation compared to the population sample. In both groups, there were increasingly higher exacerbation rates with increasing COPD severity. By including control subjects, we have adjusted for the incidence of exacerbation-like events in subjects without respiratory disease.

This confirmed our hypothesis that COPD patients from a hospital register have more exacerbations than COPD patients found in the general population and, furthermore, that using a symptom-based definition results in a higher exacerbation rate than with a utilization-based definition.

The only population-based study that provides comparable data is the PLATINO study. It estimated an exacerbation-rate of 0.58/person/yr with a symptom-based exacerbation definition.[15] The study was retrospective with a longer

recollection period, and the subjects might have been more prone to recall bias. Bowler et al[5] found an exacerbation rate of 0.65/person/yr for COPD patients using a utilization-based definition. They included all GOLD stages, including stage I. The results from the TORCH study, where the sample was from outpatient clinics and a utilization-based definition was applied, showed an annual exacerbation rate between 0.85 and 1.13.[6] In the study performed by Husebø et al,[7] they used a utilization-based definition and found an annual exacerbation rate per person to be 1.40 for their outpatient sample of COPD patients. Our results are in line with the results from the PLATINO study, but extend the previous knowledge on exacerbation rates and give enhanced understanding of the implications of how the selection of study samples and exacerbation definitions affect the results.

The independent predictors of increased exacerbation rates were belonging to the hospital sample, decreasing FEV_1/increasing airflow limitation, female sex, and receiving maintenance therapy for the utilization-based definition. For the symptom definition, the same predictors were significantly associated with higher exacerbation risk apart from female sex, which did not prove significant, and adding increasing age and influenza vaccination, which were associated with a lower risk if present.

It is a novel, but not surprising, finding that hospital samples gave higher exacerbation rates than population-based samples. The participants recruited from the hospital register can be expected to have more severe disease as seen in the newly published study by Müllerova et al[13] and therefore to exacerbate more often. Müllerova et al found a hazard ratio for hospitalization due to AECOPD at 1.12 per 5% drop of FEV_1% predicted, and those who did not exacerbate had a significantly lower BODE (Body mass index, airflow Obstruction, Dyspnea and Exercise capacity) index. We think our analyses demonstrated that studies on AECOPD recruiting from outpatient or hospital samples are biased toward higher exacerbation rates as compared with a general population. This might be not only due to differences in airflow limitation but also due to unidentified factors associated with the so-called frequent exacerbator phenotype.

The observed exacerbation risk associated with decreasing FEV_1 has previously been seen by various authors.[1,3,7,10,11,15,38] As the airflow limitation increases, even minor influences from exacerbation-causing agents may lead to a worsening where a change in medication or even hospitalization is needed.

Whether female sex is truly associated with a greater risk of COPD exacerbations is an ongoing debate. It is not known if females perceive their symptoms differently, seek medical aid more frequently, or are genuinely more prone to exacerbations than men.[39,40] Studies have shown both biological and cultural associations between sex and respiratory disease.[41] We found that female sex was only significantly associated with exacerbation risk with the utilization-based exacerbation definition. One explanation for this finding might be that women have more severe COPD exacerbations requiring medical care, as recently found by Kilic et al.[42] The alternative would be that men seek medical advice less frequently than women (a cultural explanation). In addition, the doctor's response to their patients' symptoms might differ by the patient sex.

In the multivariate analysis, receiving maintenance therapy was independently and significantly associated with elevated risk of exacerbation. We interpret this association as an expression of disease severity. The patients with the most impairing disease are also probably those advised to use medication and hence more prone to exacerbation due to their grade of disease and not due to the medication itself. This view is strengthened by the fact that 80% of the hospital samples used maintenance therapy (the group with the lowest FEV_1 and most comorbidities in our dataset) and as few as 38% of the population-based COPD cases used such medication.

Having undergone influenza vaccination was significantly associated with a lower exacerbation risk. This confirms previous results from large datasets where prophylactic vaccination is proven to reduce acute exacerbations and does not provoke exacerbations when administered.[43] We could not find an association between pneumococcal vaccination and exacerbation risk. We believe this is due to the fact that as few as 47% of the hospital-based COPD patients and 5% of the population-based COPD cases had taken this vaccine, and hence, we had no power to evaluate this effect.[43]

The main strength of our study is that we included both a population-based and a hospital-based group of COPD patients and that the analyses were performed on both groups highlighting the importance of source origin. We included two much-used definitions of an exacerbation and performed our analyses for these definitions separately on the same dataset. To our best knowledge, this has not been done before including a population-based sample. The Hokkaido cohort included several exacerbation definitions, but no population sample nor a control group.[8] Additionally, our project was prospective and had trained health personnel doing telephone interviews at intervals minimizing recall bias.[44] The overall response rate was high (79%), which enabled us to generalize our results to the Norwegian population.

Some possible weaknesses deserve mentioning. First, never-smoking subjects and subjects younger than 40 years were excluded. This was to avoid confounding with asthma patients and to ensure that potential differences between COPD cases and controls could not be explained by distinct smoking history. Second, the number of population-recruited COPD cases was lower than the number of participants from the other two groups and there were fewer with severe and very severe airflow limitation in this group. Yet, even in this group, there was a significantly increasing exacerbation risk with worsening grade of COPD, suggesting sufficient power. Third, participants of the current study were recruited from the city of Bergen, Western Norway, and eleven surrounding municipalities. However, a comparison between national Norwegian survey data for individuals older than 40 years with patients from the original cohort study that EconCOPD recruited from showed no discrepancy.[45] Finally, with our given sample size, the current analyses might have been prone to type II errors. Nevertheless, we were able to demonstrate a clear effect of the main explanatory variable (population) on the outcome.

Our results can help clinicians in identifying groups of patients at high risk of exacerbation who can benefit from better prevention of modifiable predictors and early onset of treatment, which may reduce morbidity and mortality.

We have found that COPD patients from a population sample exacerbate 2.0–2.5 times less frequently than hospital-based COPD patients, depending on the definition used. Apart from belonging to the hospital sample, increasing COPD severity gives significantly higher risk of exacerbation.

Conclusion

Our results, combined with previous findings,[46,47] demonstrate that several studies on exacerbation rate use selected populations[6,14,38] and hence suggest exaggerated rates of exacerbation, which in turn overstate the effect of medication. Thus, our finding implies that any study with AECOPD as the primary outcome should recruit from population-based samples and, if not possible, explicitly state from which population patients are recruited. Furthermore, implications of the chosen definition of AECOPD should be discussed.

Acknowledgments

The authors are indebted to Margrete Klemmetsby, Hege Marie Schnelle, Idunn Riisnes, Jan Egil Romestrand, Erik Helgeland, Jan Schille, Lene Svendsen, Tonje Lauvaasvaag, Heike Wiegmann, and Lene Kvamsdal for their contribution in collecting the data for EconCOPD. ME has recently received a research grant from AstraZeneca. Within the last 3 years, TME has received travel grants from InterMune for the AIR conferences, a grant for the MicroILD study from Boehringer Ingelheim, and speaker fees from AstraZeneca and Boehringer Ingelheim. RG reports grants from the Norwegian Association of Heart and Lung Patients and EXTRA funds from the Norwegian Foundation for Health and Rehabilitation as well as YaraPraxair during the conduct of the study, grants and personal fees from Boehringer Ingelheim, personal fees from AstraZeneca, and personal fees from GlaxoSmithKline outside the submitted work. AG has during the last 3 years participated in the advisory boards of Chesi Pharma AS, Sverige, Novartis Norge AS, Takeda Nycomed Norge, AstraZeneca Norge, and Boehringer Ingelheim, Norway. The Norway GenKOLS study, where he was the principal investigator, was supported by GlaxoSmithKline Research & Development Limited, UK.

Author contributions

Design, planning, and data collection were carried out by RG, AG, and AJ. Data management and quality control was performed by ME and RG. Statistical analyses were carried out by ME, RG, AJ, and TME. Analysis planning was done by RG, AJ, and ME. Drafting was carried out by ME. Revision and approval of drafts were performed by RG, TME, AJ, AG, PB, and ME. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax*. 2002;57(10):847–852.
2. Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. *Chest*. 2000;117(2 suppl):5S–9S.
3. Halpin DM, Decramer M, Celli B, Kesten S, Liu D, Tashkin DP. Exacerbation frequency and course of COPD. *Int J Chron Obstruct Pulmon Dis*. 2012;7:653–661.
4. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157(5 pt 1):1418–1422.
5. Bowler RP, Kim V, Regan E, et al; COPDGene Investigators. Prediction of acute respiratory disease in current and former smokers with and without COPD. *Chest*. 2014;146(4):941–950.
6. Jenkins CR, Celli B, Anderson JA, et al. Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *Eur Respir J*. 2012;39(1):38–45.
7. Husebø GR, Bakke PS, Aanerud M, et al. Predictors of exacerbations in chronic obstructive pulmonary disease – results from the Bergen COPD cohort study. *PLoS One*. 2014;9(10):e109721.

8. Suzuki M, Makita H, Ito YM, et al; Hokkaido COPD Cohort Study Investigators. Clinical features and determinants of COPD exacerbation in the Hokkaido COPD cohort study. *Eur Respir J*. 2014;43(5):1289–1297.
9. Tan WC, Bourbeau J, Hernandez P, et al; CanCOLD Collaborative Research Group. Exacerbation-like respiratory symptoms in individuals without chronic obstructive pulmonary disease: results from a population-based study. *Thorax*. 2014;69(8):709–717.
10. Niewoehner DE, Lokhnygina Y, Rice K, et al. Risk indexes for exacerbations and hospitalizations due to COPD. *Chest*. 2007;131(1):20–28.
11. Miravitlles M, Guerrero T, Mayordomo C, et al. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. The EOLO Study Group. *Respiration*. 2000;67(5):495–501.
12. Beeh KM, Glaab T, Stowasser S, et al. Characterisation of exacerbation risk and exacerbator phenotypes in the POET-COPD trial. *Respir Res*. 2013;14:116.
13. Müllerova H, Maselli DJ, Locantore N, et al; ECLIPSE Investigators. Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. *Chest*. 2015;147(4):999–1007.
14. Hurst JR, Vestbo J, Anzueto A, et al; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363(12):1128–1138.
15. de Oca MM, Tálamo C, Halbert RJ, et al. Frequency of self-reported COPD exacerbation and airflow obstruction in five Latin American cities: the Proyecto Latinoamericano de Investigacion en Obstruccion Pulmonar (PLATINO) study. *Chest*. 2009;136(1):71–78.
16. Ozyilmaz E, Kokturk N, Teksut G, Tatlicioglu T. Unsuspected risk factors of frequent exacerbations requiring hospital admission in chronic obstructive pulmonary disease. *Int J Clin Pract*. 2013;67(7):691–697.
17. Groenewegen KH, Postma DS, Hop WC, et al; COSMIC Study Group. Increased systemic inflammation is a risk factor for COPD exacerbations. *Chest*. 2008;133(2):350–357.
18. Eagan TM, Ueland T, Wagner PD, et al. Systemic inflammatory markers in COPD: results from the Bergen COPD Cohort Study. *Eur Respir J*. 2010;35(3):540–548.
19. Thomsen M, Ingebrigtsen TS, Marott JL, et al. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. *JAMA*. 2013;309(22):2353–2361.
20. Tufvesson E, Ekberg M, Bjermer L. Inflammatory biomarkers in sputum predict COPD exacerbations. *Lung*. 2013;191(4):413–416.
21. Sakae TM, Pizzichini MM, Teixeira PJ, Silva RM, Trevisol DJ, Pizzichini E. Exacerbations of COPD and symptoms of gastroesophageal reflux: a systematic review and meta-analysis. *J Bras Pneumol*. 2013;39(3):259–271.
22. Terada K, Muro S, Sato S, et al. Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation. *Thorax*. 2008;63(11):951–955.
23. Quint JK, Baghai-Ravary R, Donaldson GC, Wedzicha JA. Relationship between depression and exacerbations in COPD. *Eur Respir J*. 2008;32(1):53–60.
24. Laurin C, Moullec G, Bacon SL, Lavoie KL. Impact of anxiety and depression on chronic obstructive pulmonary disease exacerbation risk. *Am J Respir Crit Care Med*. 2012;185(9):918–923.
25. Hallin R, Koivisto-Hursti UK, Lindberg E, Janson C. Nutritional status, dietary energy intake and the risk of exacerbations in patients with chronic obstructive pulmonary disease (COPD). *Respir Med*. 2006;100(3):561–567.
26. Corhay JL, Vincken W, Schlesser M, Bossuyt P, Imschoot J. Chronic bronchitis in COPD patients is associated with increased risk of exacerbations: a cross-sectional multicentre study. *Int J Clin Pract*. 2013;67(12):1294–1301.
27. Nielsen R, Klemmetsby M, Gulsvik A. Economics of COPD: literature review and experiences from field work. *Clin Respir J*. 2008;2(suppl 1):104–110.
28. Johannessen A, Omenaas ER, Bakke PS, Gulsvik A. Implications of reversibility testing on prevalence and risk factors for chronic obstructive pulmonary disease: a community study. *Thorax*. 2005;60(10):842–847.
29. Lamprecht B, McBurnie MA, Vollmer WM, et al; BOLD Collaborative Research Group. COPD in never smokers: results from the population-based burden of obstructive lung disease study. *Chest*. 2011;139(4):752–763.
30. Gulsvik A, Tosteson T, Bakke P, Humerfelt S, Weiss ST, Speizer FE. Expiratory and inspiratory forced vital capacity and one-second forced volume in asymptomatic never-smokers in Norway. *Clin Physiol*. 2001;21(6):648–660.
31. ATS. Standardization of spirometry. *Am J Respir Crit Care Med*. 1995;1995(152):1107–1136.
32. Landis SH, Muellerova H, Mannino DM, et al. Continuing to Confront COPD International Patient Survey: methods, COPD prevalence, and disease burden in 2012–2013. *Int J Chron Obstruct Pulmon Dis*. 2014;9:597–611.
33. Jansson SA, Backman H, Stenling A, Lindberg A, Rönmark E, Lundbäck B. Health economic costs of COPD in Sweden by disease severity – has it changed during a ten years period? *Respir Med*. 2013;107(12):1931–1938.
34. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383.
35. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106(2):196–204.
36. Donaldson GC, Wedzicha JA. COPD exacerbations. 1: epidemiology. *Thorax*. 2006;61(2):164–168.
37. Keene ON, Calverley PM, Jones PW, Vestbo J, Anderson JA. Statistical analysis of exacerbation rates in COPD: TRISTAN and ISOLDE revisited. *Eur Respir J*. 2008;32(1):17–24.
38. Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. *Eur Respir J*. 2004;23(5):698–702.
39. Camp PG, Goring SM. Gender and the diagnosis, management, and surveillance of chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2007;4(8):686–691.
40. Aryal S, Diaz-Guzman E, Mannino DM. COPD and gender differences: an update. *Transl Res*. 2013;162(4):208–218.
41. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. *Thorax*. 1999;54(12):1119–1138.
42. Kilic H, Kokturk N, Sari G, Cakır M. Do females behave differently in COPD exacerbation? *Int J Chron Obstruct Pulmon Dis*. 2015;10:823–830.
43. Varkey JB, Varkey AB, Varkey B. Prophylactic vaccinations in chronic obstructive pulmonary disease: current status. *Curr Opin Pulm Med*. 2009;15(2):90–99.
44. Evans C, Crawford B. Patient self-reports in pharmacoeconomic studies. Their use and impact on study validity. *Pharmacoeconomics*. 1999;15(3):241–256.
45. Nielsen R. Costs of Chronic Obstructive Pulmonary Disease in a General Population. Methodological Aspects and Longitudinal Perspectives (dissertation). Bergen: University of Bergen; 2011.
46. Nielsen R, Johannessen A, Omenaas ER, Bakke PS, Askildsen JE, Gulsvik A. Excessive costs of COPD in ever-smokers. A longitudinal community study. *Respir Med*. 2011;105(3):485–493.
47. Erdal M, Johannessen A, Askildsen JE, Eagan T, Gulsvik A, Grønseth R. Productivity losses in chronic obstructive pulmonary disease: a population-based survey. *BMJ Open Respir Res*. 2014;1(1):e000049.

Supplementary materials

Table S1 Number of events of exacerbations of respiratory symptoms in population-recruited cases by sex, age, smoking status, education, and FEV_1% predicted

Variable	Resource-defined exacerbations	Kwallis with ties, *P*-values	Symptom-defined exacerbations	Kwallis with ties, *P*-values
Age (yrs), mean (SD)		0.0085		0.3965
<50	1.3 (1.5)		2.3 (2.9)	
50–65	0.2 (0.6)		3.9 (7.8)	
>65	0.5 (1.1)		1.5 (2.9)	
Sex, mean (SD)		0.1015		0.0910
Female	0.6 (1.2)		4.0 (5.4)	
Male	0.2 (0.8)		2.3 (6.5)	
Smoking status, mean (SD)		0.2638		0.0939
Current	0.4 (0.7)		3.3 (8.1)	
Ex-smoker	0.4 (1.1)		2.4 (3.9)	
Pack-years, mean (SD)		0.7691		0.0959
<20	0.3 (0.6)		1.8 (3.4)	
20–40	0.4 (1.0)		4.1 (8.2)	
>40	0.5 (1.3)		2.2 (5.0)	
Education, mean (SD)		0.0254		0.8132
Primary	0.2 (0.5)		3.2 (8.3)	
Secondary	0.8 (1.4)		2.9 (4.8)	
University	0.1 (0.2)		2.3 (3.7)	
FEV_1% predicted, mean (SD)		0.0437		0.7227
50–80	0.2 (0.6)		2.9 (6.6)	
30–50	0.8 (1.2)		2.4 (3.2)	
<30	2.3 (2.6)		2.5 (3.1)	
Number of comorbid conditions, mean (SD)		0.4162		0.2860
0	0.3 (0.6)		3.9 (9.2)	
1	0.4 (1.1)		2.0 (3.7)	
2	0.2 (0.4)		1.2 (1.8)	
≥3	0.9 (1.4)		4.3 (5.0)	
Maintenance therapy, mean (SD)		0.0008		0.0008
Yes	0.7 (1.2)		4.6 (8.0)	
No	0.1 (0.2)		1.1 (2.4)	
Influenza vaccination, mean (SD)		0.7422		0.2584
Yes	0.5 (1.2)		2.3 (3.4)	
No	0.3 (0.8)		3.2 (7.3)	
Pneumococcal vaccination, mean (SD)		0.8876		0.0457
Yes	0.3 (0.5)		5.3 (4.3)	
No	0.4 (1.0)		2.7 (6.3)	
BMI, mean (SD)		0.0007		0.1241
Underweight	2.7 (1.5)		8.7 (8.6)	
Normal range	0.3 (0.8)		4.1 (8.9)	
Overweight	0.3 (0.8)		1.7 (2.9)	

Notes: Exacerbations are defined by increased consumption of resources or by symptoms (Anthonisen criteria). The number of events is given as mean (SD).
Abbreviations: FEV_1, forced expiratory volume in 1 second; SD, standard deviation; Kwallis, Kruskal–Wallis; yrs, years; BMI, body mass index.

Table S2 Number of events of exacerbations of respiratory symptoms in hospital-recruited cases by sex, age, smoking status, education, and FEV_1% predicted

Variable	Resource-defined exacerbations	Kwallis with ties, *P*-values	Symptom-defined exacerbations	Kwallis with ties, *P*-values
Age (yrs), mean (SD)		0.3343		0.0370
<50	1.3 (1.3)		6.5 (5.1)	
50–65	1.1 (1.2)		7.1 (6.4)	
>65	0.9 (1.2)		5.0 (5.9)	
Sex, mean (SD)		0.0537		0.0920
Female	1.2 (1.3)		6.4 (6.0)	
Male	0.8 (1.0)		5.5 (6.3)	
Smoking status, mean (SD)		0.0539		0.0489
Current	0.8 (1.0)		4.9 (5.7)	
Ex-smoker	1.1 (1.2)		6.4 (6.3)	
Pack-years, mean (SD)		0.8827		0.8142
<20	1.0 (1.3)		5.8 (6.3)	
20–40	1.0 (1.2)		5.9 (5.9)	
>40	1.0 (1.1)		5.8 (6.5)	
Education, mean (SD)		0.2856		0.3174
Primary	1.0 (1.3)		5.5 (5.9)	
Secondary	1.0 (1.1)		5.9 (6.5)	
University	1.2 (1.1)		6.8 (5.7)	
FEV_1% predicted, mean (SD)		0.001		0.1161
50–80	0.7 (1.1)		5.2 (6.0)	
30–50	1.1 (1.1)		6.2 (5.5)	
<30	1.7 (1.2)		7.1 (7.7)	
Number of comorbid conditions, mean (SD)		0.8516		0.7727
0	0.9 (1.0)		6.0 (6.3)	
1	1.1 (1.1)		5.7 (6.4)	
2	1.1 (1.5)		5.4 (6.3)	
≥3	1.0 (1.1)		6.1 (5.8)	
Maintenance therapy, mean (SD)		0.0006		0.0006
Yes	1.1 (1.2)		6.2 (6.2)	
No	0.3 (0.4)		3.1 (5.5)	
Influenza vaccination, mean (SD)		0.2728		0.7331
Yes	1.0 (1.1)		5.5 (8.6)	
No	0.9 (1.3)		6.7 (7.4)	
Pneumococcal vaccination, mean (SD)		0.0002		0.1613
Yes	1.3 (1.2)		6.0 (5.8)	
No	0.7 (1.1)		5.7 (6.5)	
O_2 therapy, mean (SD)		0.0025		0.5706
Yes	1.8 (1.3)		6.2 (6.0)	
No	0.9 (1.1)		5.8 (6.2)	
BMI, mean (SD)		0.1172		0.8479
Underweight	1.6 (1.3)		5.4 (4.3)	
Normal range	0.9 (1.2)		5.4 (5.7)	
Overweight	1.0 (1.2)		6.2 (6.7)	

Notes: Exacerbations are defined by increased consumption of resources or by symptoms (Anthonisen criteria). The number of events are given as mean (SD).
Abbreviations: FEV_1, forced expiratory volume in 1 second; SD, standard deviation; Kwallis, Kruskal–Wallis; yrs, years; BMI, body mass index.

Table S3 IRRs (95% CI) for AECOPD with a resource-based exacerbation definition

Variable	Bivariate	Multivariate
Population		
General	Ref	Ref
Hospital	4.58 (3.19–6.60)*	1.59 (1.00–2.52)
Sex		
Male	Ref	Ref
Female	1.45 (1.02–2.05)*	1.57 (1.15–2.14)
Age, per 10-year increase	1.18 (1.00–1.39)*	0.93 (0.78–1.10)
Smoking status		
Former	Ref	Ref
Current	0.60 (0.42–0.86)*	0.79 (0.57–1.10)
Pack-years, per increase of 10	1.06 (0.98–1.14)	–
Educational level		
Primary	Ref	–
Secondary	1.06 (0.71–1.57)	–
University	0.75 (0.46–1.25)	–
COPD grade		
Control	Ref	Ref
GOLD II	4.55 (2.57–8.07)*	2.45 (1.22–4.95)
GOLD III	9.03 (5.00–16.31)*	3.43 (1.59–7.38)
GOLD IV	15.52 (8.34–28.86)*	5.67 (2.58–12.48)
Comorbidities, continuous	1.16 (1.04–1.28)*	1.03 (0.94–1.12)
Maintenance therapy		
No	Ref	Ref
Yes	4.95 (3.45–7.09)*	1.73 (1.11–2.71)
Influenza vaccination		
No	Ref	Ref
Yes	2.38 (1.69–3.35)*	0.88 (0.60–1.30)
Pneumococcal vaccination		
No	Ref	Ref
Yes	3.03 (2.17–4.25)*	1.24 (0.85–1.81)
BMI		
Underweight and normal weight	Ref	–
Overweight	0.90 (0.64–1.28)	–

Notes: *$P<0.10$. The results are from negative binomial regression models.
Abbreviations: IRR, incidence rate ratio; CI, confidence interval; AECOPD, acute exacerbations of COPD; Ref, reference; GOLD, Global Initiative on Obstructive Lung Disease; BMI, body mass index.

Table S4 IRRs (95% CI) for AECOPD with a symptom-based exacerbation definition

Variable	Bivariate	Multivariate
Population		
General	Ref	Ref
Hospital	3.81 (2.86–5.07)*	1.78 (1.20–2.64)
Sex		
Male	Ref	Ref
Female	1.15 (0.84–1.57)	1.09 (0.81–1.45)
Age, per 10-year increase	1.02 (0.87–1.21)	0.71 (0.60–0.83)
Smoking status		
Former	Ref	Ref
Current	0.74 (0.54–1.02)	0.90 (0.67–1.22)
Pack-years, per increase of 10	1.07 (0.99–1.16)	–
Educational level		
Primary	Ref	–
Secondary	0.94 (0.66–1.34)	–
University	0.78 (0.51–1.21)	–
COPD grade		
Control	Ref	Ref
GOLD II	5.91 (4.12–8.47)*	3.08 (1.96–4.84)
GOLD III	8.00 (5.23–12.22)*	3.45 (1.92–6.18)
GOLD IV	9.15 (5.45–15.38)*	4.00 (2.09–7.66)
Comorbidities, continuous	1.13 (1.03–1.24)*	1.05 (0.97–1.14)
Maintenance therapy		
No	Ref	Ref
Yes	3.49 (2.62–4.65)*	1.65 (1.15–2.36)
Influenza vaccination		
No	Ref	Ref
Yes	1.65 (1.21–2.25)*	0.71 (0.50–1.00)
Pneumococcal vaccination		
No	Ref	Ref
Yes	2.03 (1.43–2.87)*	1.15 (0.78–1.70)
BMI		
Underweight and normal weight	Ref	–
Overweight	0.96 (0.70–1.31)	–

Notes: *$P<0.10$. The results are from negative binomial regression models.
Abbreviations: IRR, incidence rate ratio; CI, confidence interval; AECOPD, acute exacerbations of COPD; Ref, reference; GOLD, Global Initiative on Obstructive Lung Disease; BMI, body mass index.

Paper IV

Respiratory Medicine: X 2 (2020) 100014

Contents lists available at ScienceDirect

Respiratory Medicine: X

journal homepage: www.journals.elsevier.com/respiratory-medicine-x

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

Marta Erdal [a,*], Ane Johannessen [b], Per Bakke [a], Amund Gulsvik [a], Tomas Mikal Eagan [a,c], Rune Nielsen [a,c]

[a] Department of Clinical Science, University of Bergen, Norway
[b] Centre for International Health, Department of Global Public Health and Primary Care, University of Bergen, Norway
[c] Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

ARTICLE INFO

Keywords:
Chronic obstructive pulmonary disease
Costs
Exacerbations
General population

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

* Corresponding author. Department of Clinical Science, University of Bergen, N-5021, Bergen, Norway.
E-mail address: marta.erdal@uib.no (M. Erdal).

https://doi.org/10.1016/j.yrmex.2020.100014
Received 26 June 2019; Received in revised form 3 February 2020; Accepted 4 February 2020
Available online 14 February 2020

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

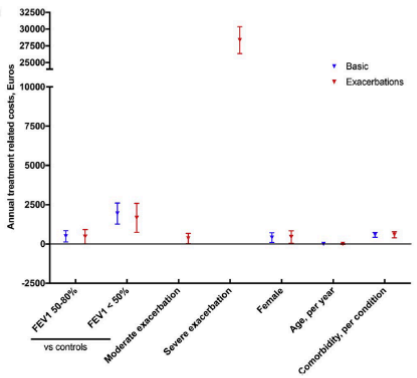


Fig. 1a. Cases and controls, multivariate median regression for treatment-related costs. "Basic" model adjusting for GOLD-stage, gender, age, per comorbid condition added, education, and packyears. "Exacerbations" model adjusting for all as in basic model + both moderate and severe exacerbations. (For 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.

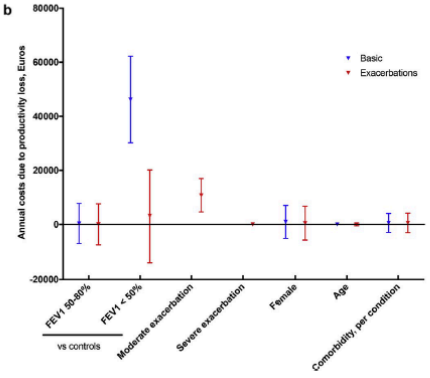


Fig. 1b. Cases and controls, multivariate median regression for productivity losses. "Basic" model adjusting for GOLD-stage, gender, age, per comorbid condition added, education, and packyears. "Exacerbations" model adjusting for all as in basic model + both moderate and severe exacerbations. (For interpretation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

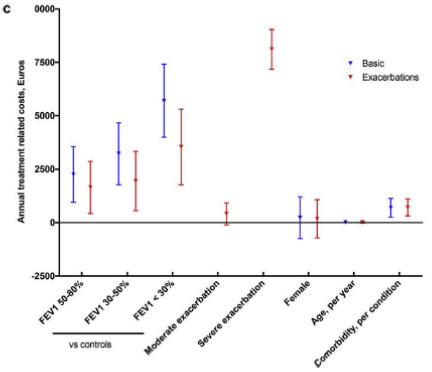


Fig. 1c. Patients and controls, multivariate median regression for treatment-related costs. "Basic" model adjusting for GOLD-stage, gender, age, per comorbid condition added, education, and packyears. "Exacerbations" model adjusting for all as in basic model + both moderate and severe exacerbations.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

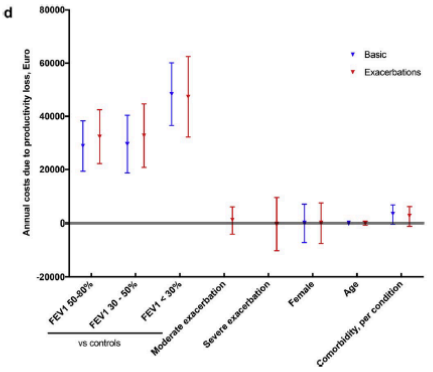


Fig. 1d. Patients and controls, multivariate median regression for productivity losses. "Basic" model adjusting for GOLD-stage, gender, age, per comorbid condition added, education, and packyears. "Exacerbations" model adjusting for all as in basic model + both moderate and severe exacerbations. (For 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.

Acknowledgements

The authors are indebted to Margrete Klemmetsby, Hege Marie Schnelle, Idunn Riisnes, Jan Egil Romestrand, Erik Helgeland, Jan Schille, Lene Svendsen, Tonje Lauvaasvaag, Heike Wiegmann, and Lene Kvamsdal for their contribution in collecting the data for EconCOPD.

We would like to thank the University of Bergen for the scholarship given to M. Erdal, making it possible to write this article as part of her PhD-grade. Further on, the Department of Thoracic Medicine at Haukeland University Hospital deserves our gratitude for supporting our study, both with logistics and skilled personnel.

Finally, we would like to express our thanks to the Norwegian Association of Heart and Lung Patients and EXTRA funds from the Norwegian Foundation for Health and Rehabilitation for the financial support of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrmex.2020.100014.

References

[1] World Health Organization, The Top 10 Causes of Death, 2018.
[2] S.D. Sullivan, S.D. Ramsey, T.A. Lee, The economic burden of COPD, Chest 117 (2 Suppl) (2000) 5S–9S.
[3] G.C. Donaldson, et al., Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease, Thorax 57 (10) (2002) 847–852.
[4] D.M. Halpin, et al., Exacerbation frequency and course of COPD, Int. J. Chronic Obstr. Pulm. Dis. 7 (2012) 653–661.
[5] T.A. Seemungal, et al., Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 157 (5 Pt 1) (1998) 1418–1422.
[6] M. Thomas, et al., COPD exacerbation frequency, pharmacotherapy and resource use: an observational study in UK primary care, COPD 11 (3) (2014) 300–309.
[7] J.A. Wedzicha, et al., Mechanisms and impact of the frequent exacerbator phenotype in chronic obstructive pulmonary disease, BMC Med. 11 (2013) 181.
[8] R. Perez-Padilla, et al., Lung function decline in subjects with and without COPD in a population-based cohort in Latin-America, PloS One 12 (5) (2017), e0177032.
[9] A. Abudagga, et al., Exacerbations among chronic bronchitis patients treated with maintenance medications from a US managed care population: an administrative claims data analysis, Int. J. Chronic Obstr. Pulm. Dis. 8 (2013) 175–185.
[10] M. Miravitlles, et al., Clinical outcomes and cost analysis of exacerbations in chronic obstructive pulmonary disease, Lung 191 (5) (2013) 523–530.
[11] J. Foo, et al., Continuing to confront COPD international patient survey: economic impact of COPD in 12 countries, PloS One 11 (4) (2016), e0152618.
[12] F. Andersson, et al., The costs of exacerbations in chronic obstructive pulmonary disease (COPD), Respir. Med. 96 (9) (2002) 700–708.
[13] C.M. Blanchette, N.J. Gross, P. Altman, Rising costs of COPD and the potential for maintenance therapy to slow the trend, Am Health Drug Benefits 7 (2) (2014) 98–106.
[14] X. Chen, et al., Costs of chronic obstructive pulmonary disease in urban areas of China: a cross-sectional study in four cities, Int. J. Chronic Obstr. Pulm. Dis. 11 (2016) 2625–2632.
[15] A. Ciapponi, et al., The epidemiology and burden of COPD in Latin America and the Caribbean: systematic review and meta-analysis, COPD 11 (3) (2014) 339–350.
[16] A.A. Dalal, et al., Impact of COPD exacerbation frequency on costs for a managed care population, J Manag Care Spec Pharm 21 (7) (2015) 575–583.
[17] A.A. Dalal, et al., Costs of COPD exacerbations in the emergency department and inpatient setting, Respir. Med. 105 (3) (2011) 454–460.
[18] K. Souliotis, et al., The direct and indirect costs of managing chronic obstructive pulmonary disease in Greece, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 1395–1400.
[19] S.A. Jansson, et al., Health economic costs of COPD in Sweden by disease severity–has it changed during a ten years period? Respir. Med. 107 (12) (2013) 1931–1938.
[20] R. Nielsen, et al., Excessive costs of COPD in ever-smokers. A longitudinal community study, Respir. Med. 105 (3) (2011) 485–493.
[21] R. Nielsen, M. Klemmetsby, A. Gulsvik, Economics of COPD: literature review and experiences from field work, Clin. Res. J 2 (Suppl 1) (2008) 104–110.
[22] A. Johannessen, et al., Implications of reversibility testing on prevalence and risk factors for chronic obstructive pulmonary disease: a community study, Thorax 60 (10) (2005) 842–847.

[23] W.C. Tan, et al., Exacerbation-like respiratory symptoms in individuals without chronic obstructive pulmonary disease: results from a population-based study, Thorax 69 (8) (2014) 709–717.
[24] Standardization of Spirometry, Update. American thoracic society, Am. J. Respir. Crit. Care Med. 152 (3) (1994) 1107–1136, 1995.
[25] A. Gulsvik, et al., Expiratory and inspiratory forced vital capacity and one-second forced volume in asymptomatic never-smokers in Norway, Clin. Physiol. 21 (6) (2001) 648–660.
[26] M.E. Charlson, et al., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chron. Dis. 40 (5) (1987) 373–383.
[27] M. Erdal, et al., Productivity losses in chronic obstructive pulmonary disease: a population-based survey, BMJ Open Respir Res 1 (1) (2014), e000049.
[28] R. Tarricone, Cost-of-illness analysis. What room in health economics? Health Pol. 77 (1) (2006) 51–63.
[29] J. Pike, S.D. Grosse, Friction cost estimates of productivity costs in cost-of-illness studies in comparison with human capital estimates: a review, Appl. Health Econ. Health Pol. 16 (6) (2018) 765–778.
[30] Statistics Norway, Arbeidskraftkostnader, 2018.
[31] R.A. Marrie, N.V. Dawson, A. Garland, Quantile regression and restricted cubic splines are useful for exploring relationships between continuous variables, J. Clin. Epidemiol. 62 (5) (2009) 511–517 e1.
[32] S.A. Jansson, et al., Costs of COPD in Sweden according to disease severity, Chest 122 (6) (2002) 1994–2002.
[33] G.M. Owens, Gender differences in health care expenditures, resource utilization, and quality of care, J. Manag. Care Pharm. 14 (3 Suppl) (2008) 2–6.
[34] P. Menn, et al., Direct medical costs of COPD–an excess cost approach based on two population-based studies, Respir. Med. 106 (4) (2012) 540–548.
[35] R. Nielsen, et al., Aspects of healthcare utilisation in self-reported obstructive lung disease, Clin. Res. J 3 (1) (2009) 34–41.
[36] B. Burrows, et al., The course and prognosis of different forms of chronic airways obstruction in a sample from the general population, N. Engl. J. Med. 317 (21) (1987) 1309–1314.
[37] L. Watson, et al., Gender differences in the management and experience of chronic obstructive pulmonary disease, Respir. Med. 98 (12) (2004) 1207–1213.
[38] S.A. Shields, A. Simon, Is awareness of bodily change in emotion related to awareness of other bodily processes? J. Pers. Assess. 57 (1) (1991) 96–109.
[39] H. Kilic, et al., Do females behave differently in COPD exacerbation? Int. J. Chronic Obstr. Pulm. Dis. 10 (2015) 823–830.
[40] D.M. Halpin, et al., Impact and prevention of severe exacerbations of COPD: a review of the evidence, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 2891–2908.
[41] D.E. Niewoehner, et al., Risk indexes for exacerbations and hospitalizations due to COPD, Chest 131 (1) (2007) 20–28.
[42] M. Miravitlles, et al., Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis, The EOLO Study Group. Respiration 67 (5) (2000) 495–501.
[43] J. Garcia-Aymerich, et al., Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. EFRAM study, Am. J. Respir. Crit. Care Med. 164 (6) (2001) 1002–1007.
[44] B.R. Celli, P.J. Barnes, Exacerbations of chronic obstructive pulmonary disease, Eur. Respir. J. 29 (6) (2007) 1224–1238.
[45] M. Maddocks, et al., Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study, Thorax 71 (11) (2016) 988–995.
[46] E. Moore, et al., Pulmonary rehabilitation as a mechanism to reduce hospitalizations for acute exacerbations of COPD: a systematic review and meta-analysis, Chest 150 (4) (2016) 837–859.
[47] G. Currie, et al., Are cost of injury studies useful? Inj. Prev. 6 (3) (2000) 175–176.
[48] D.P. Rice, Cost of illness studies: what is good about them? Inj. Prev. 6 (3) (2000) 177–179.
[49] M. Erdal, et al., Incidence of utilization- and symptom-defined COPD exacerbations in hospital- and population-recruited patients, Int. J. Chronic Obstr. Pulm. Dis. 11 (2016) 2099–2108.
[50] R. Nielsen, Costs of Chronic Obstructive Pulmonary Disease in a General Population. Methodological Aspects and Longitudinal Perspectives (Dissertation), 2011.
[51] O.B.B. M.F. Drummond, G.L. Stoddart, et al., Methods for the Economic Evaluation of Health Care Programmes, Oxford University Press., Oxford, 1997.
[52] **Statistics Norway, Labour force survey, seasonally-adjusted monthly figures (accessed 26 Feb 2014)]; Available from,** https://www.ssb.no/en/arbeid-og-lonn/statistikker/akumnd.
[53] J.S. Skouen, et al., Relative cost-effectiveness of extensive and light multidisciplinary treatment programs versus treatment as usual for patients with chronic low back pain on long-term sick leave: randomized controlled study, Spine (Phila Pa 1976) 27 (9) (2002 May 1) 901–909, discussion 909-10.
[54] W.M. Vollmer, et al., Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study, Eur. Respir. J. 34 (3) (2009) 588–597.

Supplementary material

Paper I

ONLINE SUPPLEMENT MATERIAL
METHODS
The current report includes participants from 26 sites: Guangzhou (China), Manila (Philippines), Mumbai (India) Nampicuan Talugtug (Philippines), Pune (India), Kashmir (India), Annaba (Algeria), Cape-Town (South Africa), Fes (Morocco), Ife (Nigeria), Sousse (Tunisia), Adana (Turkey), Krakow (Poland), Lisbon (Portugal), Tartu (Estonia), Tirana (Albania), Bergen (Norway), Hannover (Germany), London (United Kingdom), Maastricht (The Netherlands), Reykjavik (Iceland), Salzburg (Austria), Uppsala (Sweden), Lexington (USA), Sydney (Australia), and Vancouver (Canada).
Dyspnea was defined using the modified Medical Research Council questions with the following categories: only breathless with strenuous exercise (grade 0); short of breath when hurrying on the level or walking up a slight hill (grade 1); walk slower than people of own age or have to stop for breath when walking on own pace at level ground (grade 2); stop for breath after 100 m or a few minutes on the level (grade 3) and too breathless to leave the house or breathless when dressing or undressing (grade 4).
Multivariable analyses for the pooled data-set were conducted using multilevel mixed-effects generalized linear model (*meglm* in Stata), assuming unstructured covariance matrix with a binomial distribution and a logit link function, with study site included as random effect and with estimations of odds ratios for unemployment.
Comorbidities included in model 3 were hypertension, heart disease, diabetes, stroke and lung cancer. Respiratory symptoms included in model 5 were modified MRC dyspnea, wheezing and dyspnea, and chronic bronchitis symptoms) in addition to the Model 4 covariates.
The individual participant data meta-analyses were performed using *ipdmetan* in Stata, with binomial distribution, logit link function and robust variance estimates. The I2 statistic (range 0-100%) was reported to display the percentage of total variation across sites which was due to true site-by-site heterogeneity. I^2 is defined as 100% x (Q-df)/Q, with Q being the classical measure of heterogeneity (Cochran's Q). I^2 is a simple and easily interpretable expression of site differences. Zero% indicates no observed heterogeneity (beyond what would be expected by
chance), while <25%, 25 - 50% and > 75% is characterised as low, moderate and high heterogeneity, respectively (13).

Table S1. Participation in 26 sites of the BOLD study.

Site	Sampling design	N*	N1*	N2*	Response rate (%)	Cooperation rate (%)
Guangzhou, China	Stratified random sample	602	473	461	87	87
Adana, Turkey	Stratified cluster sample	875	806	806	82	85
Salzburg, Austria	Stratified random sample	1349	1258	1253	65	67
Capetown, South Africa	Cluster sample	896	847	844	63	68
Reykjavik, Iceland	Simple random sample	758	757	757	81	84
Hannover, Germany	Stratified random sample	713	683	680	59	61
Krakow, Poland	Stratified random sample	603	526	526	78	79
Bergen, Norway	Stratified random sample	707	658	658	68	71
Vancouver, Canada	Random digit dialling	856	827	827	26	51
Manila, Philippines	Stratified cluster sample	918	893	892	58	58
Lexington, USA	Random digit dialling	563	508	508	14	27
Sydney, Australia	Stratified random sample	585	541	541	25	33
London, England	Stratified random sample	697	677	675	17	37
Uppsala, Sweden	Stratified random sample	588	547	547	61	63
Mumbai, India	Stratified cluster sample	515	440	439	55	66
Lisbon, Portugal	Stratified cluster sample	745	714	710	10	27
Maastricht, The Netherlands	Stratified random sample	634	590	589	48	55
Nampicuan & Talugtug , Philippines	Stratified cluster sample	991	722	722	86	86
Tartu, Estonia	Stratified random sample	658	615	614	49	70
Pune, India	Simple random sample	1388	849	845	97	97
Sousse, Tunisia	Stratified cluster sample	717	661	660	90	92
Srinagar, India	Stratified cluster sample	953	763	741	86.9	88
Ife, Nigeria	Stratified cluster sample	1148	904	865	76	98
Fes, Morocco	Cluster sample	966	769	760	98	98
Tirana, Albania	Cluster sample	997	941	928	82	84
Annaba, Algeria	Stratified random sample	917	892	862	95	95

*N - Total number of responders: defined as participants who completed the core questionnaire and performed post-bronchodilator FEV1 and/or FVC; N1 – Participants with technically acceptable post-bronchodilator FEV1 and FVC; N2 – included in the current paper: participants with post-bronchodilator FEV1/FVC, age ≥ 40 years and core questionnaire information.
Response rates: total number of responders divided by the total number of eligible individuals contacted. **Cooperation rates**: total number of responders divided by the total number of responders plus active refusers.

Table S2. Prevalence of chronic airflow obstruction (CAO) in %, across 26 sites in the BOLD study, stratified by gender. N = 18 710 subjects.

Site	N	Male	Female
HIGH INCOME			
Bergen, Norway	658	15% (324)	10% (334)
Hannover, Germany	680	10% (347)	8% (333)
Krakow, Poland	526	15% (266)	12% (260)
Lexington, USA	508	14% (206)	16% (302)
Lisbon, Portugal	710	14% (331)	10% (379)
London, UK	675	16% (321)	16% (354)
Maastricht, Netherlands	589	19% (299)	17% (290)
Reykjavik, Iceland	757	9% (403)	13% (354)
Salzburg, Austria	1253	13% (683)	19% (570)
Sydney, Australia	541	8% (265)	14% (276)
Tartu, Estonia	614	9% (309)	5% (305)
Uppsala, Sweden	547	10% (283)	8% (264)
Vancouver, Canada	827	13% (344)	12% (483)
LOW-TO-MIDDLE INCOME			
Adana, Turkey	806	20% (389)	9% (417)
Annaba, Algerie	862	10% (429)	4% (433)
Cape Town, South Africa	844	24% (314)	16% (530)
Fes, Morocco	760	12% (350)	8% (410)
Guangzhou, China	461	9% (229)	6% (232)
Ile-Ife, Nigeria	865	7% (339)	7% (526)
Kashmir, India	741	18% (407)	15% (334)
Manila, Philippines	892	13% (378)	5% (514)
Mumbai, India	439	6% (275)	8% (164)
Nampicuan Talugtug, Philippines	722	16% (356)	12% (366)
Pune, India	845	6% (502)	7% (343)
Sousse, Tunisia	660	8% (309)	2% (351)
Tirana, Albania	928	13% (463)	4% (465)

Denominators for the percentages are shown in parenthesis.

Table S3. Prevalence of job status categories in % among men (blue) and women (red), across 26 sites in the BOLD study. N = 18 710 subjects.

Site	N	Paid work	Homemaker/caregiver	Unemployed	Above retirement age
HIGH INCOME					
Bergen, Norway	658	61.4 / 51.8	0.0 / 1.2	6.8 / 9.6	31.8 / 37.4
Hannover, Germany	680	50.1 / 46.6	0.3 / 10.2	19.0 / 16.2	30.6 / 27.0
Krakow, Poland	526	45.9 / 31.2	1.9 / 11.9	30.1 / 32.7	22.1 / 24.2
Lexington, USA	508	40.3 / 44.7	1.5 / 17.2	35.0 / 26.2	23.2 / 11.9
Lisbon, Portugal	710	29.6 / 30.9	0.6 / 3.2	19.9 / 22.7	49.9 / 43.2
London, UK	675	53.6 / 41.5	0.9 / 11.0	17.1 / 18.4	28.4 / 29.1
Maastricht, Netherlands	589	59.2 / 47.2	0.3 / 23.5	16.7 / 13.5	23.8 / 15.8
Reykjavik, Iceland	757	76.4 / 66.1	6.5 / 18.1	2.5 / 4.8	14.6 / 11.0
Salzburg, Austria	1253	55.0 / 47.0	0.2 / 8.1	18.3 / 21.0	26.5 / 23.9
Sydney, Australia	541	58.1 / 51.1	1.9 / 12.3	10.6 / 12.0	29.4 / 24.6
Tartu, Estonia	614	57.3 / 49.8	1.0 / 3.3	5.5 / 4.6	26.2 / 42.3
Uppsala, Sweden	547	68.2 / 66.3	0.4 / 1.5	5.3 / 8.0	26.1 / 24.2
Vancouver, Canada	827	72.4 / 57.4	0.3 / 8.3	9.0 / 11.2	18.3 / 23.1
LOW-TO-MIDDLE INCOME					
Adana, Turkey	806	60.2 / 15.8	0.8 / 19.7	20.6 / 49.2	18.4 / 15.3
Annaba, Algerie	862	59.9 / 14.8	7.5 / 76.2	19.1 / 6.7	13.5 / 2.3
Cape Town, South Africa	844	50.6 / 34.3	4.5 / 32.5	28.7 / 22.6	16.2 / 10.6
Fes, Morocco	760	45.4 / 8.1	1.4 / 41.0	33.2 / 40.2	20.0 / 10.7
Guangzhou, China	461	51.1 / 28.9	0.0 / 0.4	28.4 / 50.9	20.5 / 19.8
Ile-Ife, Nigeria	865	72.3 / 73.6	0.3 / 0.6	4.4 / 6.8	23.0 / 19.0
Kashmir, India	741	80.8 / 8.7	11.1 / 88.9	1.5 / 0.9	6.6 / 1.5
Manila, Philippines	892	71.7 / 48.6	3.7 / 26.3	11.6 / 14.2	13.0 / 10.9
Mumbai, India	439	78.6 / 5.5	1.8 / 91.5	8.4 / 2.4	11.2 / 0.6
Nampicuan Talugtug, Philippines	722	76.4 / 39.9	4.2 / 35.0	7.3 / 13.9	12.1 / 11.2
Pune, India	845	80.1 / 72.0	0.4 / 20.4	4.6 / 2.0	14.9 / 5.6
Sousse, Tunisia	660	62.1 / 22.8	0.3 / 1.1	25.9 / 65.0	11.7 / 11.1
Tirana, Albania	928	58.1 / 52.5	38.7 / 44.5	2.8 / 2.8	0.4 / 0.2

Table S4: Odds ratios (OR) with 95% confidence intervals (95%CI) for unemployment for LLN-defined CAO and other risk factors, with increasing degree of adjustment (demographic characteristics, comorbidities, FVC, and respiratory symptoms)*. Overall analyses and stratified by country income category. N = 11 675.**

	All sites	High income sites	Low to middle income sites
	Model 5	Model 5	Model 5
Spirometric CAO	1.26 (1.00, 1.57)	1.48 (0.99, 2.21)	1.04 (0.71, 1.52)
FVC, 10 percentage points decrease in %predicted	1.05 (1.01, 1.09)	1.04 (0.99, 1.10)	1.06 (1.00, 1.12)
Female gender	2.01 (1.79, 2.26)	1.35 (1.15, 1.58)	3.14 (2.58, 3.81)
Age, 10yrs increment	2.94 (2.71, 3.19)	4.09 (3.59, 4.65)	2.22 (1.98, 2.50)
Smoking Status			
Current-smoker	0.95 (0.83, 1.10)	1.31 (1.05, 1.62)	0.87 (0.70, 1.08)
Ex-smoker	1.12 (0.97, 1.28)	1.27 (1.06, 1.52)	1.09 (0.85, 1.40)
Education			
Some college	1.47 (1.20, 1.81)	1.77 (1.38, 2.28)	0.96 (0.60, 1.53)
High school	1.97 (1.65, 2.35)	2.20 (1.75, 2.76)	1.27 (0.92, 1.74)
Middle school	2.08 (1.70, 2.55)	3.13 (2.32, 4.21)	1.24 (0.89, 1.71)
Primary school	2.56 (2.08, 3.15)	3.58 (2.59, 4.94)	1.50 (1.08, 2.07)
No education	2.41 (1.84, 3.16)	2.06 (0.64, 6.62)	1.55 (1.08, 2.22)
Hypertension	1.23 (1.08, 1.39)	1.17 (0.98, 1.40)	1.21 (0.98, 1.48)
Heart disease	1.37 (1.13, 1.66)	1.36 (1.06, 1.75)	1.08 (0.77, 1.51)
Diabetes	1.41 (1.15, 1.74)	1.33 (0.99, 1.80)	1.36 (0.98, 1.88)
Stroke	1.81 (1.15, 2.85)	2.07 (1.08, 3.97)	1.64 (0.85, 3.15)
Lung cancer	2.29 (0.77, 6.86)	2.58 (0.76, 8.76)	0.97 (0.04, 24.97)
Dyspnea category			
mMRC grade 1	1.16 (0.99, 1.35)	1.29 (1.03, 1.61)	0.99 (0.78, 1.26)
mMRC grade 2	1.65 (1.34, 2.03)	2.61 (1.89, 3.59)	1.22 (0.91, 1.63)
mMRC grade 3	2.02 (1.52, 2.69)	5.05 (3.01, 8.47)	1.25 (0.86, 1.80)
mMRC grade 4	3.32 (2.14, 5.14)	6.76 (2.74, 16.68)	2.41 (1.41, 4.11)
Wheezing and dyspnea	1.05 (0.86, 1.28)	0.94 (0.71, 1.25)	1.27 (0.94, 1.73)
Chronic bronchitis symptoms	0.99 (0.79, 1.23)	1.03 (0.76, 1.39)	0.81 (0.56, 1.16)

*Adjustment variables: age, gender, education, smoking, comorbidities, FVC and respiratory symptoms.
All analyses were performed using multilevel mixed-effects generalized linear model with study site included as random effect to account for within site clustering. Reference values for categorical variables: no CAO, males, never-smokers, university education, no hypertension, no heart disease, no diabetes, no stroke, no lung cancer, no dyspnea, no wheezing and dyspnea, no chronic bronchitis symptoms.
**Retirees (age limit defined as 65 years old) and homemakers/caregivers were excluded from the analysis.

Paper II

E-table 1: Prevalence of self-reported comorbid conditions and respiratory symptoms in hospital-recruited COPD cases and population-recruited COPD cases and copntrols.

	Hospital-recruited COPD cases	Population-recruited COPD cases	Population-recruited controls
N	102	53	107
Hypertension, N (%)	20 (20%)	14 (26%)	20 (19%)
Myocardial infarction, N (%)	9 (9%)	2 (4%)	1 (1%)
Heart failure, N (%)	5 (5%)	1 (2%)	0
Diabetes, N (%)	6 (6%)	1 (2%)	4 (4%)
Depression, N (%)	11 (11%)	4 (8%)	3 (3%)
Chronic cough, N (%)	56 (55%)	20 (38%)	9 (8%)
Dyspnea, 2 flights of stairs, N (%)	75 (74%)	23 (43%)	13 (12%)
Dyspnea walking on level ground	46 (45%)	6 (11%)	0
Attacks of dyspnea	65 (63%)	17 (32%)	7 (6%)

COPD – chronic obstructive pulmonary disease, here defined by $FEV_1/FVC<0.7$ post-bronchodilation & $FEV_1<80\%$ of predicted values.

E-table 2: Regression coefficients for annual days of lost productivity in a general population and in a hospital population, showing the effect of including FEV1 in percent predicted. Quantile median regression.

Covariate	Coefficient (95% CI). Population-recruited COPD cases and controls (N=160).	Coefficient (95% CI). Hospital recruited COPD patients and population-recruited controls (N=209).
COPD status		
No COPD	Ref	Ref
COPD, FEV1< 80% of predicted	-1.74 (-11.7 to 8.2)	284.3 (267.4 to 301.2)
FEV1 % predicted, 10% increase	-3.3 (-6.0 to -0.6)	-8.0 (-10.9 to -5.0)
Sex		
Male	Ref	Ref
Female	12.3 (7.0 to 17.6)	11.4 (3.4 to 19.4)
Age, pr year	0.25 (-0.2 to 0.7)	0.73 (0.04 to 1.4)
Smoking habit		
Current smoker	Ref	Ref
Ex-smoker	-2.3 (-8.0 to 3.4)	-1.5 (-10.1 to 7.1)
Education		
University	Ref	Ref
Secondary	2.4 (-3.8 to 8.7)	7.0 (-3.2 to 17.2)
Primary	5.25 (-2.1 to 12.6)	18.2 (6.3 to 30.0)
Constant	18.40 (-13.8 to 50.6)	35.1 (-8.5 to 78.6)

95% CI – 95% confidence interval. FEV_1 – forced expiratory volume in 1 second. COPD – chronic obstructive pulmonary disease, here defined by $FEV_1/FVC<0.7$ post-bronchodilation & $FEV_1<80\%$ of predicted values.

E-table 3: Regression coefficients for annual days of lost productivity in a general population and in a hospital population, with adjustments for FEV_1 in percent predicted as well as comorbidities and exacerbations of respiratory symptoms. Quantile median regression.

Covariate	Coefficient (95% CI). Population-recruited COPD cases and controls (N=160).	Coefficient (95% CI). Hospital recruited COPD patients and population-recruited controls (N=209).
COPD status		
No COPD		
COPD, FEV_1< 80% of predicted	-8.1 (-18.6 to 2.3)	204.47 (165.86 to 243.09)
FEV_1 % predicted, 10% increase	-4.40 (-7.26 to -1.55)	-16.70 (-23.33 to -10.07)
Per added comorbidity	3.48 (0.50 to 6.45)	14.78 (8.11 to 21.45)
Per added exacerbation of respiratory symptoms	6.46 (6.04 to 6.88)	-1.28 (-3.17 to 0.61)
Sex		
Male		
Female	10.98 (5.41 to 16.55)	15.44 (-2.84 to 33.71)
Age, pr year	0.01 (-0.44 to 0.46)	1.05 (-0.48 to 2.58)
Smoking habit		
Current smoker		
Ex-smoker	-0.79 (-6.68 to 5.11)	-6.50 (-25.53 to 12.54)
Education		
University	Ref	Ref
Secondary	3.84 (-2.75 to 10.43)	5.43 (-17.99 to 28.86)
Primary	6.84 (-0.83 to 14.51)	18.99 (-7.15 to 45.14)
Constant	35.97 (1.63 to 70.31)	99.09 (-0.57 to 198.74)

95% CI – 95% confidence interval. FEV_1 – forced expiratory volume in 1 second. COPD – chronic obstructive pulmonary disease, here defined by $FEV_1/FVC<0.7$ post-bronchodilation & $FEV_1<80\%$ of predicted values.

Paper III

Supplementary material for Paper III is attached along with the paper, see pages 174 – 176.

Paper IV

Unit costs

Unit costs for hospital admissions were estimated using the accounts of Norwegian hospitals reported to Statistics Norway. Costs per day admitted in hospital are reported for diagnosis reported groups (DRG)-generating activity in hospitals, excluding capital costs.

The source of unit costs for visits to general practitioners (GP), emergency room (ER) visits, specialist physicians and physiotherapists were claims for year 2006 to The Norwegian Labour and Welfare Organisation and The Norwegian Directorate of Labour and Welfare. They administrate all claims for the Norwegian national health insurance. Co-payments were included.

Costs for visits at outpatient clinics were gathered from the Directorate for Health and Social Affairs. The estimates are based on data from 14 hospitals. Capital costs are not included.

Costs for home nursing services were based on estimates from the accounts of the city of Bergen in Western Norway. National estimates were not available. The cost of house aid is covered by the patients themselves, so we have used the participants' information concerning co-payment.

Costs for home oxygen treatment and participation in a pulmonary rehabilitation programme were gathered from the accounts of Haukeland University Hospital in Bergen, Western Norway. Unit costs for physiotherapist-led training for COPD-patients were based on official prices (co-payments and claims) for physiotherapists receiving financial support from the Norwegian government.

Costs per defined daily dose (DDD) of prescription medication were gathered from the Norwegian Pharmacy Association (NPA). NPA provided a list of all approved drugs and the maximum prize set by the Norwegian Medicines Agency. Over-the-counter (OTC) drugs were gathered from Farmastat AS who survey sales numbers from the pharmaceutical industry in Norway. All treatment-related unit costs are given in E-table 1.

E-table 1a: Unit costs as of 1st of January 2006 for the direct costs in the EconCOPD survey. All values are given in 2006 Euros.

Direct costs	Unit	Cost (Euros)
Hospital admission, all causes	1 day	972
GP visits, all causes		
at home	1 visit	91
at office	1 visit	34
ER visits, all causes		
at home	1 visit	82
at office	1 visit	43
Specialists, all causes	1 visit	88
Hospital doctor, all causes	1 visit	221
Physiotherapists	1 visit (or approx 45 mins)	29
Home nursing services	1 hour	51
Home oxygen treatment	1 year	3230
Rehabilitation programme	16 days participation	2362
Rehabilitation, physiotherapist/training – individual sessions	1 hour	35
Rehabilitation, physiotherapist/training – group sessions	1 hour	11
Medication costs	1 Defined Daily Dose (DDD)	Varies from 0.27 to 675.37.

GP – general practitioner

ER – emergency room.

E-table 1b: Unit costs as of 1st of January 2006 for the indirect costs in the EconCOPD survey. All values are given in 2006 Euros.

Indirect costs – days of lost productivity	Unit	Cost (Euros)
Male, age 40 – 50 yrs, primary education	1 day	119.3
Male, age 40 – 50 yrs, secondary education	1 day	136.2
Male, age 40 – 50 yrs, university education	1 day	186.7
Male, age 50 – 60 yrs, primary education	1 day	117.2
Male, age 50 - 60 yrs, secondary education	1 day	135.8
Male, age 50 – 60 yrs, university education	1 day	183.0
Male, age >= 60 yrs, primary education	1 day	112.2
Male, age >= 60 yrs, secondary education	1 day	132.9
Male, age >= 60 yrs, university education	1 day	181.0
Female, age 40 – 50 yrs, primary education	1 day	101.4
Female, age 40 – 50 yrs, secondary education	1 day	111.8
Female, age 40 – 50 yrs, university education	1 day	141.2
Female, age 50 – 60 yrs, primary education	1 day	100.6
Female, age 50 – 60 yrs, secondary education	1 day	109.3
Female, age 50 – 60 yrs, university education	1 day	138.3
Female, age >= 60 yrs, primary education	1 day	99.0
Female, age >= 60 yrs, secondary education	1 day	108.1
Female, age >= 60 yrs, university education	1 day	137.9

e-Table 2; Characteristics of hospital- and population-recruited COPD cases and population-recruited control subjects ≤67 years of age in the EconCOPD-study.

	Hospital-recruited COPD patients	Population-recruited COPD cases	Population-recruited controls	p-value
N	102	53	107	
Male, N (%)	57 (56%)	30 (57%)	54 (50%)	0.662
Age, mean (SD)	59.1 (5.2)	57.6 (6.2)	53.1 (6.9)	0.017
Smoking status				
Current smoker, N (%)	41 (40%)	31 (58%)	57 (53%)	0.054
Former smoker, N (%)	61 (60%)	22 (42%)	50 (47%)	
Packyears, mean (SD)	29.8 (21.8)	28.6 (17.7)	15.9 (11.9)	<0.001
Educational level				
Primary, N (%)	36 (35%)	22 (41%)	20 (19%)	<0.001
Secondary, N (%)	54 (53%)	19 (36%)	48 (45%)	
University, N (%)	12 (12%)	12 (23%)	39 (36%)	
FEV1 % predicted				
≥80%, N (%)			107 (100%)	<0.001
≥50%, <80%, N (%)	51 (50%)	47 (89%)		
≥30%, <50%, N (%)	28 (27%)	4 (7%)		
<30%, N (%)	23 (23%)	2 (4%)		
Mean FEV1 % predicted (SD)	47.0 (18.0)	65.6 (12.6)	94.3 (8.3)	<0.001
Median FEV_1 % predicted (iqr)	50.7 (29.7)	68.4 (13.3)	93.1 (10.1)	<0.001
Comorbid conditions				
Mean (SD)	1.5 (1.7)	1.0 (0.9)	0.7 (1.0)	<0.001
Median (iqr)	1 (2)	1 (1)	0 (1)	0.003
Resource-defined exacerbations				
Moderate, mean (SD)	0.8 (1.0)	0.3 (0.8)	0.1 (0.3)	<0.001
Severe, mean (SD)	0.2 (0.6)	0.0 (0.0)	0.0 (0.0)	<0.001
Maintenance therapy, N (%)	79 (77%)	22 (42%)	1 (1%)	<0.001
Undergone vaccination, N (%)				

Influenza	65 (64%)	11 (21%)	7 (7%)	<0.001
Pneumococcus	42 (41%)	3 (6%)	1 (1%)	<0.001
BMI (m/kg$^{2)}$, N (%)				
Underweight	8 (8%)	3 (6%)	1 (1%)	0.053
Normal range	42 (41%)	20 (38%)	45 (42%)	0.869
Overweight	52 (51%)	30 (57%)	61 (57%)	0.646
Oxygen therapy, N (%)	9 (9%)	0	0	0.001
Employment status at baseline, N (%)				<0.001
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)	

COPD = chronic obstructive pulmonary disease. SD = standard deviation. FEV_1 = forced expiratory volume in one second. Iqr = interquartile range. BMI = body mass index. * Students, unemployed, homemakers.

e-Table 3: Annual utilization of healthcare services and annual productivity loss according to participant status in EconCOPD.

	Hospital-recruited COPD patients	Population-recruited COPD cases	Population-recruited controls	Test for trend
Hospitalisation, all causes				$p<0.001$
Median no. of days (iqr)	0 (5)	0 (0)	0 (0)	
Total no. of days in group	1113	151	177	
Hospitalisation, resp illness				$p<0.001$
Median no. of days (iqr)	0 (0)	0 (0)	0 (0)	
Total no. of days in group	472	1	5	
Health care provider visits				
GP visits				$p<0.001$
Median no. of visits (iqr)	5 (6)	3 (5)	2 (3)	
Total no. of visits in group	1424	404	407	
Emergency room visits				$p<0.001$
Median no. of visits (iqr)	0 (1)	0 (0)	0 (0)	
Total no. of visits in group	176	26	33	
Specialist visits				$p=0.07$
Median no. of visits (iqr)	0 (1)	0 (1)	0 (1)	
Total no. of visits in group	208	74	119	
Outpatient clinic				$p<0.001$
Median no. of visits (iqr)	1 (2)	0 (2)	0 (0)	
Total no. of visits in group	382	86	91	
Physiotherapy				
Median no. of visits (iqr)	0 (0)	0 (0)	0 (0)	$p=0.735$
Total no. of visits in group	444	332	324	
No. of medicines used during the follow-up period[a]				$p<0.001$

Median no. medicines (iqr)	10 (7)	5 (6)	4 (5)	
Total no. of med. in group	2109	531	604	
No. of prescribed medicines for obstructive lung diseases[b]				$p<0.001$
Median no. medicines (iqr)	3 (2)	1 (2)	0 (0)	
Total no. of med. in group	627	108	12	
Pulmonary rehabilitation, training led by physiotherapist				$p<0.001$
Median no. sessions (iqr)	0 (1)	0 (0)	0 (0)	
Total no. of sessions in group	2598	323	22	
Pulmonary rehab progr[c]				$p<0.001$
Median participation (iqr)	0 (0)	0 (0)	0 (0)	
Total no. participants in group	28	3	0	
Long term oxygen treatm[c]				$p<0.001$
Median oxygen use (iqr)	0 (0)	0 (0)	0 (0)	
Total no oxygen users in group	19	0	0	
Home nursing services				$p<0.001$
Median no. of hours (iqr)	0 (0)	0 (0)	0 (0)	
Total no. of hours in group	1753	196	16	
Maid services[c]				$p<0.001$
Median usage (iqr)	0 (0)	0 (0)	0 (0)	
Total no. of participants using	19	3	0	
Productivity loss				
Sick leave				$p<0.001$
Median no. of days (iqr)	0 (0)	0 (0)	0 (7)	
Total no. of days in group	1288	1024	1676	
Disability pension				

Any disability[c], N (%)	69 (34)	19 (23)	9 (7)	
Median no. of days (iqr)	0 (365)	0 (0)	0 (0)	$p<0.001$
Total no. of days in group	23322	5344	2504	
Total productivity loss				
Zero days[c], N (%)	111 (54)	48 (59)	69 (52)	$p=0.042$
365 days[c], N (%)	57 (28)	13 (16)	5 (4)	
Median no. of days (iqr)	0 (365)	0 (91)	0 (15)	
Total no. of days in group	24610	6368	4180	

[a] Includes over-the-counter medication

[b] Inhaled corticosteroids, inhaled anticholinergics, B2-agonists, aminophyllines, leukotriene modifiers

[c] Variable coded as 0/1 for all participants.

Iqr – interquartile range. SD – standard deviation. Trend tests for hospital patients > population-based cases > control subjects.

e-Table 4: Annual productivity loss according to participant status in the EconCOPD study when participants >67 years of age are excluded.

	Hospital-recruited COPD patients	Population-recruited COPD cases	Population-recruited controls	Test for trend
Productivity loss				
Sick leave				*p*=0.029
Median no. of days (iqr)	0 (5)	0 (3)	1 (14)	
Total no. of days in group	1288	1024	1676	
Disability pension				
Any disability[a], N (%)	69 (68%)	19 (36)	9 (8)	
Median no. of days (iqr)	365 (365)	0 (256)	0 (0)	*p*<0.001
Total no. of days in group	23322	5344	2504	
Total productivity loss				
Zero days[a], N (%)	8 (8)	20 (38)	44 (41)	
365 days[a], N (%)	57 (56)	13 (25)	5 (5)	
Median no. of days (iqr)	365 (320)	9 (329.3)	5 (26)	
Total no. of days in group	24610	6368	4180	*p*<0.001

[a] Variable coded as 0/1 for all participants.

Iqr – interquartile range. SD – standard deviation. Trend tests for hospital patients > population-based cases > control subjects.

e-Table 5: Annual unadjusted costs per person by different indirect costs and according to participant status, for participants ≤ 67 years of age. All estimates in 2006 Euros.

(N)	Hospital-recruited COPD patients	Population-recruited COPD cases	Population-recruited controls	Test for trend
Sick leave, mean, median (iqr)	1543, 0 (693)	2369, 0 (415)	2037, 136 (1530)	$p = 0.028$
Disability pension, mean, median (iqr)	26953, 36727 (40959)	11885, 0 (25335)	2583, 0 (0)	$p < 0.001$
Total productivity loss[b], mean, median (iqr)	34195, 44072 (44310)	17105, 1471 (43198)	5544, 798 (4067)	$p < 0.001$

** non-parametric median test.

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.

e-Table 6: Cases and controls, coefficients of multivariate median regression. Basic model adjusting for COPD status, sex, age, per comorbid condition added, education, and packyears. Exacerbations model adjusts for all covariates in the basic models in addition to acute exacerbations of COPD.

	Treatment costs, Basic	Treatment costs, Exacerbations	Production loss, Basic	Production loss, Exacerbations
No COPD	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]
COPD, FEV1 50-79% of predicted	490 [132,849]	462 [7,917]	372 [-7008,7752]	48 [-7525,7621]
COPD, FEV1 < 50% of predicted	1938 [1266,2610]	1664 [740,2589]	46215 [30190,62240]	3163 [-13870,20196]
Male	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]
Female	404 [95,714]	442 [46,839]	940 [-5191,7070]	498 [-5772,6768]
Age, per year	3 [-12,18]	1 [-19,20]	-10 [-490,470]	0 [-510,510]
Per comorbid condition	578 [421,735]	585 [386,783]	534 [-2967,4035]	561 [-3037,4160]
University education	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]
Secondary	52 [-305,409]	-26 [-482,430]	416 [-6829,7661]	441 [-6931,7813]
Primary	20 [-387,427]	24 [-490,538]	372 [-7801,8544]	0 [-8301,8301]
<20 packyears smoking	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]
20-40 packyears smoking	164 [-185,513]	199 [-242,641]	-288 [-7348,6772]	0 [-7178,7178]
>40 packyears smoking	-313 [-807,182]	-444 [-1074,187]	397 [-10364,11157]	333 [-10757,11424]
Moderate exacerbations		351 [24,677]		10796 [4610,16982]
Severe exacerbations		28349 [26327,30370]		0 [0,0]
N	213	213	160	160

95% confidence intervals in brackets. FEV1 – Forced expiratory volume in 1 second. Packyear: The equivalent of smoking 20 cigarettes of tobacco daily for a year.

e-Table 7: Patients and controls, coefficients of multivariate median regression. Basic model adjusting for COPD status, sex, age, per comorbid condition added, education, and packyears. Exacerbations model adjusts for all covariates in the basic models in addition to acute exacerbations of COPD.

	Treatment costs, Basic	Treatment costs, Exacerbations	Production loss, Basic	Production loss, Exacerbations
No COPD	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]
COPD, FEV1 50-79% of predicted	2252 [947,3557]	1646 [428,2863]	28845 [19383,38307]	32354 [22229,42479]
COPD, FEV1 < 50% of predicted	3221 [1773,4669]	1943 [557,3329]	29570 [18759,40382]	32742 [20856,44627]
No COPD	5684 [3955,7412]	3539 [1771,5308]	48338 [36548,60128]	47337 [32177,62497]
Male	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]
Female	232 [-749,1212]	180 [-715,1075]	-0 [-7023,7023]	-0 [-7418,7418]
Age, per year	20 [-29,69]	18 [-27,63]	-0 [-560,560]	0 [-578,578]
Per comorbid condition	694 [254,1134]	714 [317,1111]	3294 [-154,6741]	2558 [-980,6096]
University education	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]
Secondary	21 [-1206,1248]	19 [-1091,1129]	-0 [-8698,8698]	0 [-8939,8939]
Primary	-160 [-1531,1211]	-117 [-1360,1126]	3896 [-5932,13724]	2826 [-7304,12957]
<20 packyears smoking	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]
20-40 packyears smoking	252 [-840,1344]	172 [-815,1158]	-0 [-7634,7634]	0 [-7890,7890]
>40 packyears smoking	26 [-1390,1442]	-514 [-1794,767]	725 [-10128,11579]	830 [-10284,11943]
Moderate exacerbations		407 [-108,922]		1069 [-3882,6020]
Severe exacerbations		8113 [7186,9040]		-338 [-10164,9489]

N	337	337	209	209

95% confidence intervals in brackets. FEV1 – Forced expiratory volume in 1 second. Packyear: The equivalent of smoking 20 cigarettes of tobacco daily for a year.

Appendices

Appendix A – The BOLD core questionnaire.

Country Code _____ _____ _____ 1

City Code _____ _____ 2

ID _____ _____ _____ _____ _____ _____ 3

Date: _____ _____/_____ _____/_____ _____ _____ _____ 4-6
d d m m y y y y

BOLD CORE QUESTIONNAIRE

Demographics

1. *What is the participant's sex?* Male ❑ 1 7
   Female ❑ 2

2. What is your race? _____ ___ ___ ___ 8

3. What is your date of birth? ____ ____/____ ____/____ ____ ____ ____ 9-11
   d d m m y y y y

4. How many years of schooling have you completed? ___ ___ 12

5. What is the highest level of schooling you have completed? 13
   Primary School ❑ 1
   Middle School ❑ 2
   High School ❑ 3
   Some College (Trade/Professional/Community) ❑ 4
   Four-Year College/University ❑ 5
   None ❑ 6
   Unknown ❑ 7

6. What is the highest level of schooling your father has completed? 14
   Primary School ❑ 1
   Middle School ❑ 2
   High School ❑ 3
   Some College (Trade/Professional/Community) ❑ 4
   Four Year College/University ❑ 5
   None ❑ 6
   Unknown ❑ 7

Respiratory Symptoms and Disorders

These questions pertain mainly to your chest. Please answer yes or no if possible. If you are in doubt about whether your answer is yes or no, please answer no.

Cough

7. Do you usually cough when you don't have a cold? Yes ❑ 1 15
   No ❑ 2

   *[If **yes**, continue with Question 7A; If **no**, skip to Question 8]*

   7A. Are there months in which you cough on most days? Yes ❑ 1 16
   No ❑ 2

   *[If **yes**, ask both Questions 7B & 7C; If **no**, skip to Question 8]*

ID _____ _____ _____ _____ _____ _____

7B. Do you cough on most days for as much as three months each year? — Yes ❑ 1 / No ❑ 2 — 17

7C. For how many years have you had this cough? — Less than 2 years ❑ 1 / 2-5 years ❑ 2 / More than 5 years ❑ 3 — 18

Phlegm

8. Do you usually bring up phlegm from your chest, or do you usually have phlegm in your chest that is difficult to bring up when you don't have a cold? — Yes ❑ 1 / No ❑ 2 — 19

*[If **yes**, continue with Question 8A; If **no**, skip to Question 9]*

8A. Are there months in which you have this phlegm on most days? — Yes ❑ 1 / No ❑ 2 — 20

*[If **yes**, ask both Questions 8B & 8C; If **no**, skip to Question 9]*

8B. Do you bring up this phlegm on most days for as much as three months each year? — Yes ❑ 1 / No ❑ 2 — 21

8C. For how many years have you had this phlegm? — Less than 2 years ❑ 1 / 2-5 years ❑ 2 / More than 5 years ❑ 3 — 22

Wheezing/Whistling

9. Have you had wheezing or whistling in your chest at any time in the last 12 months? — Yes ❑ 1 / No ❑ 2 — 23

*[If **yes**, ask both Questions 9A & 9B; If **no**, skip to Question 10]*

9A. In the last 12 months, have you had this wheezing or whistling only when you have a cold? — Yes ❑ 1 / No ❑ 2 — 24

9B. In the last 12 months, have you ever had an attack of wheezing or whistling that has made you feel short of breath? — Yes ❑ 1 / No ❑ 2 — 25

Breathlessness

10. Are you unable to walk due to a condition other than shortness of breath? — Yes ❑ 1 / No ❑ 2 — 26

*[If **yes** to Question 10, please describe this condition on the line below and then skip to Question 12. If **no** or unsure, go directly to Question 11.]*

Nature of condition(s): _____

ID _____ _____ _____ _____ _____ _____

11. Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill? Yes ❑ 1 No ❑ 2 27

*[If **yes**, ask Question 11A through 11D; If **no**, skip to Question 12]*

11A. Do you have to walk slower than people of your age on level ground because of shortness of breath? Yes ❑ 1 No ❑ 2 Does not apply ❑ 3 28

11B. Do you ever have to stop for breath when walking at your own pace on level ground? Yes ❑ 1 No ❑ 2 Does not apply ❑ 3 29

11C. Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on level ground? Yes ❑ 1 No ❑ 2 Does not apply ❑ 3 30

11D. Are you too short of breath to leave the house or short of breath on dressing or undressing? Yes ❑ 1 No ❑ 2 Does not apply ❑ 3 31

12. Has a doctor or other health care provider ever told you that you have emphysema? Yes ❑ 1 No ❑ 2 32

13. Has a doctor or other health care provider ever told you that you have asthma, asthmatic bronchitis or allergic bronchitis? Yes ❑ 1 No ❑ 2 33

*[If **yes**, ask Question 13A. If **no**, skip to Question 14]*

13A. Do you still have asthma, asthmatic bronchitis or allergic bronchitis? Yes ❑ 1 No ❑ 2 34

14. Has a doctor or other health care provider ever told you that you have chronic bronchitis? Yes ❑ 1 No ❑ 2 35

*[If **yes**, ask Question 14A. If **no**, skip to Question 15]*

14A. Do you still have chronic bronchitis? Yes ❑ 1 No ❑ 2 36

15. Has a doctor or other health care provider ever told you that you have chronic obstructive pulmonary disease (COPD)? Yes ❑ 1 No ❑ 2 37

ID ____ ____ ____ ____ ____ ____

Management Section

Now I am going to ask you about medicines that you may be taking to help with your breathing. I want to know about medicines that you take on a regular basis and medicines that you may take only for the relief of symptoms. I would like you to tell me each medicine that you take, what form do you take it in, and how often you take it each month.

16. In the past 12 months, have you taken any medications for your breathing (including medications for nasal congestion)? Yes ❑1 38 No ❑2

If participant does not take any medications to help their breathing, skip to Question 17.

16A.Medication Name (not entered)							
16B.Medication Code	___ ___ ___ 39	___ ___ ___ 44	___ ___ ___ 49	___ ___ ___ 54	___ ___ ___ 59	___ ___ ___ 64	___ ___ ___ 69
16C.Formulation	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7
16D.Is the Medicine taken on most days, or just when you have symptoms, or both? *(If 'most days' ask Q16E, if 'symptoms', ask Q16F, if 'both', ask both Q16E and Q16F.)*	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3
16E. When you are taking the medication, how many days a week do you take it?	_______ days 42	_______ days 47	_______ days 52	_______ days 57	_______ days 62	_______ days 67	_______ days 72
16F. When you are taking the medication, how many months in the past 12 months have you taken it?	0-3 ❑1 43 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 48 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 53 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 58 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 63 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 68 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 73 4-6 ❑2 7-9 ❑3 10-12 ❑4

ID _____ _____ _____ _____ _____ _____

17. Please tell me about any other products that you take or things you do to help your breathing that you have not already told me about.

Medicine or Activity	***Code***
	____ ____ ____ 74
	____ ____ ____ 75
	____ ____ ____ 76
	____ ____ ____ 77

18. Has a doctor or other health care provider ever had you blow into a machine or device in order to measure your lungs (i.e., a spirometer or peakflow meter)? Yes ❑ 1 No ❑ 2 78

*[If **yes**, ask Question 18A. If **no**, skip to Question 19]*

18A. Have you used such a machine in the past 12 months? Yes ❑ 1 No ❑ 2 79

19. Have you ever had a period when you had breathing problems that got so bad that they interfered with your usual daily activities or caused you to miss work? Yes ❑ 1 No ❑ 2 80

*[If **yes**, ask Question 19A. If **no**, skip to Question 20]*

19A. How many such episodes have you had in the past 12 months? ____ ____ ____ episodes 81

[If 19A >0, ask Questions 19B and 19C, else skip to Question 20]

19B. For how many of these episodes did you need to see a doctor or other health care provider in the past 12 months? _____ _____ episodes 82

19C. For how many of these episodes were you hospitalized overnight in the past 12 months? _____ _____ episodes 83

[If 19C >0, ask Question 19C1, else skip to Question 20]

19C1. All together, for how many total days were you hospitalized overnight for breathing problems in the past 12 months? ____ ____ ____ days 84

ID _____ _____ _____ _____ _____ _____

Tobacco Smoking

Now I am going to ask you about smoking. First I will ask about cigarettes.

20. Have you ever smoked cigarettes? Yes ❑ 1 85
No ❑ 2

("Yes," means more than 20 packs of cigarettes in a lifetime or more than 1 cigarette each day for a year)

*[if **yes**, ask questions 20A through 20D; otherwise, skip to Question 22)*

20A. How old were you when you first started regular cigarette smoking? _____ _____ years old 86

20B. If you have stopped smoking, how old were you when you last stopped? (If the participant has not stopped smoking, record as code '99'.) _____ _____ years old 87

20C. On average over the entire time that you smoke(d), about how many cigarettes per day do (did) you smoke? ____ ____ ____ cigarettes/day 88

20D. On average over the entire time that you smoke(d), do (did) you primarily smoke manufactured or hand-rolled cigarettes? Manufactured ❑ 1 89
Hand-rolled ❑ 2

[If the participant currently smokes cigarettes (Question 20B is '99'), then ask Questions 21A and 21B. Otherwise, skip to Question 22]

21A. In the last year, how many times have you quit smoking for at least 24 hours? ____ ____ ____ times 90

21B. Are you seriously thinking of quitting smoking? Yes, within the next 30 days ❑ 1 91
Yes, within the next 6 months ❑ 2
No, not thinking of quitting ❑ 3

22. Have you ever smoked a pipe or cigar? Yes ❑ 1 92
No ❑ 2

*[If **yes**, ask question 22A. If **no**, proceed to question 23]*

22A. Do you now smoke a pipe or cigar? Yes ❑ 1 93
No ❑ 2

*[If the participant has never smoked (answered "no" to **both** Questions 20 and 22), then skip to Question 25. Otherwise, proceed to Question 23]*

23. Has a doctor or other health care provider ever advised you to quit smoking? Yes ❑ 1 94
No ❑ 2

ID _____ _____ _____ _____ _____ _____

*[If **yes**, ask Questions 23A and 23B. If **no**, skip directly to Question 24]*

23A. Have you received medical advice to stop smoking within the past 12 months? — Yes ❑ 1 / No ❑ 2 — 95

23B. Have you used any medication (prescription or non-prescription), including a nicotine patch, to help you stop smoking? — Yes ❑ 1 / No ❑ 2 — 96

*[If **yes**, ask Question 23B1, then ask Question 24. If **no**, skip directly to Question 24]*

23B1. What kind of medication did you take to help you stop smoking? — Nicotine Replacement ❑ 1 / Buproprion ❑ 2 / Tofranil ❑ 3 / Other ❑ 4 — 97

24. Have you used or done anything else to help you stop smoking? — Yes ❑ 1 / No ❑ 2 — 98

*[If **yes**, ask Question 24A, otherwise skip to Question 25]*

24A. What did you do? — Hypnosis ❑ 1 / Acupuncture ❑ 2 / Biofeedback ❑ 3 / Other ❑ 4 — 99

Occupational Exposure

25. Have you ever worked for a year or more in a dusty job? — Yes ❑ 1 / No ❑ 2 — 100

*[If **yes**, ask Question 25A, otherwise skip to Question 26]*

25A. For how many years have you worked in dusty jobs? _____ _____ years — 101

Additional Co-morbidities

26. Has a doctor or other health care provider ever told you that you had:

26A. Heart disease — Yes ❑ 1 / No ❑ 2 — 102

26B. Hypertension — Yes ❑ 1 / No ❑ 2 — 103

26C. Diabetes — Yes ❑ 1 / No ❑ 2 — 104

26D. Lung cancer — Yes ❑ 1 / No ❑ 2 — 105

ID _____ _____ _____ _____ _____ _____

26E. Stroke — Yes ❑ 1 / No ❑ 2 — 106

26F. Tuberculosis — Yes ❑ 1 / No ❑ 2 — 107

*[If **yes** to 26F, then ask 26F1; otherwise, skip to Question 27]*

26F1. Are you currently taking medicine for tuberculosis? — Yes ❑ 1 / No ❑ 2 — 108

*[If **no** to 26F1, then ask 26F2; otherwise, skip to Question 27]*

26F2. Have you ever taken medicine for tuberculosis? — Yes ❑ 1 / No ❑ 2 — 109

27. Have you ever had an operation on your chest in which a part of your lung was removed? — Yes ❑ 1 / No ❑ 2 — 110

28. Were you hospitalized as a child for breathing problems prior to the age of 10? — Yes ❑ 1 / No ❑ 2 / Don't Know ❑ 3 — 111

29. In the past 12 months did you get a flu shot? — Yes ❑ 1 / No ❑ 2 / Don't Know ❑ 3 — 112

30. Has a doctor or other health care professional told your father, mother, sister or brother that they had a diagnosis of emphysema, chronic bronchitis or COPD? — Yes ❑ 1 / No ❑ 2 — 113

31. Has anyone living in your home (besides yourself) smoked a cigarette, pipe or cigar in your home during the past two weeks? — Yes ❑ 1 / No ❑ 2 — 114

SF-12

Interviewer: Read the following set of instructions to the participant.

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. For each of the following questions please indicate which response best describes your answer.

32. In general, would you say your health is: *(Check one.)* — Excellent ❑ 1 / Very good ❑ 2 / Good ❑ 3 / Fair ❑ 4 / Poor ❑ 5 — 115

ID _____ _____ _____ _____ _____ _____

33. The following questions are about activities you might do during a typical day. Does your health ***now*** limit you in these activities? If so, how much?

33A. ***Moderate activities,*** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	Yes, limited a lot ❑ 1 Yes, limited a little ❑ 2 No, not limited at all ❑ 3		116
33B. Climbing ***several*** flights of stairs	Yes, limited a lot ❑ 1 Yes, limited a little ❑ 2 No, not limited at all ❑ 3		117

34. During ***the past 4 weeks***, how much of the time have you had any of the following problems with your work or other regular daily activities ***as a result of your physical health***?

34A. ***Accomplished less*** than you would like	All of the time ❑ 1 Most of the time ❑ 2 Some of the time ❑ 3 A little of the time ❑ 4 None of the time ❑ 5	118
34B. Were limited in the ***kind*** of work or other activities	All of the time ❑ 1 Most of the time ❑ 2 Some of the time ❑ 3 A little of the time ❑ 4 None of the time ❑ 5	119

35. During the ***past 4 weeks,*** how much of the time have you had any of the following problems with your work or other regular daily activities ***as a result of any emotional problems*** (such as feeling depressed or anxious)?

35A. ***Accomplished less*** than you would like	All of the time ❑ 1 Most of the time ❑ 2 Some of the time ❑ 3 A little of the time ❑ 4 None of the time ❑ 5	120
35B. Did work or other activities less ***carefully*** than usual	All of the time ❑ 1 Most of the time ❑ 2 Some of the time ❑ 3 A little of the time ❑ 4 None of the time ❑ 5	121

36. During the ***past 4 weeks***, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all ❑ 1 A little bit ❑ 2 Moderately ❑ 3 Quite a bit ❑ 4 Extremely ❑ 5	122

ID _____ _____ _____ _____ _____ _____

37. These questions are about how you feel and how things have been with you ***during the past 4 weeks***. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the ***past 4 weeks…***

37A. Have you felt calm and peaceful?
All of the time ❑ 1
Most of the time ❑ 2
Some of the time ❑ 3
A little of the time ❑ 4
None of the time ❑ 5 123

37B. Did you have a lot of energy?
All of the time ❑ 1
Most of the time ❑ 2
Some of the time ❑ 3
A little of the time ❑ 4
None of the time ❑ 5 124

37C. Have you felt downhearted and depressed?
All of the time ❑ 1
Most of the time ❑ 2
Some of the time ❑ 3
A little of the time ❑ 4
None of the time ❑ 5 125

38. During ***the past 4 weeks***, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?
All of the time ❑ 1
Most of the time ❑ 2
Some of the time ❑ 3
A little of the time ❑ 4
None of the time ❑ 5 126

Economic Impact

Work Days Lost

The next questions ask about work and about times when you may have missed work due to health problems.

39. At any time in the past 12 months, did you work for income?
Yes ❑ 1
No ❑ 2 127

*[**If no**, continue with Question 39A; **if yes**, skip to Question 40]*

39A. During the past 12 months, did you not work for income mainly due to breathing problems?
Yes ❑ 1
No ❑ 2 128

39B. During the past 12 months, did you not work for income because you were a full-time homemaker or caregiver?
Yes ❑ 1
No ❑ 2 129

*[**If yes**, continue with Question 39C, **if no**, skip to Question 44]*

ID _____ _____ _____ _____ _____ _____

39C. During the past 12 months, did health problems stop you from performing your usual homemaking/caregiving tasks? Yes ❑ 1 No ❑ 2 130

*[If **yes**, continue with Questions 39D & 39E, if **no**, skip to Question 44]*

39D. During the past 12 months, how many **total days** were you unable to perform your homemaking/caregiving tasks due to your health problems? ____ ____ ____ days 131

39E. During the past 12 months, how many **total days** were you unable to perform your homemaking/caregiving tasks specifically due to breathing problems? ____ ____ ____ days 132

[Please skip to question 44]

40. During how many of the past 12 months did you work for income? _____ _____ months 133

41. During the months that you worked, how many days per week did you work for income? ____ days 134

42. What is the usual number of hours per day you work for income? _____ _____ hours 135

43. During the past 12 months, did health problems stop you from working for income? Yes ❑ 1 No ❑ 2 136

*[If **yes**, continue with Questions 43A & 43B, if **no**, skip to Question 44]*

43A. During the past 12 months, how many **total days** were you unable to work for income due to your health problems? ____ ____ ____ days 137

43B. During the past 12 months, how many **total days** were you unable to work for income specifically due to breathing problems? ____ ____ ____ days 138

Non-Work Activities Missed

The next questions ask about time when you may have missed your normal activities (such as going shopping, visiting friends/relatives, going to church, or other activities) because of health problems.

44. During the past 12 months, did health problems prevent you from participating in one or more non- work related activities? Yes ❑ 1 No ❑ 2 139

*[If **yes**, answer Questions 44A & 44B, if **no**, skip to COMPLETED BY at the end of the questionnaire.]*

ID _____ _____ _____ _____ _____ _____

44A. During the past 12 months, how many **total days** did you not participate in non-work related activities due to your health problems? ____ ____ ____ days 140

44B. During the past 12 months, how many **total days** did you not participate in non-work related activities specifically due to breathing problems? ____ ____ ____ days 141

Completed By: ____ ____ ____ ____ 142

Appendix B – EconCOPD invitation letter / consent form.

HELSE VEST
HELSE BERGEN HF
Haukeland Universitetssykehus

PROSJEKT økokols
Seksjon for Lungemedisin
Institutt for Indremedisin
Universitetet i Bergen
Telefon: 55973079, 99 44 91 29
Email: rune.nielsen@med.uib.no

Invitation to participate/consen in a study on the quality of life, exacerbations and health economics of chronic obstructive pulmonary disease (EconCOPD).

You recently paricipated in the GenKOLS survey, aiming to provide insights concerning the impact of inheritance and genes on the development of COPD.

There is a lack of knowledge on the economic consequences of COPD and exacerbations of COPD, for individual patients and the society The obectives of the EconCOPD study is to estimate costs of COPD to ensure that resources are spent in the best possible manner. To be able to compare, we also need information concerning healthcare utilization in individuals without COPD.

We would like to invite you to participate in a survey of your symptoms, your quality of life and your use of health care services.

As a part of the survey you will first be interviewed by the project physician and his co-workers at the hospital. You will thereafter be contacted, by telephone, each third month to register symptoms, drug use, and use of health care. In addition we would like you to fill in a diary to ease the recollection of the requested information. The study will last 12 months.

To reduce the extent of the interviews we also would like to gather information regarding use of health and social services from the registers of the Social Security Administration, the Norwegian Prescription Database, information from your General Practitioner and other physicians, use of healthcare from the hospitals and results from your participation in the GenKOLS study. We also would like to gather information regarding your income from Statistics Norway, your drug use from the pharmacies in Bergen and your sick leave from your employer.

This investigation has been funded by grants from The Norwegian Association of Heart and Lung Patients through EXTRA funds from the Norwegian Foundation for Health and Rehabilitation. The project has been reported to The Norwegian Social Science Data Services. Data from the Social Security Administration, the Norwegian Prescription Database, the Income Register at Statistics Norway, your GP, other physician, hospital records, the GenKOLS survey, pharmacies in Bergen or employer will not be gathered until we are permitted by The Data Inspectorate. The study has been submitted to the Regional Committee for Medical Research Ethics.

All data will be treated confidential according to the law of person-registers. When the data are analysed your personal identification number will be replaced with a code. Only the undersigned are able to connect this code to your identity. The information will kept in an unidentifiable maaner until 31.12.2025. We intend to carry through one or more follow-up studies within that time. However, follow-up studies will not be initiated unless necessary permits have been acquired.

It is voluntary to participate, and at any point of time you can withdraw from the study without having to justify this, and without any implications for your relationship to Haukeland University Hospital. If requested, your entitled to read through all recorded information concerning yourself.

Bergen, 28th of March 2005

Amund Gulsvik
Principal Investigator/Professor/Consulting Physician

Rune Nielsen
Project physician/research fellow

HELSE VEST

HELSE BERGEN HF
Haukeland Universitetssykehus

PROSJEKT økokols
Seksjon for Lungemedisin
Institutt for Indremedisin
Universitetet i Bergen
Telefon: 55973079, 99 44 91 29
Email: rune.nielsen@med.uib.no

To record the above mentioned information we need your consent to participate in this study

I have received and read this information. I have had the chance to raise questions and I am aware that I can withdraw my consent at any time without explaining why. I hereby consent to participating in this study, and that information is registered in a research database.

I consent to my results, after approval from the Data Inspectorate, can be merged with information from records of the Social Security Administration, the Norwegian Prescription Database, my General Practitioner and other physicians, hospital records, results from the GenKOLS study and my employer, the Income Register and pharmacies in Bergen. Whene these data are merged, my name and personal identification number is removed.

Study number:……

Name	Participant signature
……..……..	……..……
Date of consent	Phone
……	……

Preferred time of contact……

Appendix C – EconCOPD questionnaires (The Norwegian Cost of COPD Questionnaire-baseline (NCCQ-b), and The Norwegian Cost of COPD Questionnaire-follow-up (NCCQ-f)).

HELSE VEST
HELSE BERGEN HF
Haukeland University Hospital

PROJECT EconCOPD
Department of Thoracic Medicine
Institute of Medicine
University of Bergen
Telephone: 55 97 30 79, 99 44 91 29
Email: rune.nielsen@med.uib.no

Questionnaire for baseline interview

STICKER

Bold text indicates fill and skip-pattern
Text in italics are ment for the interviewer.
Underlining indicates words to be emphasized during the interview.

Before the interview start you should have:

1. A calculator
2. A calendar of both year 2004 and 2005
3. Pencils and notepad
4. Participants' files – address details and check lists
5. Drug codes
6. Drug sales lists

☐ Controlled by coworker (**k.1**): ⌊_⌊_⌋ (code) (**k.2**) Date: ⌊_⌊_⌊_⌊_⌊_⌊_⌋ (**k.3.**)

0. Participant tracking

0.1. Participant ID-number: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

0.2. Date of examination at outpatient clinic: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋ **0.3.** Interviewer: ⌊_⌋⌊_⌋

0.4. Appointment regarding telephone interview (time/date and phone number):

. . . . . .
. . . . . .
. . . . . .

0.5. Date of telephone interview: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋ **0.6.** Telephone interviewer: ⌊_⌋⌊_⌋

Coworkers:

01 Rune Nielsen
02 Margrete Klemmetsby
03 Idunn Riisnes
04 Jan Egil Romestrand
05 Hege Marie Schnelle

Firstly: "We have a limited amount of time available for today's questions. Some of them might be difficult to answer, but still I hope you will try to make your best guess, and answer as fast as possible. The interview is no exam, and there are no wrong answers. If I should happen to interrupt you, I hope you won't take this as a sign of disrespect. This is entirely out of respect for both your and my available time."

A Healthcare provider contact information

A1 Family physician - name: . . . . . .

A2 Family physician – address: . . . . . .
. . . . . .

A3 Family physician – phone number: _____

A4 Pharmacyk – name and address: . . . . . .
. . . . . .
. . . . . .

A5 Will the participant try to use only one pharmacy during the study?

Yes ☐ No ☐

A6 Work place – name and adress: . . . . . .
. . . . . .
. . . . . .

A7 Employer – name and address: . . . . . .
. . . . . .
. . . . . .

A8 Other regular physician contacts – title/speciality, name and address:

. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .

B. Symptoms from the airways and allergies

Symptoms from the airways

B1	Do you usually cough or clear your throat in the morning?	☐ Yes ☐ No
B2	Do you usually cough during the rest of the day?	☐ Yes ☐ No
B3	When you cough or clear your throat, do you usually bring up phlegm ?	☐ Yes ☐ No
B4	Do you have a cough for altogether three months or more in one year?	☐ Yes ☐ No
B5	During the last couple of years, have you had a cough and/or phlegm in connection with a cold for more than 3 weeks? (no/single/multiple)	☐ Yes, once ☐ Yes, several times ☐ No
B6	Are you more breathless than other people of your own age when walking uphill?	☐ Yes ☐ No
B7	Are you breathless when you climb two flights of stairs at an ordinary pace?	☐ Yes ☐ No
B8	Are you breathless when walking at a normal pace on level ground?	☐ Yes ☐ No
B9	Are you breathless while at rest?	☐ Yes ☐ No
B10	Do you sometimes experience attacks of breathlessness?	☐ Yes ☐ No
B11	Have you ever had wheezing (a wheezing sound) in your chest? *(By wheezing is meant high or low pitch sounds which can also be weak)* **If yes answer B12, if no go to B15**	☐ Yes ☐ No
B12	Have you ever had wheezing (a wheezing sound) in your chest in the last 12 months? **If yes answer B13 and B14, if no go to B15**	☐ Yes ☐ No
B13	Have you ever been breathless at the same time you have noticed a wheezing sound in your chest?	☐ Ja ☐ Nei
B14	Have you had such wheezing sounds in your chest even if you did not have a cold?	☐ Ja ☐ Nei

Allergier

B15	Have you ever had hay fever? **If yes, answer B16, no → C1**	☐ Yes ☐ No ☐ Don't know
B16	If yes, have you had hay fever within the last 12 months?	☐ Yes ☐ No ☐ Don't know

C Smoking habits

C1 Do you presently smoke daily? **If yes, answer C2, if no go to C3** ☐ Yes ☐ No

C2 Do you smoke cigarettes daily? (handrolled or factory made)? ☐ **Ja** ☐ **Nei**
Go to C5

C3 Have you smoked cigarettes daily before? ☐ **Ja** ☐ **Nei**
If yes, go to C4, if no go to D1

C4 How long is it since you quit?
☐ Less than 3 months
☐ 3 months – 1 year
☐ 1-5 years
☐ More than 5 years

C5 For how many years have you smoked daily? ⌊_⌋⌊_⌋ Number of years

C6 How many cigarettes do you smoke or did you smoke daily? Give number per day (handrolled or factory made) ⌊_⌋⌊_⌋ Number of cigarettes

C7 **If you smoke,** has any physician ever advised you to quit? ☐ Yes ☐ No

C8 Have you tried nicotine transdermal patches or nicotine gum? ☐ Yes ☐ No

C9 Have you tried the quit smoking pill Zyban? ☐ Yes ☐ No

C10 Have you participated in smoking cessation courses? ☐ Yes ☐ No

D Education

D1 Which level best describes your education?
(highest level, when difficulties – try to help the participant, but make a note of this in the margin of the questionnaire)

☐ Former primary school or present 9-year primary school

☐ Continuation school, 1-year people's college, or the like

☐ Lower or upper secondary school, or technical school

☐ College or university

☐ Don't know

1. Diagnoses

1.1. Have you been diagnosed by a physician with:

The interviewer reads the text in 1,1, and the diseases in 1.1.1.-1.1.4 for all groups. If yes, ask when they received this diagnosis.

Quest.	Diagnoses (mark)	Diagnose	Når diagnose (år siden)
1.1.1.		Chronic obstructive pulmonary disease (COPD)	
1.1.2.		Emphysema	
1.1.3.		Chronic bronchitis	
1.1.4.		Asthma	

1.2. The last week – have you had (or currently have)

□ a cold?
□ influenza?
□ pneumonia?
□ no

1.3. Do you have any other ongoing lung or airways disease? For instance disease in the sinuses, tonsilitis, tuberculosis, injuries caused by asbestos or other ((*not to be read out loudly –cancer of the lung*))?

Yes □ No □

If yes :

1.3.1. What disease?

Answer:……..

1.3.2. When was this diagnosed? ⌊_⌊_⌋ years ago
(ongoing disease: record "0")

1.4. I will now go through a list of 19 diseases. If a physician have given you one or mor of these diagnosis you please say stop. *Please specify, when affirmative answers, that we are interested in active disease – that is in terms of symptoms or treatment/follow-up.*

Diagnosis	**Mark when diagnosis**	**Number of years since diagnosed**	**Sykdoms-kode**
High blood pressure			101
Heart attack			102
Angina pectoris (angina)			103

"Smokers legs" (peripheral vascular disease)				104
Coronar valvular disease				105
Heart failure				106
Cerebral stroke or cerebral bleed				107
Other neurological disease				108
Diabetes				109
	Diabetes affected other organs (e.g. eyesight, kidneys, blood vessels, stomach/intestines)			110
Ulcer disease				111
Liver disease				112
	Mild			113
	Moderate			114
	Severe			115
Kidney disease				116
	Mild			117
	Moderate			118
	Severe			119
HIV/AIDS				120
Active cancer disease				121
	Leukemia			122
	Lymphoma			123
Skeletal/joint disease with regular use of drugs (includes osteoporosis)				124
Muscle disease with regular use of drugs				125
Depression with regular disease				126
Psychic or psychiatric disease				127
Other disease				
which disease				
None (cross)		---------- ----------		---------- ----------

Not to be read up loudly, but interviewer should evaluate this during the interview:

1.5. *Does the participant seem to be oriented (not confused)?* *Yes* ☐ *No* ☐

2. Disease activity

2.1. During the last three months, since [date for baseline interview], have you had any periods of 2 days or more with

When yes – specify that the questions concerns increases from their baseline level of function of at least 2 days in a row.

Symptom	YES	NO	Co-incidence
1) Increased dyspnoea, heavy breathing or tightness of the chest?	□	□	XXXXXX
2) Increased phlegm?	□	□	□
3) Changed color of phlegm?	□	□	□

Ved ingen 'ja' - gå rett til 2.4.

2.2. How many of these periods of at least two days with worsening of these symptoms (*optional: mention the symptoms)* have you experiencd during the last three months? (*When difficulties:* "1 period, 2 periods, 3 periods, 4 periods or more?")

⌊_⌊_⌋ perioder

evt hele tiden: □

2.3 How many days did these periods amount to altogether?

⌊_⌊_⌋ days

Specify: And this was totally, not per period? Yes □ No □

Remember: is there agreement between 2.2. and 2.3? If not – carefully suggest the inconsistency "have I understood you correctly when you say that 3 periods of at least 2 days altogether lasted 4 days?"

2.4. During the last 3 months (that is since date/month), have you had periods of at least 2 days with:

Read up loudly all symptoms. Specify that we are interested in increases from the habitual state of the participant. When inquiring "co-incidence" the interviewer lists the symptoms form question 1.1 to which the participant answered positively.

Symptom	YES	NO	Co-incidence with 2.1?
1) Nose cold or stuffed nose?	□	□	□
2) Increased wheezing from your chest?	□	□	□
3) Sore throat or coughing?	□	□	□
4) Asthenia or powerlessness?	□	□	□

2.5. How <u>many</u> of these <u>periods</u> of at least two days with worsening of these symptoms (*optional: mention the symptoms)* have you experiencd during the last three months? (*When difficulties:* "1 period, 2 periods, 3 periods, 4 periods or more?")

⌊_⌋⌊_⌋⌊_⌋ perioder

evt hele tiden: □

2.6. How many days did these periods amount to, altogether?

⌊_⌋⌊_⌋⌊_⌋ days

How many days did these periods amount to, altogether Yes □ No □

Remember: is there agreement between 2.5. and 2.6? If not – carefully suggest the inconsistency "have I understood you correctly when you say that 3 periods of at least 2 days altogether lasted 4 days?"

2.7. Have you had any symptoms of the flu the last 3 months?

Yes □ No □

Flu symptoms: fever, muscleache, headache, poor general health

3. Work and income

Work situation

3.1. What is your current work situation?

Complete 3.1. as appropriate. Anyhow – mention all possibiliies outlined below (e.g. "you don't receive any kind of disability pension?")

3.1.1. Paid work □
a. full time (≥ 35 h/week) □
b. part time (< 35 t/week) □

3.1.2. Disability pension □

Remember that disability pensioners receive age pension from 67 years of age.

a. When did you receive a disability pension? ⌊_⌋⌊_⌋ years ago

b. What is your degree of disability/pension? ⌊_⌋⌊_⌋⌊_⌋ %

c. What is the cause of disability ? (for disability pensioners only)

Airway disease □ Other disease □

Which other disease?: ……

d. What was your annual income (tax included) before you received your disability pension?

Answer.: NOK ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

e. Or – monthly income (tax included)

Svar.: NOK ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

(when less tax only: estimate using the patients income tax percentage (x/(1,00-0,yy)) wheree x is income less tax and yy is the percentage). When the percentage is unknown – use 30%).

3.1.3. Early retirement □
(and this was not disability pension?)

a. How long have you been early retired? ⌊_⌋⌊_⌋ years

b. What was the cause of early retirement?

Cause: . . . . . .

c. What was your annual income (tax included) before you received your early retirement?

Answer.: NOK ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

d. Or – monthly wage including taxes

Answer.: NOK ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

(when less tax only: estimate using the patients income tax percentage (x/(1,00-0,yy)) wheree x is income less tax and yy is the percentage). When the percentage is unknown – use 30%).

3.1.4. Student □

3.1.5. "Avtalefestet pensjon"* □

3.1.6. Age pension (> 67 years) □

3.1.7. Unemployed □

Går rett til 3.3. når ikke annet betalt arbeid

**note to English version: this is an agreement between labor unions, the employer organisations and the governmnent concerning early retirement.*

Sick leave

This sub-section is ONLY for participants involved in paid work. Others proceed to question 3.3.

3.2. During the last three months, have you received sick leave payment? (irrespective of cause)

yes □ no □

If yes, answer questions 3.2.1.-3.2.9. If no proceed to 3.3.

3.2.1. During the last three months, have you stayed home from work due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)?

Yes ☐ No ☐

If yes: answer questions 3.2.2.- 3.2.4, if no proceed to 3.2.5

3.2.2. For how many did you receive full (100%) sick leave payment the last three months?

Answer: ⌊_⌊_⌋ Days

3.2.3. For how many days did you receive graded sick leave payment (⌊_⌊_⌋ %), the last three months?

Answer: ⌊_⌊_⌋ Days

3.2.4. For how many days were you receiving "active sick leave payment the last three months?

Answer: ⌊_⌊_⌋ Days

3.2.5. During the last three months, have you received sick leave payment due to other causes than the above-mentioned?

Yes ☐ No ☐

If yes answer 3.2.6. to 3.2.9. If no, go to 3.3.

3.2.6. What was the cause of your sick leave

Enter code from question 1.3.. ⌊_⌊_⌊_⌋

Other causes: . . . . . .

3.2.7. For how many did you receive full (100%) sick leave payment the last three months?

Answer: ⌊_⌊_⌋ Days

3.2.8. For how many days did you receive graded sick leave payment (⌊_⌋⌊_⌋⌊_⌋ %), the last three months?

Answer: ⌊_⌋⌊_⌋⌊_⌋ Days

3.2.9. For how many days were you receiving "active sick leave payment the last three months?

Answer: ⌊_⌋⌊_⌋⌊_⌋ Days

Change of profession

3.3 Have you ever had to change profession or position due to asthma, COPD, or worsening of respiratory symptoms (for instance a cold)?

Yes ☐ No ☐

If No og to 3.8. If yes, answer questions 3.3.1.-3.7.

3.3.1. What was your previous occupation?

Answer:……

3.3.2. What position or occupation did you change to?
Answer:……

3.3.3 When did you change profession?

Answer: ⌊_⌋⌊_⌋ years ago

If less than a year ago, answer 3.3.4, if not proceed to 3.4

3.3.4 Is this less than 3 months ago?

Yes ☐ No ☐

3.4 Have you ever been through any re-education due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)?

Yes ☐ No ☐

Hvis ja svar på 3.4.1.-3.4.5, hvis nei gå til 3.5.

3.4.1. What re-education was this:……

3.4.2 When did this re-education take place?

Answer: ⌊_⌋⌊_⌋ years ago

If less than a year ago answer questions 3.4.3-3.4.4, if no proceed to 3.5.

3.4.3. Is it less than three months since this re-education?

Yes ☐ No ☐

3.4.4 What have your expenses been the last three months due to re-education? (What kind, and how much)

What kind:……

NOK ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

3.5 What other economic consequences than income reduction, did this change of porfession or position imply (What kind, and how much)

What kind:……

NOK ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

3.6 How much higher or lower monthly wage did this change of profession or position imly?

Answer: +/- *(cross out)* ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋ NOK

3.7. Did the change of job imply increased travel costs?

Yes ☐ No ☐

How much ? NOK ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ per month

Annual income

3.8. What is your current annual income (taxes included) according to the latest tax records?

Answer.: NOK ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Or – montly wage included taxes

Svar.: NOK ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

(when less tax only: estimate using the patients income tax percentage (x/(1,00-0,yy)) wheree x is income less tax and yy is the percentage). When the percentage is unknown – use 30%).

When difficulties – give examles in categories of 50 000, ask for one number

4. Contacts with healthcare professionals – outpatient clinic ☐, telephone ☐

4.1. During the last three months, have you had contact with any of the following health care providers (I will read a list), irrespective of cause? This does not include pulmonary rehabilitation or admissions to hospital *(Interviewer walks through the table below)*.

Yes ☐ No ☐

If yes on 4.1. complete the table below for the relevant healthcare providers. *Please mark when negative answers.When visits are due to other disease than the index-disease – please make a note on what disease in question 4.1.1.*

Healthcare profession	Asked (mark)	Number of telephone contacts	Numbers of visits at the office (number of emergency visits in parenthesis)	Number of house calls (number of emergency house calls in parenthesis)	Transportation (by own car= 1, pedestrian = 2, taxi = 3, by bus = 4,ambulance = 5, other=6)	Expenses due to travel (NOK)	Total time used per contact (hours)	Had to take time off from work? (hours in total)	Travel distance in km	Expenses related to contact *(NOK)*	Cause *(mark if airways or lung disease)**
Family physician											
GP's emergency ward											
Other GP											
Hospital doctor (except admissions)											
Specialist (outside hospital)											
Physiotherapist											
Ergotherapist											
Social worker											
Others (e.g. x-ray, laboratory)											

** If several causes for the contact – note what number was due to airways or lung diseases.*

4.1.1. Cause :. . . . . .

Name and address for contacts specified in question 4.1

4.1.2. GP's emergency ward:

. . . . . .
. . . . . .
. . . . . .

4.1.3. Other GP :

. . . . . .
. . . . . .
. . . . . .

4.1.4. Hospital:

. . . . . .
. . . . . .
. . . . . .

4.1.5. Specialist (physician)

. . . . . .
. . . . . .
. . . . . .

4.1.6. Physiotherapist:

. . . . . .
. . . . . .
. . . . . .

4.1.7. Ergotherapist:

. . . . . .
. . . . . .
. . . . . .

4.1.8. Social worker:

. . . . . .
. . . . . .
. . . . . .

4.1.9. Other healthcare provider:

. . . . . .
. . . . . .
. . . . . .

4.2. Have you reached the deductible limit, and receive healthcare services without co-payment? Yes ☐ No ☐

If yes – which deductible?

Regular ☐ Deductible limit 2 ☐

Deductible limit 2: own limit for other than doctors' visits, medication and taxi-co-payment.

If yes – when (approximate date): . . . . . .

4.3. Do others than the national health insurance cover your healthcare expenses?

Yes ☐ No ☐

If yes – who . . . . . .

For instance veterans and work-related diseases.

5. Hospital admissions

Hospital admissions due to diseases of airways and lungs

5.1 During the last three months, have you been admitted to hospital due to asthma, COPD, or worsening of respiratory symptoms (for instance a cold)? Yes ☐ No ☐

If yes answer 5.2. If no, proceed to 5.3.

5.2. How many times have you been admitted during the last three months due to asthma, COPD, or worsening of respiratory symptoms (for instance a cold)?

Answer: ☐☐ times

Complete the table for each admission.

When admitted (date)	Transportation *(1=own car, 2= bus, 3= taxi, 4= ambulance, 5=pedestrian , 6= other)*	Transportation expenses *(in total tour-retour)*	Where admitted*	Number of days in total	Days with a tube down your throat (respirator)	Days at intensive care unit	Number of days with a breathing machine	Days at regular ward

** 1 = Department of Thoracic Medicine, HUH, 2 = Department of Medicine, HUH, 3 = intensive care unit HUH, 4= Department of Medicine Haraldsplass Hospital, 5= Department of Medicine, Voss Hospital, 6= Department of Medicine, Stord Hospital, 7 = Other department – which and at what hospital*
Admission day and counts as whole day

Hospital admissions due to other diseases

5.3. Have you been admitted due to other diseases the last three months?

Yes ☐ No ☐

If yes, answer 5.3.1.-5.3.3., if no proceed to 6.0.

5.3.1. For which disease(s)?

Enter disease code from the table in question 1.4. ☐☐☐

Other causes: . . . . . .

5.3.2. What was the total length of stay for these admissions?

Answer: ☐☐ days

5.3.3. Where were you admitted (surgery, orthopaedics, gynecology, psychiatry, other)?

Department:……

Hospital:……

6. Drug utilization

When the participant arrives – ask him to show what medication he has brought. Complete the relevant tables by asking "what is this for" *and whether it is prescription medicine. When all drugs are noted, ask (tick when asked):*

□ 1. Do you take other prescription medication due to COPD, chronic bronchitis, emphysema, influenza, cold or asthma??

To make sure nothing is missed, mention all groups by saying "no inhaled drugs, no tablets, no phlegm mediation, cough suppressants or allergy tablets?"

□ 2. The last three months, have you quit taking any medication for lung or airways' disease, or taken a short course of?

□ 3. During the last three months, have you bought any over-the-counter medication for COPD, chronic bronchitis, emphysema, influenza, a cold, or asthma?
For instance pain killers, fever relievers, cough suppressants, anti-phlegm medication.

□ 4. During the last three months have you taken any other medication, irrespective of cause?
read: "blood pressure, anti-coagulants, diruetics, cholesterol medication, heart failure, medication against depression, pain killers. . This includes courses and medication that you quit taking the last three months."

Positive answers to be entered in the relevant sections.

At the end all questions in the tables are answered. This includes the questions on vaccinations (6.7.).

Review the section to ensure that all relevant information is complete.

6.0. Medication for lung/airways disease last 3 months?
Yes □ No □

6.1. Prescription medication
Yes □ No □ **If yes go to 6.1.1. If no proceed to 6.5**

6.1.1. Which?

Drug code	Date administered	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Dose *(dose pr 24h, note B if "as need medication")*	Number of doses last 24h	Date to be stopped

6.2. During the last three months, what have been your own expenses buying prescribed medication for lung diseases (*Mention the relevant medication)*?

Answer: NOK ⌊_⌊_⌊_⌊_⌋

6.3. During the last three months, have you collected any of these drugs without having to pay for them (due to crossing the deductibl limit or other causes)?

Number of times ⌊_⌊_⌋

If no on both 6.2. and 6.3., proceed to 6.5

6.4.
Which pharmacy have you been using)? (name, address – multiple answers possible)

. . . . . .

. . . . . .

. . . . . .

. . . . . .

6.5. Overt-the-counter medication for lung or airways diseases or bothers

Yes ☐ No ☐

Hvis ja, følg ut tabellen nedenfor. Hvis nei, gå til 6.7

Drug code	Date administered	Formulation *(1=tablet, 2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Dose *(dose pr 24h, note B if "as need medication")*	Number of doses last 24h

For other medication than mucolytics and anti-tussives - specify by asking– "This was due to asthma, COPD or worsening of respiratory symptoms?"

6.6. The last three months, what have your expenses been due to this over-the-counter medication? (*Mention the relevant medication)*?

Answer: NOK ⌊_⌊_⌊_⌊_⌋

6.7. Have you been vaccinated against influenza or pneumonia (pneumococcus vaccine)?

☐ yes ☐ no

If yes, anwer 6.8, if no proceed to 6.9.

6.8.

VACCINE	When vaccinated *(month and year, or time of year)*	Costs (NOK)
Influenza		
Pneumonia (pneumococcus vaccine)		

6.9 The last 3 months, have you been using medication for other diseases?

Yes ☐ No ☐

If yes, complete the table and proceed. If no, proceed to 7.0.

Drug code	Date administered	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Dose *(dose pr 24h, note B if "as need medication")*	Prescribed	Number of doses last 24h	Date to be stopped

6.10. During the last 3 months, what have your own expenses been buying medication for other diseases (*Mention the relevant medication)*?

Answer: NOK ⌊_|_|_|_⌋

6.11. The last three months, have you collected any medication without having to pay for them (due to crossing the deductible limit or other causes)?

Number of times ⌊_|_|_|_⌋

6.12. Which pharmacy have you been using? (name, address – multiple answers possible)

. . . . . .

. . . . . .

. . . . . .

. . . . . .

7. Nebulizer, ventilatory support, oxygen, other aid equipment

7.1. Do you have a nebulizer at home? Yes □ No □

Nebulizer – machine that give you medication to inhale from liquid state.

.

If yes, answer 7.2. If no porceed to 7.3.

7.2. The last three months, have you had any expenses related to your nebulizer?

Answer: NOK |_|_|_|_|

7.3. The last three months, have you had to get any aid equipment, irrespective of cause (*give examples:* hospital bed, wheel chair, roller, et cetera).

Yes □ No □

If yes, answer 7.4. and 7.5. if no – proceed to 7.6.

7.4. What aid equoment, and when where they acquired

What aid equipment	Acquired last three monts? *(cross for 'yes,' a line for no*	*Due to lung or airways disease* *

* *Ask:* Why did you get this aid equipment?

After asking 7.4 concerning one aid equipment: "Did you receive any other aid equipment the last three months?"

7.5. During the last three months, what have been your expenses due to aid equioment?

Answer: |_|_|_|_| NOK

7.6. Do you have a breathing machine at home (respirator, BiPAP, CPAP)?

Yes □ No □

If yes, answer 7.7.-7.8. If no proceed to 7.9.

7.7. What kind of machine?

- ☐ BiPAP
- ☐ CPAP
- ☐ respirator

7.8. The last three months, have you had eny expenses related to this treatment?

Answer: NOK ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

7.9. Do you use oxygen at home? Yes ☐ No ☐

If yes, answer 7.10. – 7.15. If no, proceed to 8.0

7.10. When did you start using oxygen?

Date ____/ _____ / _____

7.11. Which device do you use?

Oxygen concentrator:	☐
Liquid oxygen	☐
Bottled oxygen when traveling/exercising	☐

7.12. Who supplies you with the equipment?

Bergen health region ☐

Other:
Answer: ……

7.13. Who supplies you with oxygen?

Gasservice ☐

Other:
Answer:……

7.14. Oksygenbruk

Normal oxygen dose *(litres/minute)* rest/excercise	Increased dose last three months *(litres/minute)* Rest/excercise	Use per 24 hours usually	Increased use per 24 hours last three months

7.15. Suring the last three months, have you had any expenses related to this treatment?

Answer: NOK |_|_|_|_|

8. Undervisning, rehabilitering og trening

8.0. Have you participated in a pulmonary rehabilitation programme at Haukeland, Granheim The Glittre Clinic or other places during the last three months?

Yes □ No □

If yes – answer 8.1 if no proceed to 8.3.

8.1. Where was this?
- □ Haukeland University Hospital
- □ Haraldsplass Hospital
- □ The Glittre Clinic
- □ Granheim
- □ Voss
- □ Other Where? . . . . . .

8.2. What costs did this imply for you during the last three months?

Answer: ⌊_⌊_⌊_⌊_⌋ NOK

8.3. Har du vært til noen annen form for trening eller behandling eller oppfølgning av rehabiliteringsopphold de siste tre månedene?

8.3.1. □ yes, exercise in groups
If ticked here – please mark options below
- □ physiotherapist in private practise
- □ at Haraldsplass Hospital
- □ elsewhere Where: . . . . . .

8.3.2. □ yes, attends a physiotherapist in private practice
8.3.3. □ other
8.3.4. □ no

If yes, answer 8.4. If no go to 9.0.

8.4. What costs have you had in relation to this during the last three months?

Answer: ⌊_⌊_⌊_⌊_⌋ NOK

9. Complementary treatment

9.0. Have you ever, irespective of cause used "complementary therapy" (for instance homeopath, acupuncturist, healer or other)?

Yes ☐ No ☐

If yes, complete the table, if no proceed to 10.0.

Type	Used (mark)	*Due to airways- or respiratory disease?**	Last three months?	Number of visits last three months	Number of visits "extra," that is due to worsening of your health	Expenses (NOK) last three months
Homeopath						
Acupuncturist						
Healer						
Reflexologist						
Aromatherapist						
Naprapath						
Others (which)						

* *Ask:* What was the reason for this treatment?

10. Hjelp eller assistanse - poliklinikken ☐, telefonintervju ☐

10.0. Have you had help from any of the following groups?

Interviewer mentions all groups.

Yes ☐ No ☐

Ved ja, fyll ut tabellen, ved nei gå til 11.0.

Help or assistance from	Asked (marked)	*Due to airways- or respiratory disease?**	Help last 3 months (hours/week, deliveries/week) (totally 168 hours week)	*Usual help:* "was this different to the help you usually receive" *(hours, see note below table)*	Expenses last three months (kroner)	Prevented from work elsewhere?
Home nursing						XXXXXX
House aid						XXXXXX
Private house aid or help						XXXXXX XXXXXX
Family or friends						
Dinner delivery						XXXXXX

* *Spørres i form av:* Hva får du denne hjelpen for?

Lowest possible value = 1 hour

11. Adaptation or change of residence

11.1. Have you ever had to change residence due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)?

yes ☐ no ☐

If yes, answer 11.2. If no proceed to 11.4.

11.2. When was this?

. . . . . .

Last three months? Yes ☐ No ☐

11.3. What wxpenses did you have in relation to this change of residence?

Answer: ⌊_⌊_⌊_⌊_⌊_⌊_⌋ NOK

Does not include earnings by sale.

11.4. Have you ever had to rebuild or adapt your residence due to asthma, COPD, or worsening of respiratory symptoms (for instance a cold)?

Yes ☐ No ☐

If yes, answer 11.5. If no, go to 12.0

11.5. When was this?

. . . . . .

Last three months? Yes ☐ No ☐

11.6. What were your expences in relation to these changes of your residence?

Answer: ⌊_⌊_⌊_⌊_⌊_⌊_⌋ NOK

12. Leisure time

12.0. The last three months, how much of your leisure time has been lost due to lung disease? (for instance by using more time in the morning or not being able to do things that you would like to do")

- ☐ Less than 5 hours weekly
- ☐ 5-10 hours weekly
- ☐ 10-15 hours weekly
- ☐ 15-20 hours weekly
- ☐ 20 – 25 hours weekly
- ☐ more than 25 hours weekly

(totally 168 hours in a week)

13. Quality of Life (EQ-5D)

I will read three statements in 5 goups please indicate which statements best describe your own health state today.

13.1 Mobility

I have no problems in walking about . ❑

I have some problems in walking about ❑

I am confined to bed ❑

13.2 Self-care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I a unable to wash or dress myself eller kle meg. ❑

13.3 Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activitites ❑

I am unable to perform my usual activities ❑

13.4 Pain/Discomfort

I have no pain or discomfort. ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

13.5 Anxiety/Depression

I am not anxious or depressed ❑

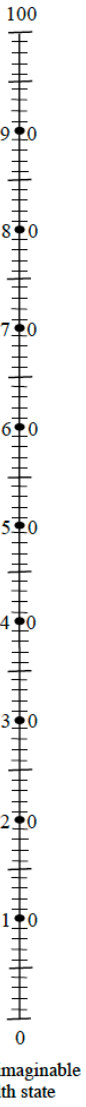
I am moderately anxious or depressed. ❑

I am extremely anxious or depressed. ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100, and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad is your own health today, in your opinion. Please do this by drawing a line form the box below to whichever point on the scale indicates how good or bad your current health state is.

Your own state of health today



14. Summary/conclusion

14.0. Other information of interest from the interview:

. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .

15. Interviewer conclusion - poliklinikken □, telefonintervju □

15.1. The last three months the participant has (one tick at the highest level of health care this period)

□ been admitted to hospital due to COPD
Number of times:

□ had an extra visit to his/her doctor due to COPD
Number of times::

□ been in contact with the doctor by telephone:
Number of times::

□ by her/himself incesed the drugs due to COPD.
Number of days:

□ more bothered by heavy breathing than usually, bot no change of medication:
Number of days:

□ no change in his/her disease

Closure:

I would like to thank you for taking time to this interveiw! Please remember to start using your diaries the first monday.

Thank you!

15.2 The interviewers evaluation of the interview:

. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .

Interview 1 - 4

Introductory information

Participant identification number: ⌊_⌊_⌊_⌊_⌋

Date of interview: ⌊_⌊_⌊_⌊_⌊_⌊_⌋ Diary start *(ask the participant)*: ⌊_⌊_⌊_⌊_⌊_⌊_⌋

Interviewed by: ⌊_⌊_⌋

01 Rune Nielsen
02 Margrete Klemmetsby
03 Idunn Riisnes
04 Jan Egil Romestrand
05 Hege Marie Schnelle
06 Tonje Knoph Lauvaasvaag
07 Heike Wiegmann
08 Lene Kvamsdal

Exempted diaries ☐

Diary not available during interview ☐

Introductory text
"Hello, my name is XX, and I'm calling from the Department of Thoracic Medicine at Haukeland University hospital. You are participating in the EconCOPD study, which you were included in a year ago. As previously agreed I'm calling to do the last telephone interview, is now a good time for you?

This interview is similar to the previous ones, but first we would like to ask you some question that you also have answered previously.

The time available for the interview is limited. Some of the questions might be difficult to answer, but still we would like you to give your best guess, and answer as rapidly as possible. The interview is not an exam, and there are no wrong answers. If I should happen to interrupt you – then it is not to be impolite, but out of respect of both your and my time. "

New interview

Note when you agreed to conduct the interview, the date today and your initials.

. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .

A.Change of contact information:

The last three months – since last interview [date of last contact] – have you changed general practitioner, pharmacy, employer or work place?

Yes ☐ No ☐

If yes: What have changed:

. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .

B. Symptoms from the airways and allergies

Symptoms from the airways

B1	Do you usually cough or clear your throat in the morning?	☐ Yes ☐ No
B2	Do you usually cough during the rest of the day?	☐ Yes ☐ No
B3	When you cough or clear your throat, do you usually bring up phlegm ?	☐ Yes ☐ No
B4	Do you have a cough for altogether three months or more in one year?	☐ Yes ☐ No
B5	During the last couple of years, have you had a cough and/or phlegm in connection with a cold for more than 3 weeks? (no/single/multiple)	☐ Yes, once ☐ Yes, several times ☐ No
B6	Are you more breathless than other people of your own age when walking uphill?	☐ Yes ☐ No
B7	Are you breathless when you climb two flights of stairs at an ordinary pace?	☐ Yes ☐ No
B8	Are you breathless when walking at a normal pace on level ground?	☐ Yes ☐ No
B9	Are you breathless while at rest?	☐ Yes ☐ No
B10	Do you sometimes experience attacks of breathlessness?	☐ Yes ☐ No
B11	Have you ever had wheezing (a wheezing sound) in your chest? *(By wheezing is meant high or low pitch sounds which can also be weak)* **If yes answer B12, if no go to B15**	☐ Yes ☐ No
B12	Have you ever had wheezing (a wheezing sound) in your chest in the last 12 months? **If yes answer B13 and B14, if no go to B15**	☐ Yes ☐ No
B13	Have you ever been breathless at the same time you have noticed a wheezing sound in your chest?	☐ Yes ☐ No
B14	Have you had such wheezing sounds in your chest even if you did not have a cold?	☐ Yes ☐ No

Allergies

B15	Have you ever had hay fever? **If yes, answer B16, no → C1**	☐ Yes	☐ No	☐ Don't know
B16	If yes, have you had hay fever within the last 12 months?	☐ Yes	☐ No	☐ Don't know

C Smoking habits

C1 Do you presently smoke daily? **If yes, answer C2, if no go to C3** ☐ Yes ☐ No

C2 Do you smoke cigarettes daily? (handrolled or factory made)? ☐ Yes ☐ No
If yes go to C5, if no answer C3

C3 Have you smoked cigarettes daily before? ☐ Yes ☐ No
If yes, go to C4, if no go to D1

C4 How long is it since you quit?
- ☐ Less than 3 months
- ☐ 3 months – 1 year
- ☐ 1-5 years
- ☐ More than 5 years

C5 For how many years have you smoked daily? ⌊_⌋⌊_⌋ Number of years

C6 How many cigarettes do you smoke or did you smoke daily? Give number per day (handrolled or factory made) ⌊_⌋⌊_⌋ Number of cigarettes

C7 **If you smoke,** has any physician ever advised you to quit? ☐ Yes ☐ No

C8 Have you tried nicotine transdermal patches or nicotine gum? ☐ Yes ☐ No

C9 Have you tried the quit smoking pill Zyban? ☐ Yes ☐ No

C10 Have you participated in smoking cessation courses? ☐ Yes ☐ No

D Education

D1 Which educational level best describes your level?
(highest level, when difficulties – try to help the participant, but make a note of this in the margin of the questionnaire)

- ☐ Former primary school or present 9-year primary school
- ☐ Continuation school, 1-year people's college, or the like
- ☐ Lower or upper secondary school, or technical school
- ☐ College or university
- ☐ Don't know

1. Disease activity

1.1. During the last 3 months, that is since [first date of last period] have you had any periods of at least 2 days with:

Presiser under hvert punkt at det dreier seg om 'økt' i forhold til deltakerens vanlige tilstand og at det er minst 2 dager på rad..

Symptom	Yes	No	Co-incidence
1) Increased dyspnoea, heavy breathing or tightness of the chest?	☐	☐	XXXXXXXXXXX
2) Increased phlegm?	☐	☐	Yes ☐ No ☐
3) Changed color of phlegm?	☐	☐	Yes ☐ No ☐

No 'yes'-answers – proceed to 1.4.

1.2. How many of these periods of at least two days with worsening of these symptoms (*optional: mention the symptoms)* have you experiencd during the last three months? (*When difficulties:* "1 period, 2 periods, 3 periods, 4 periods or more?")

⌊_⌊_⌋ periodes

or all the time:☐

1.3. How many days did these periods amount to altogether?

⌊_⌊_⌋ days

Specify: And this was totally, not per period? Yes ☐ No ☐

Remember: is there agreement between 1.2. and 1.3? If not – carefully suggest the inconsistency "have I understood you correctly when you say that 3 periods of at least 2 days altogether lasted 4 days?"

1.4. During the last 3 months (that is since date/month), have you had periods of at least 2 days with:

Read up loudly all symptoms. Specify that we are interested in increases from the habitual state of the participant. When inquiring "co-incidence" the interviewer lists the symptoms form question 1.1 to which the participant answered positively.

Symptom	Yes	No	Co-incidence with 1.1?
1) Nose cold or stuffed nose?	☐	☐	Yes ☐ No ☐
2) Increased wheezing from your chest?	☐	☐	Yes ☐ No ☐
3) Sore throat or coughing?	☐	☐	Yes ☐ No ☐

4) Asthenia or powerlessness?	☐	☐	Yes ☐ No ☐

No 'yes'-answers – proceed to 1.7.

1.5. How many of these periods of at least two days with worsening of these symptoms (*optional: mention the symptoms)* have you experiencd during the last three months? (*When difficulties:* "1 period, 2 periods, 3 periods, 4 periods or more?")

⌊_⌊_⌋ periods

or all the time:☐

1.6. How many days did these periods amount to, altogether?

⌊_⌊_⌋ days

Specify: And this was totally, not per period? Yes ☐ No ☐

Remember: is there agreement between 1.2. and 1.3? If not – carefully suggest the inconsistency "have I understood you correctly when you say that 3 periods of at least 2 days altogether lasted 4 days?"

1.7. Have you had any symptoms of the flu the last 3 months?

Yes ☐ No ☐

Flu symptoms: fever, muscleache, headache, poor general health

1.8. *To be answered by interviewer: Do the partipant have symptoms of exacerbation?*
Yes ☐ No ☐

If "yes" – please refer to this in Section 9

1.9. During the last three months, have you developed any new diseases (physician diagnosed) with a new disease, or have you experienced any symptoms that you haven't been bothered by previously?"

Yes ☐ No ☐

DISEASE CODE	DOCTORS DIAGNOSIS?	WHEN DIAGNOSED	ACTIVE DISEASE/ TREATMENT

1.10. Have you reached the deductible limit, so that you don't have to co-pay drugs or doctor visits? Or do you for other reasons not pay for health care or social services?

Yes □ No □

□ **1.10.1**. Minimum age pension. Does not have to copay drugs

1.10.1.a Granted last 3 months? Yes □ No □

□ **1.10.2.** Reached the regular deductible limit

1.10.2.a Granted last 3 months? Yes □ No □

□ **1.10.3.** Deductible limit 2, is also exempted expenses to physiotherapists et cetera

1.10.3.a. Granted last 3 months? Yes □ No □

□ **1.10.4.** Disease or injury approved as occupational

1.10.4.a Granted last 3 months? Yes □ No □

□ **1.10.5.** Other reason

Which? . . . . . .
. . . . . .
. . . . . .
. . . . . .

1.10.5.a. Granted last 3 months? Yes □ No □

2. Contacts with health care providers

2.1. During the last three months, have you had contact with any of the following health care providers (I will read a list), irrespective of cause? This does not include pulmonary rehabilitation or admissions to hospital *(Interviewer walks throug the table below)*.

Yes ☐ No ☐

If yes on 2.1. complete the table *Please mark when negative answers.When visits are due to other disease than the index-disease – please make a note on what disease in question 2.1.1.*

Health provider	Asked (mark)	Number of telephone contacts	Numbers of visits at the office (number of emergency visits in parenthesis)	Number of house calls (number of emergency house calls in parenthesis)	Transportation (by own car= 1, pedestrian = 2, taxi = 3, by bus = 4,ambulance = 5, other=6)	Expenses due to travel (kr), except petrol costs	Total time used per contact (hours)	Had to take time off from work? (hours)	Travel distance in km	Expenses related to contact *(NOK)*	Reason for contact *(mark if airways or pulmonary disease)* *
Family physician											
GP's emergency ward											
Other GP											
Hospital doctor (except admissions)											
Specialist (outside hospital)											
Physiotherapist											
Ergotherapist											
Social worker											
Others (e.g. x-ray, laboratory)											

2.1.1. Reason for contact with provider:. . . . . .

Name and address of contacts specified in question 2.1

2.1.2. GP's emergency ward:

. . . . . .

. . . . . .

. . . . . .

2.1.3. Other GP :

. . . . . .

. . . . . .

. . . . . .

2.1.4. Hospital doctor:

. . . . . .

. . . . . .

. . . . . .

2.1.5. Specialist (outside hospital)

. . . . . .

. . . . . .

. . . . . .

2.1.6. Physiotherapist

. . . . . .

. . . . . .

. . . . . .

2.1.7. Ergotherapist

. . . . . .

. . . . . .

. . . . . .

2.1.8. Social worker

. . . . . .

. . . . . .

. . . . . .

2.1.9. Other health care providers:

. . . . . .

. . . . . .

. . . . . .

3. Hospital admissions

Hospital admissions due to diseases in the airways or the lungs

3.1 Have you been admitted to hospital due to asthma, COPD or worsening of respiratory symptoms (for instance a cold), the last three months?
Yes □ No □

If yes, answer 3.2. If no proceed to 3.3.

3.2. How many times were you admitted due to asthma, COPD or worsening of respiratory symptoms (for instance a cold), the last three months?

Answer: ☐☐ times

Complete the table for each admission.

When admitted (date)	Transportation *(1=own car, 2= bus, 3= taxi, 4= ambulance. 5=pedestrian , 6= other)*	Transportation expenses *(in total tour-retour)*	Where admitted*	Number of days in total	Days with a tube down your throat (respirator)	Days at intensive care unit	Number of days with a breathing machine	Days at regular ward

** 1 = Department of Thoracic Medicine, HUH, 2 = Department of Medicine, HUH, 3 = intensive care unit HUH, 4= Department of Medicine Haraldsplass Hospital, 5= Department of Medicine, Voss Hospital, 6= Department of Medicine, Stord Hospital, 7 = Other department – which and at what hospital*

Admission day and counts as whole days

Hospital admissions due to other diseases

3.3. Have you been admitted due to other diseases the last three months?

Yes ☐ No ☐

If yes, answer 3.3.1.-3.3.3., if no go to 4.0.

3.3.1. For what disease? *Code* ⌊_⌋⌊_⌋⌊_⌋

Other cause: . . . . . .

3.3.2. For how many days did these admissions last in total?

Answer: ⌊_⌋⌊_⌋ days

3.3.3. Where were you admitted (surgery, ortophedics, gynecology, psychiatry, other)?

Department:……

Hospital:……

4. Education/rehabilitation

4.0. During the last three months, have you started a pulmonary rehabilitation program due to asthma, COPD or worsening of respiratory symptoms (for instance a cold), at Haukeland University Hospital, The Glittre clinic or Granheim?

Yes □ No □

If yes – answer 4.1 if no proceed to 4.4.

4.1. Where was this?

□ Haukeland University Hospital
□ Haraldsplass Hospital
□ The Glittre Clinic
□ Granheim
□ Voss
□ Other Where? . . . . . .

4.2. During the last three months, what costs have you had in relation to this?

Answer: ⌊_⌊_⌊_⌊_⌋ NOK

4.3. How long did this stay last? Answer: ⌊_⌊_⌋ weeks

4.3.1. How many hours per week ⌊_⌊_⌋ hours/week

4.4. During the last three months, have you participated in any other kind of exercise or treatment or follow-up of a rehabilitation program?

4.4.1. □ yes, exercise in groups
If ticked here – please mark options below
□ physiotherapist in private practise
□ at Haraldsplass Hospital
□ elsewhere Where: . . . . . .
4.4.2. □ yes, attends a physiotherapist in private practice
4.4.3. □ other
4.4.4. □ no

If yes, answer4.5., 4.6. and 4.7.If no proceed to 5.0.

4.5. What costs have you had in relation to this during the last three months?

Answer: ⌊_⌊_⌊_⌊_⌋ NOK

4.6. How many times have you used this service during the last three months?

Answer: ⌊_⌋⌊_⌋ times during the last 3 months

4.7. How long does one of these visits last? Answer: ⌊_⌋⌊_⌋ hours

5. Complementary therapy

5.0. During the last three months, have you used "complementary therapy" (for instance homeopath, acupuncturist, healer or other) irrespective of cause?

Yes ☐ No ☐

If yes, complete the table, if no proceed to 6.0.

Type	Used (mark)	*Due to airways- or respiratory disease?**	Number of visits last three months	Number of visits "extra," that is due to worsening of your health	Expenses (kroner) last three months
Homeopath					
Acupuncturist					
Healer					
Reflexologist					
Aromatherapist					
Naprapath					
Others (which)					

* *Ask:* What was the reason for this treatment?

6. Help or assistance

6.0. During the last three months, have you had help from any of the following groups, irrespective of cause?

Interviewer mentions all groups.

Yes □ No □

If yes, complete the table, if no proceed to 7.0.

Help or assistance from	Asked (marked)	*Due to airways- or respiratory disease?**	Help last 3 months (hours/week, deliveries/week) (totally 168 hours week*)*	*Usual help:* "was this different to the help you usually receive" *(hours, see note below table)*	Expenses last three months (kroner)	Prevented from work elsewhere?
Home nursing						XXXXXX
House aid						XXXXXX
Private house aid or help						XXXXXX XXXXXX
Family or friends						
Dinner delivery						XXXXXX

* *Ask:* What was the reason for this treatment?
For services where enumeration in hours is not adequate – record as one hour per week – for instance weekly administration of drugs by the home nursing services

7. Work

7.0. During the last 3 months, have your job situation or social services situation changed?

Yes ☐ No ☐

Underscore that we are interested in changes since last interview

If yes: answer 7.0.0, if no proceed to 7.1.

7.0.0. When did this change occur (date)? . . . . . .

7.0.1 What is your new job- or social service situation?

Complete 7.0.1. as it suits the participants' answers. Anyhow – go through all options (for instance "so you don't receive any kind of disability pension?")

7.0.1.1. Paid work ☐ **Must answer 7.3 - 7.7 as well**
a. full time (≥ 35 h/week) ☐
b.part time (< 35 h/week) ☐

7.0.1.2. Disability pension ☐

Please remember that disability pensioners receive age pension from 67 years and above.

a. When did you receive a disability pension? ____/_____/_____ (date)

b.What is your degree of disability/pension? ⌊_⌊_⌊_ %

7.0.1.3. Early retirement pension ☐

(this is not disability pension?)
a. From when were you early retired? ____/_____/_____ (date)

7.0.1.4. Student ☐
7.0.1.5 Homemaker/caregiver ☐
7.0.1.6. Rehabilitation support ☐
7.0.1.7. Re-education program ☐
7.0.1.8. "Avtalefestet pensjon"* ☐
7.0.1.9.Age pension (> 67 years) ☐
7.0.1.10. Unemployed ☐
7.0.1.11. Other (what): . . . . . .

Does not answer 7.2 or 7.3 unless also in paid work

* note to english version – this is an agreeement between labor unions, the authorities and the employers, giving an opportunity to retire early.

7.0.2 Due to this change, how much higher or lower did your monthly wage become?

Answer: +/- *(mark)* ⌊_⌊_⌊_⌊_⌊_⌋ NOK

7.0.3. What was the reason for this change?

☐ Disease
Respiratory ☐ or other ☐

Which : . . . . . .

☐ Other
What: . . . . . .

7.1. Are you usually in a paid job? Yes ☐ No ☐

"Yes" answer 7.2. "No" proceed to section 8.

Sick leave

This is ONLY for participant in some kind of paid work. Participants with change of job situation (and in paid work) are supposed to answer 7.3., others proceed to section 8.

7.2. During the last three months, have you received sick leave payment? (irrespective of cause)

Yes ☐ No ☐

If yes – complete the table below by first asking what the cause was Remember to ask for both categories

Cause	**Number of days receiving 100% sick leave payment**	**Number of days reveiving graded sick leave payment (percentage)**	**Number of days in "active sick leave"**
7.2.1. Asthma, COPD or worsening of respiratory symptoms (for instance a cold)			
7.2.2 Other cause			
Which other cause?			

Change of profession or position

7.3 During the last three months – have you had to chage profession or occupational position due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)?

Yes ☐ No ☐

If No go to 8.1. If yes, answer questions7.3.1.-7.6.

7.3.1. What was your previous occupation?

Answer:.....

7.3.2. What position or occupation did you change to?

Answer: . . . .

7.3.3 When did you change profession?

Answer . . . . . (approximate date)

7.4. During the last three months, have you been through any re-eductation due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)?

Yes ☐ No ☐

If yes answer 7.4.1.-7.4.5, if no proceed to 7.5.

7.4.1. What re-education was this:.....

7.4.2 When did this re-education take place?

Answer:. . . . . (time passed since the re-education started)

If this is less than a year ago please answer 7.4.3-7.4.4, if not proceed to 7.5.

7.4.3. Is it less than three months since you started this re-education?

Yes ☐ No ☐

7.4.4 What have your expenses been the last three months due to re-education? (What kind, and how much)

7.4.4.1. What kind: . . . . . .

7.4.4.2 NOK ⌊_⌊_⌊_⌊_⌊_⌊_⌋

7.5 What other economic consequences than income reduction, did this change of porfession or position imply (What kind, and how much)

7.5.1. What kind:.....

7.5.2. NOK ⌊_⌊_⌊_⌊_⌊_⌊_⌋

7.6. Did the change of job imply increased travel costs?

Yes ☐ No ☐

If yes: 7.6.1. How much ? NOK ⌊_⌊_⌊_⌊_⌋ per month

8. Leisure time

8.1. During the last three months, how much of your leisure time has been lost due to disease or issues of health?
For instance by using more time in the morning or not being able to do things that you would like to do.

Yes ☐ No ☐

8.2. During the last three months. how much of your leisure time has been lost due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)? If you have completed the column at page 8 of your diary, we will add up these numbers now

Add up the mumbers here:

=

And how many of these were due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)

Answer: ⌊_⌊_⌊_⌊_⌋ hours last three months

8.3. During the last three months, how much of your leisure time has been lost due to other disease(s)? If you have completed the column at page 8 of your diary, we will add up these numbers now

Add up the mumbers here

=

And how many of these were due to other diseases??

Svar: ⌊_⌊_⌊_⌊_⌋ hours last three months.

9. Use of drugs

9.1. During the last three months, have you taken any medication due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)?

Yes ☐ No ☐

If "yes" proceed to 9.2, if "no" ask the following control question:

9.1. k. So you have no taken any inhaled medicine, no tablets, no drugs for phlegm problems and no allergy tablets against any lung or airway trouble during the last three monhts. No regualr medication as well as no short courses or over-the-counter-medication?

Yes ☐ No ☐

***If the participant had exacerbation symptoms the last three months, this should be referred to specifically. If* "yes" answer 9.2., if "no" proceed to 9.8.**

9.2. During the last three months, have you received any new prescription medication due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)?

Yes ☐ No ☐

If yes, complete the table below, if no

9.2. k. "so your doctor has not given you any new medication due to asthma, COPD or worsening of respiratory symptoms"

Yes ☐ No ☐

If yes, complete the table below, if no proceed to next question

Drug code	Date administered	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Dose *(dose pr 24h, note B if "as need medication")*	Date to be stopped

If difficulties with answers concerning dates – ask which month this was and then whether it was in the beginning, in the middle or at the end of the month the middle = 15th, the beginning = 1st , end = the beginning of next month.

9.3. During the last three months, have you taken more than usual of any of your regular medication due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)?

Yes ☐ No ☐

If yes – complete the table below, if no:

9.3. k No transient increases of dose, or in any other way increased use of your regular medication during the last three months?

Yes ☐ No ☐

If yes, complete the table below, if no proceed to next question

Drug code	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Number of extra doses last three months (units)

9.4. During the last three months, have you received any short term courses or other transient treatment due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)? (e.g. penicillin, antibiotics, cortison, prednisolon, medrol or other)

Yes ☐ No ☐

If "yes" complete the table, if no:

9.4. k. No courses of treatment during the last three months?

Yes ☐ No ☐

If yes, complete the table below, if no proceed to next question

Drug code	Date administered	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Dose *(dose pr 24h, note B if "as need medication")*	Date to be stopped

9.5. During the last three months, have you had to use any "as need" or reliever-medication due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)?

Yes ☐ No ☐

If "yes" complete the table below, if no:

9.5. k. So you haven't been in need of any "as need" medication the last three months?

Yes ☐ No ☐

If yes, complete the table below, if no proceed to next question

Drug code	Formulation *(1=tablet,2 = mixtuer 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Number of doses last three months (units)

9.6. During the last three months, have you bought any over-the-counter medication due to asthma, COPD or worsening of respiratory symptoms (for instance a cold)? (For instance pain killers, anti-pyretics, cough relievers or phlegm medication)

Yes ☐ No ☐

If yes – complete the table, if "no":

9.6. k. So you haven't bought any over-the-counter medication due to your lung or airways trouble during the last three months?

Yes ☐ No ☐

If yes, complete the table below, if no proceed to next question

Drug code	Date administered	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Dose *(dose pr 24h, note B if "as need medication")*	Date to be stopped

9.7. During the last three months what have been your total expenses related to drugs for asthma, COPD or worsening of respiratory symptoms?

Answer: NOK ⌊_⌊_⌊_⌊_⌋ *Specify:* And this was exclusively due to asthma, COPD and airway issues?

9.8. Have you been vaccinated against pneumonia or influeza during the last three months?

Yes ☐ No ☐

If yes answer 9.8.1., if no proceed to 9.9.

9.8.1.

Vaccine	**When given (date)**	**Costs (NOK)**
Influenza		
Pneumonia		

Drugs for other diseases

9.9.0 During the last three months, have you used drugs for other diseases or bothers than asthma, COPD or airway bothers?

Yes ☐ No ☐

If yes, proceed to 9.9.1.If no, answer the control question:

9.9.0.k: So you don't use any medication for other illnesses?

Yes ☐ No ☐

If yes, proceed to 9.9.1. If "no" go to 9.11

9.9.1. During the last three months, have you received any new prescription medication due to other diseases or bothers than asthma, COPD or airway bothers?

Ja ☐ Nei ☐

If yes, complete the table below, if "no" proceed to next question:

9.9.1.k. So you have not received any new regular medication for other diseases during the last three months?

Yes ☐ No ☐

If yes, complete the table below, if no proceed to next question

Drug code	Date administered	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Dose *(dose pr 24h, note B if "as need medication")*	Date to be stopped

9.9.2. . During the last three months, have you taken more than usual of any of your regular medication due to other diseases or bothers than asthma, COPD or airway bothers?

Yes ☐ No ☐

If yes – complete the table below, if no:

9.9.2.k. So you have not taken more of medications due to other diseases during the last three months?

Yes ☐ No ☐

If yes, complete the table below, if no proceed to next question

Drug code	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Number of doses last three months (units)

9.9.3. During the last three months, have you received any short term courses or other transient treatment due to other diseases or bothers than asthma, COPD or airway bothers?

Ja ☐ Nei ☐

If "yes" complete the table below, if no:

9.9.3.k. So you have not received any courses for other diseases or bothers the last three months

Yes ☐ No ☐

If yes, complete the table below, if no proceed to next question

Drug code	Date administered	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Dose *(dose pr 24h, note B if "as need medication")*	Date to be stopped

9.9.4. During the last three months, have you had to use any "as need" or reliever-medication due to other diseases or bothers than asthma, COPD or airway bothers?

Yes ☐ No ☐

If "yes" complete the table below, if no:

9.9.4.k. So you haven't made use of any "as need"-medication the last three months?

Yes ☐ No ☐

If yes, complete the table below, if no proceed to next question

Drug code	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Number of doses last three months (units)

9.9.5 During the last three months, have you bought any over-the-counter medication due to other diseases or bothers than asthma, COPD or airway bothers?

Yes ☐ No ☐

Ved ja, fyll ut tabellen nedenfor. Ved nei:

9.9.5.k. So you haven't bought any over-the-counter medication the last three monhts?

Yes ☐ No ☐

If yes, complete the table below, if no proceed to next question

Drug code	Date administered	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Dose *(dose pr 24h, note B if "as need medication")*	Number of doses last 3 months *(only "as need" medication)*

9.10. During the last three months what have been your total expenses related to drugs for other diseases or bothers than asthma, COPD or airway bothers?

Answer: NOK ⌊_⌊_⌊_⌊_⌋ *Specify:* And this was exclusively due to other diseases?

In general

9.11. During the last three months, how many times have you been at the pharmacy and picked up medication (irrespective of cause) without having to pay for it?

Number of times ⌊_⌊_⌊_⌋

9.12. During the last three months, have you stopped taking any of our regular medication or had the dose changed?

Yes ☐ No ☐

If yes, complete the table below. I no: "so you haven't stopped taking or changed the dose of any of your medication the last three months?"

Drug code	Date stopped	Date of change	Formulation *(1=tablet,2 = mixture 3= inhaler, 4 =nebulizer, 5 = injection fluid, 6 = other)*	Strength *(unknown is to be marked by a line)*	Dose *(dose pr 24h, note B if "as need medication")*

10. Nebulizer, ventilatory support, oxygen, other aid equipment

10.1. Do you have a nebulizer at home? Yes ☐ No ☐

Nebulizer – machine that give you medication to inhale from liquid state.

If yes, answer 10.2. If no, proceed to 10.3.

10.2. The last three months, have you had any expenses related to your nebulizer?

Answer: NOK ⌊_⌊_⌊_⌊_⌋

10.3. The last three months, have you had to get any aid equipment, irrespective of cause (*give examples:* hospital bed, wheel chair, roller, et cetera)?

Yes ☐ No ☐

If yes, answer 10.4. if no proceed to 10.5.

10.4. What aid equipment was this, and what did they cost you?

What aid equipment	*Due to airway or lung disease?**	Costs last three months (NOK)

* *Ask:* Why did you get this aid equipment?

After asking 10.4 concerning one aid equipment: "Did you receive any other aid equipment the last three months?"

10.5. Do you have a breathing machine at home (respirator, BiPAP, CPAP)? Yes ☐ No ☐

If yes, answer 10.6.-10.7. If no, proceed to 10.8.

10.6. What kind of machine?

- ☐ BiPAP
- ☐ CPAP
- ☐ respirator

10.7. The last three months, have you had eny expenses related to this treatment?

Answer: NOK ⌊_⌊_⌊_⌊_⌋

If yes answer 10.10, 10.11., 10.12. and 10.13. If no proceed to 10.14

10.10. When did you start using oxygen?

Date ____/ _____ / _____

10.11. Which device do you use?

Oxygen concentrator: ☐
Liquid oxygen ☐
Bottled oxygen when traveling/exercising ☐

10.12. Who supplies you with the equipment?
Bergen health region ☐

Other:
Answer: ……

10.13. Who supplies you with oxygen?
Gasservice ☐
Other:
Answer: ……

10.14. Use of oxygen

Normal oxygen dose *(litres/minute)* rest/excercise	Increased dose last three months *(litres/minute)* Rest/excercise	Use per 24 hours usually	Increased use per 24 hours last three months

10.15 During the last three months, how many times have you received ozygen deliveries?

Answer: ⌊_⌊_⌋ ganger

10.16. During the last three months, have you had any expenses related to oxygen treatment?

Answer: NOK ⌊_|_|_|_⌋

11. Adaptation or change of residence

11.1. The last three months, have you had to move due to asthma, COPD, or worsening of respiratory symptoms?

Yes ☐ No ☐

If yes, answer 11.2. If no proceed to 11.3.

11.2. What were your expenses in relation to this change of residence?

Anwer: ⌊_|_|_|_|_|_⌋ NOK

11.3. The last three months, have you had to rebuild or adapt your residence due to asthma, COPD, or worsening of respiratory symptoms? Yes ☐ No ☐

If yes, answer 11.4. If no proceed to 12.0

11.4. What were your expences in relation to these changes of your residence?

Answer: ⌊_|_|_|_|_|_⌋ NOK

12. . Quality of Life (EQ-5D)

I will read three statements in 5 goups please indicate which statements best describe your own health state today.

12.1 Mobility

I have no problems in walking about . ❑

I have some problems in walking about ❑

I am confined to bed ❑

12.2 Self-care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I a unable to wash or dress myself eller kle meg. ❑

12.3 Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activitites ❑

I am unable to perform my usual activities ❑

12.4 Pain/Discomfort

I have no pain or discomfort. ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

12.5 Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed. ❑

I am extremely anxious or depressed. ❑

12.6 To help people say how good or bad a health state is, we would like you to imagine a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad is your own health today, in your opinion.

My state of health today ⌊_⌋⌊_⌋⌊_⌋ (0-100 – integers only)

13.Conclusion:

13.0. Other information of interest from the interview:

. . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .

13.1. Next interview: ___/___/_____

Closure text:

[varies according to which interview]

Conclusion

13.2. The last three months the participant has (one tick at the highest level of health care this period)

☐ been admitted to hospital due to COPD
Number of times:

☐ had an extra visit to his/her doctor due to COPD
Number of times::

☐ been in contact with the doctor by telephone:
Number of times::

☐ by her/himself incesed the drugs due to COPD.
Number of days:

☐ more bothered by heavy breathing than usually, bot no change of medication:
Number of days:

☐ no change in his/her disease

13.3 The interviewers evaluation of the interview:

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

uib.no

ISBN: 9788230866115 (print)
9788230852330 (PDF)