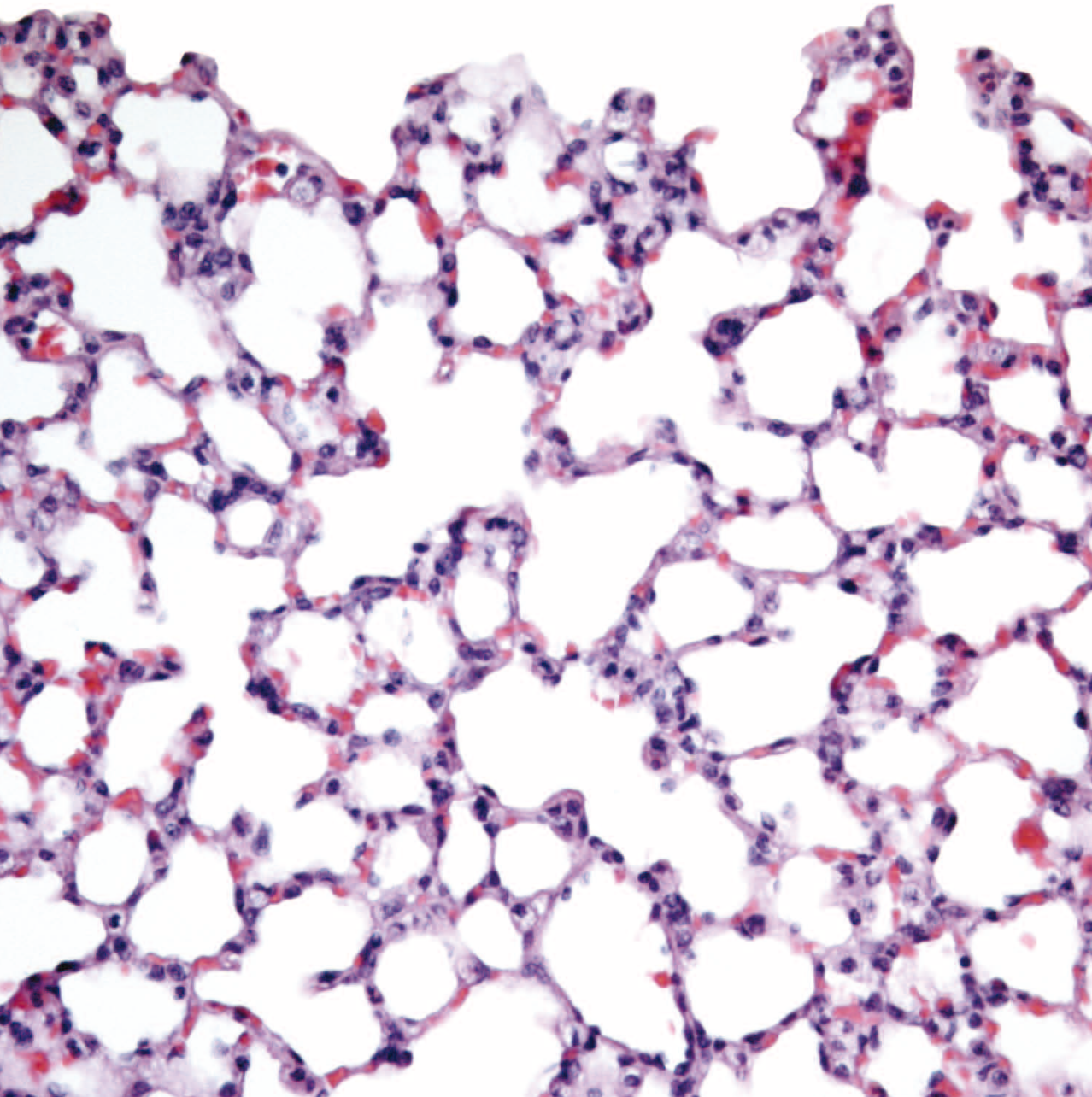
Economic impact of COPD

Empirical and model-based studies on the cost-effectiveness of treatment options

Martine Hoogendoorn



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Economic impact of COPD

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Economische impact van COPD

Empirisch en modelmatig onderzoek naar de kosteneffectiviteit van behandelmogelijkheden

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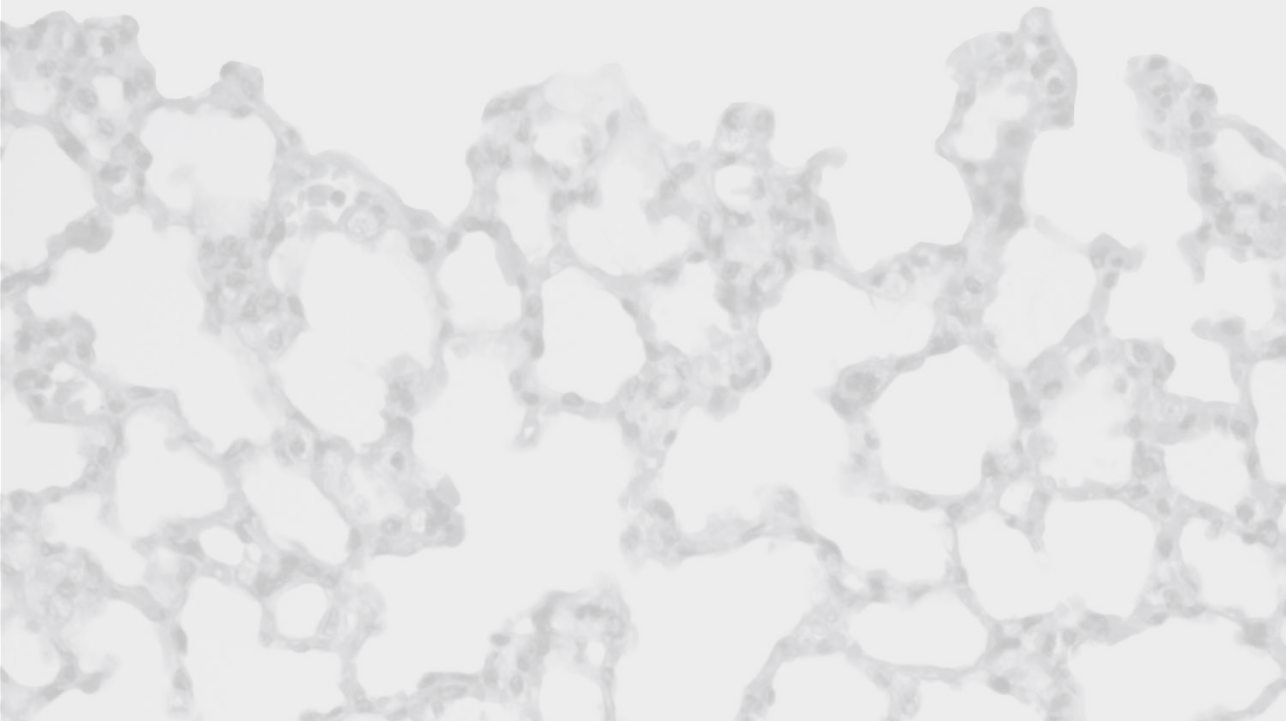
General introduction



General introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by progressive airflow limitation that is not fully reversible and is accompanied by extra-pulmonary effects that can lead to important co-morbidities. The treatment of COPD is associated with substantial healthcare costs, which are expected to increase in the future. Therefore the need for information on efficient treatment options in terms of both effects and costs is high. This thesis aims to investigate the costs and cost-effectiveness of treatment options for COPD to contribute to evidence-based policy making. This introduction provides background information on COPD and describes the disease characteristics, epidemiology, the social and economic burden and the available treatment options and their potential cost-effectiveness.

Disease characteristics

This overview starts with a description of the most important disease characteristics of COPD. The main respiratory symptoms are cough, sputum production and dyspnoea or abnormal shortness of breath [1]. In more severe stages of the disease respiratory failure can lead to right heart failure, which is an often occurring complication in COPD [2]. The most important systemic effects and co-morbidities of COPD are weight loss, loss of fat-free mass (cachexia), skeletal muscle dysfunction, cardiovascular disease, osteoporosis, diabetes, lung cancer and depression [3].

The progression of COPD is often accompanied by periods of increasing symptoms named exacerbations. A COPD exacerbation is defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD [4]. In clinical studies several definitions of an exacerbation have been used, which can be roughly divided into definitions based on an increase in symptoms (symptom-based definitions) and definitions based on an increase in healthcare use due to an increase in symptoms, such as use of antibiotics and/or oral steroids or hospitalization (event-based definitions). Although the exact cause of exacerbations remains unknown in about one third of cases, most exacerbations appear to be caused by viral and bacterial infections [5]. A large observational study showed that the best predictor of getting an exacerbation was a history of exacerbations in the year prior to the study indicating that some patients seemed to be more susceptible to exacerbations than others [6]. Exacerbations are important events in COPD because they are associated with an increase in mortality [7,8], a significant impairment of health-related quality of life [9-11] and an increase in healthcare use and associated costs [12,13], especially in case of a hospitalization [14].

Long-term smoking is the most important risk factor for the development of COPD [1,15,16]. Besides smoking, genetics and occupational exposures can play a role in the development of COPD. Factors, such as outdoor air pollution and second-hand smoke, seem to be associated with COPD, although causality is less clear [17]. In developing countries biomass fuel smoke may be an important risk factor too [18].

Diagnosis of COPD requires lung function measurement obtained by spirometry testing. Most relevant outcomes of this test to set the diagnosis of COPD are the forced expiratory volume in one second (FEV_1), the volume of air that can be expelled from maximum inspiration in the first second, and the forced vital capacity (FVC), the volume of air that can be forcibly expelled from the lung from the maximum inspiration to the maximum expiration. Airflow limitation is most often defined as a FEV_1/FVC ratio of less than 0.7, although a FEV_1/FVC ratio below the lower limit of normal (<5%) is increasingly recommended [1,19,20]. However, in daily practice the diagnosis of COPD is still often based on symptoms and a history of exposure to risk factors for the disease, especially when spirometry results are unavailable [21]. If patients are diagnosed with the disease, the severity of the COPD can be classified based on the degree of airflow obstruction. One of the most often used severity classifications for COPD based on the FEV_1 as percentage of the predicted value is the classification proposed by the Global initiative for chronic Obstructive Lung Disease (GOLD). The GOLD classification distinguishes four severity stages: mild (FEV_1% predicted ≥ 80%), moderate (50% ≤ FEV_1% predicted<80%), severe (30 ≤ FEV_1% predicted <50%) and very severe COPD (FEV_1% predicted<30%) [1]. Because COPD is more and more regarded as a multi-component disease, it is increasingly recognized that the severity of the disease should be based on more indicators than lung function alone. One of the most important factors determining disease severity of COPD is the presence of co-morbidities. Other factors influencing disease severity are the level of dyspnoea and the degree of exercise impairment. The recently performed ECLIPSE study showed that within each GOLD severity stage there was a wide variation in symptoms, number of reported exacerbations, exercise tolerance and prevalence of co-morbidities, indicating that the complexity of COPD is not captured by lung function alone [22]. In the recent past different composite measures are proposed to assess the severity of COPD. These measures combined several parameters such as body mass index (BMI), airflow obstruction, dyspnoea, exercise capacity, smoking status, age or exacerbation frequencies into one outcome [23-25]. Although these composite measures of severity are good predictors of mortality and quality of life, their usefulness in guiding treatment in routine clinical practice remains to be proven.

Prevalence

The World Health Organization (WHO) estimated that worldwide 64 million people suffer from COPD [26]. Prevalence estimates show wide variation between regions, but differences in estimates also occur as a result of differences in methods and criteria used. Two large population-based surveys performed in 17 different cities around the world reported prevalence estimates based on spirometry ranging from 7.8 to 26.1% for the population above 40 years of age, 11 to 28.7% for males and 5.6 to 25.7% for females [27,28]. A meta-analysis from 2006 by Halbert et al reported a pooled prevalence of 9.2% (95% CI: 7.7; 11.0) for studies using spirometry to diagnose COPD [29]. Pooled prevalence based on patient-report or physician diagnosis without spirometry resulted in lower estimates, 4.9% (95% CI: 2.8; 8.3) and 5.2% (95%CI: 3.3; 7.9), respectively, which may be an indication of under-diagnosis. Prevalence estimates are usually higher in men than in women [27-29], because the smoking epidemic started earlier in men than in women. In the Netherlands COPD prevalence based on general practitioner registrations was estimated to be 4.1-5.4% for the population above 40 years, 4.6-5.9% for males and 3.7-4.7% for females [30-32]. A Dutch study using a COPD diagnosis based on the combined information of spirometry and/or physician-diagnosis found a COPD prevalence of 11.6% for the population above 55 years [33]. Under-diagnosis of COPD is very common and possibly as high as 50 to 75% [34-37]. Over- diagnosis may however, also be present. The often recommended fixed value of 0.7 for the FEV_1/FVC ratio below which airflow obstruction is present may result in over-diagnosis in especially elderly patients, because the FEV_1/FVC ratio decreases with age. Using the lower limit of normal of the FEV_1/FVC ratio to identify patients with COPD would reduce this over-diagnosis [38,39]. Worldwide, the prevalence of COPD is expected to increase mainly due to ageing of the population and an increase in the prevalence of smoking, especially in the developing countries and among women. The general picture in the Netherlands and other Western countries seems to be that age-specific or age-adjusted prevalence rates are stable or even decreasing in men but still increasing in women [30,40-43]. However, due to demographic changes the absolute number of male and female COPD patients is still expected to increase in the coming decade.

Disability and mortality

COPD is a major cause of morbidity and mortality worldwide [44]. Because COPD is associated with a significant impairment in quality of life, especially in the more severe stages [45-48], COPD has a large impact in terms of morbidity. In 2004 COPD was the 7th leading global cause of years of life lost due to disability in high-income countries [26].

Due to the expected increase in prevalence, the burden of COPD is expected to increase [1,26,49]. The Global Burden of Disease Study 2004 projected COPD to be the fifth leading cause of disability worldwide in 2030. A study of Jemal et al showed that from six major causes of death COPD was the only condition for which mortality rates were increasing between 1970 and 2002 and expected to increase continuously [50]. In 2004 about 3 million people died of COPD, 5% of all deaths worldwide in that year, making it the fourth leading cause of death [26]. A similar pattern was seen in the Netherlands, where in 2007 about 6,400 people died of COPD, making COPD the fourth leading cause of death in men and the eighth cause of death in women [51]. The excess mortality among patients with COPD is high, not only because of the presence of COPD but also because of the increased prevalence of other smoking-related diseases [52]. Therefore estimates of mortality due to COPD may be even higher, because COPD is often not recorded as the primary cause of death [53].

Economic burden

In line with the high burden in terms of disability, the economic impact of COPD is also considerable. Cost-of-illness studies provide insight into the costs related to COPD in society. Costs attributable to COPD can be divided into direct medical costs and cost due to productivity loss. Direct medical costs are costs directly related to diagnosis and treatment of the disease, such as spirometry, medication, physician visits and hospitalizations, while productivity costs are costs related to inability to perform work, such as work days off or early retirement. Table 1 shows the results of eleven cost-of-illness studies for COPD performed in ten different European countries [54-64]. All costs were converted to 2011 € using purchasing power parities (PPP) and national inflation rates [65,66]. Total direct COPD-related costs varied from €19 million for Iceland to €6,000 million for Germany. Annual direct costs for COPD per patient ranged from €323 in Norway to €3,637 in Italy. Only four studies reported indirect costs varying from €82 to €1,044 per patient per year [55,57,60,63]. Comparison of cost estimates between studies is however difficult due to differences in methods, perspective, healthcare setting, unit costs and type of patients included. The studies differ for example in types of resource use included. Furthermore, most studies reported only COPD-related costs, while three studies reported the additional healthcare costs of a COPD patient compared to a healthy control or the costs of COPD and COPD-related co-morbidities [56,57,59]. The Confronting COPD survey performed in 2000/2001 was an international survey estimating the burden of COPD in seven North-American and European countries using the same methodology in each country. The annual direct costs per patient in this study ranged from $522 in France to $4,119 in the U.S [67].

Table 1: Comparison of cost of illness studies for COPD in European countries (converted to 2011, €)

First author	Country	Year	Patient selection	Type of costs included	Perspective	Annual cost per patient (2011 €)	Total annual national costs (in million 2011 €)
Nielsen., 2009 [54]	Iceland	2005	Random sample of inhabitants of Reykjavik aged >40yr and FEV_1/FVC <0.7	Visits to GP and specialists, hospitalizations, medication, rehabilitation, oxygen therapy	Healthcare	€738	€19
	Norway	2005	Random sample of inhabitants of Bergen aged >40yr and FEV_1/FVC <0.7	Visits to GP and specialists, hospitalizations, medication, rehabilitation, oxygen therapy	Healthcare	€323	€160
De Miguel Diez, 2008 [55]	Spain	2003	Primary care patients aged ≥ 40yr with an FEV_1/FVC <0.7 and FEV_1% predicted<80%	Contacts with GP, specialists, hospitalizations, medication, ER visits, diagnostic tests, oxygen therapy, vaccinations, disability leave	Societal	€2,264 (direct costs) €2,346 (total costs)	-
Bilde, 2007 [56]	Denmark	2002	Age >40yr, at least one hospitalization for COPD (J42.9-J44) between 1998-2002 and at least one contact with healthcare provider in 2002	Hospital care, contacts with GP, specialists and paramedics	Healthcare	€4,817* €1,524 (COPD primary diagnosis)	€280* €88 (COPD primary diagnosis)
Dal Negro, 2008 [57]	Italy	2002	Age >18yr, diagnosis of COPD according to GOLD guidelines, in stable phase	GP, specialist and ER visits, hospital inpatient and day care, therapeutic consumption, work days off	Societal	€2,447 (direct costs)** €2,552 (total costs)**	-
Koleva, 2007 [58]	Italy	2002	Patients recruited at pulmonary departments aged >40yr, smoker or ex-smoker, FEV_1/FVC <0.7 and FEV_1≤80%	Specialist contacts, ER visits, diagnostic and laboratory tests, LTOT, physical therapy, hospital admissions and drugs	Healthcare	€3,647	-

Table 1: Comparison of cost of illness studies for COPD in European countries (converted to 2011, €) (continued)

First author	Country	Year	Patient selection	Type of costs included	Perspective	Annual cost per patient (2011 €)	Total annual national costs (in million 2011 €)
Detournay, 2004 [59]	France	2001	Age >45yr, >15 pack-years, chronic bronchitis defined as presence of cough, sputum or dyspnoea, FEV_1/FVC<80%, no childhood asthma	Drugs, physician visits, diagnostic tests, physiotherapy, respiratory assistance, hospitalizations, rehabilitation, transportation	Societal	€5,224* €3,426 (COPD cost only)	€4,200* €2,600 (COPD cost only)
Nowak, 2004 [60]	Germany	2001	Diagnosis COPD, age ≥40yr, ≥10 pack-years, cough, sputum and dyspnoea, FEV_1≤70%	Hospital care, medication, physician contacts, oxygen, devices, rehabilitation, care, smoking cessation and other therapies, productivity loss	Societal/ Healthcare	€2,274 (healthcare) €3,541 (societal)	€1,900-6,000 (healthcare) €3,000-9,600 (societal)
Miravittles, 2003 [61]	Spain	2000	COPD according to the ATS criteria, FEV_1/FVC <0.7 and FEV_1≤80%	Drugs, oxygen therapy, outpatient visits, ER visits, hospitalizations, laboratory and diagnostic tests	Healthcare	€1,845	€498
Hoogendoorn, 2006 [62]	Netherlands	2000	Data from representative national registries and surveys (COPD: ICD 490-492, 494, 496 or ICPC R91/R95)	Hospitalizations, contacts with GP and specialists, home care, drugs, oxygen therapy, vaccinations, lung transplantation	Healthcare	€1,144	€ 350
Jansson, 2002 [63]	Sweden	1999	COPD diagnosis according to the BTS criteria or mild COPD according to the GOLD guidelines	Hospitalizations, drugs, health-care visits and contacts, oxygen therapy, devices, absence from work and disability pensions	Societal	€745 (direct costs) €1,788 (total costs)	€ 506 (direct costs) €1,200 (total costs)
Sullivan, 2000 [64]	UK	1996	Data from the National Health Service Execute	Pharmaceutical treatment, oxygen therapy, hospital-based care, primary care and community-based services	Healthcare	€2,197	€1,600

* Additional healthcare costs of a COPD patient compared to a healthy control, ** Costs of COPD and COPD-related co-morbidities

Differences in costs could not be explained by differences in unit costs only, but were thought to be the result of differences in patient characteristics and management of COPD in the individual healthcare systems. The total direct medical costs for COPD in the Netherlands in 2000 were estimated to be €280 million or €915 per patient [62]. An update of this study found estimates of €356 million and €1,110, respectively for the year 2007 [68]. The Confronting COPD survey reported a total cost estimate of €1,024 per Dutch patient of which €614 was for direct costs [69].Seven of the studies mentioned in Table 1 specified the cost by COPD severity showing a strong correlation between costs and disease severity [54,57-61,63]. The costs of a patient with very severe COPD were on average about 3 to 4 times higher than the costs of a patient with mild or moderate COPD. The most important cost drivers in COPD are hospitalizations (40-45%) and medication (25-35%) [54,55,57-61]. As hospitalizations are mainly exacerbation-related and exacerbations often require an increase in use of medication, costs of treating exacerbations are estimated to account for 50-75% of the total COPD-related costs [19]. A review of Toy et al showed a wide variation in the estimated cost per exacerbation, €95 to €8,500 (2011 €) [70-72]. The cost of a severe exacerbation defined as a hospitalization ranged from €4,520 to €9,710 [12,73], while the costs of a mild or moderate exacerbation varied between €44 and €650 [70,73,74]. The positive association between costs and increasing disease severity and the high exacerbation-related hospitalization costs show that besides primary prevention the economic burden of COPD can mainly be reduced by interventions and therapies that reduce disease progression and decrease the number of exacerbations resulting in a hospitalization.

Treatment options

Once COPD has been diagnosed the most important goal is to prevent disease progression. Smoking cessation is still the most important and well-proven to be effective intervention to slow down the disease progression in COPD [75]. The Lung Health Study showed that COPD patients who quitted smoking had an improvement in lung function in the first year and the subsequent rate of decline was half the rate observed among continued smokers [76]. Therefore, current guidelines recommend that all smoking COPD patients should be offered the most intensive smoking cessation intervention feasible [1]. Next to smoking cessation therapy, all patients should receive an annual influenza vaccination to prevent the influenza virus from triggering a COPD exacerbation. Further management of COPD mainly focuses on relieve of symptoms, improvement of exercise tolerance and quality of life and prevention of exacerbations [1]. In addition, the commonly occurring COPD-related co-morbidities should be monitored and treated [77]. With respect to the management of stable COPD, treatment of mild COPD and moderate COPD is mainly limited to pharmacotherapy, i.e. bronchodilators to reduce

symptoms. Several bronchodilating agents are available, i.e. short- and long-acting β2-agonists and short- and long-acting anticholinergics. All these agents are proven to be effective, however, regular use of long-acting bronchodilators is most effective [1]. Treatment of mild COPD is limited to the use of short-acting bronchodilators if needed. In moderate COPD the addition of long-acting bronchodilators is recommended. When the disease progresses to severe COPD treatment with inhaled glucocorticosteroids in case of recurrent exacerbations is added [1]. Recent studies showed that inhaled corticosteroids might also have a beneficial effect in less severe COPD stages [78]. Effectiveness of inhaled corticosteroids in COPD has however been discussed for many years and is still the subject of an ongoing debate [79,80].

Non-pharmacological treatment of COPD consists of pulmonary rehabilitation and in case of very severe COPD oxygen therapy or surgery (lung volume reduction surgery or lung transplantation) [1,81]. Pulmonary rehabilitation consists of exercise training, education, self-management, psychological counseling and nutritional counseling. Exercise training aims to improve or maintain exercise capacity and the general condition of patients. Education, self-management and psychological counseling focus on improvement of medication use, coping with the disease and adopting a healthy lifestyle. Nutritional counseling aims to improve the nutritional status of underweight or muscle-wasted patients by giving them nutritional advice and nutritional supplements. The beneficial effects of exercise training with or without education in terms of improving exercise capacity, dyspnoea and quality of life are well proven in patients with more severe COPD [82,83]. Self-management programs including COPD education and/or self-treatment guidelines were also shown to be effective by having a significant effect on quality of life and hospitalizations [84]. Until recently pulmonary rehabilitation was mainly indicated for patients with severe COPD and provided in the setting of a hospital or respiratory rehabilitation centre. More and more guidelines now recognize the importance of reactivation by means of exercise training and nutritional counseling for patients with less severe COPD [1,83,85]. Programs for this patient population may well be implemented in a community-based setting provided by local physiotherapists and dieticians.

Besides the above described therapies, specific treatment options for small groups of very severe patients are available, such as oxygen and lung surgeries. Oxygen therapy is usually prescribed for patients with very severe COPD with a reduced arterial oxygen pressure (PaO_2<7.3 kPa) or an oxygen saturation of less than 88-90%. Long-term administration of oxygen has shown to reduce mortality [86]. Surgeries such as lung volume reduction surgery or lung transplantation are less often applied because of the high risk involved.

For patients in all severity stages treatment of exacerbations consists of an increase of regular bronchodilating medication, a course of antibiotics and/or systemic glucocorticosteroids and in severe cases additional oxygen or other types of ventilatory support.

Cost-effectiveness of treatment options

Although the clinical evidence for most treatment options of COPD has been well established, data about costs and cost-effectiveness used to be limited. In the past decade however, the number of economic evaluations of treatments of COPD increased. For the most important preventive intervention, smoking cessation, effectiveness and cost-effectiveness have been well proven in the general population [87-91]. However, there is only some evidence of effectiveness of smoking cessation interventions targeted to COPD patients and even when including the study reported in this thesis the information about the cost-effectiveness of these interventions in this specific patient group is very limited. One study showed that the one-year cost-effectiveness of bupropion and nortriptyline compared to placebo was €2,100 and €10,600 per additional quitter, respectively [92]. The long-term cost-effectiveness of smoking cessation interventions for COPD patients was reported in a study included in this thesis [93]. This study showed that implementation of intensive counseling defined as more than 90 minutes counseling and intensive counseling plus pharmacotherapy (NRT, bupropion or nortriptyline) for patients with COPD was more effective than usual care. The costs per quality-adjusted life year (QALY) gained for both interventions were below €10,000, comparable with ratios presented for smoking cessation interventions in the general population. Although influenza vaccinations for patients with COPD are shown to be effective in reducing exacerbations [94], information about the cost-effectiveness is also scarce. A study from Hak et al showed that influenza vaccinations were cost saving in patients with chronic lung disease aged 65 years and over [95]. A study in COPD patients from Thailand reported the costs and effects of influenza vaccinations in terms of the cost of the vaccination and the resulting reduction in healthcare use. In this study the cost benefit from influenza vaccination was shown to be higher in patients with more severe airflow obstruction, because the savings in costs for hospitalizations and especially mechanical ventilation were higher in these groups compared to the group with mild airflow obstruction [96].

Information about the cost-effectiveness of pharmacotherapy for COPD has increased in the past five to ten years. A review of Rutten-van Mölken et al found thirty-five studies reporting about the cost-effectiveness of pharmacological agents for maintenance treatment in COPD [97]. The review showed that short-acting bronchodilators used in combination (β2-agonist plus ipratropium) were found to be cost saving compared to either drug alone. Evidence for the cost-effectiveness of long-acting β2-agonists was

mainly based on studies comparing salmeterol with a comparator, such as placebo or a short-acting bronchodilator. The cost per QALY for salmeterol reported in these studies varied between cost saving and $197,000. Studies investigating the cost-effectiveness of the long-acting anticholinergic agent tiotropium compared to placebo, ipratropium or salmeterol reported cost savings in the majority of studies. The remaining studies reported costs per QALY gained up to $26,000. Results for the cost-effectiveness of treatment with inhaled corticosteroids compared to placebo, no treatment or standard care were not consistent with cost per QALY ranging from about $13,000 to $78,000 or even dominance for the comparator. Studies comparing inhaled corticosteroids with salmeterol showed that the latter was more cost-effective. Almost all studies investigating the cost-effectiveness of a combination of a long-acting β2-agonist in combination with an inhaled corticosteroid found better effects and higher costs compared to the group receiving placebo, standard care or one of the single components. The cost per QALY in these studies showed a wide variation, from $24,000 to $450,000. One of the conclusions of the review of Rutten-van Mölken et al was that due to differences in methodology, comparator and time horizon used, results of the studies are difficult to compare [97,98]. To improve comparability all future studies should be more consistent in study methodology, use the same comparator and use the QALY as effectiveness outcome [97,98].

For the non-pharmacological treatment options information with regard to cost-effectiveness is limited. For pulmonary rehabilitation only three comprehensive economic evaluations, including the one reported in this thesis, have been published, two in patients with severe and one in patients with moderate to severe COPD [99-101]. The study of Goldstein et al reported the cost-effectiveness of a 2-months inpatient program followed by 4 months of outpatient training to range between $29,000 and $51,000 per patient achieving a clinical important improvement in different components of a quality of life questionnaire [99]. The one-year study of Griffiths found a 6-week outpatient program to result in better effects and to be cost saving compared to standard care [100]. The study reported in this thesis investigating the cost-effectiveness of a two-year community-based COPD management program compared to usual care in patients with less severe airflow obstruction found a cost per QALY gained of about €32,500 [101]. Besides the three comprehensive economic evaluations several studies reported about the program costs or the impact of the program on healthcare utilization, such as hospitalizations [102-105].

Evidence about cost-effectiveness was even more limited for the more specific treatment options, oxygen therapy and surgeries. No studies were found reporting about the costs per QALY using oxygen as maintenance therapy. For oxygen use in relation to treatment of a severe exacerbation two studies reported a cost-effectiveness ratio, ranging from cost saving to $45,000 per QALY [106,107]. The few other studies found only

reported about the savings in costs. Surgical procedures such as lung transplantation and lung volume reduction surgery are found to have very high cost-effectiveness ratios of $100,000 per QALY gained or higher [108,109].

Well-based information from economic evaluations is becoming more and more important for policy makers. The substantial current and increasing economic burden of COPD and the limited healthcare budgets increase the need for efficient treatment options in terms of both effects and costs.

Aim of this thesis

In 2003 the GOLD guidelines raised the issue of the lack of information on economic aspects of treatment options for COPD [110]. In the previous paragraph it is shown that this issue is still valid. The overall aim of the studies presented in this thesis was to provide new and additional data about the cost and cost-effectiveness of treatment of COPD and to contribute to evidence-based policy making for COPD in two ways:

1) by developing a decision analytic population-based COPD model, which can be used to estimate the (future) burden of COPD and the cost-effectiveness of a wide range of COPD interventions. As the epidemiology, burden and consequences of treating COPD are complex, a transparent model combining these elements can be a useful tool for policy making. A population-based COPD disease progression model has the potential to explore the implications of therapies for COPD over the whole spectrum from prevention to care, especially when direct information from long-term epidemiological studies or clinical trials is lacking. The model can be used to evaluate the short- and long-term effects of interventions of different intensity or for different target groups. Furthermore, by using the same model to estimate the cost-effectiveness of different interventions, the model can provide policy makers with comparable information.
2) by performing an empirical economic evaluation linked to a clinical trial that evaluated the effectiveness of a COPD management program. Because pulmonary rehabilitation used to be mainly indicated for patients with severe and very severe COPD, little evidence was available about the effectiveness of this kind of programs in patients with less severe COPD. Besides the issue of effectiveness and cost-effectiveness, it was also necessary to explore other settings of providing pulmonary rehabilitation programs, such as community-based instead of hospital-based, because capacity of hospitals or respiratory rehabilitation centers would not be sufficient to treat all patients who could benefit from a reactivation program. The economic evaluation presented in the second part of this thesis therefore aimed to estimate whether an interdisciplinary, community-based pulmonary rehabilitation program (INTERCOM) was cost-effective in patients with less severe airflow obstruction than the patients usually attending pulmonary rehabilitation programs.

Outline of this thesis

In the first part of this thesis, chapter two to seven, studies performed in relation to the development of the population-based COPD progression model are presented. The first version of the model was developed in 2002/2003 and presented in chapter three. The second updated and extended version of the model including exacerbations and probabilistic sensitivity analysis (2008-2010) is presented in chapter seven. Both chapter three and seven explain the structure, and input parameters of the model and examples of the potential use of the model are given, using the first or second version of the model, respectively.

Much effort was put into obtaining exacerbation-related input parameters. Chapter two, five and six show results of a thorough estimation of three types of model input parameters. In chapter two the severity distribution of COPD in the Dutch COPD population was estimated based on the GOLD classification. This distribution was used to distribute the prevalence in the model over the COPD severity stages. To include exacerbations in the second version of the model, the relation between exacerbations and lung function, mortality, lung function decline, quality of life and costs needed to be estimated. Results of the association with lung function and mortality were presented in separate manuscripts (chapter five and six). Chapter five shows the results of a review and meta-analysis performed to estimate the exacerbation rate specified by GOLD stage. Rates were estimated separately for total exacerbations defined by an increase in healthcare use (event-based), total exacerbations defined by an increase in symptoms and severe exacerbations defined as a hospitalization for COPD. Because higher mortality risks after a severe exacerbation often exceed the period of hospitalization, the case-fatality of a severe exacerbation was defined as the excess mortality associated with the exacerbation compared to the stable situation. Chapter six presents a meta-analysis estimating the case-fatality of a severe exacerbation.

An application of the model is shown in chapter four. This chapter presents the cost-effectiveness of smoking cessation interventions for COPD patients. Based on a literature review of trials evaluating a smoking cessation intervention in patients with COPD, the long-term effectiveness and cost-effectiveness of minimal counseling, intensive counseling and intensive counseling plus pharmacotherapy was estimated compared to usual care.

The second part of this thesis, chapter eight and nine, reports the two studies related to the economic evaluation of the INTERCOM trial. Chapter eight addresses the question whether this interdisciplinary community-based COPD management program is cost-effective for patients with less severe airflow obstruction. In this chapter, results of a comprehensive economic evaluation including all COPD as well as non-COPD related costs during the two years of the study are shown. Chapter nine reports a validation

study of the cost booklet that was used in the INTERCOM trial to collect resource use data. This booklet was validated against data from care-giver registrations. Furthermore, the impact of using costs based on the cost booklet or based on care-giver registrations on the cost-utility was calculated. Finally, in chapter ten the results of studies presented in chapter two to ten are discussed as well as the implications, methods used and the value of the results for policy making.

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Part one

Studies related to the development of a COPD progression model

Chapter 2

Severity distribution of chronic obstructive pulmonary disease (COPD) in Dutch general practice

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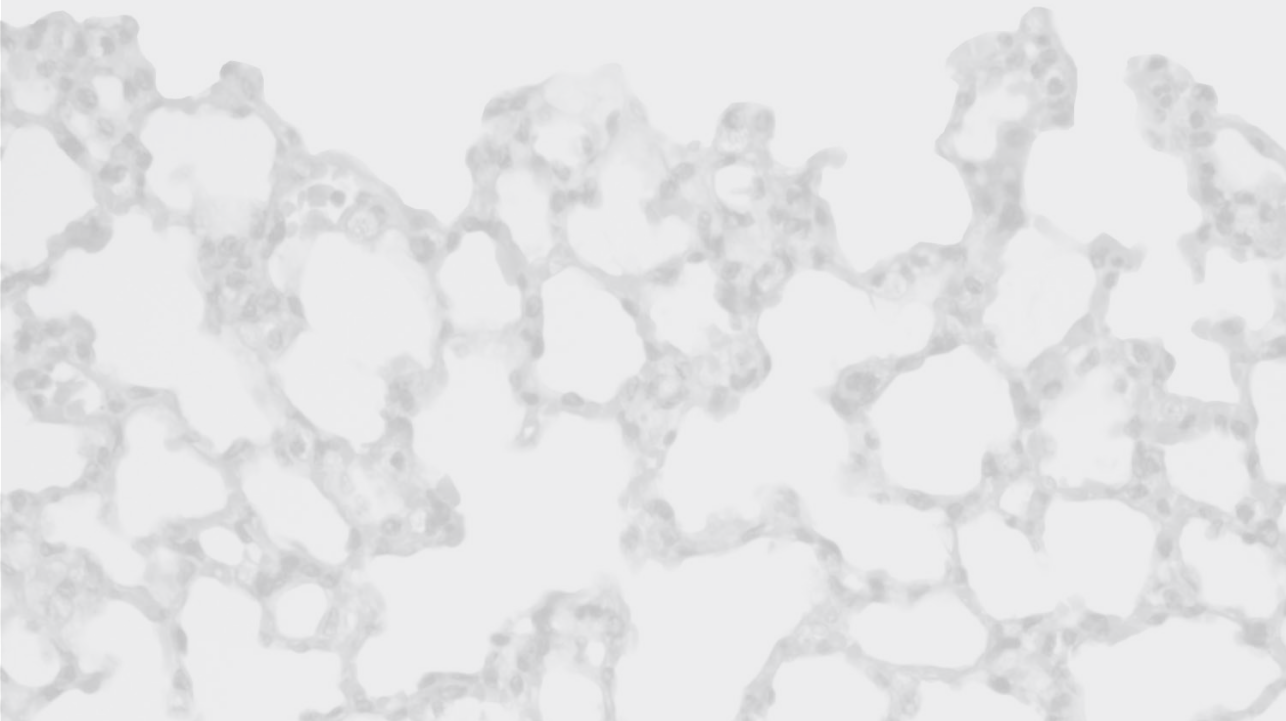

Abstract

The actual burden of chronic obstructive pulmonary disease (COPD) in terms of health-care use and costs strongly depends on the distribution of disease severity. For the Netherlands, the distribution of diagnosed COPD was estimated by classifying all patients with a physician diagnosis of COPD from two different sources of general practitioners (GP)-data into mild (27%), moderate (55%), severe (15%) or very severe COPD (3%) based on their post-bronchodilator FEV_1% predicted, according to the GOLD-guidelines. This distribution will most likely shift to the less severe stages when under-reporting and under-diagnosis are reduced.

Introduction

Worldwide, chronic obstructive pulmonary disease (COPD) causes serious health problems and disability. Models that project the future morbidity, mortality and costs of COPD show that the burden of COPD will increase during the next few decades [1, 2]. The actual burden in terms of costs strongly depends on the severity distribution of COPD in the population, as there is a powerful association between use of healthcare services and disease severity [3-5]. To project the future burden of COPD by disease severity and to evaluate the impact of different smoking cessation interventions for patients with COPD on the burden of COPD in the Netherlands, we have developed a population model that simulates disease progression over time according to severity stages [6]. To classify the prevalence of diagnosed COPD in the starting year of the simulation over the stages mild, moderate, severe and very severe COPD [7], it was necessary to know the distribution of COPD disease severity in the Dutch population of diagnosed COPD patients. Such data have not been reported in the literature before and are not routinely collected as part of any ongoing data registration. Because in the Netherlands virtually all people are registered with a general practice (GP), the prevalence of diagnosed COPD is generally derived from general practice databases. This study aimed to assess the severity distribution of COPD from GP databases in the Netherlands.

Methods

Two different sources of GP data were used. The first data source contained all patients with physician diagnosed COPD including those with co-existing asthma from five GP registrations in the Nijmegen Monitoring Project (NMP) [8]. These practices are part of the academic GP network of the University Medical Centre Nijmegen. In these practices, all patients with COPD are coded using International Classification of Primary Care [9] coding (R91/R95) and all available spirometric test results are stored electronically.

The second data source was a clinical trial that contained lung function data on COPD and asthma patients from 25 GP practices in the Amsterdam area [10]. All registered patients with a diagnosis of either COPD or asthma were asked to participate in the trial. To be enrolled in the trial, participants had to meet the following inclusion criteria: age 16 to 75 years, capable of filling in a Dutch questionnaire, no specific pulmonary disease other than COPD or asthma and absence of any disease in a terminal phase. Known asthma patients were excluded from the dataset. All patients with physician diagnosed COPD (including COPD with coexisting asthma) and patients for whom the exact GP diagnosis for the respiratory condition was unknown entered our analysis. For the latter

group, the final decision whether or not patients had COPD was based on lung function indices.

For both datasets the classification of COPD severity was based on post-bronchodilator FEV_1% predicted according to the class boundaries in the GOLD classification [7]. FEV_1% predicted was calculated using ECCS/ ERS equations [11]. Patients aged < 45 years were excluded.

For all NMP patients with a FEV_1/FVC ratio <70%, the largest FEV_1% predicted value of the two most recent consecutive years with measurements in the period 1997-2002 was used for classification. When post-bronchodilator values were not available, pre-bronchodilator values were multiplied by 1.095. This factor was based on the observed difference between pre- and post-bronchodilator values from NMP patients for whom both values were available (62%). All patients from the Amsterdam data with a FEV_1/FVC ratio <70% were classified based on the baseline lung function measurements of the clinical trial performed in the period 1995-1998.

Results

Study populations

In the NMP practices 530 patients had physician-diagnosed COPD. For 307 (58%) of them sufficient spirometric data were available. Patients with and without spirometry did not differ with respect to sex, age, co morbid conditions and number of drug prescriptions for COPD. Eighty-five patients were excluded from further analyses because their FEV_1/FVC ratio was >70%. Six additional patients were excluded because they were aged < 45 years. The remaining 216 patients (70% male) with a mean age of 67.7 years were classified according to the GOLD stages mild, moderate, severe and very severe COPD.

In the Amsterdam study 1325 patients (65%) of the 2047 patients, who met the inclusion criteria, were willing to participate. Patients who did not enter the clinical trial, were significantly younger and a higher percentage was male [10]. A total of 1308 patients had valid lung function measurements at baseline. From this group 607 patients with a diagnosis of asthma only, 400 patients with a FEV_1/FVC ratio >70% and 36 patients aged < 45 years were excluded. In total 265 COPD patients (65% male) with a mean age of 63.8 years remained for classification.

COPD severity distribution

Table 1 shows the results of the severity classification based on GOLD stages for both data sources separately as well as for both patient groups combined. Figure 1 shows

Table 1: Distribution of disease severity among COPD patients known to the general practitioner

	COPD severity by GOLD criteria, FEV_1/FVC<70%, Percentage (95%-confidence interval)			
	GOLD I	GOLD II	GOLD III	GOLD IV
	Mild: FEV_1% predicted ≥ 80%	Moderate: 50 ≤ FEV_1% predicted < 80%	Severe: 30 ≤ FEV_1% predicted < 50%	Very severe: FEV_1% predicted < 30%
NMP	31%	47%	19%	3%
Amsterdam	28%	55%	15%	2%
Total	30% (26; 34%)	52% (47; 56%)	17% (13; 20%)	2% (1; 4%)

FEV_1: Forced expiratory volume in one second
FVC: Forced vital capacity

the frequency distribution of FEV_1% predicted for the combined data. The bars show the empirical data, the continuous line the fitted normal distribution density function. Statistical testing demonstrated that the empirical data did not significantly deviate from a normal distribution with a mean FEV_1% predicted of 68.3 and a standard deviation of 19.9. For our simulation model we based the severity distribution on this normal distribution, truncated at 10 and 110 FEV_1% predicted: mild COPD 27%, moderate COPD 55%, severe COPD 15% and very severe COPD 3%.

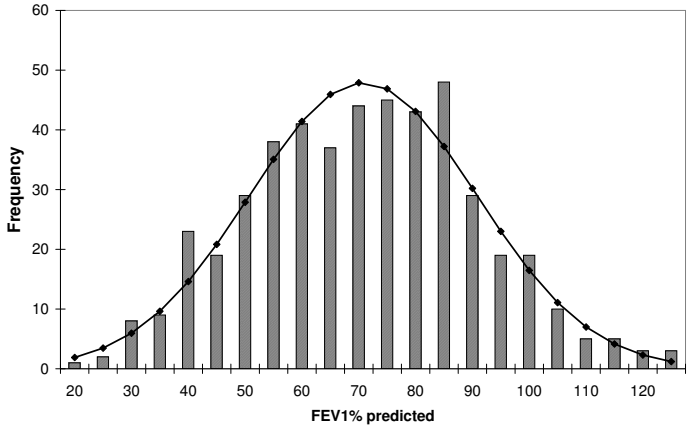

Figure 1: Frequency distribution of FEV_1% predicted of prevalent, diagnosed cases of COPD (n=481), defined as FEV_1/ FVC<70%, based on the combined data sources

Discussion

This study showed that in the Netherlands, in total, 80% of the patients with a physician diagnosis of COPD had mild or moderate disease whereas almost 20% had severe or very severe COPD. As virtually all people in the Netherlands, including those treated by pulmonologists, are registered with a GP practice, these data probably represent the population of physician-

diagnosed COPD patients fairly well. It does not reflect the COPD severity distribution in the entire Dutch community, as under-presentation and under-diagnosis is not accounted for.

Some of the patients also had a diagnosis of asthma. They were included. Excluding these patients has little impact; the proportion of patients with severe and very severe COPD changes from 19 to 22%.

The five NMP practices are known for keeping electronic records of spirometric test results. Nevertheless, spirometric data were absent in the electronic records for almost 40% of the patients with a physician diagnosis of COPD. Although no significant differences were found between the groups with and without spirometry on general characteristics, the lack of lung function data may have influenced the results. In the Amsterdam database the COPD and asthma patients who participated in the clinical trial were not completely representative for the total population of COPD and asthma patients in the 25 GP practices. Patients who refused to participate were significantly younger and a higher percentage was male. Whether this has influenced our results and to what extent is difficult to determine.

An interesting finding was that 32% of the patients with a physician diagnosis of COPD did not meet the criterion of airflow limitation as it is defined in the GOLD-guidelines (i.e., FEV_1/FVC ratio <70%). This indicates that in quite a few cases physicians do not base their diagnosis on lung function, but on criteria such as a history of smoking combined with chronic cough and dyspnoea over prolonged periods of time. As the systemic effects of COPD are increasingly recognized, it is likely that in the future COPD severity will be based on a combination of variables, like the recently published BODE-index, which combines FEV_1% predicted, dyspnoea score, 6-min walking distance and body mass index [12]. However, as this is only a recent development, no routine registrations exist that generate these data for epidemiological use yet.

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Chapter 3

A dynamic population model of disease progression in COPD

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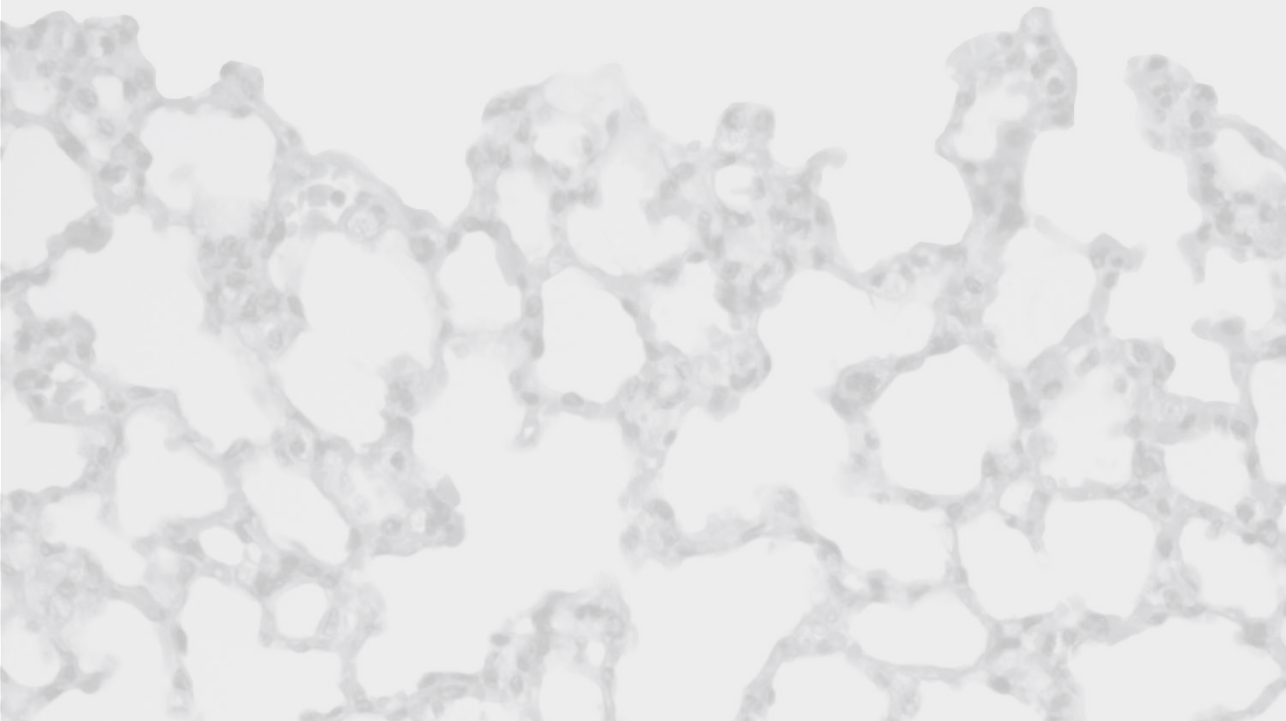

Abstract

To contribute to evidence-based policy making, a dynamic Dutch population model of chronic obstructive pulmonary disease (COPD) progression was developed. The model projects incidence, prevalence, mortality, progression and costs of diagnosed COPD by the Global Initiative for Chronic Obstructive Lung Disease-severity stage for 2000-2025 taking into account population dynamics and changes in smoking prevalence over time. It was estimated that of all diagnosed COPD patients in 2000 27% had mild, 55% had moderate, 15% had severe and 3% had very severe COPD. The severity distribution of COPD incidence was computed to be 40% mild, 55% moderate, 4% severe and 0.1% very severe COPD. Disease progression was modelled as decline in forced expiratory volume in one second (FEV_1) % predicted depending on sex, age, smoking and FEV_1% predicted. The relative mortality risk of a 10-unit decrease in FEV_1% predicted was estimated at 1.2. Projections of current practice were compared with projections assuming that each year 25% of all COPD patients receive minimal smoking cessation counseling or intensive counseling plus bupropion. In the projections of current practice prevalence rates between 2000-2025 changed from 5.1 to 11 per 1000 inhabitants for mild, from 11 to 14 per 1000 for moderate, from 3.0 to 3.9 per 1000 for severe and from 0.5 to 1.3 per 1000 for very severe COPD. Costs per inhabitant increased from €1.40 to €3.10 for mild, from €6.50 to €9.00 for moderate, from €6.20 to €8.50 for severe and from €3.40 to €9.40 for very severe COPD (price level 2000). Both smoking cessation scenarios were cost-effective with minimal counseling generating net savings. In conclusion, the COPD progression model is a useful instrument to give detailed information about the future burden of COPD and to assess the long-term impact of interventions on this burden.

Introduction

Worldwide, the increase in the prevalence, morbidity, mortality and costs of chronic obstructive pulmonary disease (COPD) that has been projected for future decades [1-3] has drawn the attention of healthcare policy makers. They realize that slowing down disease progression is one way to reduce the increasing healthcare costs, as there is a strong association between use of healthcare services and disease severity [4-7]. Currently the only available intervention proven to slow down disease progression before patients develop severe COPD is smoking cessation. The Lung Health Study (LHS) demonstrated that COPD patients who quit smoking had an improvement in lung function in the first year, and a subsequent rate of decline that was half the rate observed among continued smokers [8].

To project the future burden of COPD in the Netherlands by disease severity and to evaluate the impact of different smoking cessation interventions on the national burden of COPD, a population model has been developed that simulates COPD progression over four severity stages. The model builds further upon a dynamic multi-state life table model developed by the National Institute for Public Health and the Environment and described by Feenstra et al., which models the Dutch prevalence, incidence and mortality of COPD as a single disease state [3]. With this single-state model, the prevalence of COPD between 1994 and 2015 was projected to increase by 40% for males and 140% for females [3].

The objective of the present paper was to describe the design of the dynamic population-based COPD model with severity stages. The reason for developing this model was to provide healthcare policy makers, insurers and care-providers with detailed information about the future burden of COPD for the years 2000-2025 which can be used in planning public health strategies. The model is particularly suitable for comparing the impact of different interventions on the national burden of COPD on the long run. Therefore, the applicability of the model was illustrated by comparing two scenarios on increased use of smoking cessation interventions by COPD patients with current practice. Although the model is currently populated with Dutch data, it is likely that the trends represent other Western countries with an aging population and a history of a relatively high smoking prevalence (currently about 30% in the Netherlands).

Methods

General structure of the model

The COPD model is a dynamic population model that projects the incidence, prevalence, mortality, progression and healthcare costs of COPD per Global Initiative of Chronic

Obstructive Lung Disease (GOLD) severity stage as well as changes in the healthy population, i.e. no COPD, as present in the entire Dutch population. The multi-state model is based on the life table method as it follows births cohorts over time. Each year a new birth cohort is added, while the existing birth cohorts age by one year. Dynamics of the general population are taken into account using prognoses of birth, mortality and migration as obtained from Statistics Netherlands (Voorburg/Heerlen, The Netherlands). Within each birth cohort people can move between smoking classes, be diagnosed with COPD, move to another COPD severity stage or die, all with a certain annual probability. Changes in age and sex-specific smoking prevalence in the general population are computed by the model using the currently observed age and sex specific start, quit and restart rates that are based on data from the Dutch Foundation for Smoking and Health (STIVORO) and three Dutch cohort studies (table 1) [9-13].

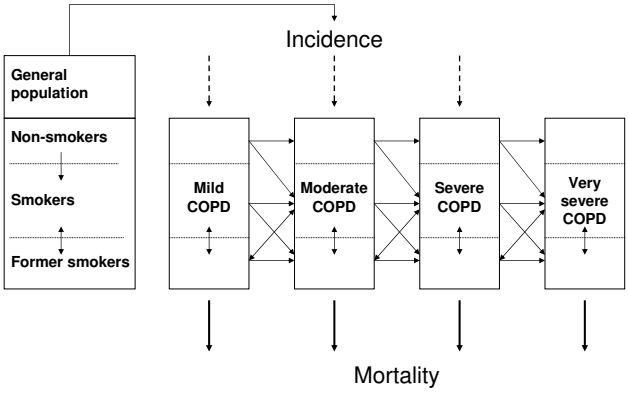

Figure 1: The four severity stages of COPD and the three classes for the risk factor smoking are the building blocks of the model. The dynamic nature is illustrated by the arrows representing the annual disease incidence, mortality, the transitioning of patients to more severe disease states and the changes between risk factor classes

COPD incidence and prevalence in the four severity stages are computed by sex and 5-yr age classes, starting at age 45 yrs and ending with at an age of >85 yrs. Incidence also depends on smoking status, defined as current smoker, non-smoker or ex-smoker. Disease progression is modelled as annual decline in forced expiratory volume in one second (FEV_1) % predicted, depending on sex, age, smoking status and FEV_1% predicted. Disease progression is then transformed into an annual transition rate, i.e. the annual probability of moving to a worse COPD stage (table 1). The effects of smoking cessation are modelled as a one-time increase in FEV_1% predicted and a reduced disease progression. COPD mortality rates (table 2) depend on FEV_1% predicted, age, sex and smoking. Competing risks have been accounted for by including smoking-related causes of death as well as other unrelated causes of death in the model. The model assumes "conditional

Table 1: Transition rates between smoking classes for the general population and the COPD population and transition rates between COPD severity stages for the year 2000

Smoking transition rates§	Start	Quit	Restart
General population	0.8%	3.6%	6.5%
COPD patients	0%	4.7%	2.6%
Severity stage transition rates#	**Non-smokers**	**Smokers**	**Former smokers**
Mild to moderate COPD	1.8%	2.5%	2.1%
Moderate to severe COPD	3.0%	3.7%	3.4%
Severe to very severe COPD	2.6%	3.1%	3.0%

§ Mean current observed smoking transition rates over all sex and age classes

Proportion of COPD patients transitioning to another severity stage associated with yearly decline in lung function

independence", i.e. within one age, sex and smoking class mortality rates for different diseases are assumed to be mutually independent. This implies for example, that given age and sex, the probability for a smoking COPD patient to die from lung cancer is the same as the probability for a smoking person without COPD. However, as there are more smokers and ex-smokers among COPD patients than among non-COPD patients, an average COPD patient has a higher risk of getting lung cancer and consequently, a higher risk of dying from it. Costs are calculated by multiplying the number of patients per sex, age and COPD severity stage with the annual costs per patient in the corresponding class. The structure, assumptions, input data and results of the model were discussed with an expert panel of scientists including pulmonologists. All mathematical details of the model have been described previously [14]. The main outcome parameters of the model were prevalence, mortality and costs specified by sex, age, smoking status, COPD severity and year.

Table 2: Prevalence#, incidence#, excess mortality^ and costs for 2000

	Prevalence	Incidence	Excess mortality	Costs per patient, €
Men				
Mild COPD	6.4	0.9	22.4	260
Moderate COPD	13.3	1.2	35.5	570
Severe COPD	3.7	0.1	54.0	1,900
Very severe COPD	0.6	0.003	77.3	6,400
Women				
Mild COPD	3.9	0.6	22.5	310
Moderate COPD	8.1	0.7	35.6	680
Severe COPD	2.3	0.06	54.3	2,300
Very severe COPD	0.4	0.002	77.4	7,600

per 1000 people in the Dutch population

^ per 1000 chronic obstructive pulmonary disease (COPD) patients in that specific severity stage

Input data

Prevalence by severity

COPD prevalence by sex and age was obtained from general practitioner (GP) registrations [15-17], indicating that it refers to "physician-diagnosed COPD". The mean prevalence rate for people aged >45 yrs was 67 per 1000 for males and 37 per 1000 for females.

To estimate the severity distribution of the prevalence of COPD in the Netherlands in the year 2000, two different sources of GP-data were used [15, 18]. The first database consisted of data from five general practices, which are part of an academic general practice network [15]. In these practices all available spirometric test results were stored in electronic patient files. The second database contained the lung function data of asthma and COPD patients from 25 GP practices at baseline of a clinical trial [18]. No specific criteria other than having a physician diagnosis of asthma or COPD and not having another pulmonary or terminal disease were used to allow patients to enter the trial. The FEV_1% predicted of all patients with a physician diagnosis of COPD, ≥45 yrs of age and airflow limitation (FEV_1/forced vital capacity <70%), from both data sources, was used to distribute COPD over mild, moderate, severe or very severe COPD according to the lung function boundaries in the GOLD-guidelines [1]. Both sources together contained a total of 481 COPD patients. The frequency distribution of their FEV_1% predicted did not significantly deviate from a normal distribution with a mean (SD) of 68.3 (19.9). From this distribution, truncated at 10 and 110 FEV_1% predicted, it was estimated that 27% (95% CI: 23; 31%) of the patients had mild COPD, 55% (95% CI: 51; 60%) moderate COPD, 15% (95% CI: 12; 19%) severe COPD and 3% (95% CI: 1; 4%) very severe COPD. This distribution was applied to each subgroup of COPD patients defined by sex, age and smoking status in the base year.

Incidence by severity

Total COPD incidence by age and sex was obtained from the same GP registrations as the prevalence data. The mean annual incidence rate for people aged >45 yrs was 6 per 1000 for males and 3 per 1000 for females. The distribution of the incidence over the severity stages was estimated mathematically such that given the prevalence, disease progression and mortality in 2000, the distribution of FEV_1% predicted in the entire COPD population in the year 2001 was not different from the distribution in the year 2000, when keeping smoking prevalence rates and population numbers constant. This resulted in a normal distribution for the incidence with a mean FEV_1% predicted of 76.4 (15.6). Using these normal distribution characteristics and the cut-off points of the COPD stages, the distribution of the incidence was estimated to be 40% in mild, 55% in moderate, 4% in severe and 0.1% in very severe COPD. This distribution was applied to the sex, age and smoking-specific incidence numbers in each year after 2000.

Decline in lung function by severity

Disease progression was modelled as annual decline in FEV_1% predicted, which depends on sex, age, smoking and FEV_1% predicted. Estimates of the decline in FEV_1%predicted were based on the Lung Health Study [8]. The original 5-year follow-up data from the 5887 COPD patients were re-analyzed using a random effect model with year, smoking cessation, sex, age, age^2, baseline FEV_1% predicted and all statistically significant second order interactions as explanatory variables (see Appendix I). The increase in FEV_1% predicted associated with smoking cessation was included in this same model. Increase and decline outside the range of the age and lung function values observed in the Lung Health Study were based on the equation given in appendix I. No data were available for non-smoking COPD patients. Therefore, decline among non-smoking COPD patients was assumed to be equal to the decline among the ex-smokers. Annual decline was transformed into stage transition rates indicating the probability of moving to a worse severity stage, from a given severity stage, e.g. from mild to moderate (see table 1). COPD patients who quit smoking could move to a less severe stage, but total remission from COPD was impossible. In the first year 0.6% of the moderate, smoking patients moved to mild COPD, 1.7% of the severe patients moved to moderate COPD and 1.8% of the very severe patients moved to severe COPD because of smoking cessation.

Mortality by severity

In the model, all cause mortality among COPD patients was divided into "excess mortality" and "mortality from other causes". Excess mortality was defined as the difference in mortality between COPD patients and the general population, which includes the increased risk of dying from other smoking related diseases.

In order to obtain a well-documented estimate of the relative risk for all-cause mortality per unit change in FEV_1% predicted, a meta-analysis was performed on papers published between 1970 and 2002, which reported the association between FEV_1% predicted and all-cause mortality in COPD patients (Appendix II). Other selection criteria were a follow-up of at least 3 yrs and a correction of the proportional hazard rate for at least age and smoking. The relative risks obtained from the different studies were combined into a weighted average, using the precision of the estimates in the study (i.e. the size of the 95% confidence intervals) as weights. Assuming a log-linear risk function, this meta-analysis resulted in an estimate of the RR per 10-unit decline of 1.20 (95% CI: 1.16; 1.23) for studies in COPD patients [19-23]. Hence, for each 10-unit decline in FEV_1% predicted, a 20% increase in excess mortality was modelled. As mortality increases with COPD severity, a 20% increase among patients with severe COPD has much more impact on absolute mortality than a 20% increase among patients with less severe COPD. Non-COPD related mortality was assumed not to depend on COPD severity, but only on sex, age and smoking.

COPD-related healthcare costs by severity

A Dutch prevalence-based cost of illness study for the year 2000 was performed. National and regional ongoing registrations or surveys were used from which the costs of GP-visits, outpatient visits, home care, day-care treatment in hospital, inpatient hospital care, nursing home and residential care, influenza vaccination, medication, oxygen therapy and lung transplantation were estimated (Appendix III). As there were no Dutch data on resource use per severity stage, a Swedish study was used to obtain ratios for the direct medical costs of a patient with moderate (2.22), severe (7.51) or very severe COPD (24.67) compared with the costs of a patient with mild COPD (1.0) [5]. These ratios were used to assign total Dutch costs within each sex and age class to the different severity stages.

Projections

Running the model for the period 2000-2025 resulted in projections of the COPD population and its cost of care for current practice. Prevalence and mortality rates were expressed as rates per 1000 inhabitants. The projections of current practice were an extrapolation of currently observed trends in smoking behaviour and disease progression. It was assumed that the age and sex specific incidence and mortality rates for each severity and smoking class remained constant. Throughout the projections, the costs per mild, moderate, severe and very severe patient were also assumed constant at the level of the year 2000.

Sensitivity analysis

To study the robustness of the projections of the model, extensive one-way sensitivity analyses were performed (SA1-SA8). In the first sensitivity analysis the severity distribution of the COPD prevalence was assumed to be age-dependent. For each year < 66 yrs (the mean age of the COPD patients the distribution was based on), the normal distribution shifted 0.5% predicted to the less severe stages, while for each year > 66 yrs it shifted 0.5% to the more severe stages. The second sensitivity analysis assumed the severity distribution of the incidence to be the same as the distribution of the prevalence, i.e. 27% of the incidence in mild COPD, 55% in moderate COPD, 15% in severe COPD and 3% in very severe COPD. The effect of the assumption that 60% of the incidence occurred in mild COPD and 40% in moderate COPD was investigated in the third sensitivity analysis. The fourth sensitivity analysis tested the effect of a 10% lower decline in FEV_1% predicted than predicted from the Lung Health Study, while the fifth sensitivity analysis tested the effect of a 10% higher decline. In the sixth sensitivity analysis the one-time increase in lung function of the COPD patients who stop smoking was assumed to be zero. The seventh sensitivity analysis assumed the decline in non-smoking COPD patients to be equal to the decline in smoking instead of former

smoking COPD patients. In sensitivity analysis eight, a more than exponential association between lung function and mortality risk (i.e. log-quadratic) was tested, because results of the meta-analysis gave indications for a deviation from the exponential model.

Evaluation of two scenarios on increased implementation of two smoking interventions

In the projections of current practice, annual changes in the number of non-smokers, smokers and ex-smokers, both in the general population and the COPD population, were modelled assuming that current age and sex-specific start, quit and restart rates for smoking remain constant over time. The current cessation probability among COPD patients was estimated to be on average 4.7% for both males and females. This current cessation rate was calculated by applying the sex and age specific cessation rates in the general population to the sex and age distribution of the COPD patients [9, 10].

To illustrate the potential use of the model in setting public health priorities, the cost-effectiveness of two smoking cessation scenarios was assessed. The first scenario assumed that smoking COPD patients were offered minimal counseling by the general practitioner, with a 12-months continuous abstinence probability of 7.9% [24, 25]. The second scenario assumed that smoking COPD patients were offered intensive counseling in combination with bupropion (IC+Bupr). The 12-months continuous abstinence of this intervention was 17.2% [26]. In both scenarios it was assumed that, each year, 25% of all COPD patients used the intervention. This implied that 25% of all smoking COPD patients had a higher smoking cessation probability of either minimal GP counseling (7.9%) or intensive counseling plus bupropion (17.2%). The remaining 75% of the smoking COPD patients kept the current cessation probability. Intervention costs of both smoking cessation interventions were based on bottom up estimates of resource use and costs per unit [27]. Estimates of resource use were based on practice guidelines and the original clinical trials from which the effectiveness data were taken. Intervention costs were €21 per patient for minimal GP counseling and €334 per patient for IC+Bupr. Both scenarios were compared with the projections made for current practice. The evaluation was performed over the period 2000-2025 and for different implementation periods of the interventions: 1, 10 or 25 yrs. Increasing the number of quitters resulted in less progression to worse severity stages, less mortality and less COPD-related costs. To calculate quality-adjusted life years (QALYs), life years were corrected for the quality of life during these years by means of the COPD severity stage specific QALY weights published by Borg et al [28]. To compute costs per life year and costs per QALY gained, the savings in COPD-related healthcare costs were subtracted from the additional costs of the smoking intervention. These net costs were divided by the gain in life years or the gain in QALYs. A discount rate of 4% was applied to both costs and effects.

Results

Prevalence and mortality

The model projected that between 2000 and 2025 the absolute number of diagnosed COPD patients increased from 188,000 to 270,000 for males and from 117,000 to 224,000 for females. The prevalence of COPD in the Dutch population of all ages was projected to increase from 24 to 33 per 1000 inhabitants for males and from 15 to 27 per 1000 inhabitants for females. The prevalence increased both in males and females, but the increase was higher for females. Figure 2 shows prevalence rates per severity stage over time. When prevalence rates for males and females were combined, they increased from

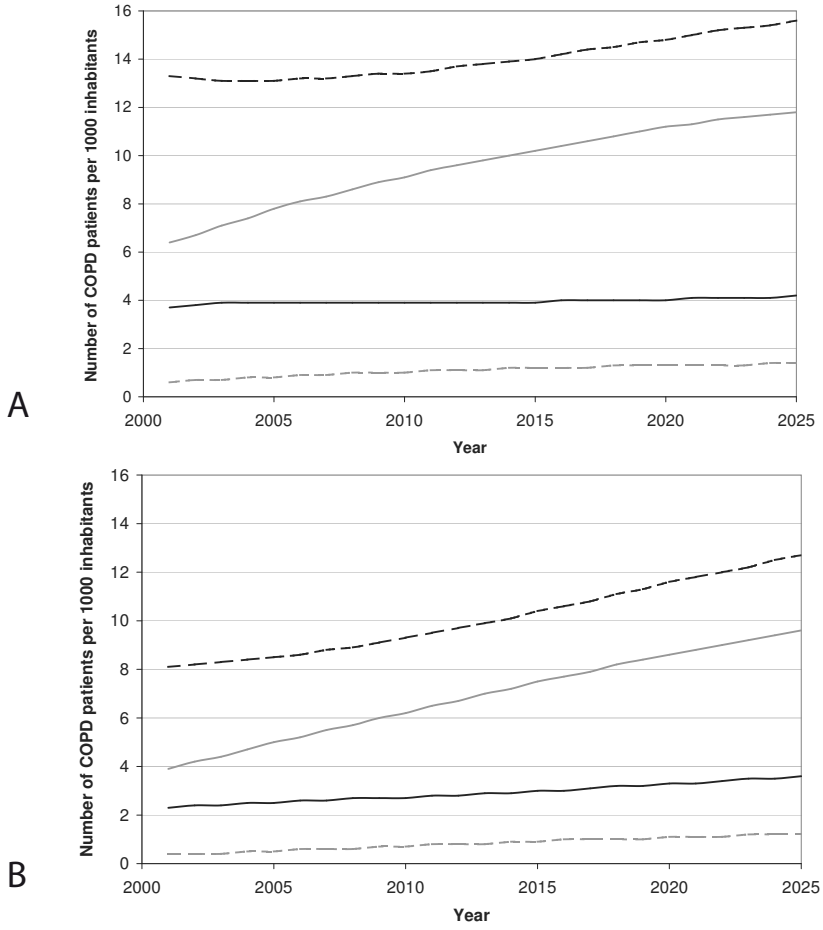

Figure 2A-B: Projections of the prevalence rates per severity stage over time for a) males and b) females. mild COPD (grey solid); moderate COPD (black dashed); severe COPD (black solid); very severe COPD (grey dashed)

5.1 to 11 per 1000 for mild COPD, from 11 to 14 per 1000 for moderate COPD, from 3.0 to 3.9 per 1000 for severe COPD and from 0.5 to 1.3 per 1000 for very severe COPD. This resulted in an increase of the total prevalence rate from 19 to 30 per 1000 inhabitants.

The absolute number of deaths among COPD patients increased from 15,000 to 23,000 for males and from 8,000 to 16,000 for females. For males the total mortality rate changed from 1.9 to 2.9 per 1000. This indicates that per 1000 males in the general population in 2025 2.9 men with COPD will die during that specific year. For females the total mortality rate increased from 1.0 to 1.9 per 1000. Figure 3 shows the absolute number of deaths among COPD patients for the different severity stages for the years 2000 and 2025. When mortality rates for males and females were combined, they increased from 0.3 to 0.7 per 1000 for mild COPD, from 0.8 to 1.1 per 1000 for moderate COPD, from 0.3 to 0.4 per 1000 for severe COPD and from 0.1 to 0.2 per 1000 for very severe COPD, resulting in an increase of the total mortality rate from 1.4 to 2.4 per 1000. These rates are expressed per 1000 inhabitants, thus reflecting that prevalence was highest for moderate COPD, followed by mild, severe and very severe COPD.

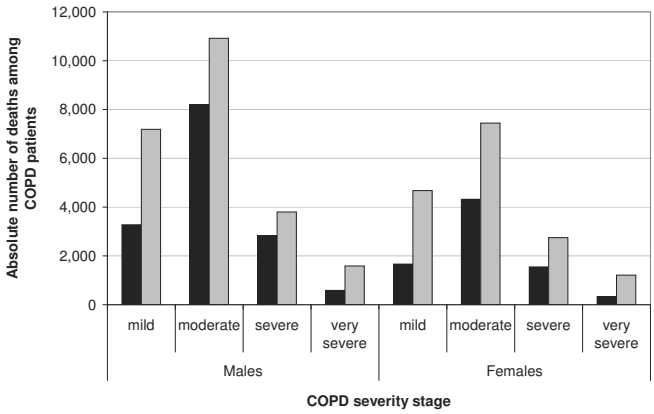

Figure 3: Absolute number of deaths among COPD patients in 2000 (black bar) and projections for 2025 (grey bar) by sex and severity stage

Healthcare costs

Total COPD-related healthcare costs in 2000 were estimated to be €280 million, €161 million for males and €119 million for females. The model projected the costs to increase to €495 million in 2025, €248 and €247 million for males and females, respectively. Because costs per patient in a severity class were kept constant over time, this increase in total costs was caused by the increase in prevalence combined with the change in the severity distribution of the COPD population. Figure 4 presents the total COPD-related healthcare costs per severity stage for the years 2000 and 2025. When expressed per

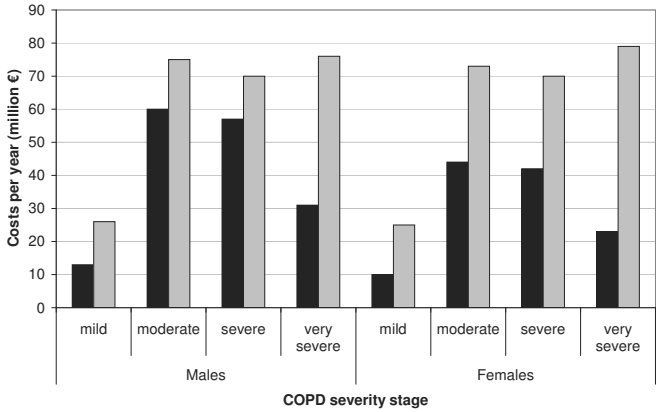

Figure 4: Total COPD-related health care costs in 2000 (black bar) and projections for 2025 (grey bar) by sex and severity stage

Dutch inhabitant, costs increased from €1.40 to €3.10 for mild COPD, from €6.50 to €9.00 for moderate COPD, from €6.20 to €8.50 for severe COPD and from €3.40 to €9.40 for very severe COPD, resulting in an increase of the total costs per inhabitant from €18 to €30.

Sensitivity analysis

Table 3 summarizes the results of the sensitivity analysis. All projections of total prevalence numbers in 2025 were within a range of 5% of the projections of the base-case.

Table 3: Sensitivity analyses on the projections of prevalence, mortality and total costs (2000, €) for 2025

	Total number of COPD patients	Percentage of COPD patients with mild, moderate, severe and very severe COPD	All-cause mortality (number of patients)	Total COPD-related healthcare costs (million €)
Base-case	494,300	36, 47, 13, 4	39,600	495
SA 1	501,200	37, 47, 12, 4	39,300	496
SA 2	475,400	26, 45, 21, 9	40,400	691
SA 3	514,000	51, 43, 4, 2	38,600	348
SA 4	496,600	37, 48, 12, 4	39,500	464
SA 5	491,900	35, 47, 13, 5	39,700	527
SA 6	492,700	35, 47, 13, 5	39,600	514
SA 7	493,900	36, 47, 13, 4	39,600	500
SA 8	492,400	36, 47, 13, 4	39,600	492

SA: sensitivity analysis; SA 1:severity distribution of the COPD prevalence is age-dependent; SA 2: severity distribution of incidence equals the distribution of the prevalence, i.e. 27% in mild, 55% in moderate, 15% in severe and 3% in very severe COPD; SA 3: severity distribution of incidence is 60% in mild and 40% in moderate COPD; SA 4: decline in FEV_1% predicted is 10% lower than estimated from the LHS; SA 5: decline in FEV_1% predicted is 10% higher than estimated from the LHS; SA 6: No increase in FEV_1% predicted after smoking cessation; SA 7: Never smoking COPD patients have the same decline as smoking COPD patients; SA 8: The association between lung function and mortality is more than exponential.

Variations in assumptions regarding the severity distribution of the prevalence by age (SA1), the decline in lung function (SA4 and 5), the decline in lung function among non-smoking COPD patients (SA7), increase after smoking cessation (SA6) or the association between lung function and mortality (SA8) hardly affected the estimates of prevalence by severity. Estimates of the COPD prevalence, mortality and costs were most sensitive to the assumption on the severity distribution of the incidence. The two assumptions regarding the distribution of incidence resulted in a shift of the severity distribution to either less severe stages (SA3) or more severe stages (SA2) compared to the base case. Projections of the costs in 2025 ranged from -30% (SA3) to +40% (SA2) of the costs projected for the base case model. When lung function decline was either 10% lower or 10% higher than predicted from the LHS data, the costs were 6% lower or higher compared to the base case.

Cost-effectiveness of smoking cessation in COPD

Increased implementation of minimal GP counseling for one year resulted in 1200 additional quitters compared to the projections of current practice. The intervention costs for 1-yr implementation were €800,000; €700 per additional quitter. In total, 4,700 additional quitters were gained after 1-yr implementation of IC+Bupr. The intervention costs for one-year implementation were €12.6 million, €2,700 per additional quitter. Table 4 shows the discounted cumulative costs and effects over a period of 25 years and the resulting cost-effectiveness ratios in terms of costs per life-year gained and costs per QALY gained.

Regardless of the implementation period, minimal GP counseling was a dominant strategy compared with current practice, because effects were higher and costs savings were higher than intervention costs. For a 25-yr implementation period at 4% discount-

Table 4: Number of (quality-adjusted) life years (Lys or QALYs) gained, total intervention costs, total savings and cost-effectiveness: cumulative over the years 2000-2025, discounted at 4% for both costs and effects (2000, €)

Duration of implementation	LYs gained	QALYs gained	Intervention costs (million)	Savings in COPD-related costs (million)	Costs per LY gained	Costs per QALY gained
1 year						
MC[#]	100	170	0.8	1.8	#	#
IC+Bupr[§]	500	790	12.6	6.9	10,600	7,300
10 years						
MC	1,100	1,700	7.1	15.2	#	#
IC+Bupr	4,000	6,200	104.6	56.6	12,000	7,700
25 years						
MC	1,400	2,500	15.3	24.5	#	#
IC+Bupr	5,400	9,300	219.1	88.0	24,500	14,100

MC = minimal GP counseling

§ IC+Bupr = intensive counseling plus bupropion

ing, 1,400 life years or 2,500 QALYs were gained. Subtracting the savings in COPD-related costs from the intervention costs over the 25-year period resulted in a net saving of €9.2 million. IC+Bupr is more effective. Over the 25-year period 5,400 life years or 9,300 QALYs were gained, but the intervention costs were much higher and not fully offset by extra savings. Costs per QALY gained were estimated to be €14,100 for IC+Bupr.

Discussion

Whenever it is important to inform policy makers about the expected future trends in the epidemiology of a disease and the long-term impact of implementation of certain interventions, modelling is required. In the present study a dynamic population model for COPD was developed that included progression of COPD over time from diagnosis of the disease to death. This model was used to project the prevalence, mortality and COPD-related healthcare costs by severity stage and to assess the long-term impact of two smoking cessation interventions.

The projections of current practice have shown that over a period of 25 years, an increase of 6 mild, 3 moderate, 0.9 severe and 0.8 very severe patients per 1000 inhabitants in the Netherlands can be expected. This increases total COPD-related healthcare costs from €280 to 495 million in 2025, an increase of almost 80%. Costs of COPD per Dutch inhabitant increase from €18 to 30. Of every 1000 inhabitants in the year 2025, 2.4 COPD patients will die compared with 1.4 in the year 2000. In absolute terms, prevalence, mortality and costs were highest for moderate COPD, but the proportional increase in these parameters between 2000 and 2025 was highest for very severe COPD and second highest for mild COPD. The latter is explained by the relative high incidence in this stage in combination with the slow progression of the disease. The first can partly be explained by the increasing number of Dutch inhabitants, especially females with a long smoking history, in the highest age categories.

The main reason to develop such a COPD model is to have an instrument with which to compare the success of various interventions in reducing the expected increase in the burden of COPD. This can only be done with a model that incorporates disease progression over time. To illustrate its use, projections of current practice were compared with two scenarios in which it was assumed that COPD patients more often get minimal counseling by a GP or IC+Bupr. The model showed that offering minimal GP counseling to 25% of all diagnosed, smoking COPD patients resulted in a gain in health and life years and net cost savings irrespective of whether the intervention was implemented for 1, 10 or 25 years. The combination of IC+Bupr to 25% of all smoking COPD patients each year, for a period of 10 years, resulted in costs per life-year gained of about €12000 (€7,700 per QALY), which is relatively low compared with other healthcare interventions.

The COPD model is embedded in a population model so that outcomes represent the Dutch setting. The Dutch COPD population, as in other high-income countries reflects the smoking epidemic of the past decades. Short-term developments depend on ageing and the effects of past smoking behaviour [3]. The current model describes these developments in detail and enables evaluation of policy measures to reduce the burden of COPD. For other countries with similar populations and comparable under-diagnosis, similar results might be expected. However, whether the cost effectiveness outcomes have validity for other countries also depends on the relative costs of different types of care. The model structure would allow translating the model to different countries using country specific data on costs, smoking behaviour and the severity distribution of incidence and prevalence.

It is important to stress that this is a model of physician-diagnosed COPD patients, since undiagnosed subjects are not modelled. Under-diagnosis is a well-known problem in COPD. However, because the model is intended to be a policy model, only diagnosed COPD is described and modelled. Undiagnosed patients may also use care for their COPD, but this care can never be related to COPD. An interesting topic for future research is the evaluation of case finding. Case finding efforts would shift the incidence distribution to the less severe cases, over time also shifting the prevalence distribution.

It is further important to note that because the model is a dynamic population model and not a cohort model that follows a group of COPD patients over time until they have all died, it does not suffer from cohort or survival effects.

In order to validate the model, outcomes of total COPD prevalence for the years 2000-2003 were compared to the prevalence as found in the Continuous Morbidity Registration (CMR) [15]. As differences in prevalence rates per 1000 between the model projections and the CMR data varied from 0.42 for females in 2003 to 3.71 for men in males, we concluded that our model projections compare quite well with this GP registration. As the CMR does not contain prevalence rates by disease severity, this registration could not be used to validate the severity distribution. The severity distribution of COPD was therefore validated with data from a Dutch study on a new regional patient management program in the Maastricht area (The Netherlands) in which all known COPD patients, treated either in primary care or by pulmonologists, underwent spirometry testing at baseline [29]. This study estimated the severity distribution of COPD in 2002/2003 to be 30% in mild, 48% in moderate, 17% in severe and 5% in very severe COPD. The current model projections for the year 2003 were 29, 52, 16 and 3%, respectively. Hence, they were quite close to the estimates from Maastricht. It is not possible to validate the model to historical data, as the severity distributions of incidence and prevalence were not available in the past, as lung function measurements did not routinely take place in GP practices.

Although modelling is a powerful tool to estimate the long-term effects of interventions that cannot be studied in clinical trials, it certainly has limitations. Due to limited

availability of suitable epidemiological data to generate robust estimates, making assumptions was inevitable. The most important assumptions will now be discussed. For simplification of the model the progression of COPD was assumed to be primarily dependent on decline in FEV_1% predicted, which in turn, depends on sex, age, smoking status and FEV_1% predicted. Of course, the progression of COPD is influenced by many other factors, such as smoking history, susceptibility to smoking and exacerbations. As the current model primarily concentrates on disease progression, it omits COPD exacerbations. Recently two studies have found indications that exacerbations accelerate the decline in lung function with about 8 ml/yr [30, 31], which seems to be relatively modest. Hence, the results presented above would probably not change much after inclusion of exacerbations. However, in order to model the cost-effectiveness of interventions that reduce the number, duration and/or severity of exacerbations, exacerbations will be included in future versions of the model. Currently, it is impossible to explicitly include treatment-related variables with a possible influence on COPD progression or survival, such as oxygen therapy or nutritional and exercise interventions, into the model, because the size of the effect in terms of lung function decline is still unknown. However, their effect is already present in the estimates of the input parameters of the model, as these were largely obtained from registries or studies that allowed patients to obtain treatment deemed necessary.

The sex- and age-specific estimates of COPD prevalence and incidence, which were obtained from regional GP registrations, were assumed to be representative for the Dutch population of diagnosed COPD patients. This assumption is reasonable, because virtually all people in the Netherlands, including those treated by pulmonologists, are registered with a GP practice. Nevertheless, the recording of spirometric results in the electronic patient records is far from perfect and when, for example, results of severe patients are more likely to be missing, the prevalence of severe and very severe COPD might be underestimated. Furthermore, data were too limited to enable specification of the severity distribution by sex, age and smoking status. In the sensitivity analysis the severity distribution by age (SA1) was varied, but the projections did not change much.

Although the Lung Health Study is the best and largest study on the effects of smoking and smoking cessation on lung function in COPD, it has limitations for the current studies purpose [8]. The study population mainly consisted of subjects with mild-to-moderate airflow obstruction aged 40-60 years. Decline (and increase after smoking cessation) for patients outside the observed age and lung function range had to be based on extrapolation of the data using the random effect model. Changing the annual decline in lung function with plus or minus 10% did not influence the outcomes greatly (SA4, 5). As non-smokers did not participate in the Lung Health Study, the decline in lung function among non-smokers was assumed to equal the decline among ex-smokers. This was thought to be more realistic than assuming that the decline equals the decline in non-

smokers in the general population. As the number of never smoking COPD patients is rather small, assuming the decline of non-smokers to be equal to the decline in smoking COPD patients did not change the results much (SA7).

Results from the sensitivity analyses show that the model projections are most sensitive to changes in the assumption about the severity distribution of the incidence. It is important to stress that the two assumptions tested in the sensitivity analysis were extremes. Such extremely different assumptions were not applied to other variables in the sensitivity analyses. The choice of these sensitivity analyses resulted from very different views of the expert panel on the incidence distribution. The assumption that 60% of the incidence occurs in mild and 40% in moderate COPD reflects the optimistic view that COPD is increasingly diagnosed in earlier stages. The assumption that the severity distribution of the incidence equals the distribution of the prevalence represents a pessimistic view with relatively many patients diagnosed when they already have advanced COPD. The real distribution is somewhere in between and probably close to what was estimated i.e. 40% in mild, 55% in moderate, 4% in severe COPD and 0.1% in very severe COPD.

In conclusion, a dynamic COPD model has been constructed that summarizes much of the current epidemiological knowledge about COPD. This model is a valuable tool for policy making, because it can represent and identify trends in the future burden and costs of COPD and assess the cost-effectiveness of interventions offered to patients with COPD in different severity stages.

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Appendix I: Calculation of annual decline in lung function

Table A1 shows the regression coefficients of the random effect model based on the original 5-yr follow-up data of the Lung Health Study. This model was used to calculate sex, age, smoking status and FEV_1% predicted dependent values of annual decline in lung function.

Annual decline was calculated by subtracting the calculated FEV_1% predicted in year 0 (given certain sex, age, smoking status and baseline FEV_1% predicted) of the FEV_1% predicted in year 1 (given certain sex, age+1, smoking status and baseline FEV_1% predicted)

Table A1: Regression coefficients of the random effect model used to calculate annual decline in lung function

Dependent variable: FEV_1% predicted	β-Coefficient	p-value
Intercept	-20.9546	0.26
Year	0.2394	0.33
Smoking cessation (0=no, 1=yes)	14.3188	<0.0001
Sex (0=male, 1=female)	7.3174	0.10
Age	1.1132	0.13
Baseline FEV_1% predicted	1.3646	<0.0001
Year*smoking cessation	0.4556	<0.0001
Year*sex	-0.1562	<0.0001
Year*age	-0.03144	<0.0001
Year*baseline FEV_1% predicted	0.006027	<0.01
Smoking cessation*sex	1.7297	<0.0001
Smoking cessation*baseline FEV_1% predicted	-0.1242	<0.0001
Sex*age	-0.4038	<0.05
Sex*baseline FEV_1% predicted	0.02723	<0.05
Age*baseline FEV_1% predicted	-0.01818	<0.05
Age^2	-0.01213	0.10
Age^2*smoking cessation	-0.00086	<0.0001
Age^2*sex	0.004299	<0.05
Age^2*baseline FEV_1% predicted	0.000197	<0.05

Appendix II: Meta-analysis on lung function and mortality

To estimate the relationship between FEV_1% predicted and all-cause mortality, a meta-analysis was performed on papers published between 1970 and 2002 reporting this association in a general or COPD population. Papers had to meet the following in- and exclusion criteria:

- ≥ 3 yrs of follow-up
- Caucasian population
- Association corrected for at least age and smoking
- Association not corrected for dyspnoea and decline in lung function
- Not in patients hospitalized for a COPD exacerbation
- Reporting standard errors (SE)

For each paper that directly reported the relative risk (RR) per unit of change in FEV_1% predicated, the relative change in mortality rate associated with a 10-unit decline in FEV_1% predicted was calculated. For each paper that reported the RRs per class of FEV_1% predicted a log-linear risk function was first fitted on the data, before the RR of a 10-unit decline in FEV_1% predicted was calculated. The RRs of all papers were combined into a weighted mean, using the precision of the estimate in each paper as a weight.

In total, 17 studies were found. Of these 11 directly reported the RRs per unit change in FEV_1% predicted [32-42] and six reported the RRs by class of FEV_1% predicted [43-48]. Only 5 of these 17 were done in COPD patients [36, 38, 39, 42, 43]. Table A2 shows the results for COPD and the general population. Two additional studies in COPD were available, but they did not report SE [49,50]. When the two studies not reporting SE were included, the mean RR in seven COPD studies, weighted for the sample size in each study, was 1.28.

Among COPD patients each 10-unit decrease in FEV_1% predicted increased the mortality risk by at least 20%. This is a significantly higher increase than the 11% increase among the general population.

Table A2: Relative mortality risks of a 10-unit decline in FEV_1% predicted

	COPD	General population
RR (95% confidence interval)	1.20 (1.16; 1.23)	1.11 (1.10; 1.12)

Appendix III: Cost of illness for COPD

A prevalence-based cost of illness study for the year 2000 was performed. Only direct medical costs were taken into account. Data on healthcare use were, as much as possible, obtained from representative national registries to obtain age- and sex-specific data. Costs per unit of resource use were also estimated. Resource use was multiplied with unit costs to calculate total costs for COPD care in the Netherlands (table A3). All costs were valued in € (price level 2000).

Table A3: Data source, unit costs and total costs per type of care

	Unit	Data source	Unit costs 2000 €	Total costs in million €
General practitioner	Visit	Confronting COPD Survey	17	13
Specialist	Outpatient visit	Confronting COPD Survey	50	27
Home care	Hour	Patient Panel Chronic Diseases	8.70	54
Hospital				
Day-care	Day	National Medical Registration	177	0.17
Inpatient care	Day	National Medical Registration	271	75
Nursing home	-	Study on Cost of illness in the Netherlands	-	34
Influenza vaccination	Vaccination	Evaluation National Influenza Vaccination Campaign	15	3.5
Medication	Prescription	Foundation for Pharmaceutical Statistics	-	60
Oxygen therapy	Day	Netherlands Organisation for Health Research and Development	4.20	11
Lung transplantation	Transplantation	Eurotransplant	186,000	1.3
Total				280

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Chapter 4

Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD

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Abstract

The aim of this study was to estimate the long-term (cost-)effectiveness of smoking cessation interventions for patients with chronic obstructive pulmonary disease (COPD). A systematic review was performed of randomized controlled trials on smoking cessation interventions in patients with COPD reporting the 12-months biochemical validated abstinence rates. The different interventions were grouped into four categories: usual care, minimal counseling, intensive counseling and intensive counseling plus pharmacotherapy (="pharmacotherapy"). For each category the average 12-month continuous abstinence rate and intervention costs were estimated. A dynamic population model for COPD was used to project the long-term (cost-)effectiveness (25 years) of 1-year implementation of the interventions for 50% of the smoking COPD patients compared with usual care. Uncertainty and one-way sensitivity analyses were performed for variations in the calculation of the abstinence rates, the type of projection, intervention costs and discount rates. Nine studies were selected. The average 12-month continuous abstinence rates were estimated to be 1.4% for usual care, 2.6% for minimal counseling, 6.0% for intensive counseling and 12.3% for pharmacotherapy. Compared with usual care, the costs per quality-adjusted life year (QALY) gained for minimal counseling, intensive counseling and pharmacotherapy were €16,900, €8,200 and €2,400, respectively. The results were most sensitive to variations in the estimation of the abstinence rates and discount rates. Compared with usual care intensive counseling and pharmacotherapy resulted in low costs per QALY gained with ratios comparable to results presented for smoking cessation in the general population. Compared with intensive counseling, pharmacotherapy was cost saving and dominated the other interventions.

Introduction

Smoking cessation is still the most important intervention to slow down the disease progression of chronic obstructive pulmonary disease (COPD) [1-3]. It decreases the annual decline in lung function [4], reduces symptoms of cough and sputum, improves health status and reduces exacerbations of COPD [5]. Because of the strong association between use of healthcare services and disease severity [6], slowing down disease progression is likely to reduce annual COPD-related healthcare costs.

Current treatment guidelines recommend that all smoking COPD patients should be offered the most intensive smoking cessation intervention feasible [7,8]. A review of five smoking cessation interventions offered to COPD patients by Wagena et al showed that only pharmacotherapy combined with intensive counseling seemed to be effective in this patient group. The effects of less intensive strategies did not reach statistical significance [9]. A more recent review concluded that counseling plus nicotine replacement therapy (NRT) had the greatest effect on prolonged abstinence rates in smokers with COPD [10]. Although almost all smoking cessation interventions targeted at smokers in the general population are cost-effective [11,12], little is known about the cost-effectiveness of smoking cessation interventions offered to patients who already have a smoking-related disease like COPD. Since information on the short-term cost-effectiveness of these interventions in COPD is already scarce, information on the long-term cost-effectiveness is virtually absent. It is however highly relevant to know the long-term cost-effectiveness, because the health benefits are small in the first year after the intervention, but will continue to increase over time.

The aim of this study was to estimate the impact of smoking cessation interventions offered to COPD patients on the future burden of COPD using a previously published dynamic population-based model of COPD disease progression [13].

Methods

Study selection

All randomized controlled trials published in English investigating the effectiveness of a smoking cessation intervention in patients with COPD confirmed by spirometry or physician-diagnosis were included if the follow-up was at least twelve months. The smoking cessation intervention or therapy had to be the primary intervention and not part of a disease management or education program and abstinence of smoking had to be biochemically validated.

Search strategy

We performed a literature search in MEDLINE using the following MeSH headings or words in the title or abstract: COPD or "chronic obstructive pulmonary disease" or "chronic bronchitis" in combination with smoking, tobacco, nicotine or smok* or nicotin* and one of the following terms: smoking cessation or tobacco use or quit* or stop* or cessat* or abstin* or abstain*. The search was performed in February 2009 and limited to randomized controlled trials published in English. We also searched the reference lists of retrieved articles and checked the systematic reviews for further references. If the search in MEDLINE resulted in studies reporting 6-month results, but the authors were aware of other publications in which the 12-month results were presented the study was included.

Methodological quality

The methodological quality of the selected studies was evaluated using the Jadad scale and the Delphi list [14,15]. The Jadad scale consists of five questions with respect to randomization and blinding. Each positive answer to a question was valued with one and a negative answer with zero, resulting in a sum score ranging from zero to five [14]. The Delphi-list consists of nine aspects regarding randomization, study population, blinding and presentation of results. Possible answers were scored as one point ("yes") or zero points ("no" or "don't know"), resulting in a sum score ranging from 0 to 9 [15]. Both scores were assigned independently by two reviewers (MH, TF, MRM). Points of disagreement were discussed until consensus was reached. Both scores were used in combination to assess the methodological quality of the studies.

Combination of abstinence rates and intervention costs

The interventions performed in the different arms of the selected trials were grouped into four categories: 1) care as usual, defined as no counseling or pharmacotherapy or any other type of smoking intervention offered as part of the trial (="usual care"), 2) minimal or brief counseling, < 90 minutes in total (="minimal counseling"), 3) intensive counseling, ≥90 minutes without pharmacotherapy (="intensive counseling") and 4) intensive counseling in combination with any type of pharmacotherapy (="pharmacotherapy"). Interventions offering pharmacotherapy on a non-compulsory basis were included in the category with pharmacotherapy if this was used by >50% of the patients. Patients in the placebo-arms of drug trials often received some form of counseling and were therefore grouped into the categories minimal or intensive counseling depending on the duration of counseling. For our model calculations we needed absolute quit rates

for at least one of the four intervention categories. We therefore used random effect meta-analysis [16] to account for study heterogeneity and estimated mean abstinence rates for all four categories. The rates were calculated separately for 12-month continuous abstinence and 12-month point prevalence abstinence. Twelve months continuous abstinence was defined as biochemical validated abstinence at all measurements up to 12 months including the 12-months measurement. Twelve months point prevalence abstinence was defined as biochemical validated abstinence at 12 months. We recalculated the abstinence rates to the intention-to-treat population assuming subjects with missing data to be smokers when this was not done in the main analysis of the article.

For studies providing sufficient details about the intervention, the costs of the intervention were estimated using Dutch unit costs for the year 2007. Based on these estimates average intervention costs for all four intervention categories were calculated as the weighted means over the studies using the numbers of patients as weights.

Model

A dynamic population model for COPD was used to estimate the impact of increased implementation of smoking cessation interventions compared with usual care [13]. The model is representative for the total Dutch COPD population (306,000 patients in 2000) and is dynamic because changes in the population, such as birth, mortality, ageing and changing smoking patterns in the population are taken into account. The model distinguishes six states: no COPD, four COPD severity stages (mild, moderate, severe and very severe COPD based on the GOLD classification) [8] and dead. The prevalence of COPD for the first year of simulation was distributed over the four COPD severity stages according to the observed severity distribution of physician-diagnosed patients in the Netherlands [17]. For each following year the model simulates the changes in the number of COPD patients, the severity distribution and annual COPD-related healthcare costs due to incidence, mortality and disease progression, i.e. annual decline in FEV_1% predicted. Incidence, mortality and disease progression are specified by sex, age, smoking status and COPD disease severity. COPD-related healthcare costs are specified by sex, age and COPD severity. The most important input parameters of the model are shown in table 1. An extensive description of the model can be found elsewhere [13]. The model can be used for projections of the Dutch COPD population over time, but more importantly, to evaluate the long-term costs and health benefits of interventions as was done for this study. The effects of smoking cessation were modelled as a one-time increase in FEV_1% predicted in the year of smoking cessation followed by a lower annual decline in FEV_1% predicted based on the Lung Health Study [4] and reduced mortality due to COPD and other smoking-related diseases. The implementation of smoking cessation interventions for COPD patients was modelled by replacing the smoking cessation rates of usual

care by the higher smoking cessation rates of the intervention for a certain period of time, for a certain (part of) the COPD population. A higher cessation rate compared to usual care results in more COPD patients quitting smoking, slower progression to worse COPD severity stages, less mortality and a reduction in COPD-related healthcare costs. The model uses 12-month abstinence rates and accounts for annual probabilities to relapse in former smokers, so former smokers may start smoking again also more than one year after quitting [13].

Outcome parameters

The long-term effectiveness of the interventions was expressed in terms of the cumulative number of life years and quality-adjusted life years (QALYs) gained and the cumulative reduction in mortality. QALYs were calculated by weighting life years for the quality of life during these years in each COPD severity stage using EQ-5D utility weights (Table 1). The cumulative number of life years, QALYs and deaths over the entire time horizon was calculated as the sum of the annual number of patients alive, the annual number of QALYs and the annual number of deaths, respectively, discounting future outcomes. The cumulative COPD-related healthcare costs were calculated as the properly discounted sum of the annual COPD-related healthcare costs over the time horizon. Finally, the cost per (quality-adjusted) life year gained was calculated as the ratio of total intervention costs minus savings in COPD-related healthcare costs compared with usual care divided by the cumulative (quality-adjusted) life years gained compared with usual care.

Table 1: Main input parameters of the COPD disease progression model [13]

		Mild COPD	Moderate COPD	Severe COPD	Very severe COPD
Prevalence per 1000 people in the general population*		5.1	10.7	3.0	0.5
Incidence per 1000 people in the general population*		0.71	0.94	0.08	0.003
Annual decline in FEV_1% predicted#	Smokers	-1.13	-1.50	-1.84	-2.13
	Ex-smokers	-0.79	-1.17	-1.51	-1.79
One-time increase in FEV_1% predicted associated with smoking cessation		0.03	2.91	5.56	7.76
Total mortality per 1000 COPD patients in a specific severity stage*	Smokers	61	73	91	114
	Ex-smokers^	51	64	82	104
COPD-related healthcare costs (2007 €)		318	700	2,389	7,847
EQ-5D utility weights [18]		0.8971	0.7551	0.7481	0.5493

*Data from the year 2000, the first year of the simulation
Data presented as the average for males and females with a mean age of 68 years, the mean age of the total Dutch COPD population
^ Standardized for the sex, age and COPD severity distribution of the smokers

Base case analysis

In the base case analysis we modelled the impact of offering minimal counseling, intensive counseling or pharmacotherapy to 50% of the Dutch smoking COPD patients (76,000 patients) for one year compared with usual care. Fifty percent was chosen because this percentage of smoking COPD patients reported a willingness to stop smoking within six months [19,20]. The base case analysis was performed using the mean 12-month continuous abstinence rates as calculated in the meta-analysis. Analyses were performed from a healthcare perspective. Effects and costs were evaluated over a time horizon of 25 years and were discounted at 1.5% and 4%, respectively, as recommended by Dutch guidelines for pharmacoeconomic evaluations [21].

Uncertainty and sensitivity analyses

The uncertainty around the outcomes due to the uncertainty around the calculated abstinence rates and intervention costs was assessed using the 95% lower and upper limit of the difference in abstinence rate compared with usual care and the minimum and maximum estimate of the intervention costs. Furthermore, a series of one-way sensitivity analyses was performed to estimate the impact of the choice of input parameters on the outcomes. In the first sensitivity analysis the impact of using the 12-months point prevalence rate was assessed. In the second analysis effects and costs were not discounted. For our base case analyses we used absolute quit rates based on random effect meta-analysis. In sensitivity analysis three we replaced these by estimating the odds ratio (OR) of minimal counseling, intensive counseling and pharmacotherapy versus usual care using a network meta-analysis approach [22] and applied these OR's to the average 12-months continuous abstinence rate for usual care. In the fourth sensitivity analysis the model was run for the cohort of Dutch COPD patients present at the start of the simulations assuming no new incidence of COPD. In contrast to the Netherlands, in many countries nortriptyline is not considered and/or used for pharmacological smoking cessation support, because it is not registered as such. In the fifth sensitivity analysis we therefore estimated the outcomes for pharmacotherapy excluding the studies on nortriptyline.

Results

The literature search identified 39 publications of which 26 were rejected in the first selection based on the title and abstract only. The remaining 13 references were reviewed in full, resulting in the further exclusion of three papers. One reported abstinence rates

Table 2: Characteristics of studies included in the review

Study	Study population	N	Severity of COPD	Intervention description (Intervention category#)
Kotz, 2009[23]	Current smokers (>10 pack-years) with previously undetected mild/moderate airflow limitation recruited from the general population, aged 35-70 years who were motivated to quit smoking	296	Mild (FEV_1pred>80%) or moderate COPD (50<FEV_1pred<80%)	Treatment group: Confrontational counseling (confrontation with spirometry results) during face-to-face sessions (160 min) plus one telephone session (5-15 min) by a respiratory nurse plus nortriptyline for 7 weeks (=pharmacotherapy) Control group 1: Face-to-face (160 min) and telephone counseling (5-15 min) by a respiratory nurse plus nortriptyline for 7 weeks (=pharmacotherapy) Control group 2: Care as usual for smoking cessation provided by the patients' own general practitioner (=minimal counseling)
Wilson, 2008[24]	Smoking COPD patients treated in an outpatient Respiratory Centre with an intention to stop smoking	91	53% mild (FEV_1>50%), 34% moderate (30<FEV_1<50%), 13% severe (FEV_1<30%)	All patients: brief advice to stop smoking by a physician (5-10 min) plus a leaflet about smoking cessation Group 1: Individual support: 5 individual support sessions (max 60 min) by a respiratory nurse. Free NRT was offered, but not compulsory (used by 59% of patients) (=pharmacotherapy) Group 2: Group support: 5 group support session (max 60 min) by a respiratory nurse. Free NRT was offered, but not compulsory (used by 41% of patients) (=intensive counseling) Group 3: Control: No further support (=minimal counseling)
Christenhusz, 2007[25]	Patients with clinically treated COPD, motivated to quit smoking, aged 40-75 years, treated in the outpatient department of an hospital	225	Moderate (50<FEV_1%pred<69%) and severe COPD (FEV_1%pred<50%)	Group 1: Smoke Stop Therapy (SST)= group counseling (360 minutes), individual face-to-face (195 min) and telephone counseling (40 min) by a respiratory nurse. In case of lapse individual sessions "recycled". Pharmacological support strongly advised. Bupropion provided free of charge (used by 100% of patients) (=pharmacotherapy) Group 2: LMIS= individual (150 min) and telephone counseling (30 min) by a respiratory nurse. Pharmacological support used by choice on own expense (used by 41% of patients) (=intensive counseling).
Tonnesen, 2006[26]	Smoking patients aged >18 years with a clinical diagnosis of COPD (FEV_1/FVC<70%, FEV1<90%) recruited from lung clinics who were willing to follow the study protocol	370	9% mild (FEV_1>80%), 53% moderate (50<FEV_1<80%), 30% severe (30<FEV_1<50%), 8% very severe COPD (FEV_1<30%)	Low-support: Individual and telephone sessions (total 150 min) by a respiratory nurse + take-home material, High support: individual and telephone sessions (total 270 min) by a respiratory nurse+ take-home material Group 1: low support plus placebo (=intensive counseling) Group 2: high support plus placebo (=intensive counseling) Group3: low support plus 12 weeks NRT sublingual tablets (=pharmacotherapy) Group 4: high support plus 12 weeks NRT sublingual tablets (=pharmacotherapy)

Table 2: Characteristics of studies included in the review (continued)

Study	Study population	N	Severity of COPD	Intervention description (Intervention category#)
Wagena, 2005/ Kaper, 2006[27,28]	Current daily smokers with COPD, smoking for at least five years, >10 cigarettes per day, aged 30-70 years, who were motivated to stop smoking	144	38% mild (FEV_1>80%), 56% moderate (50<FEV_1<80%) and 6% severe COPD (FEV_1<50%)	All patients: individual (total 60 min) and telephone counseling sessions (total30 min) by a respiratory nurse Group 1: Bupropion for 12 weeks (=pharmacotherapy) Group 2: Nortriptyline for 12 weeks (=pharmacotherapy) Group 3: Placebo for 12 weeks (=intensive counseling)
Hilberink, 2005[20]	Smoking COPD patients > 35 years treated by the GP and not under control of chest physician who were willing to participate	392	Probably mild/ moderate according to GOLD classification	Group 1: SMOCC: counseling visits to the GP (1-4 depending on the motivational stage of change) plus a maximum of 3 telephone follow-up calls by a respiratory nurse (mean 50 min per patient) (=minimal counseling) Group 2: care as usual delivered by the GP (=usual care)
Tashkin, 2001[29,31]	Current smokers with stage I or II COPD, aged >35yrs, smoking >15 cigarettes/ day for the previous year and did not quit smoking >3mnths in the previous year who were motivated to quit smoking	404	Patients with stage I (FEV_1%pred>50%) and stage II (35<FEV_1%pred<50%)	All patients received brief face-to-face counseling at each of the 9 visits to the clinic plus 1 telephone session three days after the target quit data Group 1: bupropion (=pharmacotherapy) Group 2: placebo (=intensive counseling)
Brandt, 1997[30]	Smoking patients with COPD admitted to the general medical ward of an hospital	56	Probably severe and very severe COPD according to GOLD	All patients received the same instructions on how to deal with their disease, the same encouragement to stop smoking and the same medical treatment. Group 1: use of the word "smokers lung" in all information material and by medical staff (=intensive counseling) Group 2: use of the word chronic bronchitis or emphysema (=intensive counseling)
Anthonisen, 1994[2]	Smokers aged 35-60 yrs with a FEV_1/ FVC<70% and a 55%<FEV1<90%	5887	55%<FEV_1<90%, mild and moderate COPD according to GOLD	Group 1: Physician message, individual session with interventionist for behavioral interview, group orientation meeting, 12 intensive group sessions, clinic visits every 4 months for 5 years, maintenance program for quitters, extended intervention program for patients still smoking or relapsing and NRT gum plus ipatropium bromide (Atrovent) (=pharmacotherapy) Group 2: Idem plus placebo inhaler (=pharmacotherapy) Group 3: care as usual (=usual care)

The category pharmacotherapy refers to intensive counseling in combination with pharmacotherapy

Table 3: Combined abstinence rates for the four interventions groups and associated intervention costs

	12-months continuous abstinence rates*		12-months point prevalence rates*		Weighted^ average intervention costs
	Average rate	Difference with usual care (95% confidence interval)	Average rate	Difference with usual care (95% confidence interval)	2007, €[#] (min; max)
Usual care	1.4%	-	6.8%	-	0
Minimal or brief counseling <90 min	2.6%	1.2% (-1.3; 3.7%)	9.0%	2.2% (-3.4; 7.7%)	€ 89 (22; 112)
Intensive counseling >=90 min	6.0%	4.6% (1.8; 7.4%)	12.3%	5.5% (-1.6; 12.6%)	€ 205 (93; 264)
Intensive counseling >= 90 min with pharmacotherapy	12.3%	10.9% (6.9; 15.0%)	19.0%	12.2% (0.5; 23.9%)	€ 305 (130; 452)

* Based on random effect meta-analysis performed on the absolute abstinence rates in trial arms

^ Weighted by number of patients in the study

[#] Calculated based on resource use as described in the individual papers valued using the following unit costs: general practitioner: € 2.10/min, respiratory physician: € 5.90/min, respiratory nurse: € 0.90/min, information material: € 1.00, 12 weeks NRT patches: € 194, 12 weeks NRT tablets: € 190, 12 weeks NRT gum: € 178, bupropion: € 1.30/tablet, nortriptyline € 0.16/tablet

which were not biochemically validated. The other two studies had a follow-up of six months, and to our knowledge, no other publication was available that reported the 12 months results. Two publications concerned the same study. This resulted in inclusion of ten papers reporting nine different studies [2,20,23-30]. Characteristics of these studies are shown in Table 2. The methodological quality of the selected studies is described in the Appendix. The highest scores were observed for studies comparing pharmacological treatments, because these studies score positive on items about "double-blinding". In studies comparing counseling with, for instance, usual care double-blinding is not feasible, so they received a lower quality score. All nine studies were included in the analyses. The table in the online supplement also shows the definitions of abstinence, the method of biochemical validation and the reported abstinence rates for the interventions in the different arms of the nine selected studies. Nineteen different estimates of 12-month continuous abstinence were reported, one estimate for usual care [20], three for minimal counseling [20,23,24], six for intensive counseling [24-29,31] and nine for pharmacotherapy (three for NRT, three for bupropion and three for nortriptyline) [23-29,31]. The weighted average 12-month continuous abstinence rates for intensive counseling (6.0%) and for pharmacotherapy (12.3%) were significantly higher than for usual care (1.4%). This was not the case for minimal counseling, with an abstinence rate of 2.6% (Table 3). Six studies provided sufficient details to estimate the additional costs of the interventions, minimal counseling (three estimates [20,23,24]), intensive counseling (five estimates [24-27]) and pharmacotherapy (eight estimates [23-27]), compared with usual care. Table 3 shows the weighted average intervention costs as well as the minimum and maximum costs observed within the intervention category.

Table 4 shows the results for the base case analysis, one year implementation of the intervention for 50% of the smoking COPD patients and evaluation of outcomes over a 25-year time horizon. Compared with usual care the discounted cumulative number of QALYs gained among this group of COPD patients in the Netherlands was 280 for minimal counseling, 960 for intensive counseling and 2,240 for pharmacotherapy. Figure 1 shows the undiscounted number of QALYs gained per year over the 25-year time horizon of the base case analysis. For each of the interventions, the maximum gain in QALYs was observed ten to fifteen years after implementation. Compared with usual care the net costs (difference in intervention costs minus savings in COPD-related healthcare costs) were €4.8 million for minimal counseling, €7.9 million for intensive counseling and €6.3 million for pharmacotherapy. Estimates of the cost-effectiveness compared with usual care, ranged from €2,400 for pharmacotherapy to €16,900 per QALY gained for minimal counseling. If each intervention was compared to the next most effective intervention, the cost per QALY of intensive versus minimal counseling was €4,600, while pharmacotherapy versus intensive counseling was cost saving.

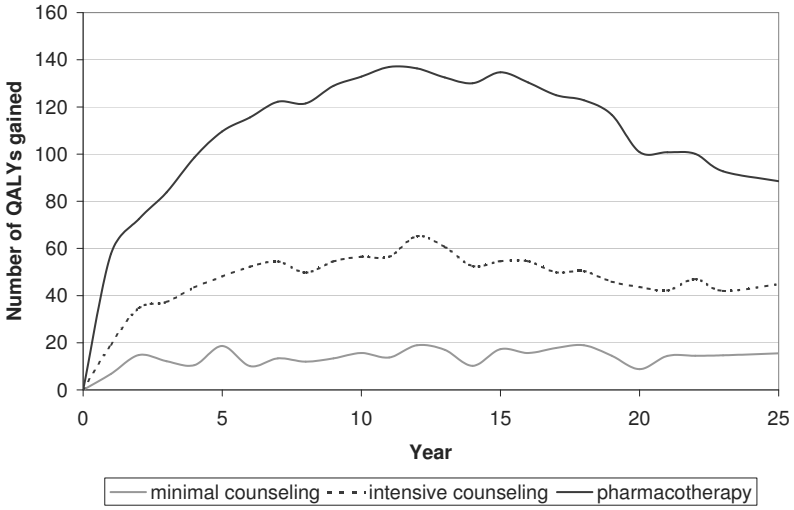

Figure 1: Annual number of quality-adjusted life years (QALYs) gained over time for 1-year implementation of minimal or brief counseling, intensive counseling without pharmacotherapy and intensive counseling with pharmacotherapy ('pharmacotherapy') compared with usual care, 0% discounting

Uncertainty and sensitivity analyses

Figure 2 shows the uncertainty around the difference in total costs and the difference in QALYs compared with usual care as a result of the uncertainty around the 12-month continuous abstinence rates and the intervention costs. For minimal counseling the results varied from less effective than usual care with higher costs to more effective with cost savings. The results for intensive counseling ranged from more effective and cost saving to a maximum possible cost per QALY gained of €44,800, while for pharmacotherapy results ranged from more effective and cost saving to a maximum of €15,700 per QALY gained. The results of the different sensitivity analyses for all interventions compared with usual care are shown in Table 4. Using the 12-months point prevalence rates for each of the three types of interventions and usual care resulted in a slightly lower estimate of the cost per QALY gained for minimal counseling and slightly higher estimates for intensive counseling and pharmacotherapy versus usual care compared with the base case analysis. No discounting for both effects and costs also resulted in lower estimates of the cost per QALY gained with pharmacotherapy even being cost saving. The third sensitivity analysis resulted in OR's of 2.4, 4.7 and 9.8 for minimal counseling, intensive counseling and pharmacotherapy compared with usual care, respectively. Applying these to the 12-month continuous abstinence rate of usual care (1.4%) resulted in the following abstinence rates of 3.3%, 6.4% and 13.2% for minimal counseling, intensive counseling and pharmacotherapy, respectively. Consequently, the cost-effectiveness of

Table 4: Results of the base case and sensitivity analyses in 2007 €: one year implementation of minimal counseling, intensive counseling or intensive counseling in combination with pharmacotherapy ("pharmacotherapy") compared with usual care, time horizon 25 years#

Inter-vention:	Type of analysis: base case or sensitivity analysis (SA)	Life years gained	QALYs gained	Reduction in mortality*	Difference in intervention costs (million)	Savings in COPD-related costs (million)	Cost per life year gained	Cost per QALY gained
Minimal counseling	Base case analysis	210	280	90	6.8	2.0	22,400	16,900
	SA1: 12-m point prev rates	210	300	160	6.8	2.5	20,900	14,400
	SA2: No discounting	260	340	100	6.8	3.0	14,300	11,000
	SA3: Network meta-analysis	310	420	150	6.8	3.1	11,800	8,800
	SA4: Cohort instead of dynamic	200	260	100	6.8	1.9	24,600	18,200
Intensive counseling	Base case analysis	690	960	340	15.6	7.6	11,600	8,200
	SA1: 12-m point prev rates	600	810	280	15.6	5.9	16,200	11,900
	SA2: No discounting	850	1,160	380	15.6	11.5	4,800	3,500
	SA3: Network meta-analysis	750	1,050	370	15.6	8.3	9,600	6,900
	SA4: Cohort instead of dynamic	680	950	390	15.6	7.4	12,000	8,600
Pharmaco-therapy	Base case analysis	1,590	2,240	830	23.2	17.9	3,300	2,400
	SA1: 12-m point prev rates	1,260	1,740	630	23.2	13.0	8,000	5,800
	SA2: No discounting	1,960	2,690	910	23.2	26.8	Cost saving	Cost saving
	SA3: Network meta-analysis	1,710	2,400	920	23.3	19.2	2,300	1,600
	SA4: Cohort instead of dynamic	1,550	2,170	850	23.2	17.1	3,900	2,800
	SA5: Excluding studies with nortriptyline	1,570	2,190	820	30.6	17.3	8,500	6,100

#Results for pharmcotherapy versus intensive counseling or intensive versus minimal counseling can be calculated as follows: ((intervention $costs_{intervention\_B}$ - savings in COPD-related $cost_{intervention\_B}$) - ((intervention $costs_{intervention\_A}$-savings in COPD-related $cost_{intervention\_A}$)) / ($QALYs_{intervention\_B}$ – $QALYs_{intervention\_A}$)

* Number of deaths avoided over the time horizon of the analyses

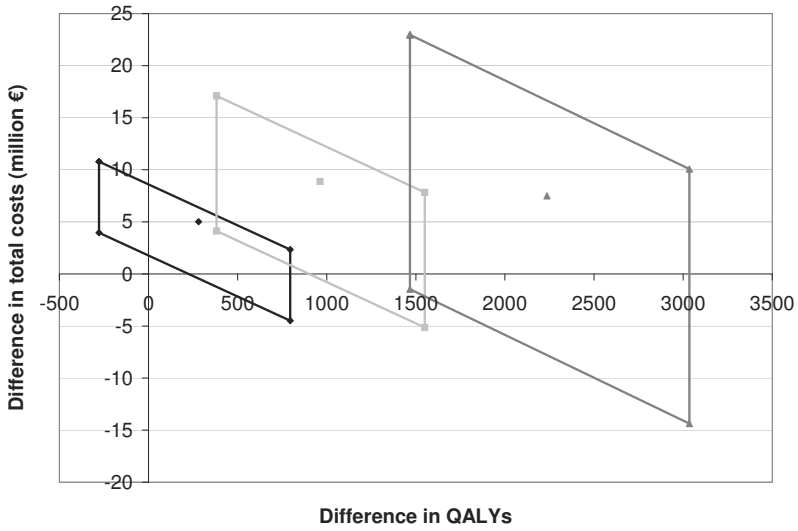

Figure 2: Uncertainty around the difference in total costs and the difference in quality-adjusted life years (QALYs) for the base case analysis, 1-year implementation of the intervention compared with usual care over a time horizon of 25 years, discount rate for effects 1.5% and for costs 4%. (♦ = minimal or brief counseling, ■ = intensive counseling and ▲= intensive counseling + pharmacotherapy)

all three interventions was (slightly) better than the base case analysis. Outcomes based on a cohort of COPD patients instead of using the dynamic version of the model did not have much influence on the results. The fifth sensitivity analysis based on the 12-months continuous abstinence rate and the weighted average intervention costs excluding the studies on nortriptyline (12.0% and €403, respectively) showed an increase of the cost per QALY for pharmacotherapy compared with usual care from €2,400 to €6,100.

Discussion

This study estimated the impact of offering different types of smoking cessation interventions to patients with COPD. Meta-analysis showed that both intensive counseling (defined as >90 minutes counseling) as well as intensive counseling with any type of pharmacotherapy were significantly more effective than usual care. The cost-effectiveness ratio's for both types of intervention were low and below €20,000 per QALY gained, the often mentioned threshold for an intervention to be considered cost-effective in the Netherlands [32]. Comparison of pharmacotherapy with intensive counseling resulted in cost savings making pharmacotherapy the most favourable intervention. The cost per QALY gained for minimal or brief counseling (defined as counseling <90 minutes) was also below €20,000, but the effectiveness was not significantly different from usual care.

Our literature search on studies reporting the effectiveness of smoking cessation interventions in patients with COPD resulted in nine studies. It was therefore impossible to group the interventions into more than three or four categories, although we acknowledge that differences in methods and interventions within one category existed. Minimal and intensive counseling are commonly used classifications in smoking cessation studies and reviews. The pharmacotherapy category was too small to subdivide by type, intensity or duration of pharmacotherapy. Longer duration or greater intensity of pharmacotherapy would probably lead to higher abstinence rates, although it is not clear whether this is also true for COPD patients. With regard to type of pharmacotherapy, the meta-analysis included three estimates on each type of pharmacotherapy (bupropion, nortriptyline and NRT). If, despite the low numbers, the category pharmacotherapy was subdivided into intensive counseling plus NRT and intensive counseling plus antidepressant, the cost per QALY gained would have been €10,400 for NRT and €600 for antidepressants, both low ratios. However, more research on the effectiveness of pharmacotherapies in COPD patients is needed to give better estimates of the cost-effectiveness specified by type, intensity of supportive counseling and duration of pharmacotherapy. Our estimate of pharmacotherapy included the results of studies offering pharmacotherapy on a non-compulsory basis, if this was used by more than 50% of the patients. This might have resulted in a potential underestimation of the effect of pharmacotherapy. Exclusion of the two trials with non-compulsory pharmacotherapy, however, only had a small effect on the incremental cost-effectiveness ratio of pharmacotherapy (€1,900 instead of €2,400 per QALY gained).

Our estimates of the 12-month continuous abstinence rates of intensive counseling (6.0%) and pharmacotherapy (12.3%) were still relatively low and lower than observed in the general population (10 and 17%, respectively) [33,34]. These results suggest that abstinence rates in patients with COPD are lower than in "healthy" smokers. This finding was also observed in a study by Wagena et al which showed that patients with COPD had a 30% higher chance of relapsing than smokers at risk of COPD [27]. By increasing the intensity and duration of counseling and/or pharmacotherapy, the abstinence rates in COPD may possibly increase as shown by the Lung Health study also included in our meta-analysis [2]. This study is unique in terms of intensity of the intervention, monitoring of patients and follow-up, which resulted in remarkably high abstinence rates for the smoking intervention group but also for the usual care group. Although the current guidelines advocate the most intensive smoking cessation intervention, it is questionable whether an intervention with such a high intensity as the Lung Health Study is feasible in daily practice.

Results for the cost-effectiveness of pharmacotherapy and intensive counseling in COPD were comparable with the cost per QALY gained for smoking cessation support in the general population. For the general population studies on nicotine replacement

therapy (NRT), bupropion and nortriptyline have showed cost-effectiveness ratios consistently below €10,000 per (quality adjusted) life year [12,35-38]. The cost-effectiveness ratio for minimal counseling in COPD is somewhat higher than in studies in the general public [11,12]. This is probably a result of the lower abstinence rate and the relatively high intervention costs compared with other studies on minimal counseling. In our study minimal counseling for COPD patients still consisted of an average of about 25 minutes counseling, while in most general population studies minimal counseling is defined as less than 10 minutes of cessation advice.

The common approach in reviews evaluating the effectiveness of smoking cessation interventions is to report the RR or OR of one comparator with the other [9,33,34]. The best method to retain randomization would be a network meta-analysis. However, in addition, for a cost-effectiveness analysis the absolute quit rate for at least one of the interventions or usual care need to be estimated. We decided instead to use the averages of the absolute quit rates as obtained from random effect meta-analysis in our base case analysis. Estimating OR's and applying them to the absolute quit rate of usual care would have resulted in slightly more favourable cost per QALY estimates for all interventions, but would not have changed the conclusions much (third sensitivity analysis).

In conclusion, compared with usual care implementation of both intensive counseling with and without pharmacotherapy for COPD patients resulted in low costs per QALY gained with ratios in the range of results presented for smoking cessation support in the general population. Implementation of minimal counseling was also cost-effective, but the effectiveness was not significantly different from usual care. Pharmacotherapy in combination with intensive counseling was cost saving compared with intensive counseling alone and dominated the other interventions. These results confirm the advice given in the guidelines that COPD patients should be offered the most intensive smoking cessation intervention feasible, not only from a clinical, but also from an economic perspective.

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Table A1: Methodological quality and abstinence rates presented in the selected studies

	Methodological quality*	Definition abstinence	Validation technique	Abstinence rates
Kotz, 2009	Jadad: 3 Delphi: 6	Point prevalence abstinence at 12 months	Urine cotinine <50ng/ml	Treatment (n=116): 11.2% Control1 (n=112): 12.5% Control2 (n=68): 10.3%
		Prolonged abstinence: abstinent at all three follow-up visits at week 5, 6 and 52	Urine cotinine <50ng/ml	Treatment (n=116): 11.2% Control1 (n=112): 11.6% Control2 (n=68): 5.9%
Wilson, 2008	Jadad: 3 Delphi:5	Complete cessation: abstinent at 2, 3, 6,9 and 12 months	Exhaled carbon monoxide <=10ppm Salivary cotinine <10ng/ml	Individual support (n=27): 0% Group support (n=29): 0% Control (n=35): 0%
		Intermittent cessation: abstinent at either 2, 3, 6,9 or 12 months	Exhaled carbon monoxide <=10ppm Salivary cotinine <10ng/ml	Individual support (n=27): 0% Group support (n=29): 10.3% Control (n=35): 5.7%
Christenhusz, 2007	Jadad: 3 Delphi:3	Point prevalence abstinence at 12 months	Salivary cotinine < 20ng/ml	SST (n=114): 20.2% LMIS (n=111): 11.7%
		Continuous abstinence at 12 months: abstinent at 6 and 12 months	Salivary cotinine < 20ng/ml	SST (n=114): 17.5% LMIS (n=111): 8.1%
Tonnesen, 2006	Jadad: 5 Delphi: 7	Point prevalence abstinence at 12 months	Exhaled carbon monoxide <10ppm	Low support/placebo (n=88): 5.7% High support/placebo (n=97):13.4% Low support/NRT (n=95):16.8% High support/NRT (n=90:17.8%
		Sustained abstinence: abstinent at all visits between week two and month 12	Exhaled carbon monoxide <10ppm	Low support/placebo (n=88): 4.5% High support/placebo (n=97):6.2% Low support/NRT (n=95):13.7% High support/NRT (n=90):14.4%
Wagena, 2005/ Kaper, 2006	Jadad: 5 Delphi:9	Prolonged abstinence: abstinent at week 4, week 12, 6 months and 12 months	Urine cotinine < 60ng/ml	Bupropion (n=44): 20.4% Nortriptyline (n=52): 19.2% Placebo (n=48): 6.3%

Table A1: Methodological quality and abstinence rates presented in the selected studies (continued)

	Methodological quality*	Definition abstinence	Validation technique	Abstinence rates
Hilberink, 2005	Jadad: 2 Delphi: 4	Point prevalence abstinence at 12 months (unpublished)	Urine cotinine <80 ng/ml	SMOCC (n=243): 8.6% Usual Care (n=148): 4.1%
		Continuous abstinence at 12 months: abstinent since start of the intervention (unpublished	Urine cotinine <80 ng/ml	SMOCC (n=243): 2.5% Usual Care (n=148): 1.4%
Tashkin, 2001	Jadad: 5 Delphi: 8	Continuous abstinence at 6 months: abstinent at week 4, 5, 6, 7, 10,12 and 26	Exhaled carbon monoxide < 10ppm	Bupropion (n=204): 15.7% Placebo (n=200): 9.0%
		Prolonged abstinence at 12 months (Review Wagena)	Exhaled carbon monoxide < 10ppm	Bupropion (n=204): 10.3% Placebo (n=200): 8.5%
Brandt, 1997	Jadad: 2 Delphi: 3	Point prevalence abstinence at 12 months	Exhaled carbon monoxide	Treatment (n=25): 32.0% Control (n=31): 16.1%
Anthonisen, 1994	Jadad: 3 Delphi: 5	Point prevalence abstinence at 12 months	Salivary cotinine <20ng/mL or exhaled CO< 10ppm	Treatment (smoking intervention) (n=3923): 34.5% Usual care (n=1964): 9.0%

*Methodological quality of the study based on the Jadad score (0-5) and the Delphi-index (0-9)

Chapter 5

Association between lung function and exacerbation frequency in patients with COPD

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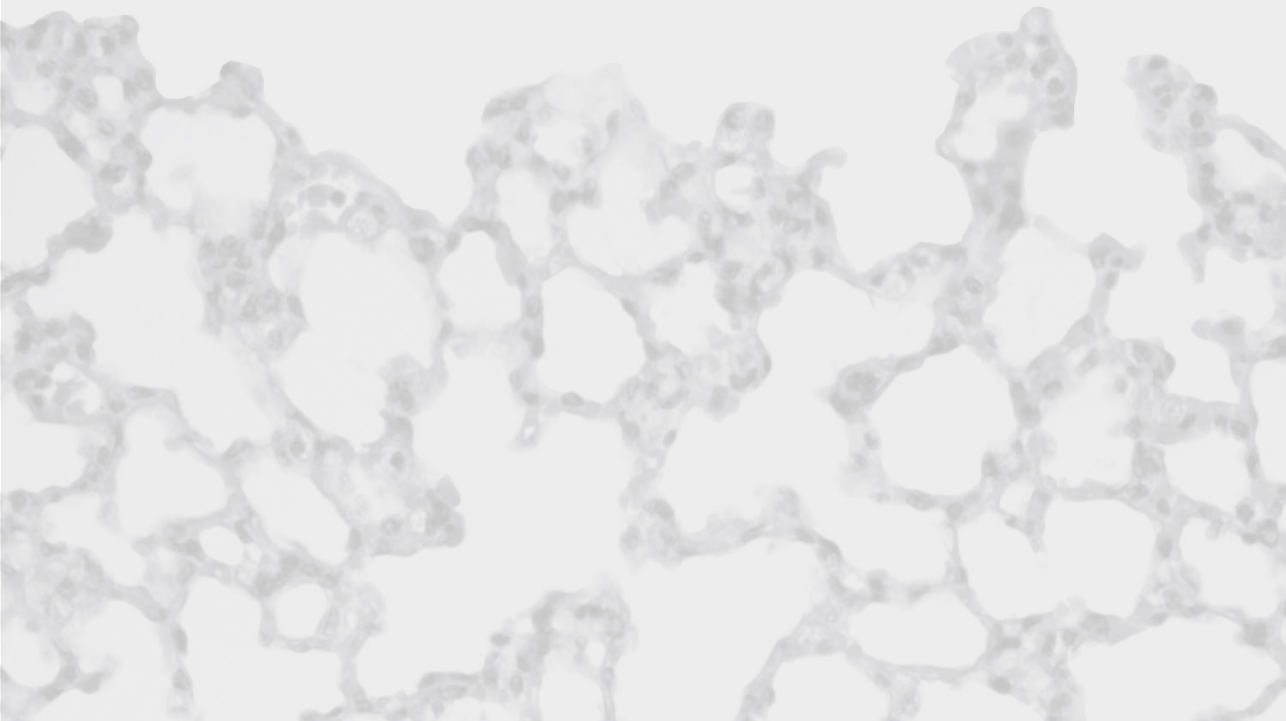

Abstract

The objective of this study was to quantify the relationship between severity of chronic obstructive pulmonary disease (COPD) as expressed by GOLD stage and the annual exacerbation frequency in patients with COPD. We performed a systematic literature review to identify randomized controlled trials and cohort studies reporting the exacerbation frequency in COPD patients receiving usual care or placebo. Annual frequencies were determined for: total exacerbations defined by an increase use of healthcare (event-based), total exacerbations defined by an increase of symptoms and severe exacerbations defined by a hospitalization. The association between the mean FEV_1% predicted of study populations and the exacerbation frequencies was estimated using weighted log linear regression with random effects. The regression equations were applied to the mean FEV_1% predicted for each GOLD stage to estimate the frequency per stage. Thirty-seven relevant studies were found with 43 reports of total exacerbation frequency (event-based: n=19, symptom-based: n=24) and 14 reports of frequency of severe exacerbations. Annual event-based exacerbation frequencies per GOLD stage were estimated at 0.82 (95% uncertainty interval (UI): 0.46; 1.49) for mild, 1.17 (0.93; 1.50) for moderate, 1.61 (1.51; 1.74) for severe and 2.10 (1.51; 2.94) for very severe COPD. Annual symptom-based frequencies were 1.15 (95% UI: 0.67; 2.07), 1.44 (1.14; 1.87), 1.76 (1.70; 1.88) and 2.09 (1.57; 2.82), respectively. For severe exacerbations, annual frequencies were 0.11 (95% UI: 0.02; 0.56), 0.16 (0.07; 0.33), 0.22 (0.20; 0.23) and 0.28 (0.14; 0.63), respectively. Study duration or type of study (cohort versus trial) did not significantly affect the outcomes. This study provides an estimate of the exacerbation frequency per GOLD stage, which can be used for health economic and modelling purposes.

Introduction

The progression of chronic obstructive pulmonary disease (COPD) is often accompanied by periods of increasing symptoms, such as dyspnoea, cough and sputum production known as exacerbations. Exacerbations are important events because they are associated with an increase in mortality [1,2], significant impairment of health-related quality of life [3-5] and an increase in healthcare use and associated costs [6,7], especially the event of a hospitalization [8]. The exacerbation frequency is therefore an important outcome parameter in COPD [9,10].

However, quantification of the average exacerbation frequency is difficult. Many studies report the exacerbation frequency but results can not be compared directly, because different definitions are used, exacerbations are measured in different seasons [9] or data come from different types of studies, e.g. clinical trials or cohort studies, each using specific inclusion criteria [10]. Use of different definitions in particular seems to have a large influence.

Definitions of exacerbations can be roughly divided into two groups: i.e. the symptom-based definitions and event-based definitions. Studies defining exacerbations as self-reported changes in symptoms (symptom-based definition) generally result in higher estimates than studies using event-based definitions, because they also include exacerbations which do not present to physicians [11]. When symptoms are closely monitored using diaries, these "unreported" exacerbations are thought to account for about 50% of all exacerbations [4]. Event-based definitions use more objective criteria, such as a doctor's visit, use of antibiotics and/or systemic steroids or hospitalization. However, event-based definitions are sensitive to differences in treatment patterns between settings.

Another source of variation between studies is the method used to classify the severity of an exacerbation. Most studies classify exacerbations based on the treatment required, i.e. either an increase of short-acting bronchodilator or maintenance medication use, additional antibiotics and/or systemic corticosteroids or hospitalization [12].

Despite the difficulties in measuring exacerbations, the general pattern is that the frequency of exacerbations increases with decreasing lung function [9,10,13]. However, as far as we know no studies have quantified this relationship. The present study aimed to quantify the relationship between degree of airflow obstruction expressed as the FEV_1% predicted, and the annual exacerbation frequency, using previously published data. The association was estimated separately for symptom-based and event-based exacerbations and for total and severe exacerbations. Furthermore, we explored the impact of study duration and type of study, i.e. clinical trial or cohort study, on this relationship. This study arose out of the need to estimate the average exacerbation frequency for the different COPD severity stages as defined by the Global Initiative for Chronic Obstructive

Lung Disease (GOLD) that were used as input parameters in a COPD disease progression model [14,15]. Because this model aims to simulate the long-term cost-effectiveness of interventions which successfully prevent exacerbations compared with minimal care, the exacerbation frequency in patients receiving minimal care was essential.

Methods

A systematic literature review was performed to identify randomized controlled trials and cohort studies reporting the exacerbation frequency in patients receiving care as usual or placebo. MEDLINE, EMBASE and the Cochrane database were searched using the key words "chronic obstructive pulmonary disease" or COPD or "chronic bronchitis" in combination with exacerbat* and the specification "cohort or survey or observation* or the selection "clinical trial". Studies were included if they were published after 1990, had a follow-up of at least three months, used an event- or symptom-based definition for an exacerbation and, included a group of patients that received either usual care or placebo (e.g. the placebo arm of a long-acting bronchodilator trial or a combination treatment trial). Studies that included a subgroup of COPD patients selected based on criteria other than lung function were excluded (e.g. studies only including patients admitted to hospital or patients with an acute exacerbation at baseline). Retrospective studies based on administrative or claims data were excluded because the algorithms to identify exacerbations in these databases are often quite different from the definitions used in prospective cohort studies or clinical trials. Finally references of the studies that met the inclusion and exclusion criteria were checked.

Primary outcomes

The three main outcomes of the study were the annual frequency of total exacerbations using an event-based definition, the annual frequency of total exacerbations using a symptom-based definition and the annual frequency of severe exacerbations as defined by a hospitalization. One study could provide more than one estimate of the exacerbation frequency by presenting separate rates for total and severe exacerbations or rates based on both a symptom- and an event-based definition or by presenting rates for different lung function classes.

Data extraction

Because the comparator arm in our model needed to reflect minimal care, we only extracted exacerbation data for the groups of patients that received either usual care

or placebo. The following data were extracted: percentage males, mean age, mean lung function (in FEV_1% predicted of the study population), follow-up duration, definition of exacerbation used (symptom- or event-based) and the annual exacerbation frequency. If the mean FEV_1 was only given in liters, the mean FEV_1% predicted of the study population was calculated using the association between the absolute value and percentage predicted from other studies. If the exacerbation frequency was presented for different classes of the FEV_1% predicted and the mean within-class FEV_1% predicted was not specified, the mean FEV_1% predicted was estimated based on the mean and the standard deviation of the FEV_1% predicted in the total population assuming a normal distribution or it was assumed to be the middle FEV_1% predicted of that specific class.

Data on the exacerbation frequency were recalculated to annual exacerbation rates, if necessary. The annual exacerbation rate was calculated by dividing the total number of exacerbations by the total number of patient years on the assumption that drop-outs count for half of the follow-up time.

Data analysis

As almost all studies provided only point estimates of exacerbation rates, uncertainty around the exacerbation rates was estimated assuming the exacerbations to follow a Poisson distribution within each study. To quantify the relationship between the FEV_1% predicted and the annual exacerbation frequency, weighted log linear regression analysis with random effects was performed. Log linear regression was chosen in order to symmetrize the skewed distribution of the exacerbation rates and approximate a normal distribution of the residuals in the linear regression analysis. A random effect model was chosen to account for study heterogeneity. The logarithm of the annual exacerbation frequency was used as dependent variable and the mean FEV_1% predicted of the study as independent variable. The regression analysis was performed using the S-plus routine general linear model for mixed-effects models [16]. Analyses were performed separately for total event-based, total symptom-based and severe exacerbations. From the resulting regression equation the predicted log exacerbation rate for a specific FEV_1% predicted could be calculated. Simply taking the exponential function of the logarithm of the exacerbation rate, in order to re-transform the data into a normal exacerbation rate introduces bias and inconsistency [17]. Therefore we have used the non-parametric smearing factor, which was calculated following the method of Duan et al [17,18]. According to this method, the smearing factor φ can be calculated as the weighted mean of the exponential of the differences between the logarithm of the observed and predicted exacerbation rates in the selected studies using the number of exacerbations in a study as a weight. This smearing factor is then multiplied by the uncorrected predicted exacerbation rates to find corrected predicted exacerbation rates

Table 1: Characteristics of included studies

Type of study	First author	N	% males	Mean age (years)	Mean FEV_1% pred	Follow-up (months)	Definition used for an exacerbation	Annual total exacerbation rate	Annual severe exacerbation rate
Trial	Monninkhof, 2003 [21]	121	84	65	58	12	Event-based	1.51	0.14
Trial	Coultas, 2005 [22]	51	54	69	46	6	-	-	0.20
Trial	Rea, 2004 [23]	52	41	68	50	12	-	-	0.67
Trial	Littlejohns, 1991 [24]	65	63	63	50	12	-	-	0.31
Trial	Gallefoss, 1999 [25]	31	52	58	56	12	-	-	0.14
Trial	Brusasco, 2003 [26]	400	76	65	39	6	Symptom-based	1.49	0.15
Trial	Casaburi, 2002 [27]	371	63	65	38	12	Symptom-based	0.95	0.16
Trial	Niewoehner, 2005 [28]	915	99	68	36	6	Symptom-based	1.05	0.25
Trial	Vincken, 2002 [29]	179	86	65	39	12	Symptom-based	0.96	0.16
Trial	Dusser, 2006 [30]	510	87	65	48	12	-	-	0.15
		280	-	-	67	12	Event-based	1.97	-
		230	-	-	31	12	Event-based	2.70	-
Trial	Calverley, 2003a [31]	361	75	63	44	12	Event-based	1.30	-
Trial	Calverley, 2003b [32]	256	75	65	36	12	Event-based	1.80	-
Trial	Szafranski, 2003 [33]	205	83	65	36	12	Event-based	1.87	-
Trial	Calverley, 2007[34]	1524	76	65	44	36	Event-based	1.13	0.19
Trial	Dal Negro, 2003 [35]	6	83	40-76	50	12	Event-based	4.17	-
Trial	Wonsurakiat, 2004 [36]	125	95	68	60	12	Symptom-based	1.35	0.06
Trial	Allegra, 1996 [37]	218	71	59	70	6	Symptom-based	1.32	-
Trial	Bontognali, 1991 [38]	30	57	59	75	3	Event-based	1.27	-
Trial	Decramer, 2005 [39]	258	79	62	57	36	Event-based	1.31	-
Trial	Grassi, 1994 [40]	41	79	62	57	3	Symptom-based	5.37	-
Trial	Hansen, 1994 [41]	70	46	52	85	5	Symptom-based	1.95	-
Trial	Malerba, 2004 [42]	119	76	61	70	12	Symptom-based	0.87	-
Trial	Meister, 1999 [43]	124	41	58	79	6	Symptom-based	1.20	-
Trial	Moretti, 2004 [44]	61	75	68	59	8	Symptom-based	2.07	-
Trial	Pela, 1999 [45]	84	71	66	59	6	Symptom-based	3.50	-

Table 1: Characteristics of included studies (continued)

Type of study	First author	N	% males	Mean age (years)	Mean FEV_1% pred	Follow-up (months)	Definition used for an exacerbation	Annual total exacerbation rate	Annual severe exacerbation rate
Trial	Burge, 2000 [46]	370	74	64	50	36	Event-based	1.90	-
Trial	Van Grunsven, 1999 [47]	88	90	61	44	24	Event-based	1.00	-
Trial	Vestbo, 1999 [48]	145	62	59	87	36	Symptom-based	0.45	-
Cohort	Llor, 2008 [49]	136	96	70	49	24	Symptom-based	0.93	
Cohort	Mittmann, 2008 [50]	609	58	69	44	12	Symptom-based	1.39	0.27
		609	58	69	44	12	Event-based	1.13	
Cohort	Langsetmo, 2008 [51]	421	57	67	46	6	Symptom-based	2.70	
Cohort	Hutchinson, 2007 [52]	92	63	72	40	Median 10.8	Symptom-based	1.79	
Cohort	O'Reilly, 2006 [53]	127	62	69	50	12	-	-	-
		57	-	-	66	12	Symptom-based	2.20	
		69	-	-	36	12	Symptom-based	2.50	
		57	-	-	66	12	Event-based	2.30	
		69	-	-	36	12	Event-based	3.20	
Cohort	Miravitlles, 2004 [3]	441	98	66	33	24	Symptom-based	1.50	
Cohort	Donaldson, 2003 [54]	132	69	68	38	Median 30	-	-	0.17
		94	-	-	47	Median 30	Symptom-based	2.68	-
		38	-	-	26	Median 30	Symptom-based	3.43	-
Cohort	Andersson, 2002 [6]	191	59	64	62	4.5	-	-	-
		32			90	4.5	Event-based	0.67	-
		72			70	4.5	Event-based	0.70	-
		63			50	4.5	Event-based	1.06	-
		24			30	4.5	Event-based	2.56	-
Cohort	Greenberg, 2000 [55]	30	43	67	68	Mean 26	Symptom-based	1.80	-
		32	41	64	36	Mean 26	Symptom-based	3.0	-

for a given FEV_1% predicted. As a result, the relationship between the annual exacerbation frequency and the FEV_1% predicted is:

Annual exacerbation frequency = φ * exp[a+b*FEV_1% predicted] whereby
φ = smearing factor
a = intercept (estimated in the regression analysis)
b= coefficient for FEV_1% predicted (estimated in the regression analysis)

This equation was used to calculate the annual exacerbation frequency in the four COPD severity stages according to the GOLD classification [19] using a mean FEV_1% predicted of 90 for mild, 65 for moderate, 42 for severe and 23 for very severe COPD [20]. To include the uncertainty around the smearing factor jointly with the uncertainty around the regression coefficients, the uncertainty around the exacerbation rates per GOLD stage was estimated by Monte Carlo simulation, i.e.1000 random draws were taken from the joint distribution of the intercept and the coefficient for FEV_1% predicted. For each combination of intercept and coefficient the accompanying smearing factor was calculated using the formula described above. The mean FEV_1%predicted per GOLD stage was then applied to each of the 1000 combinations of intercept, coefficient for FEV_1% predicted and smearing factor, resulting in 1000 estimates of the exacerbation rate per GOLD stage. The 2.5% and 97.5% percentiles of these 1000 estimates formed the 95% uncertainty interval.

Additional regression analyses were performed adding follow-up duration (in months) and type of study (cohort versus trial) to FEV_1% predicted as dependent variables. The analyses were performed with Splus 8.1 (TIBCO Spotfire S+ Version 8.1.1 HF-001 for Microsoft Windows, 2008).

Results

The literature review identified 86 references for trials and cohort studies published after 1990 that seemed eligible based on the title. Of these 86 references that were obtained in full another 44 studies were excluded because they did not present exacerbation frequencies or numbers (n=13), were based on a selective subgroup of COPD patients (n=11), were based on a cross-sectional study or on administrative or claims data (n=8), had a follow-up less than 3 months (n=9) or used a deviant definition for an exacerbation (n=3). The final 42 references referred to 37 unique studies, 28 trials [21-48] and nine cohort studies [3,6,49-55]. This resulted in 43 estimates for the total exacerbation frequency and 14 estimates of the frequency of severe exacerbations. Of the 43 estimates of the total exacerbation frequency, 19 used the event-based definition and 24

the symptom-based definition. Characteristics of all included studies with their annual exacerbation rates are presented in Table 1. The left three graphs in figure 1 show the logarithm of the annual total and severe exacerbation frequency plotted against the mean FEV_1% predicted of each study, as well as the estimated relation between the two obtained from the regression analyses. The estimated coefficients for the relationship between the mean FEV_1% predicted and the exacerbation frequency are shown in Table 2. Lung function was a predictor of borderline significance (p=0.053) for event-based

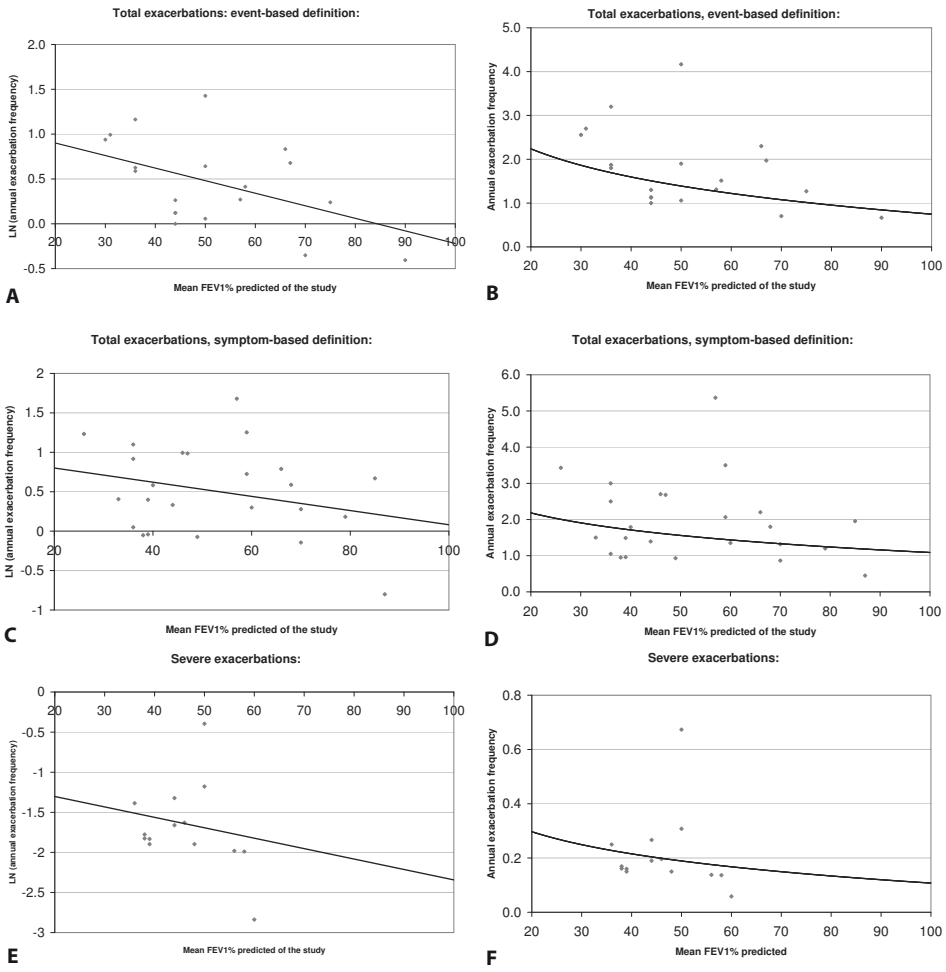

Figure1A-F: Left graphs: Logarithm of the annual total or severe exacerbation frequency plotted against the mean FEV_1% predicted of the study, line= estimated relation obtained from the log-linear regression. Right graphs: Annual total or severe exacerbation frequency plotted against the mean FEV_1% predicted of the study, line= relation based on the re-transformed exacerbation rates using the smearing factor

Table 2: Estimates of the regression coefficients, covariance and smearing factors for the relation between FEV_1% predicted and annual exacerbation rate described as: Annual exacerbation frequency = φ * exp[a+b*FEV_1% predicted]

	Total exacerbations: event-based definition#	Total exacerbations: symptom-based definition#	Severe exacerbations#
Intercept: a	1.181 (0.351), p=0.004	0.981 (0.364), p=0.01	-1.043 (0.904), p=0.27
Coefficient FEV_1% predicted: b	-0.014 (0.007), p=0.053	-0.009 (0.007), p=0.19	-0.013 (0.020), p=0.51
Covariance intercept and coefficient	-0.00227	-0.00227	-0.0176
Smearing factor: φ	0.893	0.960	1.072

Values are mean (SE), p-value

Table 3: Estimated annual exacerbation frequency per GOLD stage based on the regression equations (95% uncertainty interval)

GOLD stage	Mean FEV_1% predicted	Total exacerbations: event-based definition	Total exacerbations: symptom-based definition	Severe exacerbations
I, Mild COPD (FEV_1% pred ≥80%)	90	0.82 (0.46; 1.49)	1.15 (0.67; 2.07)	0.11 (0.02; 0.56)
II, Moderate COPD (50%≤ FEV_1% pred< 80%)	65	1.17 (0.93; 1.50)	1.44 (1.14; 1.87)	0.16 (0.07; 0.33)
III, Severe COPD (30%≤ FEV_1% pred<50%)	42	1.61 (1.51;.74))	1.76 (1.70; 1.88)	0.22 (0.20; 0.23)
IV, Very severe COPD (FEV_1% pred<30%)	23	2.10 (1.51; 2.94)	2.09 (1.57; 2.82)	0.28 (0.14; 0.63)

exacerbations only (symptom-based: p=0.19, severe exacerbations: p=0.51). The final association between the FEV_1% predicted and the exacerbation frequency after retransforming the predicted log exacerbation rate into normal exacerbation rate, are shown in the right three graphs in figure 1. Results for the mean exacerbation frequencies for the different GOLD stages based on the regression equations are presented in Table 3.

Using an event-based definition the total exacerbation frequency was significantly higher in patients with an FEV_1% predicted below 50% compared with patients having an FEV_1% predicted above 50%. Regression analyses with additional covariates showed no significant effect of duration of follow-up of the study or type of study (cohort versus trial) was found. The duration of follow-up was of borderline significance for total exacerbations using the symptom-based definition with longer follow-up resulting in lower rates (Table 4).

Table 4: Random effect regression analysis of FEV_1%predicted and annual exacerbation frequency: significance of the covariates, type of study and duration of follow-up

	P-value for type of study (cohort versus trial)	P-value for duration of follow-up
Total exacerbations, event-based definition	0.80	0.57
Total exacerbations, symptom-based definition	0.24	0.05
Severe exacerbations	0.86	0.99

Discussion

Although many trials and cohort studies report on the important outcome i.e. exacerbation frequency, the association between lung function and exacerbation frequency is less often investigated. The current study systematically reviewed the information contained in the literature and combined it into an estimate of exacerbation frequency as a function of FEV_1% predicted. The coefficient for lung function showed borderline significance for total exacerbations using the event-based definition (p=0.053), and was insignificant for total exacerbations using a symptom-based definition and severe exacerbations. Based on the estimated equation the final estimates of the total exacerbation frequency per GOLD severity stage using the event-based definition were 0.82 for mild, 1.17 for moderate, 1.61 for severe and 2.10 for very severe COPD. In spite of the overlapping uncertainty intervals, these estimates are useful for health economic/modelling purposes, as long as they are accompanied by an appropriate uncertainty probabilistic sensitivity analysis. In this way, the 95% confidence intervals vary substantially per GOLD stage, which would be ignored using a single exacerbation frequency for all GOLD stages.

In accordance with the general finding that using the symptom-based definition results in higher estimates of the total exacerbation frequency, we found slightly higher estimates for mild, moderate and severe COPD using the symptom-based definition compared with the event-based definition. However, this difference was not significant and seemed to get smaller with increasing severity of COPD. We also did not see an effect of follow-up duration. The mean follow-up in the studies in this review was 14 months, ranging from three to 36 months.

The study had a couple of limitations and strengths. A reason why the relationship between lung function and exacerbation frequency in our study was relatively weak may be our use of published data. Regression on study summary estimates, as done in this study, has substantially less power than regression on patient-level data [56]. It is likely that variation in lung function across studies is lower than variation in lung function across patient-level data within studies. By plotting the mean exacerbation frequency against the mean FEV_1% predicted of a particular study, the within study variation was not accounted for. Thus, a limitation of our study was that the heterogeneity in mean lung function between the studies in our review was relatively limited, especially for severe exacerbations. The majority of studies had a mean FEV_1% predicted between 35 and 60% and studies with a very low (<30%) and a very high mean FEV_1% predicted (>80%) were scarce or completely lacking. However, using a systematic review, the current study reflects the full evidence present in the current literature. This is preferable to using a single patient-level study, which may be biased towards the specific population under study.

Another limitation may be that most of the data were obtained from patients participating in clinical trials each using specific inclusion criteria. We included data from 28 clinical trials with in total 6780 patients and nine cohort studies with in total 2211 patients. Trial populations may be biased towards a lower exacerbation frequency because they include clinically stable patients with no other major co morbidities and who are motivated to participate in a trial. However, an overestimation could also be possible because a large number of trials included only patients with at least one or two exacerbations in the year before inclusion. The cohort studies included in our review used similar inclusion criteria as the trials and therefore probably included similar patient populations. No systematic difference in exacerbation rate was found between the cohort studies and trials. How these compare with the COPD population seen in daily practice is difficult to determine. One indication may be found in large retrospective database analyses [57-59]. These studies used event-based definitions and usually found lower exacerbation frequencies than our study, which gives us confidence that we did not underestimate exacerbation frequencies.

Exacerbations depend on the season and are more likely to occur in winter [3]. Therefore, according to recommendations [12], studies need to have a follow-up of at least twelve months or recruitment should be spread throughout the year to give reliable estimates of the exacerbation frequency. One of the strengths of our study is that the majority of studies, 89%, had a follow-up of at least six months and 65% had a follow-up of at least one year. Conversion of exacerbation rates from studies with a follow-up less than 12 months to annual rates may however have overestimated or underestimated the exacerbation frequency. However, we did not find a significant difference between studies with a follow-up duration shorter and longer than 12 months.

To validate the exacerbation frequencies found in our study, they may be compared with the limited patient-level data on the exacerbation frequency specified by subgroup of lung function. The cohort study of Andersson et al, which was included in the review, was the only study providing estimates for four COPD severity stages, using almost the same cut-off points for the stages as the GOLD classification [6]. The study used an event-based definition for exacerbations and found an annual exacerbation frequency of 0.67 for mild, 0.70 for moderate, 1.06 for severe and 2.56 for very severe COPD, which was somewhat lower than our estimates, except for very severe COPD. Vestbo et al reported on the exacerbation frequencies in several cohort studies and placebo-arms of trials in relation to the FEV_1% predicted and also found exacerbation frequencies below 1.0, for patients with an FEV_1% predicted above 50%. The average values for exacerbations for patients with an FEV_1% predicted between 40 and 50% ranged between 1.0 and 1.5, which was comparable with our results [10]. Burge et al showed the number of exacerbations per year in the placebo-arm of the ISOLDE trial using an event-based definition and specified the frequency for three lung function categories: <1.25, 1.25-1.54 and >1.54

liter (about comparable with <45%, 44-55% and >55% predicted). Below 45% predicted a mean of 2.6 exacerbations was found, while above >55% the average value was about 1.2 [13]. From the above described studies the general picture seems to be that above 50% predicted the total annual exacerbation frequency is around or slightly below 1.0, while below 40-45% predicted the exacerbation rate increases significantly, to about two or more exacerbations per year. The results of our study showed the same picture.

In conclusion, the current study provides an estimate of the association between annual exacerbation frequency and FEV_1% predicted in COPD, based on aggregated, summary data from individual studies. Results were in line with the few studies reporting on this relationship using patient-level data. The resulting GOLD stage specific exacerbation frequencies show overlapping uncertainty intervals, and hence any analysis based on these rates should be accompanied by a proper sensitivity analysis.

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Chapter 6

Case-fatality of COPD exacerbations: a meta-analysis and statistical modeling approach

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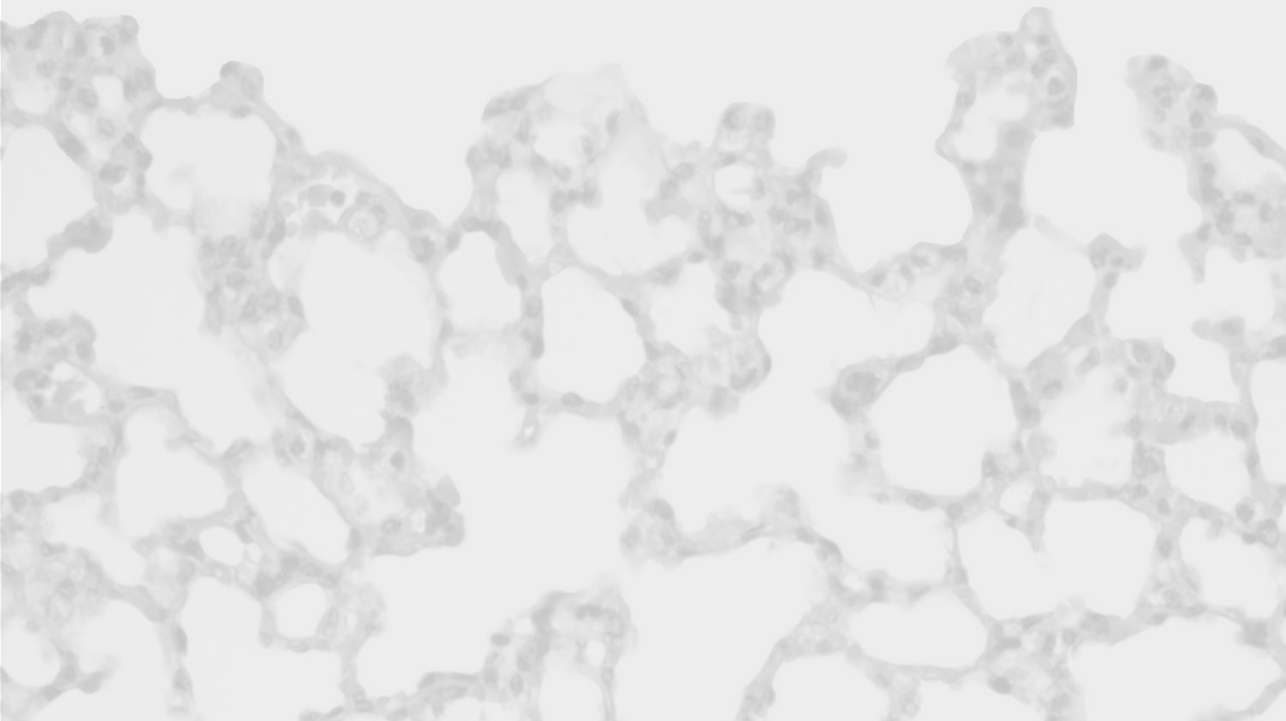

Abstract

The aim of our study was to estimate the case-fatality of a severe exacerbation from long-term survival data presented in the literature. A literature search identified studies reporting≥1.5 year survival after a severe chronic obstructive pulmonary disease (COPD) exacerbation resulting in hospitalization. The survival curve of each study was divided into a critical and a stable period. Mortality during the stable period was then estimated by extrapolating the survival curve during the stable period back to the time of exacerbation onset. Case-fatality was defined as the excess mortality that results from an exacerbation and was calculated as 1 minus the (backwardly) extrapolated survival during the stable period at the time of exacerbation onset. The 95% confidence intervals (CI) of the estimated case-fatalities were obtained by bootstrapping. A random effect model was used to combine all estimates into a weighted average with 95%-CI. The meta-analysis based on six studies that fulfilled the inclusion criteria resulted in a weighted average case-fatality rate of 15.6% (95% CI: 10.9%; 20.3%), ranging from 11.4% to 19.0% for the individual studies. A severe COPD exacerbation requiring hospitalization not only results in higher mortality risks during hospitalization, but also in the time period after discharge and contributes substantially to total COPD mortality.

Introduction

Worldwide, mortality due to chronic obstructive pulmonary disease (COPD) is high. According to the World Health Organization (WHO), at least 2.7 million deaths every year are due to COPD [1]. The 30-yr projections from the Global Burden of Disease Study show a striking increase in COPD as a cause of death to the third place worldwide in 2020 [2]. This increase largely results from a worldwide increase in the prevalence of smoking - especially in the developing countries and among females - and ageing of the population. The excess mortality among patients with COPD is high, not only because of the presence of COPD but also because of the increased prevalence of other smoking-related diseases [3].

Many studies have analyzed predictors of mortality in COPD. Among the factors independently associated with mortality in COPD are age, lung function (forced expiratory volume in 1 second, inspiratory capacity divided by total lung capacity), dyspnoea, co-morbidity, body mass index (BMI), fat-free mass, exercise capacity, arterial oxygen tension, C-reactive protein, the BODE-index (BMI, the degree of airflow obstruction, dyspnoea, and exercise capacity) and the number of previous hospitalizations [4,5].

Because patients with COPD are often recorded as dying from other causes, it has been suggested that all-cause mortality is probably the best mortality measure to use in COPD [5]. Nevertheless, it is well known that many patients dying do so during a severe COPD-exacerbation, when they experience acute respiratory failure [6]. However, there is a relative scarcity of knowledge on mortality rates from COPD exacerbations. Unlike in myocardial infarction and stroke [7] no estimates of the case-fatality of a COPD exacerbation exist. This may be associated with the absence of consensus on the length of the critical period during which the mortality risk is increased.

The most frequently reported outcome of death due to COPD exacerbations is short-term, in-hospital mortality [8]. Previous studies have estimated in-hospital mortality after hospitalization for a COPD exacerbation to range from 2.5% to 14% [9,10]. Mortality among patients admitted to intensive care units is much higher, i.e. up to 30% [11]. In-hospital mortality is insufficient to assess case-fatality for at least two reasons. There is a selection bias towards patients with longer hospital stays and it does not incorporate the mortality that occurs after hospital discharge but is still attributable to the index exacerbation. Therefore, our study aimed to estimate the case-fatality of a severe COPD exacerbation including the time period after hospitalization. This study arose out of our need to capture the impact of exacerbations on mortality within the context of a dynamic COPD progression model [12,13] used to evaluate the impact of different COPD interventions. To fully simulate the potential long-term impact of interventions which successfully prevent or treat exacerbations the impact of severe exacerbations on mortality needed to be estimated. As the COPD population in the model is specified by age, which is a significant predictor of mortality in COPD [5], we also investigated the association between age and mortality after a severe exacerbation.

Methods

We performed a comprehensive literature search in MEDLINE and EMBASE for journal articles published after 1990 reporting mortality or survival during and after hospitalization for an exacerbation of COPD using the MESH (sub) headings "chronic obstructive pulmonary disease or COPD or chronic bronchitis" in combination with "mortality or dead or death* or life expectancy or survival or prognosis" and "hospital* or admission* or admitt* or exacerbation* or disease episodes". We also searched references listed from articles retrieved. Studies were excluded if the patient population was a subgroup of hospitalized COPD patients, such as patients requiring mechanical ventilation. Inclusion criteria were: European, American or Australian study population; a follow-up period that started at hospital entry and lasted ≥1.5 year and presenting mortality rates at three or more time-points after hospital admission, or presenting a survival curve. Studies that fulfilled all inclusion criteria except for a follow-up of 1.5 year or the presence of three data points were used to complete the information on the average mortality rates at different time-points after a severe exacerbation as presented in the literature. In addition to information on the average mortality rates at different time-points, data on the association between mortality and age was extracted from the studies.

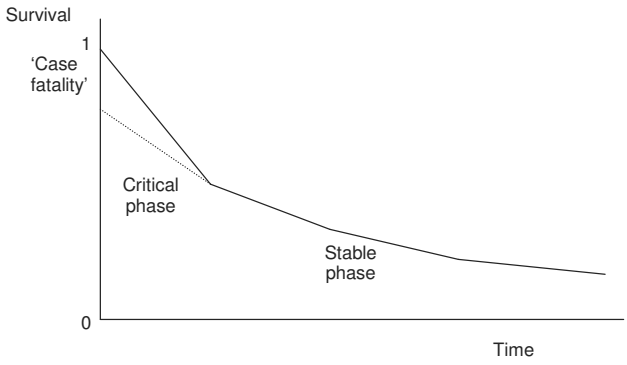

Figure 1: Survival curve after hospitalization for an exacerbation of COPD. The dotted line represents the extrapolated curve during the stable phase

Our general approach was as follows (figure1). For each study, we extracted the survival curve presented in the article or estimated the curve from the presented data ourselves. We roughly distinguished between the critical and the stable period after hospital admission with the survival curve during the stable period being flatter than the one during the critical period. Several data points from the curve during the stable period were extracted to estimate survival during this period. Only data points well after

the critical period were included. For each study, the survival function during the stable period was then parameterized using three parameters:

$$S(t) = (1-g)\,\mathrm{Exp}[-\alpha t - \beta t^2]$$

with
- t time, with t=0 being time of hospital admission
- $S(t)$ survival probability
- α, β parameters that define the non-linear change in survival over time
- g case-fatality of the exacerbation

The survival curve was fitted by minimizing the sum of squared differences with the points that were extracted from the curve, or given in the publication. We then extrapolated the survival curve during the stable period back to the time of hospital admission and calculated where the curve intersected the vertical axis (i.e. the start of hospital admission). The case-fatality was defined as the excess mortality that results from an exacerbation and equals g=1-S(0). Uncertainty intervals for each parameter were obtained from bootstrapping. Based on the given initial sample size and the calculated survival probabilities for each interval during the follow-up period, we randomly draw new survival numbers assuming binomial distributions. In this way we generated new survival curves, resulting in newly calculated values for the model parameters. The 2.5% and 97.5% percentile values correspond with the 95% uncertainty interval. Finally, estimates from all studies were combined to calculate the weighted average for g, using random effect meta-analysis [14]. The weights were based on a combination of the sampling error (variance of case-fatality within each study) and the random-effect variance (variance of case-fatality between all studies).

To estimate the association between age and mortality after a severe exacerbation, the relative risks of age on mortality within a study, if reported, were extracted from the retrieved references. The association with age within each separate study was investigated, because there was little difference in the mean age between the different studies. The weighted average relative risk was calculated using the variance in the individual studies as a weight.

Results

After first selection 60 references were obtained in full (figure 2). An entire review of these remaining publications resulted in the exclusion of another 44 studies for different reasons (figure 2). The main reasons for exclusion were that the association between hospitalization for COPD and mortality was not reported (13 studies) and that the study

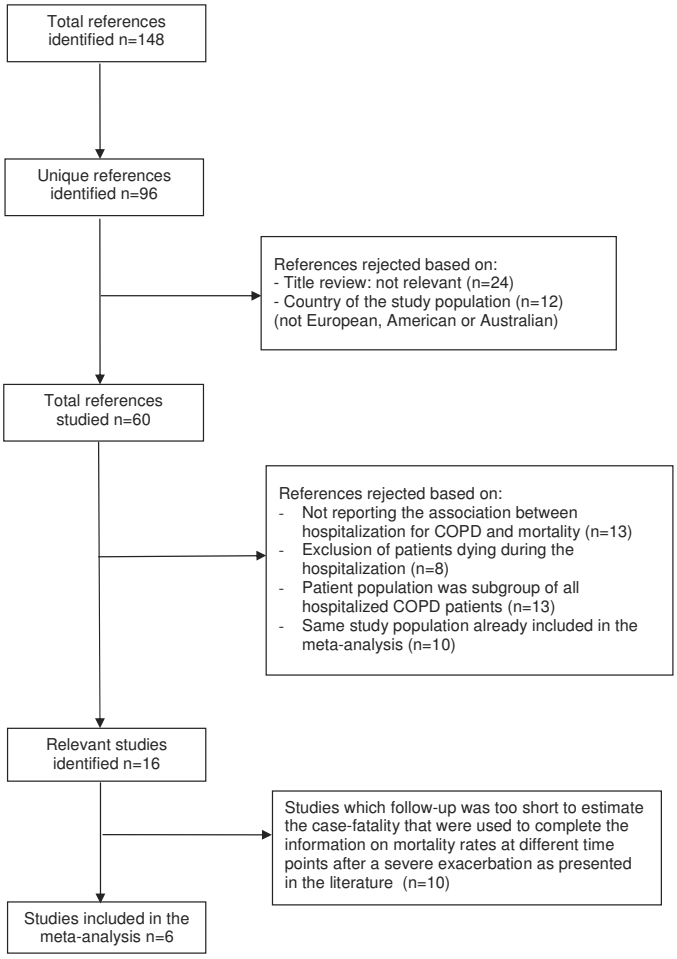

Figure 2: Results of the systematic literature search

population consisted of a selective subgroup of hospitalized patients (13 studies). Of the latter 13 studies, six studies included patients admitted to ICU or requiring (non-) mechanical ventilation only, three included patients treated in ER or pre-hospital setting only, two included hospitalizations for diagnoses other than COPD, while two studies included patients with a first admission or a very mild exacerbation only. Of the remaining 16 studies, 10 studies met all inclusion criteria except for the 1.5 years of follow-up. Hence, a total of six studies were finally included in the meta-analysis to calculate the case-fatality rate [15-20]. None of these studies evaluated the effect of an intervention as they were all cohort studies. For one of these six studies, the study of Brekke et al [20], we had access to the patient level data. For the other five studies results were based on the data presented in the article. Characteristics of the studies included are shown in Table 1.

Table 1: Characteristics of studies included in the meta-analysis that aimed to calculate the case-fatality of a COPD exacerbation

1st author of the study, year of publication	N	% Males	Mean age	Mean FEV_1% predicted	Patient selection	Definition exacerbation	Mean hospital length of stay (days)	Country
Connors, 1996 [15]	1,016	51	70	0.80L about 30% pred	Patients (age>18yr) with clinical diagnosis of COPD recorded by a physician	Hospitalization in combination with breathlessness, respiratory failure, or change in mental status due to COPD as main reason for admission and PaCO2>=50mmHg	9	USA
Vestbo, 1998 [16]	487	55	67	60	Patients (age>20yr) admitted for COPD (Copenhagen City Heart Study)	Hospitalization (>24 hours) with primary diagnosis ICD-8:491-492	Not reported	Denmark
Groenewegen, 2003 [17]	171	61	70	35	Patients with COPD (ATS criteria), with a FEV_1<70% and reversibility<11% who were admitted	Increase of two of three symptoms: dyspnea, cough, sputum severe enough to warrant hospitalization	11.7	Netherlands
Gunen, 2005 [18]	205	88	65	38	Patients with COPD (ATS criteria) who were admitted	Hospitalization for severe increase of symptoms (cough, purulent sputum and dyspnea), cyanosis and oedema, confusion, lethargy, coma, use of accessory muscles for ventilation, treatment failure, acidosis, hypoxemia and/or hypercapnia or new arrhythmias	11.6	Turkey
McGhan, 2007 [19]	54,269	97	69	Not reported	Patients admitted for COPD	Hospitalization with primary diagnosis ICD-9: 490-492 or 496 or diagnosis related group code of COPD with a primary or secondary discharge diagnosis of COPD	6.5	USA
Brekke, 2008 [20]	996	49	71	47	Patients (age>40 yr) admitted for COPD	Hospitalization with primary discharge diagnosis ICD-10:J44.0, J44.1, J44.x with J13-J18.9	Not reported	Norway

Case-fatality

Table 2 presents the results of the curve fitting procedure for each of the six selected studies. Details about the parameter values for each study are presented in the Appendix. The estimated average case-fatality rate for the individual studies varied between 11.4% and 19.0%. The overall weighted mean value of the case-fatality of an exacerbation was 15.6% (95% CI: 10.9; 20.3%).

Table 2: Estimated case-fatality of a COPD exacerbation

1st author of the study, year of publication	N	Estimated mean case-fatality (95% confidence limits)
Connors, 1996	1,016	17.2% (11.5; 23.1%)
Vestbo, 1998	487	12.3% (5.8; 18.4%)
Groenewegen, 2003	171	17.7% (10.2; 25.8%)
Gunen, 2005	205	16.7% (7.9; 25.4%)
McGhan, 2007	54,269	11.4% (10.6; 12.2%)
Brekke, 2008	996	19.0% (18.7; 19.3%)#
Overall estimate*		15.6% (10.9; 20.3%)

Based on patient-level data

*Overall weighted average case-fatality based on random effects analysis.

Association between mortality and age

All of the six studies included in the meta-analysis reported on the association between mortality after a hospitalization for an exacerbation and age. Age was a significant predictor of mortality in univariate analyses (five studies) and remained an independent predictor after correction for other explanatory variables in multivariate analyses (4 studies). On average the probability of dying after a hospitalization for an exacerbation increased by 4.1% per year increase in age (RR=1.041 95%CI: 1.037; 1.045) (six studies).

Average mortality rates at different time-points presented in the literature

Characteristics of the ten studies with an insufficient length of follow-up are shown in table 3 [9,10,21-28]. Table 4 shows the average mortality probabilities at different time-points for both these ten studies as well as the six studies that were included in the meta-analysis. Based on all sixteen studies combined, the average in-hospital mortality rate was 6.7%. The average mortality rates at three and six months were 18% and 26%, respectively.

Table 3: Characteristics of studies with a follow-up less than 1.5 years, excluded from the meta-analysis used to obtain information on mortality rates at different time-points after a severe exacerbation as presented in the literature

1st author of the study, year of publication	N	% Males	Mean age	Mean FEV_1% predicted	Patient selection	Definition exacerbation	Mean hospital length of stay (days)	Country
Fuso, 1995 [10]	590	79	68	Not reported	Patients with COPD (ATS criteria) who were admitted	Increased dyspnea, reduced usual performance with or without change in sputum, blood temperature and body weight less than 5 days prior to hospitalization	Not reported	Italy
Cydulka, 1997 [21]	131,974	49	75	Not reported	Patients (age>65yr) admitted for COPD	Hospitalization with first diagnosis ICD-9: 490-492, 496	6	USA
Eriksen, 2003 [22]	300	40	71	35	Patients with COPD confirmed by physician or spirometry that were admitted	Hospitalization for COPD exacerbation: J44.0, 44.1, 44.8, 44.9	9.9	Denmark
Patil, 2003 [9]	71,130	44	70	Not reported	Patients (age>40 yr) admitted for COPD	Hospitalization with discharge code ICD-9: 491.21	5	USA
Yohannes, 2005 [23]	104	48	73	40	Patients (age >60yr) admitted for COPD	Hospitalization for exacerbation defined as: presence of ≥2 symptoms: increased sputum purulence or volume, dyspnea, wheeze, chest tightness, or fluid retention	15	UK
Wang, 2005 [24]	282	41	71	36	Patients (>40yr), smoker/ex-smoker, FEV_1<80%, FEV_1/FVC<70%, no other lung disease who were admitted	Hospital admission for an acute exacerbation of COPD	10	Canada
Price, 2006 [25]	7529		Not reported	Not reported	Patients with physician-diagnosed COPD who were admitted	Acute hospital admission for COPD	8.3	UK
Bustamente, 2007 [26]	763	81	76	47	Patients (age>45yr) with COPD according to GOLD who were admitted	Hospitalization with diagnosis: ICD-9: 491.21	10.6	Spain
Kinnunen, 2007 [27]	72,896#	74	72	Not reported	Patients (age>44yr) admitted for COPD	Hospital admission with primary diagnosis ICD-8,9: 491, 942, 496 ICD-10: J41, 42, 43, 44	8.1	Finland
Dransfield, 2008 [28]	825	50	66	Not reported	Patients admitted for COPD	Hospitalization with primary discharge code ICD-9: 491.21 or primary diagnosis of respiratory failure 518.81 with second. diagnosis COPD exacerbation	5.7	USA

Number of admissions instead of number of patients

Table 4: Mortality rates after hospitalization for a COPD exacerbation at different time-points for the six studies included and the ten studies excluded from the meta-analysis fulfilling all inclusion criteria except for a follow-up more than 1.5 years.

		Mortality rate					
	N	In-hospital	3 months	6 months	1 year	2 year	5 year
Studies included in the meta-analysis							
Connors, 1996	1,016	11%	-	33%	43%	49%	-
Vestbo, 1998	487	-	-	-	-	-	44%
Groenewegen, 2003	171	8%	16%	18%	23%	-	-
Gunen, 2005	205	8.3%	-	24%	33%	39%	-
McGhan, 2007	54,269	3.6%	-	-	24%	-	57%
Brekke, 2008	996	9.9%	22%	27%	32%	41%	-
Studies (follow-up<1.5 years) excluded from the meta-analysis							
Fuso, 1995	590	14%	-	-	-	-	-
Cydulka*, 1997	131,974	6%	-	-	-	-	-
Eriksen, 2003	300	8.6%	19%	-	36%	-	-
Patil, 2003	71,130	2.5%	-	-	-	-	-
Yohannes, 2005	104	3.8%	-	-	38%	-	-
Wang, 2005	282	9.9%	-	-	-	-	-
Price, 2006	7,529	7.4%	15%	-	-	-	-
Bustamente, 2007	763	6.4%	-	-	-	-	-
Kinnunen, 2007	72,896#	3.2%	-	-	-	-	-
Dransfield, 2008	825	5.2%	-	-	-	-	-
Overall estimate based on all 16 studies (95% confidence limits)$		**6.7% (5.7;7.7%)**	**18% (14;22%)**	**26% (20;32%)**	**33% (25;40%)**	**43% (37;50%)**	**51% (38;63%)**

* Results year 1991

Number of admissions instead of number of patients

- Not reported

$Overall weighted average mortality rates based on random effects analysis.

Discussion

In this study the case-fatality of an exacerbation was calculated by extrapolating the survival curve during the stable period to the time of exacerbation onset. The weighted average case-fatality rate was estimated to be 15.6%, with the individual studies varying from 11.4% to 19.0%. The average in-hospital mortality rate was 6.7%, which strongly supports the notion that the critical period indeed exceeds the duration of the hospitalization.

However, we would like to emphasize that the estimated case fatality can not be compared with the mortality rates at different time-points as these represent different concepts. The case fatality was calculated as one minus the survival that would have been expected if the patient would have been stable (Figure 1), while mortality at a certain time-point was calculated as one minus the survival at that specific point in time. This also implies that the exact distinction between the critical and stable period after exacerbation onset however, could not be determined by comparing the case fatality rate with mortality rates at different points in time. The critical period was defined as the period in which mortality is increased compared to the stable situation. Therefore, this period ranges from the hospital admission until the point were the estimated survival curve during the stable period approaches the actual observed survival curve (figure 1). Estimating the point where the two survival curves approach each other is only possible if patient-level data are available or when we make additional assumptions on how the case-fatality changes over time within the critical period. We had patient-level data from one study, the study of Brekke et al [20]. For this study the critical period was estimated to last 4.4 months. The length of the critical period is likely to vary according to the population studied; in patients with several co-morbidities the exacerbation may have both more severe [9,19] and longer lasting impact and similarly the critical period could last longer in the elderly.

Due to limited data and the homogeneity of the different studies we were not able to specify the case-fatality by subgroups such as COPD severity (defined by lung function), sex or age. Therefore we searched for information about the association of these variables with mortality within the extracted studies. Within the studies the relation of mortality due to an exacerbation with disease severity or sex was less clear. Mortality after a hospitalization for an exacerbation was however highly dependent on age (RR=1.041 per increase in year of age).

As the study populations of the six studies selected for the meta-analysis were almost the same with respect to the mean age, 65 to 71 years, age did no influence the between-study comparison of case-fatalities. The studies included have sampled data spanning a time period of more than 10 years but no obvious pattern of change over time in case-fatality can be seen. This could be the result of the variation in treatment

and management between the different countries but was actually also observed in within one of the included studies [16]. In contrast, a very recent study found indications of a slight improvement of exacerbation-related mortality over time [29].

Despite the homogeneity between the studies with respect to age, the study populations may have differed on other aspects. Although we selected studies from Western countries, the criteria used for hospitalization for example are not similar across countries. This is related to local treatment patterns, which in turn may be driven by local guidelines, medical traditions, cultural aspects, financing and reimbursement schemes etc. In our selected studies the mean length of stay was significantly longer in the European studies compared to studies from the USA, 11 versus 7 days. However, the mean in-hospital mortality rate did not differ. One study aspect which seemed to have an influence on the results was whether patients included in the study had physician- or spirometry-confirmed COPD. Studies including patients with confirmed COPD reported higher mortality rates than studies including patients with hospitalization for COPD based on ICD-coding. The mean in-hospital mortality rate for both groups were 9.2% (95% CI: 7.4; 10.9) and 4.8% (95% CI: 3.5; 6.1), respectively. Two of the studies used in the meta-analysis included patients with a hospitalization for COPD based on ICD-coding. If the largest of these two studies, the study of McGhan [19], was excluded from the meta-analysis, the average case fatality rate would have been higher, i.e. 17.9% (95% CI: 15.8; 20). Studies using ICD-coding only to define COPD may report lower mortality rates because they also included mild patients or patients with for example asthma that were wrongly coded.

In conclusion, mortality in COPD is common and severe exacerbations of COPD are one of the major causes of death in COPD. In this study the case-fatality rate of a severe exacerbation resulting in hospitalization was estimated to be 15.6%, showing the substantial impact of exacerbations on mortality.

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Appendix

The survival function during the stable period for each study was parameterized using three parameters:

$$S(t) = (1-g)\,\mathrm{Exp}[-\alpha t - \beta t^2]$$

with
- t time, with t=0 being time of onset of exacerbation
- $S(t)$ survival probability
- α, β parameters that define the non-linear change over time
- g case-fatality of an exacerbation

Table A1: Median parameter values (95% uncertainty interval) of the survival function

1st author of the study, year of publication	α	β	g
Connors, 1996 [1]	0.482 (0.353;0.608)	-0.117 (-0.164; -0.071)	0.174 (0.115;0.231)
Vestbo, 1998 [2]	0.132 (0.055;0.204)	0.001 (-0.013;0.018)	0.126 (0.058;0.184)
Groenewegen, 2003 [3]	-0.006 (-0.087;0.069)	0.016 (0;0.033)	0.179 (0.102;0.258)
Gunen, 2005 [4]	0.135 (0.058;0.228)	-0.014 (-0.03;0.002)	0.17 (0.079;0.254)
McGhan, 2007 [5]	0.229 (0.22;0.238)	-0.01 (-0.012;- 0.008)	0.114 (0.106;0.122)
Brekke, 2008 [6]#	0.191 (0.187;0.195)	-0.017 (-0.018;-0.016)	0.190 (0.187;0.193)

Based on patient-level data

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Chapter 7

Developing and applying a stochastic dynamic population model for chronic obstructive pulmonary disease

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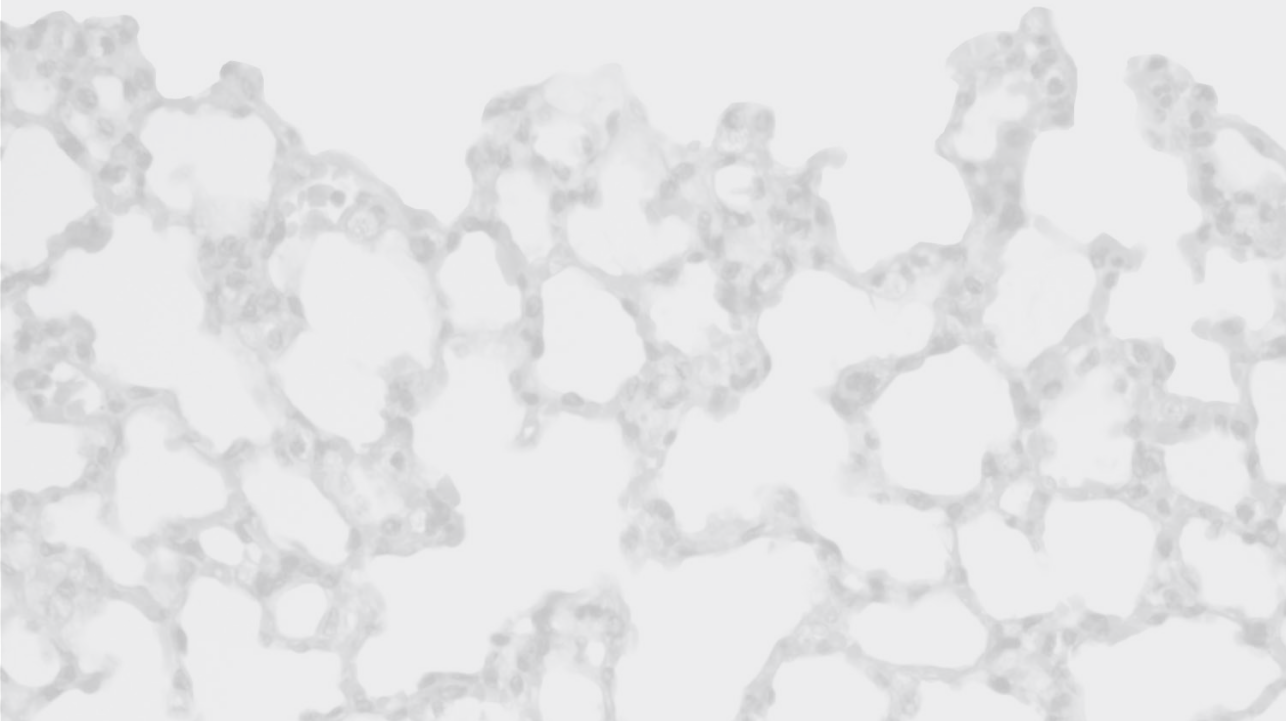

Abstract

The objective of the study was to develop a stochastic population model of disease progression in COPD that includes the impact of COPD exacerbations on health-related quality of life, costs, disease progression and mortality and can be used to assess the impact of a wide range of interventions. The model is a multistate Markov model with time varying transition rates specified by age, sex, smoking status, COPD disease severity, and/or exacerbation type. The model simulates annual changes in COPD prevalence, due to COPD incidence, exacerbations, disease progression (annual decline in FEV_1% predicted) and mortality. The main outcome variables are (quality-adjusted) life years (QALYs), total exacerbations and COPD-related healthcare costs. Exacerbation-related input parameters were based on quantitative meta-analysis. All important model parameters are entered into the model as probability distributions. To illustrate the potential use of the model, costs and effects were calculated for three-year implementation of three different COPD interventions, one pharmacological, one on smoking cessation and one on pulmonary rehabilitation using a time horizon of ten years for reporting outcomes. Compared with minimal treatment the cost per QALY gained was €8,300 for the pharmacological intervention, €10,800 for the smoking cessation therapy, €8,700 for the combination of the pharmacological intervention and the smoking cessation therapy and €17,200 for the pulmonary rehabilitation program. The probability of the interventions to be cost-effective at a ceiling ratio of €20,000 varied from 58 to 100%. The COPD model provides policy makers with information about the long-term costs and effects of interventions over the entire chain of care, from primary prevention to care for very severe COPD and includes uncertainty around the outcomes.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation, which is not fully reversible [1]. The main risk factor is smoking and the most important symptoms are chronic dyspnoea, cough and sputum production. The progression of COPD is often accompanied by periods of increasing symptoms, known as exacerbations, which were found to be associated with increased mortality, impaired health-related quality of life and increased healthcare use [2,3].

The worldwide burden of COPD in terms of morbidity, mortality and healthcare costs is substantial and is expected to increase in the future, mainly due to ageing and continuing tobacco use. A US study showed that from six major causes of death COPD was the only condition for which mortality rates have increased between 1970 and 2002 and these rates were expected to increase continuously [4]. Furthermore, COPD was projected to be one of the leading causes of mortality and disability in 2020 worldwide [5]. Against this background health policy makers need information about the options for prevention and treatment of COPD in terms of both effects and costs.

In a slowly progressing disease such as COPD, modelling can be a useful tool to estimate the medium and long-term effects and costs of interventions. Next to that, modelling is also useful to combine existing knowledge from various sources in a consistent way. In the past decade nine different COPD progression models have been published [6-14]. All these models are Markov models and comparable with respect to COPD severity based on FEV_1% predicted, progression based on decline in lung function and inclusion of exacerbations. Structural differences between the models exist regarding the number of COPD severity stages, duration of the Markov cycles, inclusion of the risk factors age and smoking, distinction in severity of exacerbations and inclusion of COPD incidence. Furthermore, the models substantially differ in utility values assigned to COPD stages and utility decrements assigned to exacerbations [15]. Finally, not all the models take into account the uncertainty around the input parameters, which is currently regarded as essential in cost-effectiveness analyses [16,17].

Because most of the COPD models were built to evaluate a specific intervention in a specific population, mostly to support reimbursement negotiations of new medications, they may be less suitable to evaluate other types of interventions. This is for example reflected in the fact that model parameters such as transition probabilities and exacerbation rates were often obtained from one or a few clinical trials investigating the medication of interest. In such models, disease progression is often similar regardless sex, age and smoking status which make these models less suitable to simulate the impact of for example smoking cessation interventions on disease progression.

The aim of this study was to develop a dynamic population model of disease progression in COPD from diagnosis of the disease until death. In contrast to our earlier model

[9,18], the new model includes the impact of COPD exacerbations, allows for probabilistic sensitivity analysis and can be used to evaluate a wide range of COPD interventions, from prevention to treatment. This paper primarily describes the structure of the new model and the estimation of the new exacerbation-related input parameters. The potential use of the new model is illustrated by calculating the cost-effectiveness of three different COPD interventions compared with minimal treatment.

Methods

Description of the model structure

The COPD model is not a straightforward simple discrete stage Markov model, but it may be classified as a Markov-type model, because the Markov property is a prominent aspect of the entire model. The model has six main health states, no COPD, four COPD severity stages based on the Global Initiative for chronic Obstructive Lung Disease (GOLD) classification [1] and death, which are further stratified by sex, age and smoking status. COPD severity stages are further characterized by their distribution of lung function, the forced expiratory volume in one second (FEV_1) as percentage of the predicted value. The cycle length of the model is one year and the time horizon of the analyses can vary between one year and life-time. Figure 1 illustrates the structure of the model. The model follows birth cohorts over time. Each year a new birth cohort is added, while the existing cohorts age with one year. Within each birth cohort people can move between smoking classes, be diagnosed with COPD, move to another COPD severity stage or die, all with a certain annual probability. These probabilities depend on the relevant co variables age, sex, lung function and smoking status. The model starts with the Dutch general population and the COPD patient population in 2007 specified by sex, one-year age classes, smoking status (smokers/ former smokers/never smokers) and COPD severity. COPD patients are divided into four severity stages according to their lung function, expressed as the FEV_1% predicted. The model then simulates the annual changes in the general population as well as the COPD population. The dynamics in the Dutch general population are taken into account using prognoses of birth and mortality as well as estimates of the start-, stop and restart rates of smoking, while changes in the COPD population are the result of incidence, changes in smoking status, disease progression and mortality (figure 1). In each severity stage COPD patients have an annual probability to experience exacerbations. Exacerbations in the model were defined based on an increase in healthcare use, i.e. an event-based definition. A distinction was made between moderate (non-severe) and severe exacerbations. A moderate exacerbation was defined as an exacerbation leading to a prescription of systemic corticosteroids and/or antibiotics and

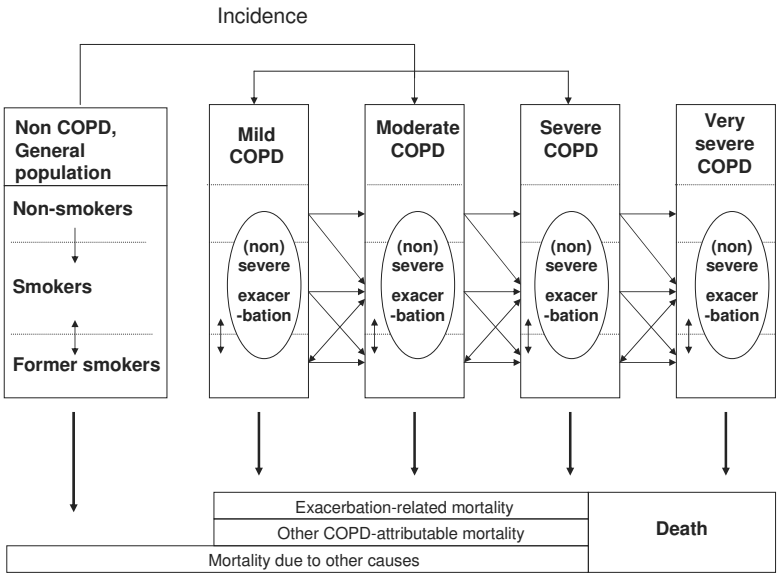

Figure 1. Description of the Dutch COPD population model

a severe exacerbation was defined as a hospitalization for COPD. Total exacerbations were calculated as the sum of both moderate and severe exacerbations. Exacerbations were modelled to affect disease progression, mortality, quality of life and costs.

Mortality among COPD patients consists of mortality attributable to COPD and mortality due to other causes. COPD-attributable mortality was defined as the independent mortality risk related to having COPD, i.e. which is adjusted for the mortality risk from smoking. This adjusted COPD-related mortality risk is smaller than the unadjusted risk, since having COPD is largely correlated with smoking, and smoking increases the mortality risk through many more chronic diseases other than COPD. COPD-attributable mortality was modelled as being dependent on sex, age and FEV_1% predicted (RR=1.2 (95% CI: 1.16; 1.23) per 10-unit decline [19] and was further divided into exacerbation-related mortality and remaining COPD attributable mortality. Mortality from other causes was modelled to depend on sex, age and smoking status and included the mortality from other smoking-related diseases. To avoid double counting, COPD attributable mortality was not modelled to depend on smoking status because the impact of smoking on mortality due to COPD is already captured by the increased incidence and prevalence of COPD among smokers and former smokers. This means that a smoking and former smoking patient with the same sex, age and COPD severity stage were assumed to have the same risk to die of COPD. Smoking patients, however, have a higher COPD-attributable mortality risk over time, because they progress faster to more severe COPD stages, which are associated with a higher mortality risk. More details about the model structure can be found in [20].

Outcomes

The main outcome variables of the model are the total annual number of life years, quality-adjusted life years (QALYs), moderate and severe COPD exacerbations, total mortality and total COPD-related healthcare costs. The annual number of life years is calculated as the annual number of patients alive. The annual number of QALYs is calculated as the annual number of life years weighted by their quality of life during these years using EQ-5D utility weights specified by COPD severity [6]. For each exacerbation a decrement in utility weights is applied [21,22]. Total mortality is defined as the annual number of deaths with a COPD-related cause plus the annual number of deaths due to other causes. The annual COPD-related healthcare costs are calculated by multiplying the number of patients alive with the COPD-related maintenance costs per patient specified by sex, age and COPD severity and adding the additional costs of exacerbations.

Demographic, smoking and COPD non-exacerbation related input parameters

Data on demography and prognoses of birth and mortality for the year 2007 were obtained from Statistic Netherlands [23], while prevalence of smoking and changes in smoking status in the population, i.e. start, stop and restart rates, were based on data from STIVORO [24-26], all specified by sex and one-year age classes.

Data on COPD prevalence, incidence and mortality for 2007 including uncertainty were obtained from GP registrations [27,28]. As almost all Dutch citizens are registered at a GP, the model is representative of the Dutch population of diagnosed COPD patients. Prevalence, incidence and mortality by sex and age were further specified by smoking status using the relative risks of smokers and former smokers to die of COPD [29,30]. The COPD prevalence within each subclass by sex, age and smoking status was then further divided over the four GOLD stages of COPD severity [1] using the estimated normal distribution of the FEV_1% predicted of COPD patients in two Dutch GP practices (mean: 68.3, SD: 19.9), which led to the following distribution: 27% mild (FEV_1 predicted ≥80%), 55% moderate (FEV_1 predicted <80% and ≥50%), 15% severe (FEV_1 predicted <50% and ≥30%) and 3% very severe COPD (FEV_1 predicted <30%) [31]. The severity distribution of the incidence was estimated by the model and defined as the distribution that -given disease progression and mortality- would not change the FEV_1% predicted among the prevalent cases in the first year of the model. Based on this estimated normal distribution (mean: 76.4, SD: 15.6), the severity distribution of the incidence was estimated to be 40% in mild, 55% in moderate, 4% in severe and 0.1% in very severe COPD.

Disease progression was modelled as the annual decline in FEV_1% predicted based on a re-analysis of the original 5-yr Lung Health Study data [32,33]. A random effect model was used to estimate the annual decline in FEV_1% predicted depending on sex, age,

Table 1: Main input parameters for the model for the reference scenario specified by sex and/or COPD severity stage

		COPD severity stage			
		Mild	Moderate	Severe	Very severe
Prevalence (2007) as % of general population >45yrs:					
- Males	Never smokers	0.03	0.06	0.02	0.003
	Smokers	0.41	0.85	0.24	0.04
	Former smokers	0.98	2.05	0.57	0.10
- Females	Never smokers	0.12	0.25	0.07	0.01
	Smokers	0.36	0.74	0.21	0.04
	Former smokers	0.64	1.34	0.37	0.06
Incidence (2007) as % of general population >45yrs:					
- Males	Never smokers	0.005	0.007	0.0005	0.00001
	Smokers	0.08	0.11	0.008	0.0002
	Former smokers	0.17	0.24	0.02	0.0004
- Females	Never smokers	0.02	0.03	0.002	0.00005
	Smokers	0.07	0.10	0.007	0.0002
	Former smokers	0.11	0.15	0.01	0.0003
Annual decline in FEV_1% predicted#:					
- Males	Never smokers/former smokers	-0.83	-1.20	-1.56	-1.85
	Smokers	-1.16	-1.54	-1.89	-2.18
- Females	Never smokers/former smokers	-0.79	-1.17	-1.52	-1.81
	Smokers	-1.13	-1.51	-1.86	-2.15
COPD attributable mortality (2007)#:					
- Males		2.8%	4.5%	6.9%	9.6%
- Females		1.9%	3.0%	4.6%	6.3%
Mortality due to other causes (2007) #:					
-Never smokers			Males:1.0%, females: 0.6%		
-Smokers			Males: 2.4%, females: 1.4%		
-Former smokers			Males: 1.2%, Females: 0.7%		
Utilities:		0.8971 (0.1117)	0.7551 (0.2747)	0.7481 (0.2991)	0.5493 (0.3129)
COPD costs for maintenance per patient (€, 2007)#:					
- Males		€135 (20)	€169 (25)	€187 (28)	€277(42)
- Females		€326 (49)	€405 (61)	€452 (68)	€671 (101)
Smoking prevalence in the general population >45yrs:					
- Never smokers			Males: 18%, females: 39%		
- Smokers			Males: 27%, females: 22%		
- Former smokers			Males: 54%, females: 39%		
Smoking transition rates in the general population >45yrs:					
- Start			Males: 0.5%, females: 0.1%		
- Stop			Males: 6.5%, females: 6.5%		
- Restart			Males: 1.3%, females:1.4%		

Data has been specified by age. The table presents values for age 69 years, the mean age of the COPD population in the model

smoking status and baseline FEV_1% predicted [9]. The values found were not translated into transition rates as is common in all other models, but modelled directly as the change in the distribution of FEV_1% predicted for the total group of patients within a certain COPD state. A new division over the severity stages was made at each annual step after all changes had been simulated using the cut-off points for the different GOLD severity stages (FEV_1predicted of 80%, 50% and 30%).

The main input parameters for mortality were all-cause mortality obtained from Statistic Netherlands [34] and COPD excess mortality [28]. The COPD-attributable mortality was calculated as the COPD excess mortality adjusted for smoking status. Mortality due to other causes was estimated as the total mortality among COPD patients minus the COPD-attributable mortality.

The total direct medical costs for COPD in the Netherlands specified by sex and age were obtained from a previous cost of illness study for the year 2000 [35]. These costs were updated to the year 2007 using consumer price indices [36]. We did not update these data using newer cost of illness studies, because we aimed to represent minimal treatment and the resource use estimates of 2000 best reflected this type of treatment. The COPD-related maintenance costs were calculated as the total direct medical cost per sex and age class minus the exacerbation-related costs per sex and age class. The maintenance costs within each sex and age class were further divided over the severity stages using ratios for the total COPD costs of a patient with moderate (1.24), severe (1.39) or very severe COPD (2.06) compared to the costs of a patient with mild COPD (1.0) as observed in Dutch studies [10,37]. The main input parameters of the model are shown in Table 1 and further specified in reference [20].

COPD exacerbation-related input parameters

The new exacerbation-related parameters were based on quantitative meta-analyses. These parameter estimates can be regarded as results of this study, but are presented in the methods section because it concerns input parameters.

Exacerbation frequency by COPD severity

The frequency of total and severe exacerbations by GOLD severity stage was based on a systematic literature review and meta-analysis of randomized controlled trials and cohort studies reporting altogether 19 different estimates of the total exacerbation frequency and 14 different estimates of the severe exacerbation frequency in patients receiving usual care or placebo. The association between the mean FEV_1% predicted of the study populations in the selected studies and the annual exacerbation frequencies was estimated. The estimated equations were used to calculate the total number and the number of severe exacerbations per GOLD stage. Based on the mean FEV_1% predicted

per GOLD severity stage in the first year, the average number of total exacerbations in the first year was estimated to be 0.82 (95% CI:0.46; 1.49) for mild, 1.17 (0.93; 1.50) for moderate, 1.61 (1.51; 1.74) for severe and 2.10 (1.51; 2.94) for very severe COPD. The severe exacerbations rates were 0.11 (95% CI: 0.02; 0.56), 0.16 (0.07; 0.33), 0.22 (0.20; 0.23) and 0.28 (0.14; 0.63), respectively. The estimated regression equations were built into the model to capture the impact of changes in mean FEV_1% predicted over time within a severity stage on the exacerbation frequency. All details about the estimation of the exacerbation frequencies specified by GOLD severity stage have been reported in a separate manuscript [38].

Case-fatality of exacerbations

Mortality was assumed to be increased after a severe exacerbation only, not after a moderate exacerbation. The case-fatality was calculated as the probability of mortality after a severe exacerbation corrected for the mortality probability during a stable disease period. This was based on six studies reporting at least 1.5 year survival after a severe exacerbation that allowed us to separate the survival curve after hospital admission into a critical and a stable period. The case-fatality of a severe exacerbation was estimated to be 15.6% (95% CI: 10.9; 20.3%) on average. This case-fatality was applied to the mean age of the COPD population in the papers selected from the literature, i.e. 69 years. The relation between age and mortality was also estimated (RR=1.041 (95% CI: 1.037; 1.045) per year increase in age) and used in the model to make the case-fatality rate age-dependent. Further details about the estimation of the case-fatality of a severe COPD exacerbation have been reported in a separate manuscript [39].

Exacerbations and lung function decline

Five studies were found reporting the relation between exacerbations and lung function decline [40,41-44]. Only one study directly reported the decline in lung function per lower respiratory illness [42]. For the other studies the decline in lung function due to an exacerbation was estimated by dividing the difference in lung function decline between patients with infrequent and frequent exacerbations as defined in the specific study by the difference in exacerbations between the two groups. The average decline in lung function per exacerbation was estimated to be 0.19% predicted (95% CI: 0.092; 0.29).

Exacerbations and quality of life

Only two studies reported about exacerbations and quality of life using the EuroQol (EQ-5D), one for severe and one for moderate exacerbations. O'Reilley et al presented utility values at admission and discharge for a COPD hospitalization based on the UK value set [22]. Based on these values, -0.077 and 0.576 respectively, the mean length of hospitalization of 11 days, the assumption that the utility value would have returned to

normal, i.e. 0.689, after 4.5 months [39] and the assumption of a linear increase between admission and discharge and discharge and baseline, the annual utility loss due to a severe exacerbation was estimated to be 4.82% (95% CI: 3.11; 6.53) from the baseline utility value. The annual utility loss due to a moderate exacerbation, 1.66% (95% CI: 1.23; 2.09) of the baseline value, was derived from a study of Goossens et al, who measured utility scores during a moderate exacerbation at four different time points over a period of six weeks [21].

Costs of exacerbations

The costs per moderate and severe exacerbation were based on a study from Oostenbrink et al [45]. Because of the difference in exacerbation definition with our model we slightly modified the cost estimate of a moderate exacerbation by deleting the inpatient hospital costs for a non-severe exacerbation. The final cost estimates were updated to the year 2007 resulting in a cost estimate of €94 (95% CI: 80; 108) for a moderate and €4100 (95% CI: 2348; 5852) for a severe exacerbation.

Intervention scenarios

All reference values of the input parameters were as far as possible estimated from data sources in which patients received minimal treatment. Data were obtained from cohorts receiving usual care in older studies or from the placebo-arm of a trial or the arm receiving a non-intensive intervention. Therefore a model simulation using the reference values of the input parameters reflects the situation in which patients receive minimal treatment ("minimal treatment scenario"). To illustrate the possibilities of the model we calculated the cost-effectiveness for four scenarios (three different interventions) compared with minimal treatment. For ease of interpretation, all cost-effectiveness analyses were performed for a fixed cohort of patients, that is setting COPD incidence to zero.

The first scenario evaluated was the implementation of a pharmacological combination therapy of a long-acting β2 agonist with an inhaled corticosteroid (ICS/LABA). Effects of this therapy were modelled as a reduction in lung function decline, exacerbation frequency and all-cause mortality. The size of these benefits was obtained from the TORCH trial [44,46] and given in Table 2. Directly applying the RR's to all three parameters independently would overestimate the effect of the intervention, because lung function, exacerbation rate and mortality are related to each other in the model. Therefore the effect of the intervention was modelled in three steps. In step one the effect on lung function decline was applied. If the effect of the decrease in decline on exacerbation frequency was smaller than the effect seen in the trial, the effect of the intervention on exacerbation frequency was adjusted till the magnitude of the effect observed in the trial (step two). After that, the effect of the first two steps on all-cause

Table 2: Input data for the intervention scenarios (95% confidence interval)

	Combination of a long-acting bronchodilator and an inhaled corticosteroid	Intensive counseling plus pharmacotherapy for smoking cessation	Pulmonary rehabilitation
Target population	Moderate and severe COPD	Mild, moderate, severe and very severe COPD	Moderate and severe COPD
Percentage of patients receiving the intervention	50%	50%	15%
Annual smoking cessation rate	-	+10.9% (6.0;15.0%)	-
Annual decline in lung function	RR=0.60 (0.45;0.76)	-	-
Total exacerbation frequency	RR=0.75 (0.69;0.81)	-	-
All-cause mortality at three year	HR=0.825 (0.681;1.002)	-	-
Annual change in utility	-	-	+0.043 (-0.005;0.090)
Annual intervention costs	€773	€305	€745

mortality was determined. Finally, in step three the effect on mortality was adjusted till the effect seen in the trial. The second scenario assumed increased implementation of intensive counseling plus pharmacotherapy for smoking COPD patients, leading to increased smoking cessation rates (Table 2) [18]. In the model, increased smoking cessation leads to a one-time increase in FEV_1% predicted, a lower annual decline in lung function (based on the Lung Health Study [33]) and reduced mortality due to COPD and other smoking-related diseases. In scenario three implementation of the combination of the first two interventions, ICS/LABA for all patients with moderate and severe COPD and intensive counseling plus pharmacotherapy for all smoking COPD patients was evaluated. Because the TORCH trial did not found a significant interaction between treatment and smoking status [46], we assumed no interaction effect between the pharmacological intervention and the smoking cessation therapy, i.e. effects were assumed additive. In scenario four, implementation of an interdisciplinary community-based pulmonary rehabilitation program was simulated, using a trial-based estimate of its costs and effect on quality of life (Table 2) [47].

Table 2 also shows the type and percentage of patients receiving the intervention and the intervention costs. All interventions were assumed to be implemented for three years and evaluated using a time horizon of ten years. A three-year implementation period implied that the benefits and costs of the interventions were applied for three years and that after three years all input parameters returned to the reference values, representing minimal treatment. The four intervention scenarios were compared with the minimal treatment scenario to estimate the number of QALYs gained, the number of exacerbations avoided, the incremental intervention costs and the savings in COPD-related healthcare costs. Health outcomes were discounted by 1.5%, costs by 4% [48].

The costs per QALY gained and exacerbation avoided for each intervention scenario were calculated as the total incremental intervention costs minus savings in COPD-related healthcare costs divided by the gain in QALY or the number of exacerbations avoided, respectively.

Sensitivity analyses

To estimate the impact of the uncertainty around the different input parameters on the outcomes a probabilistic sensitivity analysis was performed. The parameters included in the sensitivity analysis with their mean and SE and applied distribution have been described in appendix I. Monte Carlo simulation was conducted by drawing random values from all parameters distributions, after which the model was run for each set of parameters and results of each run were collected. Monotonicity was enforced for the utility weights and COPD-related maintenance costs by COPD severity. For utility values for example this means that in each simulation the randomly drawn value for mild COPD needed to be higher than the value drawn for moderate COPD and the value for moderate needed to be higher than for severe COPD etc. The current analyses were based on 1000 simulations, providing the 95% uncertainty interval around the effects and costs. The uncertainty was displayed in cost-effectiveness planes and acceptability curves [49-51].

In addition to the probabilistic sensitivity analyses we performed several one-way sensitivity analyses for all intervention scenarios for a number of key model parameters and for model parameters for which a probabilistic approach was not appropriate, such as discount rate. In the first sensitivity analysis we investigated the effect of a 50% higher or lower annual decline in FEV_1% predicted. In sensitivity analysis two to six we investigated the impact of using either the 95% lower limit or the 95% upper limit of the five exacerbation-related parameters: the baseline exacerbation frequencies per severity stage, the case-fatality, the decline in lung function, the utility loss and the costs. In sensitivity analysis seven the 95% CI limits for the utility values by COPD severity stage were applied. In sensitivity analysis eight we investigated the impact of using a lower smoking cessation rate for COPD patients in the reference scenario, 1.4% [52]. The impact of a ten percent reduction or increase in intervention costs was assessed in sensitivity analysis nine. Using discount rates of 0% or 4% for both costs and effects was investigated in sensitivity analysis ten and in sensitivity analysis eleven we performed analyses using a time horizon of five and twenty years.

Results

The COPD population in 2007, the starting year of the simulation, consisted of 321,000 patients above 45 years of age. Forty-six percent of the patients were female and the mean age was 69 years. Thirty percent of the patients were estimated to be current smokers, while 64% were former smokers. The majority of patients (82%) had mild or moderate COPD. About two-third of the total COPD-related healthcare costs of €352.8 million in 2007 for a minimal treatment scenario were exacerbation-related. The results for the four interventions scenarios are shown in table 3. The mean cost per QALY gained compared with minimal treatment varied between €8,300 and €17,200. The costs per exacerbation avoided varied between €2,600 for the ICS/LABA intervention and around €400,000 for the smoking cessation scenario. The latter ratio is high because smoking cessation extends life expectancy and patients are therefore longer at risk to get an exacerbation. Pulmonary rehabilitation was not assumed to affect exacerbation frequency, so the costs per exacerbation avoided were not calculated.

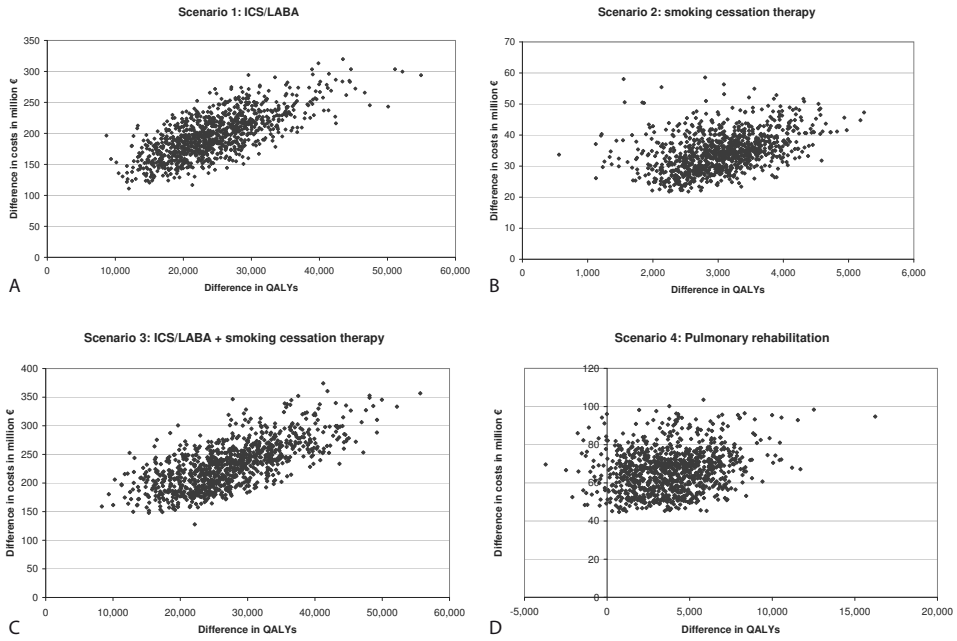

Figure 2A – 2D: Cost-effectiveness planes for three year implementation of 1) inhaled corticosteroid (ICS) with long-acting bronchodilator (LABA), 2) pharmacotherapy plus intensive counseling for smoking cessation, 3) combination of ICS/LABA and pharmacotherapy plus intensive counseling for smoking cessation and 4) pulmonary rehabilitation program. All compared with minimal treatment, time horizon ten years, discount rates: 1.5% effects, 4% costs

Table 3: Cost-effectiveness for four scenarios of three year implementation of three different interventions offered to the cohort of Dutch COPD patients in 2007 compared to the reference scenario (=minimal treatment), time horizon 10 years, discount rates 1.5% for effect, 4% for costs, data are mean (95% confidence interval), costs in €

	Total exacerbations avoided	QALYs gained	Difference in intervention costs (million)	Savings in COPD-related health costs (million)	Cost per exacerbation avoided	Costs per QALY gained	Gain in life expectancy in years
1. ICS/LABA for 50% of the patients with moderate and severe COPD (n=113,783)	77,700 (44,500;118,500)	23,800 (13,600;39,900)	236.5 (170.9;321.7)	37.9 (12.0;69.3)	2,600	8,300	0.26
2. Pharmacotherapy plus intensive counseling for 50% of smoking COPD patients (n=48,541)	90 (-4,200;3,900)	3,200 (1,800;4,300)	33.7 (23.9;45.5)	-0.9 (-8.2;3.6)	383,700	10,800	0.073
3. Combination of ICS/LABA for 50% of the patients with moderate and severe COPD ánd pharmacotherapy plus intensive counseling for 50% of smoking COPD patients (n=145,137)	78,500 (39,900;128,700)	26,900 (14,200;43,600)	270.4 (198.3;368.6)	37.2 (4.6;77.2)	3,000	8,700	0.23
4. Interdisciplinary, community-based pulmonary rehabilitation program for 15% of the patients with moderate and severe COPD (n=34,135)	0	3,900 (-400;8,400)	67.2 (48.1;92.9)	0	-	17,200	0

The results of the probabilistic sensitivity analysis are shown in figure 2 and 3. For scenario one to three, i.e. implementation of ICS/LABA, intensive counseling plus pharmacotherapy for smoking cessation or a combination of these two interventions, 100% of all model replications fell in the upper right quadrant indicating more QALYs and higher costs compared to minimal treatment. For scenario four on pulmonary rehabilitation this percentage was 96%. The probability to be cost-effective at a willingness-to-pay value of €20,000 per QALY gained was 99.9% for ICS/LABA, 97.3% for pharmacotherapy for smoking cessation, 99.8% for the combination of ICS/LABA and smoking cessation and 58% for pulmonary rehabilitation (Figure 3).

The one-way sensitivity analyses showed that for the first three scenarios the cost per QALY gained was most sensitive to the time horizon chosen and the baseline exacerbation frequencies (Appendix II). For the scenario on pulmonary rehabilitation a 10% reduction or increase in intervention costs or changes in utility values for the COPD severity stages had the highest impact on the cost per QALY.

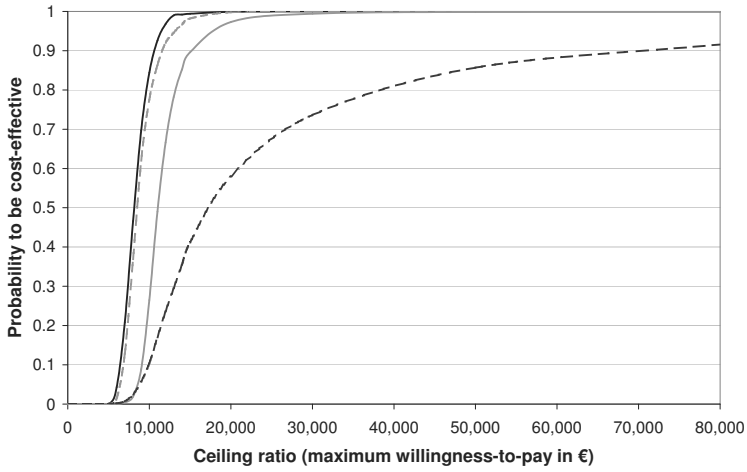

Figure 3: Acceptability curves ICS/LABA=black solid, pharmacotherapy for smoking cessation=grey solid, combination of ICS/LABA and pharmacotherapy for smoking therapy=grey dashed, pulmonary rehabilitation=black dashed

Discussion

This study aimed to develop a dynamic, stochastic population model of disease progression in COPD including the impact of exacerbations. The paper described the structure of the model and showed the potential of the model by evaluating three different COPD interventions. One of the strengths of the model is that many of the input parameters of the model were obtained from systematic reviews, using quantitative analysis to

combine data from multiple sources. The annual frequency of moderate and severe exacerbations, the case-fatality of a severe exacerbation, and the impact of exacerbations on lung function decline and quality of life were all estimated by quantitative meta-analysis, which improves the quality of the parameter estimates.

The model is also up-to-date as it can generate uncertainty around the estimated results using probabilistic sensitivity analyses. The uncertainty around estimates of all important parameters has been included. We did not take into account structural model uncertainty [16]. This means for example that a reduction in the number of severe exacerbations always results in a reduction of the case-fatality and a gain in utility. However, these assumptions are clinically very plausible.

A limitation of the model is that the severity and progression of COPD are only based on lung function, i.e. FEV_1% predicted. It is well-know from the literature that the severity of COPD is also determined by the severity of symptoms, especially breathlessness and fatigue, the level of exercise impairment and the existence of co-morbidities [1]. Composite measures, such as the BODE, DOSE or ADO, which include variables such as BMI, airflow obstruction, dyspnoea, exercise capacity, age, smoking status or exacerbation frequency are better predictors of disease severity than lung function alone [53-55]. The progression of COPD is also not only influenced by the decline in lung function [56]. It is however very difficult if not impossible to obtain detailed data for so many different variables from national registries and hospital and GP databases. For reasons of availability and simplicity the severity and progression of COPD in the model is therefore only based on lung function as is done in all other available COPD models.

Up to now, besides our model, eight other COPD models have been published [6-8,10-14]. Seven of the models take into account uncertainty around input parameters in a more or less elaborate way [6-10,12,14] and three are population-based, i.e. representative for a total nationwide COPD population [9,11,13]. The majority of the models has been developed with financial support of pharmaceutical companies and six models were built to evaluate a specific pharmacological treatment. Five models were used to investigate the impact of implementation of inhaled corticosteroids with or without long-acting β2-agonist bronchodilator for a (sub-)group of COPD patients [7,8,11,12,14], while one model was used to evaluate implementation of the long-acting anticholinergic bronchodilator, tiotropium [10]. Because these models have been built to evaluate a specific intervention, input parameters not relevant for the intervention under evaluation, such as disease progression are often modelled as one single value of FEV_1 decline that is not depending on sex, age or smoking. This type of simplifications in input parameters and assumptions can make a model less suitable to evaluate other types of interventions.

The potential of our model was demonstrated by showing the results for four intervention scenarios. By choosing three completely different interventions we tried to

emphasize that the model can be used to evaluate a wide range of interventions. The model can be used to evaluate interventions that have an effect on COPD incidence rates, smoking rates, lung function decline, quality of life, mortality and/or frequency and severity of exacerbations. To make the results of the scenarios as realistic as possible, we applied the intervention to a realistic target population in terms of disease severity and percentage of patients receiving the intervention. To make the results of the scenarios more valid, effectiveness should have been taken from a systemic review, and not from one trial as was done for two interventions. This will be part of future research. To increase comparability between the scenarios we applied the same implementation duration and time horizon for all scenarios. The optimal time horizon was however different for each scenario. For pharmacotherapy a time horizon of ten years seemed plausible, but for the smoking cessation scenario that was too short to capture all health gains because the annual gain in QALYs was maximal around ten years. Extensive one-way sensitivity analyses showed that results of the scenarios were very sensitive for the time horizon used. It is therefore very important to use a well-based estimate of the most realistic time horizon for each intervention. For the scenarios on pharmacotherapy and smoking cessation baseline exacerbation frequencies also influenced the results substantially. We are however rather confident about the exacerbation frequencies as these were obtained from a systematic review.

Although a large part of the input data of the model are based on international data, the model as described in this paper is representative for the Dutch COPD population, because it filled with Dutch data on epidemiology of COPD and costs. To transfer the model to another country, setting-specific input data on prevalence, incidence, mortality, smoking prevalence and costs should replace the Dutch data (if they are expected to differ). All of these input data are listed in separate files that are imported into the model and are therefore easy to adapt.

In conclusion, this paper described the structure of an up-to-date COPD progression model, with input parameters as much as possible based on systematic reviews. The model can be used to provide policy makers with information about the long-term costs and effects of interventions over the entire chain from primary prevention to care for very severe COPD. Furthermore it also gives insight into the uncertainty around the outcomes. The model has been developed without any industry support and hence provides an independent tool for evaluation.

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Appendix I: Details about the probabilistic sensitivity analysis

Table A1: Details about the distribution and parameter values of variables included in the probabilistic sensitivity analysis*

Type of data	Parameters	Distribution, mean (SE)	Remarks
Severity distribution of the COPD population in the starting year	Mean and SD of the normal distribution of the FEV_1% pred. at baseline	Normal distribution: Mean: 68.3 (0.91) SD: 19.93 (0.644)	
Annual change of lung function	Annual decrease in FEV_1% predicted	Normal, with parameters see [1]	Based on the uncertainty around the coefficients of the regression equation to estimate the decline in lung function
	Increase after smoking cessation	Normal, with parameters see [1]	Idem
Annual probability of total exacerbations	Coefficients of the regression equation (see methods)	Normal, with parameters: Intercept: 1.181 (0.351) Coefficient: -0.014 (0.007) [2]	
Annual probability of severe exacerbations	Coefficients of the regression equation (see methods)	Normal, with parameters: Intercept: -1.043 (0.904) Coefficient: -0.013 (0.020) [2]	
Case fatality of an exacerbation	Case fatality rate	Normal, with parameters: 15.6 (0.0235) [3]	
	Association case fatality and age, RR	RR=1.041 per year increase in age (0.002) [3]	
QALY-weights for 4 COPD severity classes		Normal, with parameters: Mild: 0.8971 (0.0194) Moderate: 0.7551 (0.0309) Severe: 0.7481 (0.0352) Very Severe: 0.5493 (0.0591) [4]	Monotonicity was enforced: QALY_severity stage > QALY_severity stage+1
QALY loss as a result of an exacerbation	Moderate exacerbation	Normal, with parameters: 0.0166 (0.0022)	
	Severe exacerbation	Normal, with parameters: 0.0482 (0.0087)	
Effect of lung function on mortality	RRFEVtot	Logarithm of RRFEVtot is normal distributed, with parameters 0.0182 (0.0015) / % decline	

Table A1: Details about the distribution and parameter values of variables included in the probabilistic sensitivity analysis* (continued)

Type of data	Parameters	Distribution, mean (SE)	Remarks
Effect exacerbations on lung function decline.		Normal, with parameters: 0.19 (0.05)	
COPD-related healthcare costs	Maintenance costs	Normal, with an SE of 15% of the mean sex and age specific maintenance costs)	Monotonicity was enforced: Costs_severity stage < Costs_severity stage+1
	Costs of exacerbations	Normal, with parameters: Moderate exac: 94 (7) Severe exacerbation: 4100 (894)	
Prevalence, incidence and mortality of COPD and other modelled disease		Random effects models with polynomials of age as explanatory variable were estimated simultaneously. Uncertainty intervals were constructed by taking random draws from the joint distribution of the prevalence, incidence and mortality	Parameterized over age and sex

*All input parameters were treated as independent in the probabilistic sensitivity analysis

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Appendix II: Results of the one-way sensitivity analyses

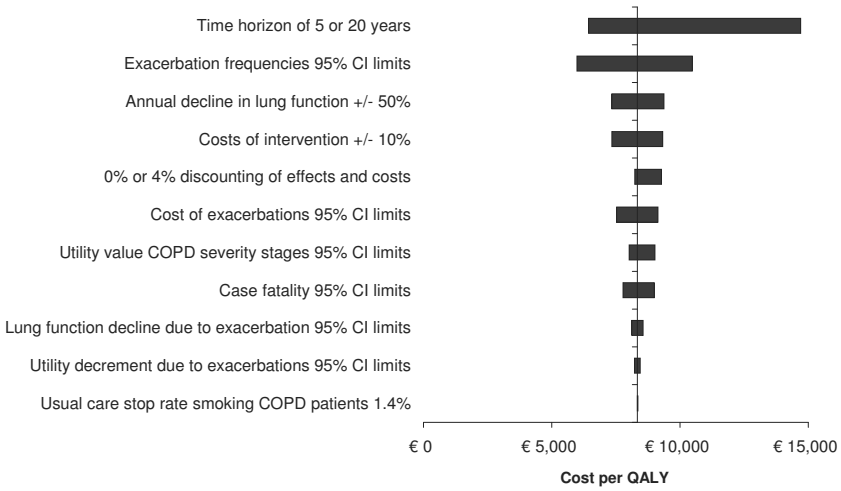

Figure A1: Sensitivity analyses for the cost per QALY gained of three year implementation of a combination of ICS/LABA for 50% of the COPD patients with moderate or severe COPD in 2007, time horizon ten years

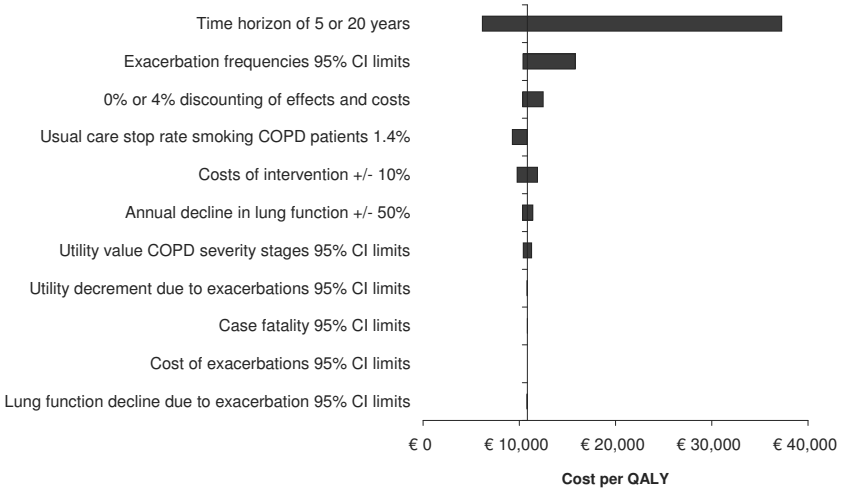

Figure A2: Sensitivity analyses for the cost per QALY gained of three year implementation of intensive counseling plus pharmacotherapy for smoking cessation for 50% of the smoking COPD patients in 2007, time horizon ten years

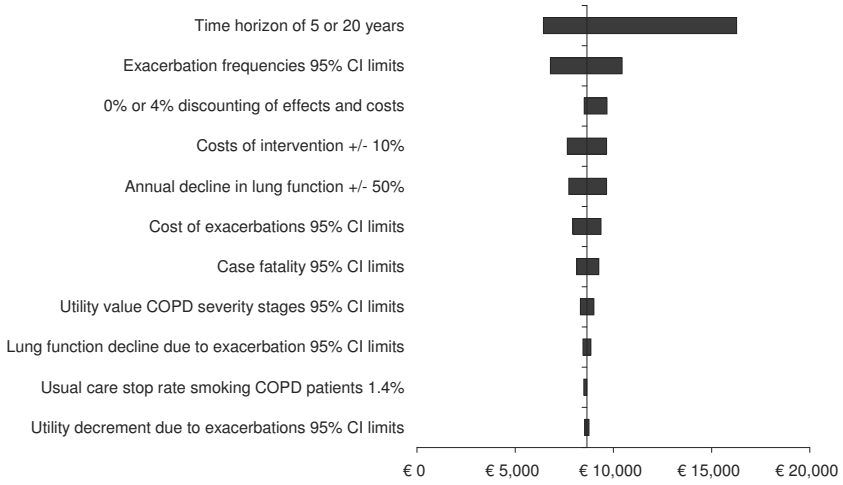

Figure A3: Sensitivity analyses for the cost per QALY gained of three year implementation of a combination of ICS/LABA for 50% of the COPD patients with moderate or severe COPD, and three year implementation of intensive counseling plus pharmacotherapy for smoking cessation for 50% of the smoking COPD patients in 2007, time horizon ten years

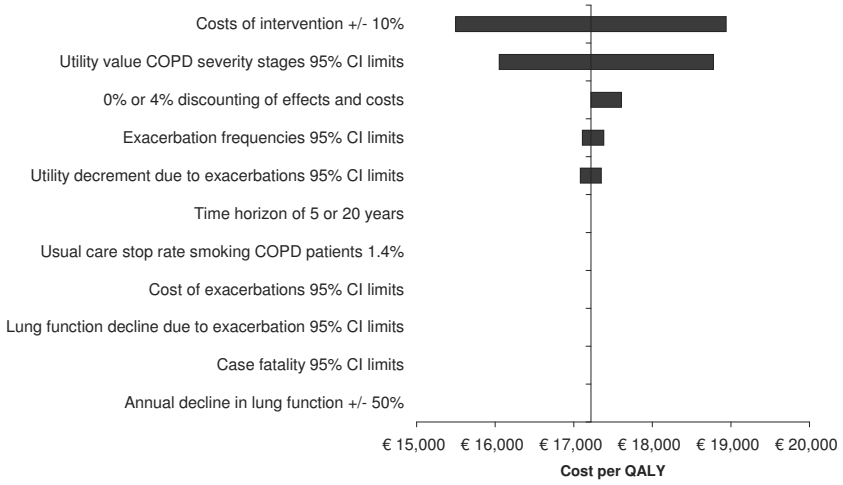

Figure A4: Sensitivity analyses for the cost per QALY gained of three year implementation of an interdisciplinary community-based pulmonary rehabilitation program for 15% of the COPD patients with moderate or severe COPD in 2007, time horizon ten years

Part two

Studies related to the economic evaluation of an interdisciplinary community-based COPD management program

Chapter 8

Is INTERdisciplinary COMmunity-based COPD management (INTERCOM) cost-effective?

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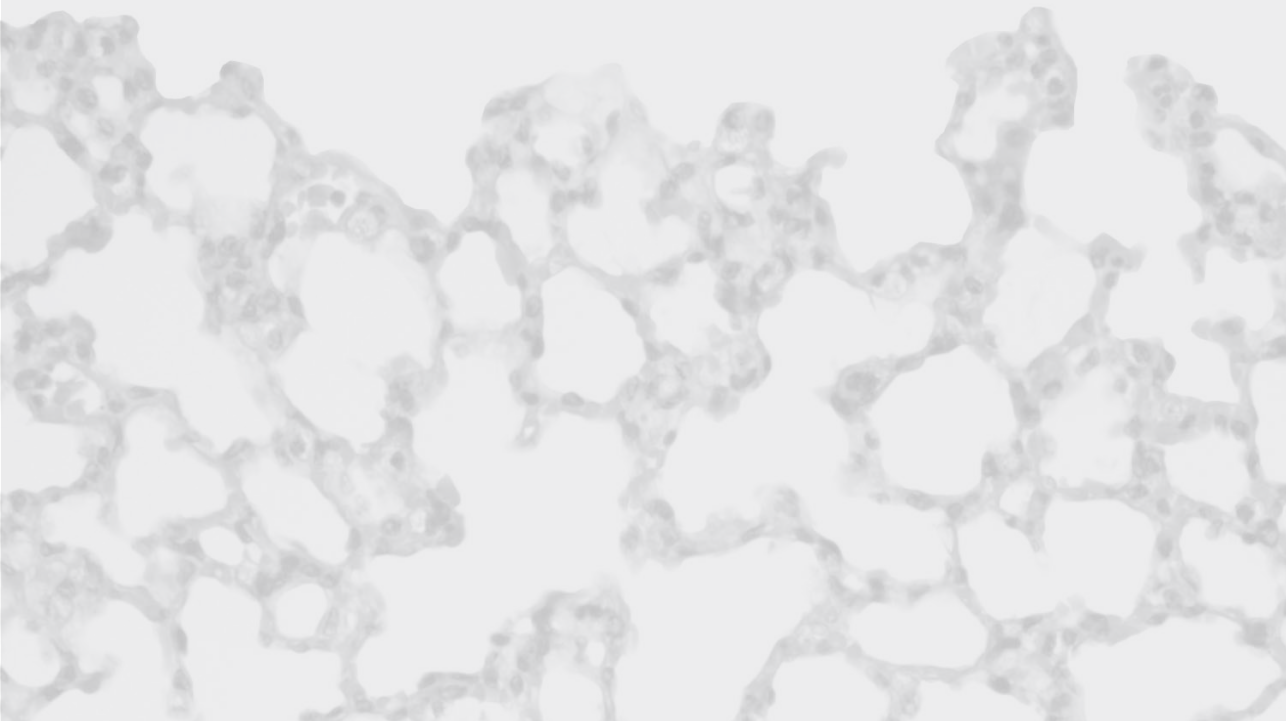


Abstract

The study aimed to estimate the cost-effectiveness of interdisciplinary community-based chronic obstructive pulmonary disease (COPD) management in patients with COPD. We conducted a cost-effectiveness analysis alongside a two-yr randomized controlled trial in which 199 patients with less advanced airflow obstruction and impaired exercise capacity were assigned to the INTERCOM program or usual care. The INTERCOM program consisted of exercise training, education, nutritional therapy and smoking cessation counseling offered by community-based physiotherapists and dieticians and hospital-based respiratory nurses. All-cause resource use during two yrs was obtained by self-report and from hospital and pharmacy records. Health outcomes were the St George's Respiratory Questionnaire (SGRQ), exacerbations and quality-adjusted life years (QALYs). The INTERCOM group had 30% (95% CI: 3; 56%) more patients with a clinically relevant improvement in SGRQ total score, 0.08 (95% CI: -0.01; 0.18) more QALYs per patient, but a higher mean number of exacerbations, 0.84 (95% CI: -0.07; 1.78). Mean total two-yr costs were €2,751 (95% CI: -632; 6,372) higher for INTERCOM than for usual care, which resulted in an incremental cost-effectiveness ratio of €9,078 per additional patient with a relevant improvement in SGRQ or €32,425 per QALY. INTERCOM significantly improved disease-specific quality of life, but did not affect exacerbation rate. The cost per QALY ratio was moderate, but within the range of what is generally considered to be acceptable.

Introduction

The importance of pulmonary rehabilitation [1] in treating chronic obstructive pulmonary disease (COPD) is increasingly recognized as COPD is becoming more and more regarded as a systemic disease, that does not only affect the lungs [2]. In patients with severe COPD the beneficial effects of both in-patient and hospital-based outpatient pulmonary rehabilitation programs have been well established in terms of improving exercise capacity, dyspnoea and quality of life [3]. With regard to the cost-effectiveness of pulmonary rehabilitation the evidence is still very limited. Nevertheless, it is often stated in the literature that pulmonary rehabilitation is cost-effective, because it reduces healthcare costs [1, 4]. However, most studies only reported the program costs or the impact on just a limited number of healthcare services such as hospital admissions [5-10]. Only two comprehensive economic evaluations of pulmonary rehabilitation programs have been published [11,12]. Both studies included patients with severe COPD and were performed in the inpatient or outpatient setting of a hospital. Evidence of cost-effectiveness in less severe patients or in community settings is not available. In general it is assumed that the substitution of hospital care by community care reduces total costs and improves cost-effectiveness. We aimed to conduct a comprehensive cost-effectiveness analysis (CEA) of a community-based multidisciplinary rehabilitation program for COPD patients with less severe airflow obstruction than that of patients traditionally included in secondary-care or tertiary-care pulmonary rehabilitation programs. This CEA was performed alongside a two-year randomized controlled trial evaluating the effect of an INTERdisciplinary COMmunity-based COPD management program (INTERCOM) compared to usual care. Full clinical results of this trial have been reported elsewhere [13-15]. In brief, results over the total two-year period showed that there were statistically significantly better effects in the INTERCOM group than for usual care in St. George's Respiratory Questionnaire (SGRQ) total score, Medical Research Council (MRC) dyspnoea score, 6-min walking distance (6MWD) and cycle endurance time in a constant work rate test at 70% of peak exercise capacity. No significant differences were found for exacerbations, muscle function and body composition. Both patient and caregiver assessment of effectiveness significantly favoured the INTERCOM program.

Methods

Patients and design

One hundred ninety-nine patients with GOLD stage 2 or 3 COPD and impaired exercise capacity (maximum work (Wmax) <70% predicted), recruited by respiratory physicians

of two general hospitals in the Netherlands, were randomized to the INTERCOM program (n=102) or to usual care (n=97) (Figure 1). Patients did not have prior rehabilitation or serious co-morbidity that precluded exercise training. At inclusion, they were judged by their respiratory physician to be clinically stable and pharmacotherapy was optimized. The time horizon of the study was two years and disease-specific and generic quality of life and functional parameters were single-blinded evaluated at baseline and, 4, 12 and 24 months. All patients gave written informed consent and ethical approval was granted by the Medical Ethical Committee of the two hospitals.

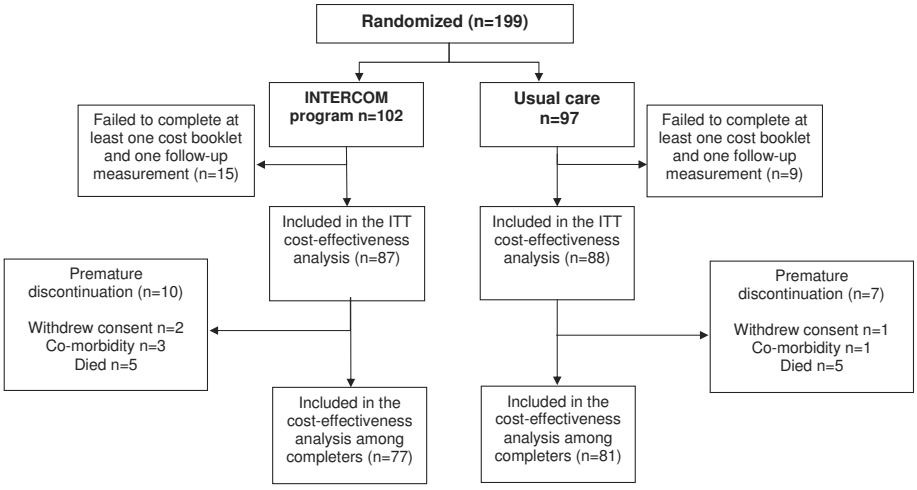


Figure 1: Patient disposition. INTERCOM: interdisciplinary community-based chronic obstructive pulmonary disease management program; ITT=intention-to-treat.

INTERCOM program

The core elements of the INTERCOM program were exercise training, education, nutritional therapy and smoking cessation counseling (the latter two upon indication) [13]. During the 4-month standardized, supervised, intensive intervention phase individual exercise training sessions were given twice a week by physiotherapists in the proximity of the patients' home. Patients were also instructed and motivated to perform the exercises at home and to walk and cycle twice a day. Smoking cessation counseling, if applicable, as well as education to improve the knowledge of COPD and its treatments and to teach self-management skills was provided by respiratory nurses in the hospital (average of four sessions). Nutritionally depleted patients were scheduled to visit a local dietician four times in the first four months. Nutritional therapy consisted of counseling to improve nutritional intake and three oral liquid (3x125ml) supplements (Respifor®, Nutricia BV, Zoetermeer, the Netherlands) per 24 hours for a period of four months. Dur-

ing the less intensive, less-standardized 20-month maintenance phase, patients visited the physiotherapist once a month. In case of insufficient recovery from an exacerbation, additional training sessions (maximum of six) could be started. During the maintenance phase, patients visited the dietician four times, while they visited the respiratory nurse according to an individualized schedule.

Usual care

Patients assigned to usual care received pharmacotherapy according to accepted guidelines, a short smoking cessation advice from their respiratory physician and short nutritional advice to eat more and better in case they were nutritionally depleted.

Perspective

The cost-effectiveness study was performed according to the good research practices for cost-effectiveness analyses alongside clinical trials [16]. The study was conducted from a societal perspective, including all COPD and non-COPD related healthcare costs, travel expenses and cost of productivity losses. A separate analysis was done from a third party payers' perspective. All costs related to conducting the trial and developing the intervention have been excluded.

Healthcare utilization and unit costs

In both treatment groups, patients kept a weekly record of contacts with healthcare providers, "over-the-counter medication", medical devices, hospital admissions, time lost from paid work, hours of (un)paid household help, travel expenses and nutritional supplements using cost booklets. Each booklet covered a period of four weeks and was collected every two months. Whenever necessary, patients were contacted by telephone for further clarification. To ensure that no hospitalizations were missed, data on hospital admissions were extracted from the electronic hospital records of the two hospitals involved in the study. Information on the dispense and costs of outpatient medication was obtained from each patients' local pharmacy. For twelve patients using oxygen during exercise, the start and stop date of oxygen supply were obtained from their oxygen supplier. Resource utilization was valued in euros (€) using Dutch guideline prices updated to the year 2007 (Table 1) [17]. Because of the small number of patients with a paid job and the homogeneity of this group, the weekly number of hours absent from paid work was valued with the average gross hourly earnings weighted for sex and age, €46.61 per hour. The calculation of productivity loss was based on the friction cost

Table 1: Unit costs for the most important types of resource utilization (2007, €)

Type of healthcare	Unit	Unit costs
Contacts with care providers:		
General practitioner	Contact	21
Medical specialist, general hospital	Contact	59
Physiotherapist	Contact	24
Dietician	Contact	31
Respiratory nurse	Contact	27
Other therapists	Contact	24-75
Hospital care		
General hospital	Day	356
University hospital	Day	502
Daycare treatment	Day	242
Emergency Department	Visit	147
Ambulance	Ride	359
Pulmonary rehabilitation centre		
Inpatient day	Day	379
Paid and unpaid help		
Home care	Hour	32
Informal care/ unpaid household help	Hour	8.70
Oxygen therapy	Day	4.00
Respifor®	Unit	2.76
Travel expenses, public transport/ car	Km	0.17
Productivity cost	Hour	46.61

approach [18], using a friction period of 154 days [17]. No discounting was applied to costs or effects, because of the limited study period.

Health outcomes

It was pre-specified which of the wide range of health outcome measures applied in the clinical trial would be used in the cost-effectiveness study. These were: 1) the net proportion of patients with a clinically relevant improvement (≥ four units) in disease specific quality of life as measured by the SGRQ total score [19, 20]; 2) the total number of COPD-exacerbations (moderate plus severe); and 3) the number of quality-adjusted life years (QALYs) based on EuroQol-5D (EQ-5D) utility values [21, 22]. SGRQ and exacerbations were the co-primary outcomes of the clinical study, whereas QALYs is the outcome preferably used in economic evaluations. The SGRQ and the EQ-5D were administered at baseline and, 4, 12 and 24 months, while exacerbations were measured continuously over the 2-yr period.

The net proportion of patients with an improvement of four or more units in SGRQ total score was calculated as the proportion of patients with four or more units improvement between baseline and 24 months minus the proportion of patients with four or more units deterioration. A moderate exacerbation was defined as a visit to the general

practitioner or respiratory physician in combination with a prescription of antibiotics and/or prednisolone or a visit to the emergency department or day care of a hospital, which according to the patient, was related to a COPD exacerbation. A severe exacerbation was defined as a hospitalization for a COPD exacerbation. The number of QALYs for each patient was calculated by summing the days under observation weighted by their EQ-5D utilities [21, 22] using linear interpolation.

Cost-effectiveness

Cost-effectiveness was expressed as the incremental cost-effectiveness ratio (ICER), which was calculated as the difference in mean costs between the INTERCOM and usual care group divided by the difference in mean health outcome. Three different ICERs were planned: costs per additional patient with a relevant improvement in SGRQ total score, costs per exacerbation avoided and costs per QALY.

Statistical analyses

The analysis was performed according to the intention-to-treat (ITT) approach. All randomised patients who had at least one outcome measurement after the start of treatment and who completed at least one cost booklet were included in the cost-effectiveness analysis. Differences in baseline characteristics of patients completing the trial and drop-outs were statistically tested using independent sample unpaired t-tests for continuous, normally distributed data, Wilcoxon Mann-Whitney U tests for continuous non-normally distributed data and Chi-square tests for categorical variables.

To account for costs and health outcomes that were missing after patients prematurely dropped out from the trial and the additional uncertainty that these missing values introduced, the multiple imputation technique was used [23]. Each missing value was replaced by ten simulated values using the propensity score method in SAS V8 [24, 25]. In summary this method implied that for patients who dropped out values were imputed that were randomly drawn from the data of patients who did not drop out, but had a similar probability to have missing data given several baseline and other variables. This meant that for patients with a worse health status that dropped out the trial, random draws of data of patients with a similar health status who did not drop out, were imputed. The logistic regression to calculate the probability to have missing data (i.e. the propensity score) included the following independent variables: age, sex, smoking status, forced expiratory volume in one second (FEV_1) as percentage of predicted normal, number of co-morbidities, body mass index (BMI), 6MWD, SGRQ total score and EQ-5D utility index scores, at baseline and, 4, 12 and 24 months, monthly exacerbation

rates and monthly costs. Multiple imputation was carried out separately for both treatment groups and health outcomes and costs were imputed simultaneously.

Each of the ten complete datasets was further analyzed by non-parametric bootstrapping using 10,000 bootstraps per dataset [26]. The 95% confidence interval around the difference in mean costs and health outcomes was determined by taking the 2.5th percentile and the 97.5th percentile of these bootstrap replications. The bootstrap replicates were plotted in cost-effectiveness planes (CE-planes). A CE-plane is an x-y-diagram with the x-axis representing the difference in health outcome between the treatment and usual care group and the y-axis representing the difference in costs. By plotting all bootstrap replicates in this diagram the uncertainty around the point estimates of the ICERs was displayed. In addition, the information in the CE-planes was summarized in cost-effectiveness acceptability curves, which shows the probability that the ICER of the INTERCOM program falls below various ceiling ratios. These ceiling ratios reflect the maximum that a decision maker would be willing to pay to have one additional patient with a relevant improvement in SGRQ, one exacerbation avoided or one additional QALY [27, 28]. All analyses were performed with either SPSS version 13.0 or SAS V8.

Sensitivity analyses

In addition to the probabilistic sensitivity analyses presented in the CE-planes and the acceptability curve, univariate sensitivity analyses were conducted to assess the impact of assumptions made or analytic methods used on the results. In the first sensitivity analysis (SA1) only data from patients who fully completed the trial were analyzed. In addition two sensitivity analyses on time horizon were conducted, showing the results at four months (SA2) and at twelve months (SA3). Finally, a sensitivity analysis was performed in which patients referred to inpatient pulmonary rehabilitation during the trial were excluded from the analyses (SA4).

Results

Patients

Baseline characteristics of the 199 randomized patients did not differ between the two groups (Table 2). Of the total of 199 patients 13 dropped out after randomization and before start of the treatment. From the 186 patients that actually started treatment, 175 patients completed the first four months, while 158 completed the 2-yr study period (79%), 75% in the INTERCOM group and 84% in the usual care group. Length of stay in the trial was significantly shorter for drop-outs in the INTERCOM group than in the usual

care group, with mean (SD) of 262 (192) and 505 (225) days, respectively. In the INTERCOM group drop-outs were older, tended to have more co-morbidities and worse scores on functional and quality of life parameters at baseline than completers, which was not the case in the usual care group. 175 patients had at least one outcome measurement after the start of treatment and completed at least one cost booklet and were therefore included in the cost-effectiveness analysis (figure 1). A more detailed patient enrolment and disposition scheme is given elsewhere [13].

Table 2: Baseline characteristics

	INTERCOM (n=102)*	Usual care (n=97)*
Women	30 (29%)	28 (29%)
Age (years)	66 (9)	67 (9)
Number of co-morbidities	1.6 (1.6)	1.5 (1.4)
Number of exacerbations in 12 months before trial	1.2 (1.4)	1.0 (1.5)
Number of COPD hospital admissions in 12 months before trial	0.2 (0.5)	0.2 (0.5)
Current smokers	32 (33%)	22 (24%)
Post-bronchodilator FEV_1% predicted	58% (17)	60% (15)
FEV_1/FVC, %	49% (11)	51% (12)
Wmax % predicted	60% (19)	61% (17)
Fat Free Mass (kg/m^2)	17 (2)	18 (2)
SGRQ Total score (0-100 scale)#	39 (15)	38 (15)
SGRQ-symptom score (0-100 scale)#	45 (19)	41 (21)
SGRQ-Activity score (0-100 scale)#	55 (18)	56 (19)
SGRQ-Impact score (0-100 scale)#	27 (16)	25 (15)
EQ-5D utility index score	0.79 (0.21)	0.79 (0.15)
MRC dyspnea score (0-4 scale)$	1.7 (1.0)	1.5 (0.9)

*Data are n (%) or mean (SD)

St. George's respiratory questionnaire: a higher score indicates a worse quality of life

$ modified Medical Research Council (MRC)

Resource use

Table 3 shows the mean resource use per patient as observed during the 2-yr trial.

Overall, the percentages of item level missing data plus the missing data due to drop-out for the different data sources was about 5 to 7% except for prescribed medication for which this percentage was 9.2%. Missing data was primarily due to drop-out before completing the trial. To prevent bias related to differences in the length of the observation time, multiple imputation was applied to costs and health outcomes before statistically testing differences between the treatment groups.

Table 3: Mean total healthcare utilization and days of absenteeism per patient as observed during the trial

	INTERCOM (n=87)*	Usual care (n=88)*
General practitioner, visits	7.2 (7.0)	7.9 (8.1)
Chest physician, visits	4.4 (3.1)	3.5 (3.6)
Cardiologist, visits	1.6 (2.9)	1.4 (2.0)
Internist, visits	0.4 (1.6)	1.1 (2.2)
Other specialist, visits	2.6 (4.7)	3.8 (5.7)
Physiotherapist, visits	51 (18)	11 (21)
Dietician, visits	2.1 (3.4)	0.6 (2.1)
Respiratory nurse, visits	5.2 (3.1)	0.8 (1.6)
Respifor®, units of 125ml	111 (314)	3.6 (23)
Other healthcare providers, visits#	1.3 (5.7)	2.1 (9.1)
Home care, hours	37 (115)	38 (118)
Paid household help, hours	36 (103)	26 (73)
Unpaid household help, hours	10 (44)	25 (150)
Ambulance rides	0.19 (0.65)	0.23 (0.54)
Hospital admissions	0.75 (1.29)	0.96 (1.35)
Hospital admissions for COPD	0.36 (1.00)	0.40 (0.78)
Total hospital days	7.8 (16)	9.3 (15)
Total hospital days for COPD	4.9 (14)	4.3 (10)
Pulmonary rehabilitation (inpatient days)	3.3 (16)	0.7 (6.8)
Hours unable to work	22 (89)	6.8 (40)

*Data are mean (SD)

#Other healthcare providers included other and alternative therapists, social workers and psychologists

Costs

Table 4 shows the mean 2-yr costs per patient after multiple imputation. Mean total costs, irrespective of whether they were related to COPD or not, were €13,565 for the INTERCOM group and €10,814 for the usual care group, a difference of €2,751 (95% CI: -631; 6,372). Total direct healthcare costs were €2,147 (95% CI: -1,091; 5,649) higher in the INTERCOM group. Because the INTERCOM program is tailored to the individual patient, resulting in a variable number of contacts with the INTERCOM care givers, the intervention costs were best estimated as the difference in costs for the physiotherapist, dietician, respiratory nurse and diet nutrition between the two groups, €1,520 per patient. Based on the study protocol the 2-yr intervention costs were €1,650 per patient, ranging from €1,350 for patients visiting the physiotherapists and the respiratory nurse to €2,500 for nutritional depleted patients receiving additional dietary counseling and Respifor.

Table 4: Mean total 2-year costs per patient for different categories of resource use after multiple imputation (2007, €)

	INTERCOM (n=87)	Usual care (n=88)	Difference	95% CI
General practitioner	163	175	-12	(-59; 36)
Specialist	570	610	-40	(-178; 101)
Physiotherapist	1,290	265	1025	(882; 1,167)
Dietician	70	20	50	(24; 77)
Respiratory nurse	147	22	125	(106; 145)
Hospital admissions	2,944	3,353	-408	(-2,084; 1,365)
Diet nutrition	320	31	290	(118; 486)
Prescribed medication	3,532	3,318	214	(-239; 667)
Oxygen use	196	57	139	(-13; 304)
Other direct medical costs*	2,911	2,148	763	(-1,207; 2,909)
Subtotal direct healthcare costs	12,145	9,998	2,147	(-1,091; 5,649)
Costs paid by the patient#	423	486	-63	(-472; 269)
Subtotal direct costs	12,568	10,484	2,084	(-1,198; 5,614)
Productivity costs	997	330	667	(-124; 1,566)
Total costs	13,565	10,814	2,751	(-631; 6,372)

*Other direct medical costs included costs of visits to other therapists, alternative therapists, social workers and psychologists, home care, ambulance transportation, pulmonary rehabilitation, psychiatric hospital admissions and medical devices.

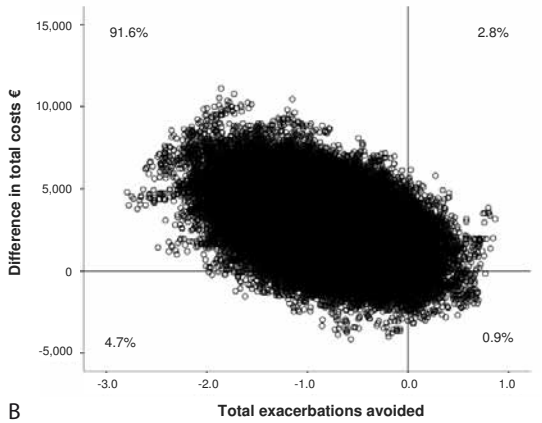
#Costs paid by the patient included costs of over the counter medication, paid and unpaid household help and travel expenses

Health outcomes

In the INTERCOM group 43% of the patients had an improvement of four or more units in SGRQ total score, while 29% had a deterioration of four or more units, resulting in a net improvement of 13%. In the usual care group 29% improved and 46% deteriorated more than four units, resulting in a net improvement of -17%. The difference in net proportion of patients with an improvement in SGRQ total score was significantly different between the two groups, 30% (95% CI: 3; 56). Over the entire 2-yr period the INTERCOM group had 3.02 exacerbations per patient compared to 2.18 in the usual care group, a not significant two-year difference of 0.84 (95% CI: -0.07; 1.78). The mean number of QALYs per patient was 1.62 and 1.54 in the INTERCOM and the usual care group respectively, i.e. a difference of 0.08, which was not significantly different (95% CI: -0.01; 0.18).

Cost-effectiveness

From a societal perspective, the ICERs of the INTERCOM program compared to usual care were €9,078 per additional patient with a relevant improvement in SGRQ total score and €32,425 per QALY. Because the INTERCOM group had a higher number of mean exacerbations, the costs per exacerbation avoided were negative. The CE-planes with SGRQ and



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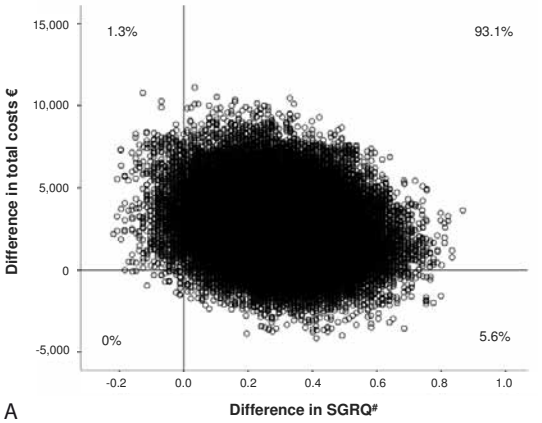

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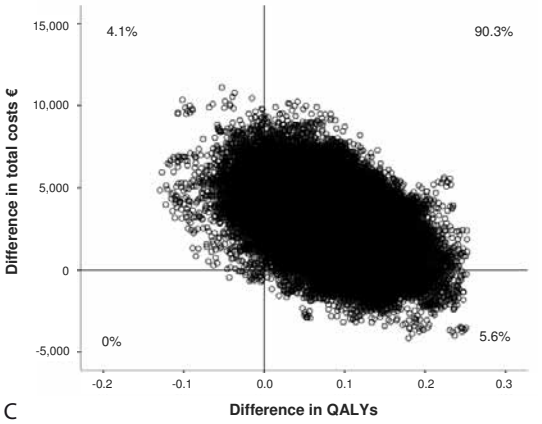

C

Figure 2A – **2C:** Cost-effectiveness plane: A) cost per additional patient with a relevant improvement in SGRQ total score, B) cost per exacerbation avoided and C) cost per QALY. #: difference in net proportion of patients with a relevant improvement in SGRQ total score

QALYs as outcomes showed that the majority of bootstrap replications (>90%) fell within the upper-right quadrant indicating that the INTERCOM program resulted in higher costs but more patients had a relevant improvement in SGRQ and a higher gain in QALYs, respectively (Figure 2). For total exacerbations most bootstrap replications fell in the upper-left quadrant indicating higher costs and more exacerbations. The accompanying acceptability curves are shown in Figure 3. The probability that the INTERCOM program is cost-effective at a willingness-to-pay of €20,000 and €50,000 per QALY gained was 33% and 67%, respectively. From a third party payer's perspective the ICERS were slightly lower, i.e. €7,086 per additional patient with a relevant improvement in SGRQ total score and €25,309 per QALY, resulting in slightly higher probabilities that the INTERCOM program was cost-effective.

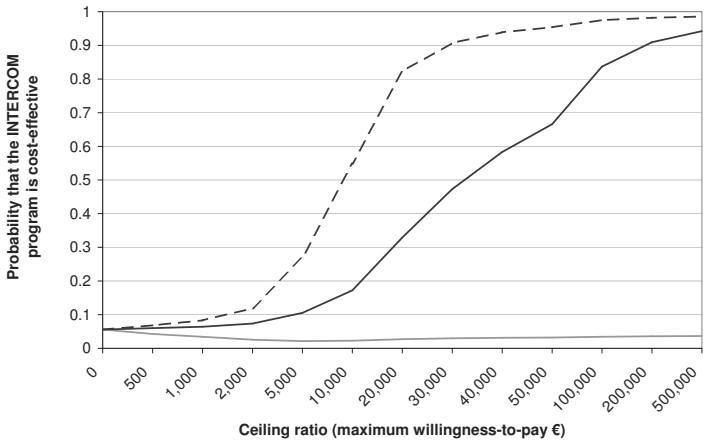

Figure 3: Cost-effectiveness acceptability curves: probability that the INTERCOM program is cost-effective in relation to willingness to pay for one additional patient with a relevant improvement in SGRQ (black dashed), one exacerbation avoided (grey solid) or one additional QALY (black solid)

Sensitivity analyses

Results for the sensitivity analyses (Table 5) showed that when only patients that completed the trial were included in the analysis (SA1), the costs per QALY were comparable to the base case analysis. The results for the sensitivity analyses on time horizon showed that the difference in mean number of QALYs between the two groups increased over time (SA2 and SA3). It is important to note that part of the cost increase in the INTERCOM group was due to four patients who were referred to inpatient pulmonary rehabilitation compared to one patient in the usual care group. When these five patients were excluded from the analyses (SA4), the difference in cost between the two groups reduced to €909 and the incremental costs per QALY reduced to €8,421. For all sensitivity analyses the ICERs for total exacerbations avoided were negative as a result of a higher number of exacerbations in the INTERCOM group (data not shown).

Table 5: Sensitivity analyses (SAs) on imputation methods for missing data and time horizon. Data are mean or proportion (95% confidence interval)

	Difference in mean total costs in €	Difference in net proportion of patients with ≥4 units improvement in SGRQ total score*	Cost per additional patient with ≥4 units improvement in SGRQ total score	Difference in mean QALYs	Cost per QALY gained €	Probability that INTERCOM is cost-effective at €20,000 per QALY	Probability that INTERCOM is cost-effective at €50,000 per QALY
Base case	2,751 (631; 6,372)	0.30 (0.03; 0.56)	9,078	0.08 (-0.01; 0.18)	32,425	0.33	0.67
Imputation method:							
SA1: completers	2,684 (-932; 6,466)	0.36 (0.09; 0.62)	7,538	0.08 (-0.04; 0.19)	34,187	0.36	0.62
Time horizon							
SA2: 4 months	1,024 (534; 1,525)	0.34 (0.11; 0.57)	2,976	0.01 (0; 0.03)	90,990	0.01	0.19
SA3: 12 months	1,042 (-730; 2,895)	0.11 (-0.14; 0.36)	9,303	0.04 (0; 0.09)	23,894	0.44	0.74
SA4: excluding patients referred to inpatient pulmonary rehabilitation	909 (-1,665; 3519)	0.36 (0.09; 0.62)	2,641	0.11 (0.01; 0.20)	8,421	0.74	0.92

Discussion

This comprehensive cost-effectiveness analysis of an interdisciplinary community-based COPD management program (INTERCOM) compared to usual care has shown that such a program can significantly improve disease-specific quality of life in patient with less advanced COPD and impaired exercise performance, but the price that has to be paid is a cost increase of €2,751 per patient over 2 yrs. All other outcomes showed a consistent pattern toward better effects in the INTERCOM group compared to usual care group and statistical significance was reached for 6 MWD, cycle endurance time, dyspnoea and patient and caregiver global assessment of effectiveness [13]. These positive effects could not be explained by differences in medication use between the two groups, as this was similar. The only exception to the pattern of better effects in the INTERCOM group was the number of exacerbations that was slightly, but not significantly higher in the INTERCOM group. Given the consistency of the outcome pattern and considering that the 2-yr costs for medication alone were €3,300 and the total 2-yr costs for usual care were €10,800, the cost increase of €2,751 per patient seems reasonable for such an intensive and comprehensive COPD management program.

The incremental costs per QALY gained of the INTERCOM program were estimated to be €32,425. This is the ratio of the additional costs of INTERCOM over usual care divided by the gain in QALYs due to INTERCOM. In the Netherlands treatments with a cost-effectiveness ratio below €20,000 per QALY gained are generally regarded by policy makers as very cost-effective. The maximum acceptable cost per QALY ratio is subject of ongoing debate. An advisory board of the Dutch government has recently proposed to adopt a maximum willingness-to-pay for a QALY that depends on the burden of disease for which the treatment is developed [29]. The maximum acceptable ratio in their proposal would be €80,000 per QALY gained for diseases with the highest burden of disease. With a ratio of €32,425 per QALY gained the INTERCOM program would be considered as moderately cost-effective, although the uncertainty around this ICER was substantial. Currently, for COPD patients, the costs of the separate components of the INTERCOM program (i.e. physiotherapy, dietary counseling, counseling by a respiratory nurse and diet nutrition) are covered by the nationwide obligatory basic healthcare insurance in the Netherlands. However, this situation may change in the nearby future as the Dutch minister of health considers introducing one reimbursement package for 'chained and integrated COPD care', in which pre-defined types of healthcare are included. Whether a program such as INTERCOM would be included in this package is unclear. Other healthcare interventions with comparable, but also much higher cost-effectiveness ratios [30-33] are currently reimbursed, providing an indication that a ratio of around €30,000 as found in the current study was previously considered acceptable for reimbursement. It is obvious however, that other criteria, such as budget impact, necessity of care, own

responsibility and affordability by the patient also play a role in the decision whether a healthcare service should be covered by social healthcare insurance. Interpreting the costs per additional patient with a relevant improvement in SGRQ total score is more difficult, because no reference data are available and up to now only one study used this outcome in a cost-effectiveness analysis [34].

The estimated average intervention costs of the entire INTERCOM program were approximately €1,500 per patient. As expected, these intervention costs were much lower than the intervention costs for inpatient rehabilitation [11]. Given the duration and intensity of the program, the costs of our community-based intervention seemed also low compared to several outpatient programs [7,8,12,35,36].

The increase in costs in the INTERCOM group was higher than the intervention costs. Although not significant, patients in the INTERCOM group had higher productivity costs and other direct medical costs (see table 4). The latter was mainly caused the fact that four patients in the INTERCOM group were referred to inpatient pulmonary rehabilitation during their participation in the trial compared to only one patient in the usual care group. This difference may be coincidence, but could also be related to the frequent contact between patient and caregivers resulting in earlier signalling of insufficient improvements or significant worsening. In retrospect, it was also speculated that these patients should never have been included because their condition was so severely impaired that this community-based program was not sufficiently intensive. However, according to the intention to treat principle, these patients were kept in the trial and the costs of these inpatient rehabilitation programs were included. If the difference in referrals to inpatient pulmonary rehabilitation between the two groups indeed is an unexpected side effect of implementing a community-based program, including these costs in the analyses might have improved the generalizability of the results to common daily practice.

In both the base case analysis and sensitivity analysis, the ICERs for exacerbations avoided were negative, because the number of COPD exacerbations was slightly higher in the INTERCOM group. The definition of an exacerbation in this study was based on resource use reported by the patient (moderate exacerbations) and obtained from hospital records (severe exacerbations). The frequently scheduled caregiver contacts might have increased the opportunity to detect an exacerbation. In addition, improved self-management skills in the INTERCOM group might have enhanced the ability to recognize and report exacerbations sooner as has also been seen in other studies [37,38].

Only two comprehensive economic evaluations on pulmonary rehabilitation have been published previously [11,12]. The study of Goldstein et al reported the cost-effectiveness of a 2-month inpatient rehabilitation program followed by 4 months of outpatient training in patients with severe stable COPD. The cost required for a single patient to achieve a clinically important improvement in different components of the health related quality of life questionnaire ranged from $28,993 for mastery to $51,027

for fatigue (Canadian dollars). The second study is a 1-yr study by Griffiths et al that reported the cost-utility of a 6-week multidisciplinary outpatient rehabilitation program. Compared to standard care the incremental costs of the program were £-152 (95% CI: -881; 577) per patient, while the incremental utility per patient was 0.030 (95% CI: 0.002; 0.058), suggesting that the health improvements were accompanied by net savings. Comparison of the studies of Goldstein and Griffiths with our study is complicated by differences in the type of intervention, outcome measures and patient population. Both the study of Goldstein and Griffiths included patients with severe COPD/ lung disease reflected by a mean FEV_1% predicted of 35% and 40% respectively, whereas in our study this was 60%. We have not found a full economic evaluation on outpatient or home-based pulmonary rehabilitation in less severe patients.

Whether an in interdisciplinary program such as the INTERCOM program can be implemented in other countries than the Netherlands depends, among other things, on the organizational structure of the healthcare system, the reimbursement system, the costs of health services for COPD and the geographical circumstances. Furthermore, it is important that COPD is acknowledged as a systemic disease, requiring regular assessments other than lung function, and a collaborative network of the different healthcare providers in the local community is needed.

From the combined results of the clinical analyses published elsewhere [13-15] and the cost-effectiveness analyses presented here, we conclude that compared to usual care, the INTERCOM program resulted in significant improvements in SGRQ total score and several exercise performance and dyspnoea measures at a cost increase of €2,751 per patient. In terms of costs per QALY the program is moderately cost-effective.

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Trial registration

Trial started before before January 2006 and was registered retrospectively at www.clinicaltrials.gov (NCT00840892).

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Chapter 9

Self-report versus care provider registration of healthcare utilization: impact on cost and cost-utility

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Abstract

The aim of this study was to compare the impact of two different sources of resource use, self-report versus care provider registrations, on cost and cost utility. Data were gathered for a cost-effectiveness study performed alongside a 2-yr randomized controlled trial evaluating the effect of an INTERdisciplinary COMmunity-based management program (INTERCOM) for patients with chronic obstructive pulmonary disease (COPD). The program was offered by physiotherapists, dieticians and respiratory nurses. During the 2-yr period patients reported all resource use in a cost booklet. In addition, data on hospital admissions and outpatient visits, visits to the physiotherapist, dietician or respiratory nurse, diet nutrition and outpatient medication were obtained from administrative records. The cost per quality-adjusted life year (QALY) was calculated in two ways, using data from the cost booklet or registrations. In total 175 patients were included in the study. Agreement between self-report and registrations was almost perfect for hospitalizations (rho=0.93) and physiotherapist visits (rho=0.86), but above 0.55, moderate, for all other types of care. The total cost difference between the registrations and the cost booklet was €464 with the highest difference for hospitalizations €386. Based on the cost booklet the cost difference between the treatment group and usual care was €2,444 (95% CI: -819: 5,950), which resulted in a cost-utility of €29,100 per QALY. For the registrations, the results were €2,498 (95% CI: -88; 6,084) and €29,390 per QALY, respectively. This study showed that the use of self-reported data or data from registrations effected within-group costs, but not between-group costs or the cost utility.

Introduction

In cost-effectiveness studies performed alongside clinical trials, healthcare utilization can be measured using questionnaires or diaries completed by the patients in the trial or obtained from medical, billing or other administrative records. The latter is often regarded as more accurate than the first. However, retrieving data from medical or administrative records can be time consuming and costly, especially when patients contact many different care providers. Furthermore, data on services for which the patient pays out-of-pocket, such as over-the counter medication or alternative therapists, are missed using medical or administrative records only. Self-reported surveys, such as questionnaires or diaries, can provide data on all types of healthcare utilization, but can be less valid due to recall-bias. Several studies compared self-reported healthcare utilization with data from medical records, but results are inconclusive. Some studies found good agreement between both sources [1-4], but others reported substantial differences [5-7]. In general, agreement seems fairly good on major events such as hospitalizations or visits to the emergency department, but self-report of outpatient visits, visits to the general practitioner and diagnostic, laboratory or imaging procedures seems less valid compared to medical records [8-12]. Although several studies reported about the extent of agreement between self-reported healthcare utilization and data from medical records [4,7,9-11], the impact of the different types of data collection on cost(-effectiveness) has not been studied. This is an important issue, because almost perfect agreement in hospitalizations between two data sources can still result in a substantial difference in costs as a result of the high costs of an inpatient day. On the other hand, a substantial difference in visits to the general practitioner may have little impact on costs, because of its low unit costs. The aim of this study was to compare the impact of using either self-reported resource use or resource use as obtained from administrative data of healthcare providers on costs and cost-effectiveness in a sample of patients with chronic obstructive pulmonary disease (COPD). Furthermore, we explored whether differences in costs estimates between the two different types of data sources were related to patient characteristics.

Methods

Design of the trial, the intervention and the cost-effectiveness study

Data were obtained as part of a cost-effectiveness study performed alongside a 2-yr randomized controlled trial evaluating the effect of an INTERdisciplinary COMmunity-based COPD management program (INTERCOM) [13]. The trial included patients with COPD

and impaired exercise performance who were recruited from two general hospitals in the Netherlands. One-hundred ninety-nine patients were randomized to the INTERCOM program (n=102) or usual care (n=97).

The INTERCOM program consisted of exercise training, education and smoking cessation support offered by local physiotherapists in the proximity of the patient's home and by respiratory nurses in the hospital. Nutritionally depleted patients in the INTERCOM group were referred to a local dietician for counseling and nutritional supplements (Respifor®). The program was divided in a 4-month intensive intervention phase followed by a 20-month maintenance phase. During the intensive intervention phase all patients visited the physiotherapist twice a week, the respiratory nurse on average two times and the dietician four times if they were nutritionally depleted. In the maintenance phase, these frequencies were lower: once a month for the physiotherapist and at 6, 9, 12 and 24 months for the dietician. Visits to the respiratory nurse during the maintenance phase were upon request and varied widely between patients from 0 to 16 visits. Patients assigned to usual care received pharmacotherapy according to accepted guidelines, a short smoking cessation advice by their respiratory physician and short nutritional advice to eat more and better in case they were nutritionally depleted. Quality of life and several functional parameters were assessed at baseline, 4, 12 and 24 months. All patients gave written informed consent.

The cost-effectiveness study was conducted from a societal perspective including all COPD and non-COPD related healthcare costs, travel expenses and costs of productivity losses. All costs related to conducting the trial have been excluded. Health outcomes were expressed in terms of quality-adjusted life years gained (QALYs), using EQ-5D utility values.

Self-report versus care provider registrations of resource use

During the whole 2-yr study period healthcare utilization was recorded weekly in a cost booklet. In this booklet patients recorded visits to general practitioners, medical specialists, physiotherapists, dieticians, respiratory nurses, alternative therapists, psychologists, social workers, use of over-the counter medication and medical devices, hospital admissions, ambulance rides, time lost from paid work, hours of (un)paid household help, number of units of Respifor® used and use of other nutritional supplements. For all visits to care providers the travel distance was recorded to be able to calculate travel expenses. Each booklet covered a period of 4 weeks and was collected every 2 months. In case the recorded information was unclear, patients were contacted by the investigators by telephone for further clarification.

Next to the self-reported data from the cost booklet resource use was obtained from administrative data of different care providers. Information on the delivery and costs

of outpatient medication was obtained from the patients' local pharmacies. For twelve patients using oxygen the start en stop date of oxygen supply were obtained from their oxygen supplier. The number of hospitalizations, inpatient hospital days and outpatient visits to medical specialists were obtained from the administrative systems of the two hospitals in the study. All seventeen local physiotherapists who treated patients in the INTERCOM group provided information about the number of contacts, the date, duration of the visits and whether treatment was for the INTERCOM study or not. The six respiratory nurses involved in the study provided the same information for outpatient visits to the respiratory nurses for all patients in the INTERCOM group. The five local dieticians who treated nutritionally depleted patients in the INTERCOM group provided detailed information about the visits to the dietician. Finally, the number of units of Respifor® supplied to all nutritionally depleted patients in the treatment group was obtained from the supplier (Nutricia Netherlands).

Resource utilization was valued using Dutch guideline prices updated to the year 2007 [14]. More details about the cost calculation and the cost per unit used can be found elsewhere [13], but the most important unit costs are summarized in the Appendix (Table A1).

Two-different estimates of cost-utility

Cost-utility was calculated in two different ways. In the first analysis, data on healthcare utilization were based entirely on self-reported data from the cost booklet. Only data on outpatient medication and oxygen use were obtained from registrations as no self-reported data were available. In the second analysis, data on healthcare utilization were based on registrations. This implied that outpatient medication, oxygen use, hospitalizations and visits to the medical specialist in the two hospitals in the study, visits to local physiotherapists and respiratory nurses in the hospital and visits to local dieticians and units of Respifor® used were based on registrations. The travel expenses for visits obtained from the registrations were calculated based on the average distance to the healthcare provider (hospital: 7.0, local physiotherapist: 1.8 and local dietician: 3.9 kilometres) [14]. Data on visits to other care providers, use of over the counter medication and medical devices, ambulance rides, time lost from paid work, hours of (un) paid household help, travel expenses for visits to other care providers and use of other nutritional supplements besides Respifor® were based on the cost booklet, because data from registrations were not available for these data sources.

Statistical analyses

All randomized patients who had at least one outcome measurement after start of treatment and completed at least one cost booklet were included in this study. Missing data could be the result of drop-out or unavailability of registrations or cost booklets while patients were (still) in the trial. The percentage of missing data for the different data sources was calculated as the total number of weeks with missing data summed over all patients divided by the maximum number of observable weeks if all patients had complete data for the entire 2-yr study period (=18200).

Correlation between resource use data from the registration and self-reported resource use from the cost booklet was calculated using Spearman's rank correlation coefficient (rho). Furthermore, the proportion of perfect agreement between the two data sources was determined, where perfect agreement was defined as no difference between the two data sources. The correlation between the registrations and the cost booklet was calculated for the whole 2-yr period, but also for 0 to 4 months, 4 to12 months and 12 to 24 months to see whether correlation changes over time.

After valuation of resource use the absolute difference in total costs was calculated for each patient as the total costs based on the registrations minus the total costs based on the cost booklet. Multivariate linear regression analysis with the absolute difference in costs as depend variable was performed to investigate whether treatment group, drop-out, sex, age, number of co-morbidities at baseline, disease severity, health status and total costs were associated with either under- or over reporting. Underreporting was defined as higher costs based on the registrations compared to the cost booklet, while over reporting was defined as higher costs as obtained from the cost booklet compared to the registrations. In this analysis data from patients who did not complete the full two years of the trial were included in the analyses up until the moment patients dropped out and no imputation of missing data was done.

To account for costs and health outcomes that were missing due to drop-out and the additional uncertainty that these missing values introduce, 'multiple imputation' was applied before calculating the cost-utility [15]. This was done separately for missing costs based on self-reported resource use from the cost booklet and missing costs based on resource use from registrations. Each missing value was replaced by ten simulated values using the propensity score method in SAS V8 [16,17]. Missing EQ-5D scores were imputed simultaneously with costs. More details about the multiple imputation are described elsewhere [13].

Each of the ten complete datasets was further analyzed by nonparametric bootstrapping using 10,000 replications per dataset [18]. The 2.5th percentile and the 97.5th percentile of these bootstrap replications form the 95% confidence interval of the difference in costs and QALYs. The uncertainty around the point estimates of the incremental cost

effectiveness ratios (ICERs) was displayed by plotting the bootstrap replications in cost-effectiveness planes (CE-planes). In addition, cost-effectiveness acceptability curves were drawn, which show the probability that the INTERCOM program is cost-effective at several values of the willingness-to-pay for one additional QALY [19,20]. All analyses were performed with either SPSS version 13.0 or SAS V8.

Results

Subjects

In total 175 of the 199 randomized patients were included in this cost-effectiveness study, because they had at least one outcome measurement after start of treatment and completed at least one cost booklet. Mean age was 67 years (SD 7), 26% was female, FEV_1% predicted was 60% (SD 16), EQ-5D utility index score at baseline was 0.80 (SD 0.18) and patients had on average 1.5 (SD 1.5) co-morbidities at baseline. Baseline characteristics of patients in the INTERCOM and the usual care group were comparable. Of the 87 patients in the INTERCOM group that were included, all visited the physiotherapist and the respiratory nurses and 21 received additional nutritional advice and Respifor®. One hundred fifty-eight patients completed the 2-yr study period; 75% in the INTERCOM group and 84% in the usual care group, which was not a statistically significant difference. Drop-outs in the INTERCOM group had a significantly shorter length of stay in the trial than drop-outs in the usual care group. Besides that, drop-out in the INTERCOM group was related to a more impaired health status compared to completers, which was not the case in the usual care group.

Availability of data

Information about hospitalizations and outpatient visits to medical specialists obtained from hospital records was available for 171 patients (97.7%). All other registrations were 100% complete. Eighty-three percent of the 158 patients who completed the study filled in the cost booklet for the exact 2-yr period, while the remaining seventeen percent missed on average 2.6 weeks. The missing number of cost booklets in drop-outs was higher. Seventy-one percent of the seventeen drop-outs did not complete the cost booklets until their formal date of drop-out with an average of 8.3 weeks missing. After the formal date of drop-out the number of weeks with missing data was on average 37.8 per patient. For all data sources the total percentage of missing data was below 10% (Table 1).

Table 1: Mean resource use per patient and correlations between self-report and care provider registrations for the complete 2-year study period before multiple imputation of missing data (n=175)

	Number of patients	Care provider registrations		Self-reported cost booklet		Absolute difference	Spearman rank correlation coefficient	Percentage of perfect agreement
Hospital		Mean	Missing[a]	Mean	Missing[a]			
Daycare treatment	175	0.25	6.0%	0.08	4.5%	0.17	0.55	87%
Daycare treatment for COPD	175	0.035	6.0%	0.006	4.5%	0.03	0.49	98%
Hospital admissions	175	0.79	6.0%	0.69	4.5%	0.10	0.93	88%
Hospital admissions for COPD	175	0.36	6.0%	0.33	4.5%	0.03	0.94	95%
Total hospital days	175	8.0	6.0%	6.6	4.5%	1.4	0.91	79%
Total hospital days for COPD	175	4.3	6.0%	3.6	4.5%	0.7	0.93	93%
Visits to medical specialists	175	10.5	6.0%	9.2	4.5%	1.3	0.70	8%
Visits to the physiotherapist*	87	48.4	5.7%	49.9	6.4%	-1.4	0.86	7%
Visits to the respiratory nurse*	87	7.5	5.7%	5.1	6.4%	2.4	0.65	11%
Visits to the dietician#	21	8.1	2.7%	6.6	2.7%	1.5	0.64	29%
Units Respifor® used#	21	491	2.7%	461	2.7%	30	0.68	10%

[a]The percentage of missingness was calculated as the total number of weeks with missing data summed over all patients divided by the maximum number of observable weeks if all patients had complete data for the entire two year study period (=18200).

* Only applicable to patients in the INTERCOM group, # Only applicable to nutritionally depleted patients in the INTERCOM group

Agreement

For all types of resource use, the mean unimputed resource use as obtained from the registrations was higher, except for visits to the physiotherapist, for which the mean number of visits obtained from the cost booklet was slightly higher (Table 1). Agreement was almost perfect for number of COPD-related and total hospital admissions, number of COPD-related and total hospital days and number of visits to the physiotherapists (all rho>0.8). Agreement was substantial for visits to the medical specialists, the respiratory nurse and the dietician and the number of units Respifor® used (rho>0.6), while agreement for COPD-related and total daycare treatment was moderate (rho>0.4). The percentage of perfect agreement decreased as the mean resource use increased. Agreement did not worsen or improve over time (Appendix, Table A2).

Variables related to differences in costs based on self-report or care provider registrations

Comparison of the total unimputed costs between the two data sources showed that 106 of 175 patients (61%) were underreporting, i.e. they had higher costs based on the registrations compared to the cost booklet. Sixty-five patients (37%) were over

reporting, because they had higher costs based on the cost booklets compared to the registrations. For the remaining four patients, the absolute difference between the two data sources could not be calculated, because data for visits to the medical specialist and hospitalizations were not available from the registrations. In the multivariate linear regression, the degree of underreporting was significantly independently associated with drop-out and total costs. Patients who dropped out during the trial and patients with higher total costs had larger differences in costs between the registrations and the cost booklet compared to patient who completed the study and patients with lower total costs, respectively. The degree of over reporting was only associated with total costs with higher total costs resulting in more over reporting. The association of drop-out with underreporting was confirmed using the logarithm of costs as the dependent variable. No association was found with treatment group, sex, age, number of co-morbidities at baseline, health status or indicators of disease severity.

Costs and costs-utility

The figure in the appendix shows the difference in costs between registrations and the cost booklet after multiple imputation. These are the final cost estimates used in the cost-utility calculations. The cost difference was highest for hospitalizations, approximately €390 and lowest for visits to the dietician, approximately €50.

Table 2 shows the mean costs by treatment group after applying multiple imputation separately for costs based on the registrations or the cost booklet. Costs for visits to the physiotherapist, respiratory nurse, dietician and the use of diet nutrition, all elements of the INTERCOM program, were, as expected, significantly higher for the INTERCOM group, irrespective of the data source used. Costs for visits to the medical specialist were significantly higher in the usual care group based on the registrations, while this was

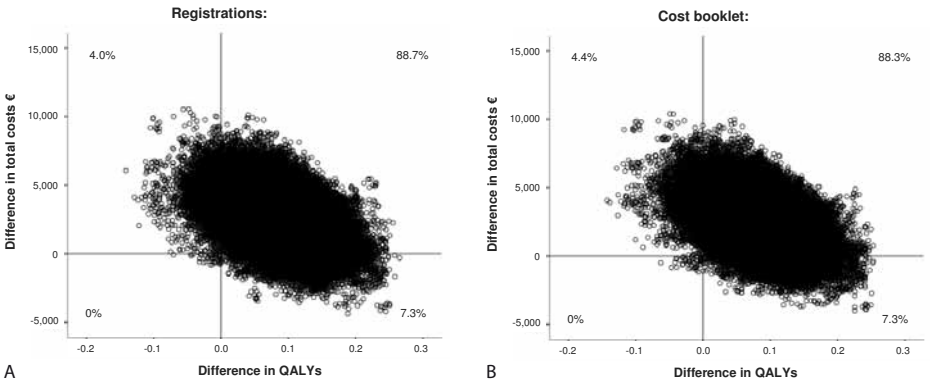

Figure 1A - 1B: Cost-effectiveness planes, cost per QALY

Table 2: Mean costs per patient for different categories of care based on care provider registrations or the self-reported cost booklet after multiple imputation of missing data* (2007, €)

	INTERCOM (n=87)*		Usual Care (n=88)*		Difference in costs INTERCOM and Usual Care (95% confidence interval)*	
	Care provider registrations	Self-reported cost booklet	Care provider registrations	Self-reported cost booklet	Care provider registrations	Self-reported cost booklet
General practitioner	162	162	175	175	-12 (-60; 35)	-13 (-61; 34)
Medical specialist	582	571	738	609	-156 (-276; -33)	-38 (-175; 102)
Physiotherapist	1,236	1,290	265	264	971 (834; 1,104)	1,026 (882; 1,168)
Dietician	81	70	20	20	62 (32; 92)	50 (23; 76)
Respiratory nurse	215	148	22	22	193 (171; 215)	125 (106; 145)
Hospital admissions	2,793	2,341	3,342	3,021	-549 (-2,204; 1,204)	-679 (-2,116; 866)
Diet nutrition	340	318	31	31	309 (145; 500)	287 (115; 483)
Prescribed medication	3,525	3,528	3,313	3,321	212 (-243; 665)	208 (-248; 659)
Oxygen use	198	197	56	57	141 (-10; 306)	141 (-11; 305)
Other direct medical costs[#]	2,908	2,901	2,147	2,148	760 (-1,204; 2,893)	754 (-1,231; 2,889)
Costs paid by the patient[$]	386	424	486	491	-100 (-509; 233)	-67 (-475; 266)
Productivity costs	996	983	330	330	667 (-123; 1,563)	653 (-136; 1,552)
Total costs	13,423	12,932	10,925	10,488	2,498 (-855; 6,084)	2,444 (-819; 5,950)

* Grey cells contain data obtained from the two different data sources. Data in white cells are based on the same data source either the self-reported cost booklet or care provider registrations. Small differences in the white cells are the result of the multiple imputation procedure.

[#] Other direct medical costs included costs of visits to other therapists, alternative therapists, social workers and psychologists, home care, ambulance transportation, pulmonary rehabilitation (daycare treatment and inpatient), psychiatric hospital admissions and medical devices.

[$] Costs paid by the patient included costs of over the counter medication, paid and unpaid household help and travel expense

not the case when costs were based on the cost booklet. However, differences between the two data sources were small across all types of resource use (Table 2). The difference in total costs between the two treatment groups was comparable for both data sources €2,498 (95% CI: -88; 6,084) based on the registrations and €2,444 (95% CI: -819; 5,950) based on the cost booklet. The gain in QALYs due to the INTERCOM program was 0.08 (95% CI: -0.01; 0.18). This resulted in ICERs of €29,390 per QALY based on the registrations and €29,100 per QALY based on the cost booklet. CE-planes for both data sources were similar (Figure 1). For both the registrations and the cost booklet about 88% of the bootstrap replications fell in the upper-right quadrant indicating that the INTERCOM program has a higher gain in QALYs, but also higher costs. The acceptability curves were also comparable. The probability that the INTERCOM program is cost-effective at a willingness-to-pay of €20,000 and €50,000 per QALY gained was in both data sources 37% and 69%, respectively.

Discussion

This study showed the impact of self-report or registration based resource use on costs and cost-utility. Agreement between self-reported resource use and resource use based on registrations was good or substantial for most types of care. Because inaccuracy increases with longer recall periods [11], the relatively short recall period in our study may have contributed to this high agreement. The cost booklets were designed to record resource use per week and each booklet covered four weeks. The booklets were collected every two months. This is a relatively short recall period compared to other studies using recall periods of six or even twelve months [8-10,12]. The high agreement between the two data sources for hospital admissions/days were in accordance with other studies showing a high agreement for major events [10-12]. The agreement for visits to the physiotherapist was higher than in other studies [3,5], probably because the visits took place on a regular basis, two times a week in the first four months and once a month thereafter. Agreement for daycare treatment in hospital was poor. This may have been related to the fact that the cost booklet did not explicitly specify daycare treatment in hospital separately from inpatient hospitalizations including an overnight stay. It identified daycare treatment when the date of admission and discharge was the same.

Our study confirmed that self-report results in underestimation. For all categories of care, except one, mean resource use was lower for the cost booklet than for the registrations. Analyses of the difference in total costs based on either the cost booklet or the registrations showed that both under- and over reporting were associated with total costs. The association between increased visit frequency and underreporting was reported by several studies before [2,6,11]. As total resource use increases patients are more likely to forget visits or unwilling to write everything down. The relation between increased visit frequency and over reporting has also been found in other studies [6,9]. With an increase of resource use, it is more difficult to remember the exact date of a certain visit. As a result visits that occurred outside the actual recall period may have been included.

The absolute difference in costs between the registrations and the cost booklet was about €460. Despite the almost perfect agreement for hospitalizations and hospital days, the cost difference between the registrations and self-reported resource use was highest for this type of care, about €390. For visits to the dietician the cost difference was lowest, about €50, although agreement for this type of care between the two data sources was only substantial. Hence, good agreement between self-reported resource use and resource use from registrations does not automatically result in good agreement in costs, when unit costs are high. Van den Brink et al also investigated the effect of different data sources on costs for a limited number of types of care [4]. They found that cost estimates for medication and stoma care products based on self-report were

substantially lower compared to providers' records .The cost estimates for hospital admissions however did not differ much between the two data sources in contrast to what we found in our study.

The observed difference in total costs of about €500 between the registrations and the cost booklet *within* treatment groups did not have an influence on the difference in costs *between* treatment groups. The cost difference between treatment groups was only slightly different, €2,498 based on registrations versus €2,444 based on the cost booklet. As a result the CE-ratio, CE-planes and acceptability curves were comparable.

A limitation of our study was that we did not have both data sources for all types of resource use. Although it is common in economic evaluations to combine resource use data obtained from different sources, it is unusual to have multiple sources for a single type of resource use. It is not common practice to validate resource use data obtained from one source with a second source. We collected data from several care provider registrations in addition to the data from the cost booklet for the specific purpose to validate the booklet. Of the two items with the highest costs in our study, i.e. medication and hospitalizations, only the latter was available from both self-report and registrations. Information on outpatient medication was only available from the administrative systems of patients' local pharmacies. Given the length of the study, two years, and the large number of different medications used by COPD patients, the choice for registrations was made in order to limit the burden of data registration. For other high costs categories, such as "other direct medical costs" and "productivity costs", getting data from registrations would have been very difficult if not impossible. However, if only items with two data sources would have been included in the cost-effectiveness analysis, the cost difference between treatment groups would have been €730 based on registrations versus €704 based on the cost booklet, resulting in ICERs of €8,590 and €8,379 per QALY, which would not have changed the conclusions.

The final estimate of costs used in the original cost-effectiveness study was based on a combination of both sources. Most resource use information was obtained from the cost booklet except for outpatient medication and oxygen, which were obtained from registrations. For hospitalizations we combined both sources and counted all hospitalizations irrespective of whether they were recorded by patients only, in the registrations only or in both sources. This resulted in higher costs for hospitalizations compared to the data presented in this paper and therefore in somewhat different estimates for the cost difference between treatment groups and the cost-effectiveness, €2,751 (95%CI:-632; 6,372) and €32,425 per QALY, respectively [13].

In conclusion, we showed that self-reported resource use led to different cost estimates than care provider registrations, but it did so in both treatment groups. As a result, estimates of the difference in costs between two treatment groups and estimates of the cost-utility of the INTERCOM program were comparable between the two methods of resource use measurement.

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Appendix

Table A1: Unit costs for the most important types of resource utilization (2007, €)

Type of healthcare	Unit	Unit costs
Contacts with care providers:		
Medical specialist, general hospital	Contact	59
Physiotherapist	Contact	24
Dietician	Contact	31
Respiratory nurse	Contact	27
Hospital care		
General hospital	Day	356
Daycare treatment	Day	242
Respifor®	Unit	2.76
Travel expenses, public transport/ car	Km	0.17

Table A2: Mean resource use per patient and correlation between self-report and care provider registration over time before multiple imputation of missing data

	Time period	Care provider registrations		Self-reported cost booklet		Absolute difference	Spearman rank correlation coefficient
		N	Mean	N	Mean		
Hospital admissions	0-4 months	170	0.07	175	0.07	0.00	1.0
	4-12 months	170	0.20	174	0.18	0.02	0.93
	12-24 months	165	0.53	167	0.46	0.08	0.94
Hospital days	0-4 months	170	0.74	175	0.71	0.02	1.0
	4-12 months	170	1.87	174	1.65	0.22	0.93
	12-24 months	165	5.55	167	4.46	1.08	0.93
Visits to medical specialists	0-4 months	170	1.45	175	1.65	-0.20	0.63
	4-12 months	170	3.44	174	3.24	0.19	0.60
	12-24 months	165	5.82	167	4.54	1.27	0.64
Visits to the physiotherapist	0-4 months	87	21.4	87	22.6	-1.2	0.74
	4-12 months	87	13.1	86	14.0	-0.8	0.82
	12-24 months	81	14.9	80	14.7	0.2	0.77
Visits to the respiratory nurse	0-4 months	87	2.03	87	1.49	0.54	0.55
	4-12 months	87	2.33	86	1.76	0.58	0.68
	12-24 months	81	3.41	80	2.03	1.38	0.61
Visits to the dietician	0-4 months	21	2.43	21	2.62	-0.19	0.65
	4-12 months	21	2.67	21	2.00	0.67	0.58
	12-24 months	20	3.15	20	2.01	1.1	0.55
Units of Respifor® used	0-4 months	21	272	21	180	91	0.54
	4-12 months	21	91	21	128	-38	0.52
	12-24 months	20	135	20	160	-25	0.57

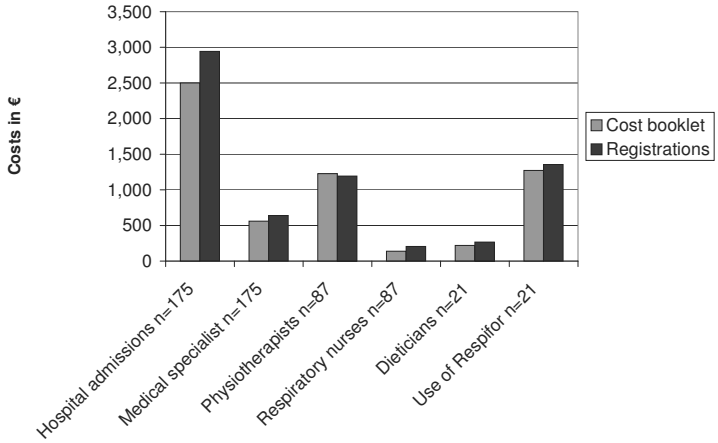

Figure A1: Costs per patient based on the self-reported cost booklet or care provider registrations after multiple imputation of missing data

Chapter 10

General discussion

Discussion

The main goal of this thesis was to develop tools that enable the assessment of the cost-effectiveness of treatment options for COPD and to provide such information. Two different approaches were used to obtain this information. First, a population-based COPD progression model was developed which can be used to evaluate the cost-effectiveness of a wide range of COPD interventions over a long time horizon and can provide policy makers with comparable information on a nationwide level. Secondly, an empirical economic evaluation was performed alongside a clinical trial evaluating the effectiveness of a COPD management program. In this chapter, results of both approaches will be discussed separately. Furthermore, the advantages, disadvantages and complementary nature of both methods will be presented. It will also be discussed how the outcomes of the studies in this thesis can be used in policy making with respect to COPD care. Finally, recommendations for further research will be given.

Part one: studies related to the development of a COPD progression model

The first part of this thesis presented papers describing the estimation of the input parameters and the structure of the COPD model. Furthermore, examples of the possible use of the model were included as well as a paper describing the cost-effectiveness of smoking cessation interventions in COPD patients using the COPD model. Models synthesize data from various sources in a systematic way and combine these data into a consistent framework. In the COPD model described in this thesis data on COPD prevalence, incidence, mortality, decline in lung function, smoking prevalence and smoking transition rates, exacerbation-related parameters, quality of life and costs were combined into a population-based COPD disease progression model describing the course of the disease from diagnosis till death. The model aims to be representative for all patients with a physician-diagnosis of COPD. Patients with undiagnosed COPD are not included, because data on prevalence and incidence are based on a physician-diagnosis of COPD obtained from registrations of general practices. A model including undiagnosed patients is hard to fill with evidence-based estimates of input parameters, because the number of undiagnosed patients and their COPD-related resource use is completely unknown because it is not registered as such. The model is a dynamic population model which means that dynamics influencing the incidence of COPD in the Dutch general population, such as prognosis of birth, migration and mortality and changes in smoking prevalence are taken into account [1]. An advantage of the model being dynamic is that the model projects the changes in the total Dutch COPD popula-

tion over time. The model can also be used to follow a pre-specified fixed cohort of patients over time by selecting patients within a certain age range, adjusting the COPD severity distribution at the start of the simulation and setting the number of newborns and the COPD incidence to zero.

Summary of findings

Chapter two to seven described the structure and input parameters of the first and the second version of the COPD model. The most interesting input parameters of the models and the most important outcomes will be discussed in this paragraph. The total number of COPD patients in 2000 was estimated to be 305,000 (chapter three). The majority of these patients had mild or moderate airflow obstruction (82%) according to the GOLD classification (chapter two). For the period 2000-2025 the prevalence of COPD was projected to increase by about 40% in males and 90% in females. Total COPD-related healthcare costs were projected to increase from €280 to €495 million (chapter three). Several GP registries combined resulted in a prevalence estimate for 2007 of 321,000 patients (uncertainty interval: 225,100; 395,500), which was used as input data for the second version of the model. For this version of the model all exacerbation-related input parameters except for costs were estimated by means of a meta-analysis. The annual total exacerbation frequency by COPD severity stage was found to range from 0.82 (95% uncertainty interval (UI): 0.46;1.49) for mild to 2.1 (1.51; 2.94) for very severe COPD. The frequency of severe exacerbations increased from 0.11 (0.02; 0.56) in mild to 0.28 (0.14; 0.63) in very severe COPD (chapter five). The FEV_1 decline due to an exacerbation was estimated to be 0.19 % predicted (95% CI: 0.092; 0.29) per exacerbation (chapter seven). The case-fatality of a severe exacerbation was found to be 15.6% (95% CI: 10.9; 20.3) (chapter six). The association between exacerbations and quality of life was derived from studies from Goossens and O'Reilly that reported utility values during a moderate and severe exacerbation, respectively. Based on these values the annual utility loss due to an exacerbation was estimated to be 1.66% (95% CI: 1.23; 2.09) of the baseline utility value for a moderate exacerbation and 4.82% (3.11; 6.53) of the baseline value for a severe exacerbation ([2,3].

Chapter three, four and seven included examples of the potential of the model for cost-effectiveness analyses. Chapter three presented two examples of cost-effectiveness calculations assuming increased implementation of smoking cessation interventions for COPD patients. Compared with usual care, one-year implementation of minimal counseling (10 minutes) by the general practitioner was estimated to be cost saving and the cost per QALY for intensive counseling plus bupropion was estimated to be €7,300, both using a time horizon of 25 years. Due to a lack of data at that time, the 12-month continuous abstinence rates that were used in this study had to be based on

studies among smokers in the general population. However, abstinence rates for the same intervention are currently assumed to be higher in the general population than in COPD patients [4,5]. It took some years before the number of studies evaluating smoking cessation interventions in COPD patients was sufficient to be able to calculate better estimates of the cost-effectiveness of smoking cessation interventions using abstinence rates specific for COPD patients (chapter four). Compared with usual care the costs per QALY gained of one year implementation of minimal counseling (less than 90 minutes), intensive counseling (≥ 90 minutes) and intensive counseling plus pharmacotherapy (NRT, bupropion or nortriptyline) were estimated to be €16,900, €8,200 and €2,400, respectively, using a time horizon of twenty-five years. The calculations of the cost-effectiveness of smoking cessation in chapter three and four were done with the first version of the COPD model. Using the second version of the model (chapter 7), the cost-effectiveness ratio for intensive counseling plus pharmacotherapy was estimated to be €10,800 per QALY gained (chapter seven). However, this estimate was based on calculations assuming a longer implementation period than in chapter four, i.e. three years instead of one year(s). Moreover, effects were evaluated over a shorter time horizon, ten years instead of twenty-five years. Using the same implementation period and time horizon as in the study in chapter four would have resulted in a ratio of €5,700 per QALY gained, which was not significantly different from the result in chapter four taking into account the uncertainty around the outcomes. Chapter seven also presented the cost per QALY gained for three-year implementation of the combination of ICS/LABA (€8,300) and three year implementation of a pulmonary rehabilitation program, the INTERCOM program (€17,200) both using a time horizon of ten years. The latter estimate included the additional intervention costs directly related to the program, e.g. physiotherapist, dietician, respiratory nurse and diet nutrition above the costs for maintenance therapy and exacerbations already included in the model. Because the INTERCOM trial did not provide evidence that the intervention significantly affected other types of costs, such as for example a reduction in costs for hospitalizations, we did not model any changes in the costs for maintenance treatment and exacerbations as a result of the intervention. This is the main explanation for the difference in cost per QALY of the model-based estimate compared with the trial-based estimate, €32,400 (chapter eight).

Input parameters

As described above the model is filled with several input parameters. According to the principles of good practice for modelling [6], all key input parameters should be based on systematic reviews. This increases the validity and generalizability of the model outcomes substantially, because in this way input data are based on the evidence available in the current literature and are not biased towards one single study population. All

exacerbation-related parameters, except for costs, were based on systematic reviews and meta-analyses (chapter five, six and seven). However, due to data limitations it is sometimes unavoidable to base input parameters on only a few or even one data source. A disadvantage of systematic reviews and meta-analyses based on just a few studies is that this often results in one mean estimate, which can not be further specified by subgroup. An example of this is the case-fatality of a COPD exacerbation, which should preferably be further specified by sex and age (chapter six). Another example is the smoking abstinence rates presented in chapter four. Preferably, rates would have been specified by COPD severity and the group intensive counseling plus pharmacotherapy to support smoking cessation would have been further specified by type of pharmacotherapy. For the epidemiological input parameters of the model a meta-analysis of all available evidence in the literature would not be appropriate, because the model was intended to be representative for the Dutch COPD population. Therefore the model was filled with Dutch data on prevalence, incidence, smoking data and costs, mostly obtained from one or a couple of data sources. Mortality data were obtained from the DYNAMO-HIA project and originally based on the General Practice Research Database (GPRD) from the UK [7]. The model could be transferred to different settings by replacing the epidemiological input data by setting-specific data.

Severity of COPD

One of the major difficulties in developing a COPD model is the concept of COPD disease severity. In the current version of the model disease severity and disease progression was based on the degree of airflow obstruction defined in terms of the FEV_1% predicted, as has been done in all other available COPD models [8-15]. Chapter two showed the results of the estimation of the severity distribution of COPD in the Netherlands based on lung function. The complexity of COPD severity can however not be described by the degree of airflow obstruction alone, because patients within each GOLD severity stage can vary substantially in terms of symptoms, exacerbations and prevalence of co-morbidities [16]. The same is true for disease progression, which was defined as annual decline in lung function based on data from the Lung Health Study, a large study in patients with mild and moderate airflow obstruction [17]. Although the decline in lung function was specified by sex, age, smoking status and baseline FEV_1% and influenced by exacerbations, other acknowledged prognostic factors, such as BMI, health status, and dyspnoea [18] were not taken into account due to data limitations. Several composite measures based on multiple parameters have been proposed as better ways to define disease severity in COPD [19-21]. The recently published Dutch "Zorgstandaard COPD" also chose not to use a severity distribution based on lung function alone, but proposed a new classification based on burden of disease (="ziektelast") specified as mild, moder-

ate or severe burden of disease [22]. This new classification includes parameters such as diagnostic problems, achievement of treatment goals, lung function, dyspnoea, coping, nutritional status, exacerbations and co-morbidity and would better reflect the true disease severity of COPD and the health problems patients experience. A clear exact definition of this concept of burden of disease is still missing, which makes the comparison between groups and interventions difficult. The exact distinction between the three proposed severity stages is also difficult because scientific evidence for cut-off points for the different parameters is still insufficient. Another difficulty is that the burden of disease of a patient is dynamic and can vary within a patient over time [22]. Using a severity distribution based on multiple parameters in the model would be challenging, because it requires continuous monitoring of changes in all of these parameters. Therefore the COPD severity in the model was only based on lung function.

Model validation

Validation is an important step in the development of a model [23]. Different types of model validation can be distinguished: internal validation, between-model validation, predictive or prospective validation and external validation [23,24]. The internal validity of the developed COPD model was secured by performing fifteen different model checks to prevent internal inconsistencies. This was done by setting several major input parameters at zero or at extreme values to see whether the model outcomes responded as expected [25]. Furthermore, model results for certain subgroups were compared, such as smokers versus former smokers and mild versus severe COPD to see whether the model outcomes were plausible. Finally, the mean life expectancy of a COPD patient above 45 years of age was calculated and compared with published data. The mean age of the COPD patients in the model was 69 years. The mean life expectancy of these patients calculated by the model was 10.5 years, which was comparable with the mean life expectancy of 10 to 12 years for a patient with a mean age of 65-70 years estimated by Van Baal et al (adapted from [7,26]. Given that the life expectancy of a 65-70 year old person in the general population is about 14 to 17 years for males and 17 to 21 years for females our estimate of the life expectancy of a COPD patient seemed reliable [27]. Internal validation refers to the situation that if the model is filled with input parameters that are obtained from one particular trial it should be able to reproduce the outcomes of that trial. Although internal validation was not completely possible in our case, because input data were obtained from multiple resources, we tried to check the internal validity of the COPD model using data from the TORCH trial [28,29]. We used the model to simulate the cohort of patients included in the TORCH trial by selecting patients between 40 and 80 years of age and adjusting the severity distribution at baseline. Furthermore we replaced the exacerbation rates and all-cause mortality rates in the model at baseline by the rates observed in the

trial. Table 1 shows that the model outcomes after three years resembled the trial data fairly well, except for the all-cause mortality rate in very severe COPD which was about 1.4% lower in the COPD model. This is probably the result of the higher percentage of males in the very severe COPD group in the trial (83%) compared with our model (54%) in combination with the higher all-cause mortality rates in males compared with females (chapter seven). Based on the outcomes of the internal checks and simulation of the TORCH trial we concluded that the COPD model was internally valid.

Table 1: Internal validation of the COPD model using input data of the TORCH trial

	Outcomes of the TORCH trial after three years [28,29]		Outcomes of the COPD model after three years	
	Annual exacerbation rate	All-cause mortality at three years	Annual exacerbation rate	All-cause mortality at three years
Moderate COPD	0.82	11.4%	0.84	11.7%
Severe COPD	1.24	15.2%	1.27	15.3%
Very severe COPD	1.79	24.3%	1.82	22.9%
Overall	1.17*	15.2%	1.20	15.2%

* Weighted mean based on the severity distribution of the population. The overall annual exacerbation rate published by Calverley et al was based on negative bionomial regression.

The prospective validity of the first version of the model (chapter three) was checked by comparing the prevalence projections of this model for the year 2007 with prevalence data for this year obtained from GP registrations [26]. Based on this comparison the prospective validity of the first version of the model seemed good for female COPD patients, but less so for male COPD patients. For males, the model projected an increase from 188,000 patients in 2000 to 216,000 in 2007, while the actual prevalence in 2007 was 172,000. Figure 1 shows that this was mainly the result of an overestimation of the prevalence in the highest age groups. The latter was probably caused by a change in the number of smokers at older ages. The updated smoking prevalence figures for the year 2007 showed that especially in older males the smoking prevalence decreased substantially in the past years and faster than expected in 2000 [30,31]. The smoking prevalence in the cohort of 65-70 year old males for example was projected by the model to decrease from 31% in 2000 to 24% in 2007, while the new input data for the year 2007 reported a smoking prevalence rate of 14% for this group of patients. For female patients the model performed quite well by projecting an increase in total number of patients from 117,000 in 2000 to 147,000 in 2007, which was comparable to the prevalence observed in 2007, 149,000. However, figure 1 shows that also for females the prevalence was slightly overestimated in the older ages.

Two comments should be made regarding the assessment of the prospective validity of the model. First, it should be noted that the data sources for the prevalence for the year 2000 and 2007 were not completely the same. For the year 2000 data on prevalence

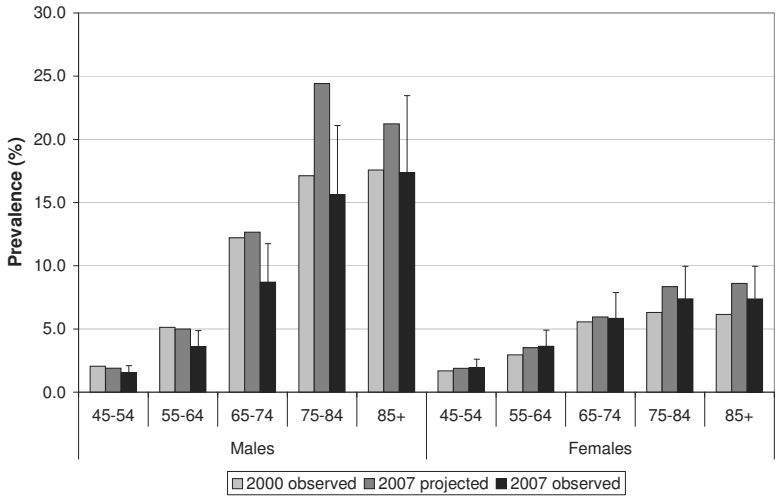

Figure 1: Comparison of observed and projected age-specific prevalence rates

were based on three general practice registrations (CMR, RNH and Transition-project) [26]. The new prevalence estimates for 2007 were also based on three general practice registrations, but the data from the Transition-project were replaced by data from the RNHUH-LEO, because the Transition-project seems to overestimate current prevalence [32]. This may imply that the prevalence estimates for 2000, the start of the simulation, were already too high. To check the real prospective validity of the model prevalence estimates for the years 2000 and 2007 should be based on the same data registrations to ensure that differences in prevalence could not be the result of methodological differences. Secondly, the differences in prevalence estimates between the different GP registrations were substantial and therefore uncertainty around the prevalence rates for 2007 was high [32]. This was probably also the case for the prevalence rates for 2000, but in the first version of the model we did not take into account uncertainty. For 2007, all age-specific prevalence rates could vary from 25% lower to 35% higher rates. The prevalence projections for females for 2007 using the first version of the model fell within this uncertainty interval. For males this was not the case indicating that prevalence projections for 2007 of the first version of the model were probably too high.

To assess the between-model validity of the model the outcomes of the newest version of the model were compared with other published models. A model-based study of Earnshaw et al used input data from the TORCH trial to estimate the cost-effectiveness of treatment with ICS/LABA [15]. Compared with placebo the cost-effectiveness of lifetime treatment with ICS/LABA was estimated to be $33,900 per QALY (about €29,800 per QALY in 2007€). Using the same treatment effects for ICS/LABA on exacerbation frequency and all-cause mortality, the same study population and equal intervention

costs, our COPD model found a cost-effectiveness ratio of €36,600, slightly higher than the results of Earnshaw.

External validation of the model by comparing the model outcomes with other sources not used as input for the model was difficult, because such data sources were not available for the Dutch setting. The only parameter of the model we were able to validate with independent data was the COPD severity distribution, which was assumed to be 27% in mild, 55% in moderate, 15% in severe and 3% in very COPD. This finding was confirmed by a study from Steuten et al, which also reported that almost 80% of Dutch primary care COPD patients were classified as having mild or moderate COPD [33].

Recommendations for future research with respect to COPD modelling

Several aspects in the field of COPD modelling require more research. One of the items for future research is the concept of COPD disease severity. To better reflect the complexity of the disease, future COPD models should incorporate other ways to define disease severity than based on lung function alone. This involves including other parameters such as BMI, fat-free mass, dyspnoea, exercise capacity, exacerbation history and co-morbidities. The severity distribution based on burden of disease proposed by the Zorgstandaard COPD is no realistic alternative yet, because the concept of burden of disease needs to be further elaborated and a uniform definition should be made before it can be used in daily practice [22]. Currently, all published COPD models are Markov models. Because one of the aspects of a Markov model is that patients can only be in one state, including more parameters to define COPD severity would increase the number of states exponentially. Therefore a Markov model may not be the most appropriate approach to use when developing a COPD model including several parameters to define COPD severity. Patient-level simulation may then be a better way to model the natural history and complexity of a disease such as COPD. However, data to fill models are often lacking [34]. A Markov model may also be less suitable for modelling COPD because of its property that transitions or probabilities do not depend on past values. In this way the probability to get an exacerbation can not depend on the number of exacerbations in the past, although it has clearly been shown that the most important predictor for a COPD exacerbation is a history of exacerbations [35].

With respect to the input parameters of the COPD model more research should be done on the utility decrement during exacerbations, the COPD-related costs specified by GOLD or other severity stage and data on COPD-related productivity losses. With respect to the first point, most COPD models made assumptions because data on the utility decrement during exacerbations were completely lacking. Only recently, two studies published results about the utility decrement in either a moderate or a severe hospitalization [2,3]. However, the information on this type of parameter is still very

limited. With respect to costs, no Dutch study published COPD-related costs by disease severity. If data on both costs and lung function are available the sample is often too small to give reliable estimates. With respect to the third point representative data about the mean annual number of days absent from work or data on early retirement due to COPD are still limited which is the main reason that up to now our model only included direct medical costs. A large population-based study or patient registry should be done to investigate COPD-related healthcare costs by disease severity and to yield data on days absent from work and early retirement. A good example of such a type of study is the ECLIPSE study in which unfortunately no data on healthcare utilization were collected [36]. If representative data on days of work loss would become available, we would be able to include COPD-related costs of productivity losses and perform the cost-effectiveness analyses from a societal perspective.

The introduction of this thesis showed that information on the cost-effectiveness of especially non-pharmacological treatment options is still limited. Despite the lack of data on cost-effectiveness of COPD interventions, many of these interventions are included in national and international guidelines, such as the Zorgstandaard COPD and the GOLD guidelines [22,37]. Given the increasing healthcare expenditures and the limited healthcare budgets taking into account cost-effectiveness data in guideline development seems appropriate. Therefore, more studies should be done investigating the cost-effectiveness of COPD care, especially in real life.

Part two: studies related to the economic evaluation of an interdisciplinary community-based COPD management program

Aim of the second part of this thesis was to estimate the (cost-)effectiveness of an interdisciplinary, community-based COPD management program (INTERCOM) in patients with less advanced airflow obstruction and impaired exercise capacity (peak exercise capacity during an incremental cycle ergometer test <70%). Effectiveness of this program was evaluated in a large, two-year randomized controlled trial comparing the INTERCOM program, consisting of exercise training, education, nutritional therapy and smoking cessation support with care as usual [38]. Furthermore, an economic evaluation was performed alongside the clinical trial. This thesis presented a paper describing the cost-effectiveness of the program, as well as a paper describing a methodological issue in performing economic evaluations based on patient data.

Summary of findings

The clinical evaluation showed that at four months patients in the INTERCOM group had significantly improvements in disease-specific quality of life, dyspnoea, exercise capacity, muscle function and body composition compared with patients receiving usual care. Over the total two-year period significant differences were found in disease-specific quality of life, dyspnoea, exercise capacity, but not in the number of exacerbations. The INTERCOM study furthermore showed that implementation of a COPD program in a community-based hospital-guided setting seemed feasible, but adequate coordination of the program and repeated education of participating local care providers seems very important for the success or failure of the program [38]. The economic evaluation of the program (chapter eight) found that the total two-year costs in the INTERCOM group were €2,751 (95% CI: -632; 6,372) higher than in the usual care group. The gain in QALYs in the INTERCOM group was 0.08 (95% CI: -0.01; 0.18) resulting in an incremental cost-effectiveness ratio of €32,400 per QALY gained.

Because the INTERCOM program was compared with usual care only, results for effectiveness and cost-effectiveness only apply to the INTERCOM program as an integrated package of care, i.e. the combination of exercise, education and for some patients nutritional therapy and smoking cessation support. The study design did not allow us to draw firm conclusions about the cost-effectiveness of the separate components of the program. In a post-hoc analysis the INTERCOM group was split in the group of muscle wasted patients (fat free mass index ≤15 (female)/ ≤16 (male) kg/m^2) receiving exercise, education and nutritional therapy and the group of non-muscle-wasted patients receiving exercise and education only. This analysis showed that over two years the group receiving nutritional therapy had significant improvements in fat free mass index and BMI, which were not found in the group receiving exercise and education only. Part of the higher costs for nutritional counseling and supplements in the muscle-wasted group were compensated by significantly lower hospitalization costs [39]. However, these findings were based on a low number of patients and the study was not designed to test the additional effect of nutritional therapy properly.

The increase in total costs in the INTERCOM group was higher than the costs of the program (about €1,500 per patient), which was mainly the result of higher costs for inpatient pulmonary rehabilitation. During the trial five patients were referred to an inpatient pulmonary rehabilitation program, four in the INTERCOM group and one in the usual care group. Because these inpatient rehabilitation programs lasted on average about 70 days, the costs involved with these programs were substantial. The difference in referral to inpatient pulmonary rehabilitation between the INTERCOM group and the usual care group could have been coincidence, but it could also have been an unexpected side effect of the program. The high frequency of visits to care providers in the

INTERCOM group could have resulted in earlier signalling of significant worsening of the disease and a need for more intensive therapy. In retrospect, these patients should probably not have been included in the trial, because a community-based program was not intensive enough given their severe condition. To hold on to the intention-to-treat principle and to improve the generalizability to daily practice, the costs for inpatient pulmonary rehabilitation were included in the analyses. Exclusion of the patients referred to inpatient pulmonary rehabilitation from the analysis would have reduced the cost per QALY for the INTERCOM program from €32,400 to €8,400.

Collection of resource use data

The cost-effectiveness study of the INTERCOM program was performed from a societal perspective including all COPD as well as non-COPD related costs. An advantage of this approach was that the potential effect of the intervention on the costs of treatments for co-morbidities can be taken into account. However, we did not explicitly ask patients to specify whether the reported healthcare use was COPD-related or not, except for hospitalizations. Therefore it was not possible to make a distinction between COPD- and non-COPD related healthcare costs afterwards. During the total two-year study period, data on total healthcare utilization was recorded weekly in cost booklets filled in by the patients themselves. Each booklet covered a period of four weeks and was collected every two months, which made the recall period relatively short in comparison to other studies [40]. Chapter ten showed that using self-reported data resulted in general in an underestimation of healthcare use when compared to caregiver registrations. Although the agreement in number of hospitalization days between the cost booklet and registrations was almost perfect, the underestimation of costs was highest for this type of care due to the high unit costs per inpatient day. This problem was already accounted for in the original economic evaluation presented in chapter nine, where hospitalizations were based on the combined data of the cost booklet and electronic hospital records. Although the use of self-reported data was shown to have an effect on the within-group costs, it did not affect the difference in costs between the INTERCOM group and the cost utility (chapter nine).

Generalizability of the results

The INTERCOM trial included patients with impaired exercise performance recruited by chest physicians in general hospitals. Therefore the results and outcomes of the INTERCOM trial can not be generalized directly to all patients with less severe airflow obstruction. This was also not the intention as the main aim of the study was to see whether patients with an impaired exercise performance regardless of their degree of

airflow obstruction could benefit from pulmonary rehabilitation. By including patients with impaired exercise capacity the patient population in the trial probably had a more impaired health status compared to the total COPD patient population. The patients with an impaired exercise capacity included in the trial showed for example a decreased hand grip force, quadriceps force and maximal inspiratory and expiratory pressure, expressed as percentage of predicted normal [41]. The clinical analyses of the trial furthermore showed that the patients randomized to usual care had an impressive decline in exercise capacity, especially the muscle-wasted patient indicating the severity of the condition of the patient population included in the trial [39]. Another indication that the patients included in the trial had a more impaired health status than the average COPD patient was provided by comparing the mean annual number of inpatient hospital days for COPD for patients in the usual care group of the INTERCOM trial and the total COPD population. The mean number of hospital days for COPD was around two in the usual care group compared with 0.9 for the average COPD patient based on national registrations [42].

Recommendations for further research with respect to integrated COPD care

With respect to pulmonary rehabilitation additional studies should be done investigating the effect of these types of programs in patients with less advanced airflow obstruction and impaired exercise capacity. The latter criterion was in the current study based on the results of a cycle ergometer test. Because it is not feasible to perform this test in a community-based setting other methods to easily measure exercise capacity should be explored. Whether a program such as the INTERCOM is also effective in patients with an impaired exercise capacity based on other parameters need to be investigated. Furthermore, additional research should be done investigating the effectiveness and cost-effectiveness of the major components of pulmonary rehabilitation programs, such as nutritional supplements in combination with exercise versus exercise alone. Up to now, most studies evaluated the effectiveness of a total program including multiple components (exercise, education and self-management) compared with patients receiving care as usual. The INTERCOM program was provided by community-based healthcare providers (local physiotherapists and dieticians) and hospital-based respiratory nurses and supervised by a hospital-based physiotherapist. Whether is would be feasible to transfer a program such as the INTERCOM program completely to a community-based setting needs to be investigated.

Trial-based versus modelling-based cost-effectiveness studies

The two methods used to obtain cost-effectiveness information, trial-based and model-based studies are complementary. Modelling studies can not be done without trials and observational studies providing model input data, while trials usually do not have a sufficient follow-up time to find estimates of long-term effects. Modelling is then needed to assess these effects. Therefore trial-based and model-based studies are a valuable supplement to each other. Different aspects of both methods will be discussed in this paragraph. Trial-based cost-effectiveness studies have the advantage that effects and costs are obtained from the same patient population. This means that effects and costs are directly related, where in model-based studies data from various sources are combined. One of the consequences of the latter is that variables in probabilistic sensitivity analysis are often treated as independent, because data on the correlation between variables are lacking, while in bootstrapping patient-level data the association between effects and costs of a patient is taken into account. Another advantage of trials is that they have a high internal validity. However, the external validity may be limited, because patients included in trials are often not representative for the whole patient population as a lot of trials use multiple inclusion and exclusion criteria [43]. One of the most often used inclusion criterion in COPD trials is that patients need to be in a stable state of the disease at study entry, while presence of an acute life-threatening condition is the most important reason to exclude patients. Because a lot of COPD patients suffer from (severe) co-morbidities [44], part of the probably more severe COPD population is excluded from trials. The generalizability of model-based studies is dependent on the external validity of the input data. Using systematic reviews and meta-analysis to estimate input data using data from trials as well as observational studies improves the validity and external validity of the results [6].

The main advantage of modelling is that results can be extrapolated beyond the study duration. With regard to this aspect modelling is only useful if the beneficial effects of the intervention are expected to continue after the trial duration. A perfect example of such an intervention is a stop-smoking therapy as presented in chapter four and chapter seven for which the maximum annual number of QALYs gained due to the intervention is reached ten to fifteen years after its implementation (chapter four). For these studies the short-term effectiveness in terms of percentage of additional quitters was obtained from clinical trials, while the long-term effects on disease progression and mortality needed to be based on modelling. However, extrapolation of effects beyond the study duration may require making assumptions about the continuation of the effect. In the pharmacological scenario presented in chapter seven the effect of treatment with a combination of ICS/LABA was obtained from a three-year clinical trial, while effects were assumed to remain constant in the years four to ten thereafter. These kinds of assump-

tions should be accompanied with proper sensitivity analyses. If interventions only have an effect on quality of life, which is not expected to continue after the trial, modelling does not have an additional value with regard to the extrapolation effect. This was for example shown by the scenario on pulmonary rehabilitation in chapter seven, which was assumed to have an effect on quality of life only. This positive effect on quality of life was applied the first three years and not to the years thereafter. Because all costs and health benefits related to the intervention occurred in the first three years, the cost-effectiveness of three-year implementation of this intervention was the same using a five, ten and twenty year time horizon. Modelling can also be relevant to translate intermediate endpoints into final endpoints relevant for policy makes, such as mortality or QALYs. This was shown in the scenario analysis in chapter three, four, and seven in which a difference in smoking abstinence after one year or a difference in lung function decline, exacerbation frequency and all-cause mortality was translated into a difference in QALYs.

Role of the study outcomes in policy making

Cost-effectiveness information can play a role in several phases of the development and use of medical technology [45], such as the decision about reimbursement. Currently costs of all interventions investigated in this thesis are already covered by the nationwide obligatory basic healthcare insurance in the Netherlands. For the INTERCOM program applies that all separate components of the program, physiotherapy, dietary counseling, counseling by a respiratory nurse and diet nutrition are currently reimbursed for COPD patients. In the recent past a new financing system of COPD care was proposed next to the currently available reimbursement system. Since July 2010, an integrated payment system or bundled payment approach for "chained and integrated COPD care" has been introduced [46,47]. This new reimbursement system primarily aims to improve the quality of care for patients with chronic diseases by increasing the cooperation between healthcare providers in the primary care setting (such as GP's, practice nurses, physiotherapists and dieticians) and by better targeting the patient's needs [47]. In the new situation health insurers contract groups of care providers called "care-groups" by paying them prospectively a fixed price per patient. This fee covers the full range of COPD care services for a fixed period, mostly one year. The care groups either provide all necessary care themselves or contract other individual care providers if a certain type of care can not provided by the care group. Insurers only contract care groups that provide care according to the "COPD care standard". Up-to-now only costs of services are included in the new system; drugs, diagnostics and medical devices are not (yet) included. Cost-effectiveness information of COPD interventions as presented in

this thesis can contribute to the development of the "COPD care standard" and therefore indirectly influence the type of COPD care provided by the care groups and the type of COPD care potentially reimbursed by the healthcare insurers.

In addition to informing reimbursement decisions cost-effectiveness information can also play a role in the planning phase of a new technology or intervention or for its use in daily practice [45] The information presented in this thesis can contribute to evidence-based policy making and guideline development for COPD, such as the Zorgstandaard COPD, CBO guideline for diagnosis and treatment of COPD, "NHG-standaard COPD" or the international GOLD guidelines [22,37,48,49]. The first part of the thesis described the COPD model that can be used to estimate the cost-effectiveness of a wide range of interventions from prevention to care for very severe COPD patients and allows comparing interventions of different intensity and target group. A major advantage of using a model is that the results for the different interventions are comparable because there are no methodological differences [50]. The model can also be used to calculate the cost-effectiveness of a combination of interventions, i.e. integrated approaches, since single interventions or treatments will probably not reduce the burden of COPD sufficiently (chapter seven). Results from the second part of this thesis, the results from the INTERCOM trial, increased the information on cost-effectiveness of non-pharmacological interventions for patients with less severe COPD and informed policy makers developing treatment guidelines for pulmonary rehabilitation. Up to the publication of the INTERCOM trial there was hardly any information about the effectiveness of pulmonary rehabilitation programs in patients with less severe airflow obstruction and data on cost-effectiveness of these programs in this patient group were completely lacking. The significant (faster) deterioration in quality of life, dyspnoea, exercise capacity and muscle function observed in the usual care group and the positive effects of the INTERCOM program stress the need not to wait with pulmonary rehabilitation till patients have severe airflow obstruction, but to start at earlier stages of the disease [38].

Several chapters in this thesis provided new and additional data on cost-effectiveness of treatment options for COPD. The costs per QALY ratios for the different COPD interventions reported ranged between €2,400 for smoking cessation and €32,400 for pulmonary rehabilitation, both compared with usual care. Whether all these interventions could be considered cost-effective depends on the threshold value used. In the past, interventions with a cost per QALY below the often quoted threshold value of €20,000 were considered very cost-effective in the Netherlands. More recently, an advisory board of the Dutch government (RVZ) proposed a variable willingness to pay for a QALY depending on the burden of the disease under study [51]. They proposed a maximum acceptable ratio ranging from €8,000 for diseases with a disease burden of 0.1 to €80,000 for diseases with the maximum burden of 1.0. According to the same report the burden of disease for COPD is 0.61, which would correspond with a maximum willingness-to-pay

for a QALY of about €48,000. The burden of disease based on the utility values included in the model would however be lower, resulting in a maximum acceptable cost per QALY ranging from €8,000 for mild COPD to €35,000 for very severe COPD. Based on all these possible maximum willingness-to-pay values for COPD care increased implementation of smoking cessation interventions for smoking COPD patients can be regarded as cost-effective. The probability that the cost per QALY of intensive counseling plus pharmacotherapy for smoking cessation falls below a maximum willingness-to-pay of €20,000 was 97%, respectively. The findings for smoking cessation support the advice given in guidelines that COPD patients should be offered the most intensive smoking cessation intervention feasible not only from a clinical but also from an economic perspective. Treatment with ICS/LABA for all patients with moderate and severe COPD can also be considered cost-effective based on the calculation performed for this thesis. The probability of ICS/LABA to be cost-effective using a maximum willingness- to-pay of €20,000, the maximum willingness-to-pay for a moderate COPD patient, was 100%. However, it should be noted that effectiveness of this intervention was based on one trial assuming an effect on lung function decline, exacerbation frequency and mortality. The mean burden of disease for the patients included in the INTERCOM trial was 0.21, which would correspond with a threshold value of about €16,000 per QALY. Therefore the INTERCOM program could not be labelled as very cost-effective, but the ratio was below the mentioned threshold values of €35,000 and €48,000 per QALY gained.

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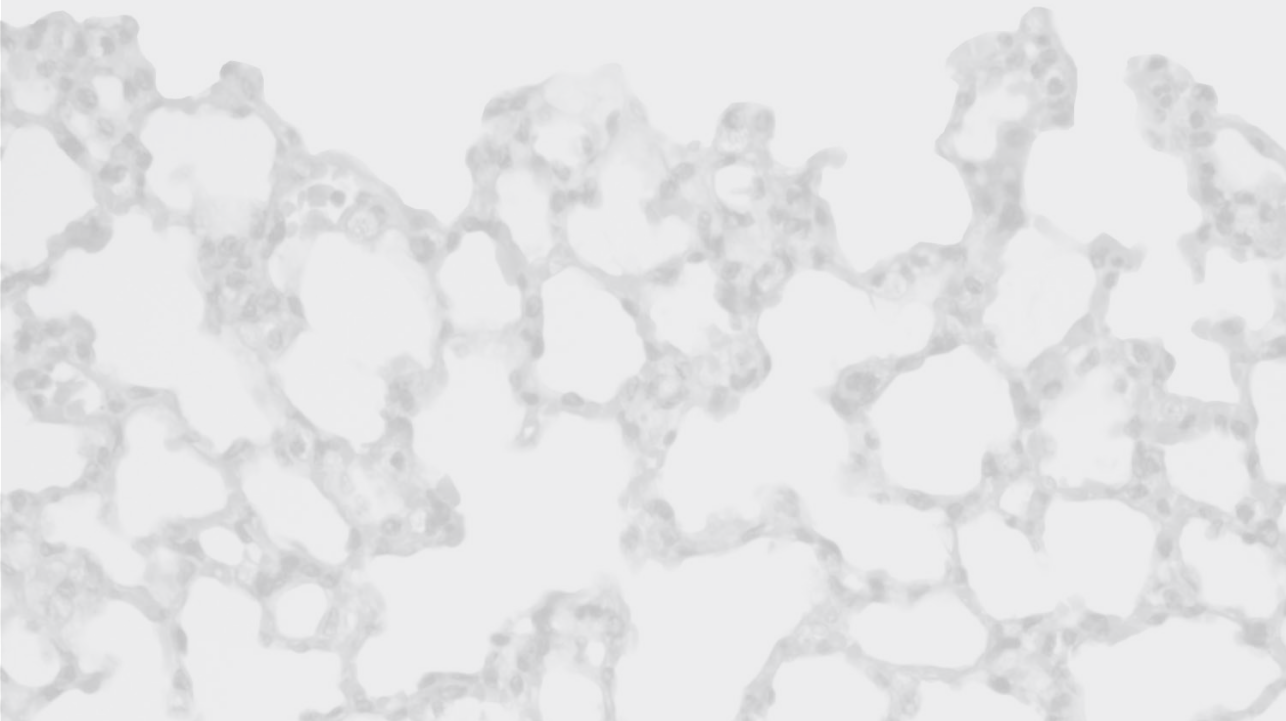
Summary/Samenvatting



Summary

Introduction: Chronic obstructive pulmonary disease (COPD) is a disease characterized by progressive airflow limitation that is not fully reversible and its progression is often accompanied by periods of increasing symptoms (cough, sputum production and dyspnoea) named exacerbations. The main risk factor for COPD is long-term smoking. Treatment of COPD mainly consists of support for smoking cessation, pharmacotherapy such as short- and long-acting bronchodilators and inhaled corticosteroids, and non-pharmacological treatment, such as pulmonary rehabilitation and self-management programs. The burden of COPD in terms of prevalence, disability and healthcare costs is high and is projected to increase in the nearby future. Therefore the need for information on efficient treatment options in terms of both effects and costs is high. The aim of this thesis was to develop tools that enable the assessment of the cost-effectiveness of treatment options for COPD and to provide such information. This information was obtained in two ways:

- by developing a population-based COPD model, which can be used to estimate the cost-effectiveness of a wide range of COPD interventions.
- by performing an empirical economic evaluation linked to a clinical trial that evaluated the effectiveness of a COPD management program

Part one: studies related to the development of a COPD progression model

In **chapter two** the severity distribution of COPD in the Dutch COPD population in terms of the degree of airflow obstruction was estimated. This distribution was used as starting distribution of the COPD prevalence in the COPD model. For this study all patients with a physician-diagnosis of COPD from two different sources of general practitioners data were selected. Patients were classified into four COPD severity stages based on their FEV_1% predicted using the GOLD classification. The distribution among Dutch COPD patients was estimated to be 27% mild, 55% moderate, 15% severe and 3% very severe airflow obstruction.

Chapter three described the structure and input parameters of the first version of the COPD model developed in 2002/2003. The COPD model is a dynamic population model that projects the Dutch incidence, prevalence, mortality, disease progression and healthcare costs of COPD over time, taking into account population dynamics such as prognosis of birth and mortality and changes in smoking prevalence. The model is a Markov model with six main states, no COPD, four COPD severity stages based on lung function, and death. All states are specified by sex, age and smoking status. Transition between

COPD severity stages was based on the annual decline in lung function depending on sex, age, smoking and lung function at start. Furthermore, each COPD severity stage was associated with a probability to die, a utility value and COPD-related healthcare costs. The model was used to make projections of current practice for the period 2000-2025 to estimate the future burden of COPD. These projections showed that the prevalence of COPD was estimated to increase from 24 to 33 per 1000 for males and from 15 to 27 per 1000 for females. The associated healthcare costs were expected to increase from €280 to €495 million. The model was also used to estimate the cost-effectiveness of two smoking cessation interventions for COPD patients, minimal counseling by the GP and intensive counseling plus bupropion.

An application of the first version of the model is shown in **chapter four**. This chapter presented the cost-effectiveness of smoking cessation interventions for COPD patients. First, a systematic review was performed of randomized controlled trials evaluating smoking cessation interventions in COPD patients. A meta-analysis was done to calculate the 12-month continuous abstinence rates for four categories of interventions: usual care, minimal counseling (<90 minutes), intensive counseling (≥90 minutes) and intensive counseling plus pharmacotherapy (NRT, bupropion or nortriptyline). The estimated abstinence rates were used in the COPD model to estimate the cost-effectiveness of one-year implementation of the three interventions for 50% of the smoking COPD patients compared with usual care, using a time horizon of 25 years. Compared with usual care, the cost per QALY gained were €16,900 for minimal counseling, €8,200 for intensive counseling and €2,400 or intensive counseling plus pharmacotherapy. The latter two categories of interventions resulted in low cost per QALY gained comparable to results for smoking cessation support in the general population. Compared with intensive counseling, intensive counseling plus pharmacotherapy was cost saving and should therefore be the option of first choice.

The first version of the model did not include COPD exacerbations. To improve this model several exacerbation-related parameters needed to be estimated. One, of these parameters, the exacerbation frequency specified by GOLD severity stage, was described in **chapter five**. A systematic review was performed to identify randomized controlled trials and cohort studies reporting the exacerbation frequency in COPD patients receiving usual care or placebo. The association between the mean FEV_1% predicted of study populations and the exacerbation frequencies was estimated using weighted log linear regression with random effects. The association was estimated separately for the total number of exacerbations defined as an increased use of healthcare (event-based definition) and severe exacerbations defined by a hospitalization. The estimated regression equations were used to estimate the exacerbation frequencies by GOLD stage using

the mean FEV_1% predicted for each stage. Based on the 37 relevant studies found, the annual event-based frequencies per GOLD stage were estimated to be 0.82 (95% uncertainty interval (UI): 0.46; 1.49) for mild COPD, 1.17 (0.93; 1.50) for moderate COPD, 1.61 (1.51; 1.74) for severe COPD and 2.10 (1.51; 2.94) for very severe COPD. For severe exacerbations, the annual frequencies were estimated to be 0.11 (0.02; 0.56), 0.16 (0.07; 0.33), 0.22 (0.20; 0.23) and 0.28 (0.14; 0.63), respectively.

Another exacerbation-related parameter, the case-fatality of a severe exacerbation, was addressed in **chapter six**. A literature search was performed for studies reporting mortality or survival during and after a hospitalization for an exacerbation of COPD. Studies needed to have a follow-up of at least 1.5 years and they needed to present a survival curve or mortality rates on at least three time-points after hospital admission. For each study the reported or estimated survival curve was divided into a critical and a stable period. Mortality during the stable period was then estimated by extrapolating the survival curve during the stable period back to the time of exacerbation onset. The case-fatality of the exacerbation was defined as the excess mortality related to the exacerbation and was calculated as 1 minus the backwardly extrapolated survival during the stable period at the time of exacerbation onset. For the six selected studies the case-fatality was found to range between 11.4% and 19.0%. The weighted average case -fatality rate was estimated to be 15.6% (95 CI: 10.9; 20.3).

In **chapter seven** the second updated and extended version of the COPD model (2008-2010) was presented. Compared with the first version all input parameters on demography, prevalence, incidence, and mortality of COPD, smoking prevalence and costs were updated to the year 2007. Furthermore, exacerbations were built into the model by including an annual probability to experience a moderate or severe exacerbation for each COPD severity stage. Exacerbations were modeled to affect lung function decline, mortality, quality of life and costs. The average decline in lung function per exacerbation was estimated to be 0.19% predicted (95% CI: 0.092; 0.29). The annual utility loss due a moderate and a severe exacerbation were estimated to be 1.66% (95% CI: 1.23; 2.09) and 4.82% (3.11; 6.53) from the baseline utility value, respectively. The costs were estimated to be €94 (95% CI: 80; 108) for a moderate and €4100 (2348; 5852) for a severe exacerbation. In contrast to the first version of the model, the second version of the model included probabilistic sensitivity analysis because the important model parameters were entered into the model as probability distributions. The potential use of the model was shown by calculating the ten-year cost-effectiveness for four scenarios of three year implementation of three different COPD interventions. Compared with minimal treatment the cost per QALY was €8,300 for the pharmacological intervention, €10,800 for the smoking cessation therapy, €8,700 for the combination of the pharmaco-

logical intervention and the smoking cessation therapy and €17,200 for the pulmonary rehabilitation program. The probability of the interventions to be cost-effective at a ceiling ratio of €20,000 varied from 58% for the pulmonary rehabilitation program to 100% for the pharmacological intervention.

Part two: studies related to the economic evaluation of an interdisciplinary community-based COPD management program

The second part of this thesis started with an economic evaluation performed alongside the INTERCOM trial, a trial evaluating the effectiveness of an interdisciplinary community-based COPD management program for patients with less severe airflow obstruction than usually included in pulmonary rehabilitation programs (**chapter eight**). In this two-year trial 199 patients with less advanced airflow obstruction and impaired exercise performance were randomized to the INTERCOM program or usual care. The INTERCOM program consisted of exercise training and an educational intervention for all patients and smoking cessation counseling, nutritional therapy and nutritional supplements upon indication. These interventions were offered by local physiotherapists and dieticians and hospital-based respiratory nurses. The total two-year costs, COPD- plus non-COPD related costs, were related to three health outcomes: the St. George's Respiratory Questionnaire (SGRQ), the total number of exacerbations and the number of QALYs. Mean total 2-year costs per patient were €13,565 in the INTERCOM group and €10,814 in the usual care group, resulting in a difference of €2751 (95% CI: -631; 6372). The cost-effectiveness ratios were estimated to be €9,078 per additional patient with a relevant improvement in SGRQ total score and €32,425 per QALY. The costs per exacerbation avoided were negative, because the INTERCOM group had a higher number of exacerbations. Exclusion of five patients that were referred to in-patient pulmonary rehabilitation during the trial (4 in the INTERCOM group, 1 in the usual care group), would have reduced the incremental cost-effectiveness ratio to €8412 per QALY gained.

Chapter nine reported a validation study of the cost booklet that was used in the INTERCOM trial to collect resource use data. Data on the number of hospital admissions, outpatient visits, visits to the physiotherapists, dietician and respiratory nurse and nutritional supplements used were obtained from administrative records or caregiver registrations and compared with the numbers reported by the patients in the cost booklet. What was new in this study is that we calculated the impact of using costs based on the cost booklet or based on care-giver registrations on the cost-utility. Total costs based on the cost booklet were €464 lower compared with the costs based on the care-giver registrations (two treatments combined). The cost difference between the INTERCOM and the usual care group based on the cost booklet was €2,444 (95% CI: -819; 5950),

resulting in a cost-utility of €29,100 per QALY. For the care-giver registrations the results were comparable, a cost difference of €2498 (95% CI: -88; 6084) and a cost per QALY of €29,390. In this study the use of self-reported data did have an effect on within-group costs, but not on the between-group costs or the cost-utility.

Discussion: With respect to part one, the development and application of the dynamic COPD population model, this chapter summarized the findings and comparisons were made between model outcomes for the cost-effectiveness of smoking cessation interventions based on the first and second version of the model. It further discussed three different aspect of the model: the input parameters, the definition of severity of COPD and the validation of the model. The COPD model was extensively validated and was found to have a good internal validity and acceptable between-model validity. The predictive validity of the first model in terms of the prediction of future prevalence was good for female patients, but it overestimated the prevalence for male patients somewhat. The discussion about the second part of this thesis, the empirical study on multidisciplinary, integrated COPD care, also started with a summary of the main findings and addressed the aspects of the cost-effectiveness of the total program in comparison with its different components. It also discussed the impact of the inclusion of five patients referred to inpatient pulmonary rehabilitation during the trial. Other aspects discussed were the collection of the resource use data by means of cost booklets and care-giver registrations and the generalizability of the results. The comparison between part one, the model-based and part two, the trial-based studies in the discussion showed that both approaches have their own advantages, but moreover that both methods are complementary. Finally, the role of the studies for policy making was discussed. The studies in this thesis showed that the COPD model can be regarded as an up-to-date COPD progression model that is useful to provide policy makers with information on the long-term costs and effects of a wide range of COPD interventions including the uncertainty. The results of the COPD interventions evaluated showed that smoking cessation interventions and especially intensive counseling with pharmacotherapy can be regarded as cost-effective for COPD patients. Based on the cost per QALY the INTERCOM program can be considered moderately cost-effective. These data could be used to support evidence-based guideline development for COPD.

Samenvatting

Introductie: Chronisch obstructief longlijden (COPD) is een ziekte die gekenmerkt wordt door luchtwegobstructie die progressief en niet volledig omkeerbaar is. De belangrijkste symptomen van COPD zijn hoesten, productie van slijm en kortademigheid. Patiënten met COPD hebben regelmatig last van periodes waarin de symptomen toenemen. Deze plotselinge verergeringen van de klachten worden exacerbaties genoemd. De belangrijkste risicofactor voor COPD is langdurig roken. De behandeling van COPD bestaat voornamelijk uit medicamenteuze behandeling, zoals het gebruik van kort- en langwerkende luchtwegverwijders en inhalatiecorticosteroïden en niet-medicamenteuze behandeling, zoals het ondersteunen van het stoppen met roken en het volgen van longrevalidatie en zelfmanagement programma's. De prevalentie, het gezondheidsverlies en de zorgkosten voor COPD zijn hoog en het is de verwachting dat dit in komende jaren toeneemt. Daarom is het voor beleidsmakers relevant om informatie te hebben over de kosten en effecten van interventies bij COPD om zo de meest efficiënte behandelmogelijkheden te vinden. Het doel van dit proefschrift was om instrumenten te ontwikkelen om de kosteneffectiviteit van behandelingen bij COPD te kunnen bepalen en deze instrumenten in te zetten om informatie over de kosteneffectiviteit te verschaffen. Op twee manieren is geprobeerd dit doel te bereiken:

Door het ontwikkelen van een populatiemodel voor COPD, dat gebruikt kan worden om de kosteneffectiviteit van een breed scala aan behandelingen voor COPD door te rekenen

Door het uitvoeren van een economische evaluatie parallel aan een gerandomiseerde klinische studie die de effectiviteit van een multidisciplinair management programma voor COPD onderzocht.

Deel 1: Studies gerelateerd aan het COPD-model:

In **hoofdstuk twee** is op basis van de mate van luchtwegobstructie een ernstindeling gemaakt van de COPD-populatie in Nederland. Deze verdeling is gebruikt om de COPD-prevalentie in het COPD-model bij start van de simulatie te verdelen naar ernst. Voor dit onderzoek zijn alle patiënten met een diagnose COPD uit twee verschillende bronnen met huisartsgegevens geselecteerd. De geselecteerde patiënten werden op basis van hun longfunctie, de FEV_1 als percentage van voorspeld, ingedeeld in vier COPD-ernststadia: milde, matige, ernstige of zeer ernstige COPD (GOLD-classificatie). Op deze manier werd de ernstverdeling voor de COPD patiënten in Nederland geschat op: 27% milde, 55% matige, 15% ernstige en 3% zeer ernstige luchtwegobstructie.

Hoofdstuk drie beschrijft de structuur en invoerwaarden van de eerste versie van het COPD-model dat ontwikkeld is in 2002/2003. Het COPD-model is een dynamisch populatiemodel wat de incidentie, prevalentie, sterfte, het ziektebeloop en de zorgkosten voor COPD simuleert over de tijd. Het model houdt hierbij rekening met de dynamiek in de algemene bevolking als gevolg van geboorte, sterfte en veranderingen in rookgedrag. Het model is een Markovmodel met zes verschillende gezondheidstoestanden: geen COPD, vier COPD ernstklassen en dood, die allemaal gespecificeerd zijn naar geslacht, leeftijd en rookstatus. De overgang tussen de verschillende COPD-ernstklassen is gebaseerd op de jaarlijkse afname in longfunctie, welke afhankelijk is van geslacht, leeftijd, rookstatus en de longfunctie bij aanvang. Elke COPD-toestand is geassocieerd met een kans op overlijden, een utiliteitswaarde en COPD-gerelateerde zorgkosten. Het model is gebruikt om projecties te maken van de toekomstige prevalentie en zorgkosten voor COPD voor de periode 2000 tot 2025. Deze projecties lieten een stijging zien van de prevalentie van 24 naar 33 per 1000 voor mannen en van 15 naar 27 per 1000 voor vrouwen. De zorgkosten voor COPD werden geschat te stijgen van €280 naar €495 miljoen. Het model is daarnaast gebruikt om de kosteneffectiviteit van twee stoproken interventies voor COPD patiënten te berekenen, de minimale interventiestrategie stoppen met roken voor de huisartspraktijk en intensieve ondersteuning in combinatie met bupropion.

Een toepassing van de eerste versie van het model is gegeven in **hoofdstuk vier** van dit proefschrift. In dit hoofdstuk wordt de kosteneffectiviteit van verschillende typen stoproken interventies voor COPD-patiënten gepresenteerd. Voor dit onderzoek werd eerst een systematisch literatuurstudie gedaan naar gerandomiseerde, klinische studies die de effectiviteit van stop-roken interventies bij COPD-patiënten onderzochten. De data uit de gevonden studies werden gecombineerd in een meta-analyse om de continue abstinentie op 12 maanden voor vier verschillende typen interventies te berekenen: standaard zorg (geen specifieke stop-roken interventie), minimale ondersteuning (< 90 minuten), intensieve ondersteuning (≥ 90 minuten) en intensieve ondersteuning in combinatie met stop-roken medicatie (nicotinevervangers, bupropion of nortriptyline). De geschatte stopkansen werden gebruikt in het COPD-model om de kosteneffectiviteit van één jaar implementatie van de drie typen interventies voor 50% van de rokende COPD patiënten door te rekenen in vergelijking met standaardzorg over een tijdshorizon van 25 jaar. In vergelijking met standaardzorg waren de kosten per gewonnen QALY €16900 voor minimale ondersteuning, €8200 voor intensieve ondersteuning en €2400 voor intensieve ondersteuning in combinatie met medicatie. De kosteneffectiviteitsratio van intensieve ondersteuning met en zonder medicatie was vergelijkbaar met de ratio die gevonden is voor een vergelijkbare interventie voor rokers in de algemene bevolking. Intensieve ondersteuning in combinatie met stop-roken medicatie was kos-

tenbesparend in vergelijking met intensieve ondersteuning zonder medicatie en zou daarom de eerste keus bij stop-roken ondersteuning van COPD patiënten moeten zijn.

In de eerste versie van het model werd geen rekening gehouden met de impact van COPD-exacerbaties. Om de invloed van exacerbaties op het ziekteverloop mee te nemen te kunnen nemen in het model moesten verschillende exacerbatie-gerelateerde parameters geschat worden. Eén van deze parameters was de exacerbatiefrequentie uitgesplitst naar COPD-ernstklasse (**hoofdstuk vijf**). Om deze frequentie te bepalen werd een systematische review gedaan naar gerandomiseerde klinische studies en cohortstudies die de exacerbatiefrequentie bij COPD-patiënten rapporteerden. Vervolgens werd het verband tussen de gemiddelde FEV_1 als percentage van voorspeld van de studiepopulaties en de exacerbatiefrequentie geschat m.b.v. gewogen, random-effect loglineaire regressie. Het verband tussen de longfunctie en de exacerbatiefrequentie werd apart geschat voor het totaal aantal exacerbaties en het aantal ernstige exacerbaties. Een exacerbatie werd hierbij gedefinieerd als een toename in symptomen en klachten leidend tot een toename van het zorggebruik. Een ernstige exacerbatie werd gedefinieerd als een exacerbatie-gerelateerde ziekenhuisopname. De geschatte regressievergelijkingen werden gebruikt om de exacerbatiefrequentie per GOLD-ernstklasse te bepalen door de gemiddelde FEV_1 als percentage van voorspeld per ernstklasse in te vullen in de geschatte vergelijking. In totaal werden 37 relevante studies gevonden. De totale exacerbatiefrequentie per jaar werd geschat op 0.82 (95% onzekerheidsinterval (UI):0.46-1.49) voor mild COPD, 1.17 (0.93-1.50) voor matig COPD, 1.61 (1.51-1.74) voor ernstig COPD en 2.10 (1.51-2.94) voor zeer ernstig COPD. Voor ernstige exacerbaties werd de frequentie per jaar per ernstklasse geschat op respectievelijk 0.11 (0.02-0.56), 0.16 (0.07-0.33), 0.22 (0.20-0.23) and 0.28 (0.14-0.63).

Om het risico op sterfte ten gevolge van een ernstige exacerbatie te schatten (**hoofdstuk zes**) werd een literatuuronderzoek gedaan naar studies die sterfte of overleving rapporteerden na een ziekenhuisopname voor een COPD-exacerbatie. De studies moesten een duur van tenminste 1,5 jaar hebben. Daarnaast moesten de studies de overleving op tenminste drie momenten in de tijd rapporteren of een overlevingscurve presenteren. Voor elke studie werd de overlevingscurve opgesplitst in twee stukken, de curve tijdens de kritieke fase en de curve tijdens de stabiele fase. De sterftekans tijdens de stabiele fase werd vervolgens geschat door de overlevingscurve tijdens de stabiele fase terug te extrapoleren naar het begin van de exacerbatie. De extra sterfte, gedefinieerd als 1 min de teruggeëxtrapoleerde sterfte tijdens de stabiele fase, werd toegeschreven aan de exacerbatie. De literatuurstudie leverde zes relevante studies op. De gewogen gemiddelde sterftekans ten gevolg van een ernstige exacerbatie werd

geschat op 15.6% (95% betrouwbaarheidsinterval (BI): 10.9-20.3). Binnen deze studies varieerde de kans op sterfte tussen de 11.4% en 19%.

In **hoofdstuk zeven** is de tweede, vernieuwde en uitgebreide versie van het COPD-model (2008-2010) beschreven. In vergelijking met de eerste versie is het model op een aantal punten veranderd. Allereerst zijn de invoerwaarden voor demografie, COPD-prevalentie, incidentie en sterfte, de prevalentie van roken en de kosten geactualiseerd naar het jaar 2007. Verder is de invloed van exacerbaties in het model ingebracht. Voor elke COPD-ernstklasse is een jaarlijkse kans gespecificeerd op het krijgen van een niet-ernstige en ernstige exacerbatie. Exacerbaties hebben in het model invloed op de daling in longfunctie, sterfte, kwaliteit van leven en de kosten. De gemiddelde afname in longfunctie ten gevolg van een exacerbatie is geschat op 0.19% van voorspeld (95% BI: 0.092-0.29). Het effect van exacerbaties op de kwaliteit van leven is geschat als procentuele daling in de utiliteitswaarde op jaarbasis ten opzichte van de utiliteit bij start. Deze is geschat op 1.66% (95% BI: 1.23-2.09) voor een niet-ernstige exacerbatie en 4.82% (95% BI: 3.11-6.53) voor een ernstige exacerbatie. De kosten van een exacerbatie werden geschat op €94 (95% BI: 80-108) voor een niet-ernstige en €4100 (95% BI: 2348-5852) voor een ernstige exacerbatie. Ten derde is het met de vernieuwde versie van het model mogelijk om probabilistische sensitiviteitsanalyses te doen, omdat rekening gehouden is met de onzekerheid rond de belangrijkste invoerwaarden. De mogelijkheden van het model zijn geïllustreerd door in een aantal scenario's de kosteneffectiviteit van drie verschillende behandelingen ten opzichte van minimale behandeling door te rekenen. Hierbij werd verondersteld dat de interventies drie jaar werden geïmplementeerd en werden de kosten en effecten geëvalueerd over een periode van tien jaar. De kosteneffectiviteit was €8300 per gewonnen QALY voor de medicamenteuze interventie, €10800 voor de stoproken interventie, €8,700 voor de combinatie van deze twee interventies en €17200 voor het longrevalidatieprogramma.

De kans dat de kosteneffectiviteitsratio van de verschillende interventies onder de €20000 per gewonnen QALY was, varieerde van 58% voor het longrevalidatieprogramma tot 100% voor de medicamenteuze interventie.

Deel 2: Studies gerelateerd aan de economische evaluatie van een transmuraal, interdisciplinair COPD managementprogramma

Het tweede deel van dit proefschrift begint met de economische evaluatie die uitgevoerd is parallel aan de INTERCOM trial (**hoofdstuk acht**). Deze trial onderzocht de effectiviteit van een transmuraal, interdisciplinair COPD-managementprogramma bij patiënten met een minder ernstige mate van luchtwegobstructie dan de patiënten

die normaal gesproken deelnemen aan longrevalidatieprogramma's. In de twee jaar durende studie zijn 199 patiënten met een matig ernstige luchtwegobstructie en inspanningsbeperking random toegewezen aan de groep die het INTERCOM programma kreeg of de controlegroep. Het INTERCOM programma bestond uit een trainings- en educatieprogramma. Daarnaast participeerden patiënten op indicatie in een stoprokenprogramma en/of kregen zij voedingsadvies en supplementen. De verschillende onderdelen van het programma werden uitgevoerd door fysiotherapeuten en diëtisten in de directe woonomgeving van de patiënt en door longverpleegkundigen in het ziekenhuis. Het programma omvatte vier maanden revalidatie gevolgd door een actieve onderhoudsfase van 20 maanden. De gemiddelde totale COPD en niet-COPD gerelateerde kosten per patiënt over 24 maanden waren €13565 voor de INTERCOM groep en €10814 voor de controlegroep. Het kostenverschil tussen beide groepen was €2751 (95% BI: -631;6372). De kosteneffectiviteitsratio's werden geschat op €9078 per extra patiënt met een klinische relevante verbetering in de SGRQ totaal score en €32400 per gewonnen QALY. Een deel van de kostenstijging in de INTERCOM groep werd veroorzaakt door vier patiënten die tijdens de studie verwezen werden naar een longrevalidatiecentrum ten opzichte van één patiënt in de controlegroep. Wanneer deze patiënten uit de analyses werden gelaten, daalden de kosten per QALY naar €8412.

Hoofdstuk negen beschrijft de validatie van het kostenweekboek wat gebruikt is in de INTERCOM studie om het zorggebruik van de patiënten in kaart te brengen. Voor deze studie zijn extra gegevens verzameld uit ziekenhuisregistraties en registraties van de verschillende zorgverleners. Vervolgens is voor ziekenhuisopnames, bezoeken aan de specialist, de fysiotherapeut, de diëtist en de longverpleegkundige en voor voedingssupplementen een vergelijking gemaakt tussen het aantal verkregen uit de registraties en de gegevens zoals ingevuld door de patiënten in het kostenweekboek.

Verder is gekeken naar de invloed van de kostenbron, registraties versus kostenweekboek, op de kosteneffectiviteit. De totale kosten per patiënt gebaseerd op gegevens uit het kostenweekboek waren €464 lager dan de kosten gebaseerd op gegevens uit de registraties (beide behandelingen gecombineerd). Het verschil in kosten tussen de INTERCOM en de controlegroep op basis van het kostenweekboek was €2444 (95% BI: -819;5950), wat resulteerde in een kosteneffectiviteitsratio van €29100. De resultaten op basis van de registraties waren vergelijkbaar. Het kostenverschil op basis van de registraties was €2498 (95% BI: -88;6084) en de kosteneffectiviteitsratio was €29390. Het gebruik van gegevens op basis van zelfrapportage had in deze studie dus wel een invloed op de kosten binnen een behandelgroep, maar niet op het verschil in kosten tussen de beide behandelgroepen of de kosteneffectiviteit.

Discussie: In dit hoofdstuk zijn allereerst de resultaten van deel één van dit proefschrift, de studies over de ontwikkeling en toepassing van het dynamische populatiemodel voor COPD, samengevat en besproken. Verder zijn de modeluitkomsten voor de kosteneffectiviteit van stop-roken interventies van de eerste en tweede versie van het model vergeleken. Daarnaast zijn drie verschillende aspecten van het model belicht: de invoerwaarden, de definitie voor ernst van de COPD die gebruikt is in het model en de validatie van het model. Vooral het laatste punt wordt uitgebreid besproken. Het model bleek een goede interne validiteit te hebben en een redelijke tussen-modelvaliditeit. De voorspellende validiteit is getest door te kijken naar hoe goed de eerste versie van het model de toekomstige prevalentie van COPD kon simuleren. Deze voorspellende validiteit bleek goed te zijn voor het aantal vrouwelijke patiënten. Voor mannen werd de toekomstige prevalentie wat overschat door het model. De discussie wat betreft het tweede deel van dit proefschrift, de empirische studie naar het transmurale, interdisciplinaire COPD managementprogramma, begint ook met een samenvatting van de belangrijkste resultaten. Daarnaast komen de volgende punten aan bod: de kosteneffectiviteit van het totale programma versus de verschillende individuele componenten, de impact van inclusie van vijf patiënten die tijdens de studie verwezen werden naar een intern longrevalidatieprogramma op de resultaten, de manier waarop het zorggebruik in de studie gemeten is en de generaliseerbaarheid van de uitkomsten. Een vergelijking van deel één, de modelstudies, en deel twee, de empirische studies, laat zien dat beide methoden hun eigen voordelen hebben, maar bovenal complementair aan elkaar zijn.

Tenslotte is de rol van de uitkomsten bij het bepalen van beleid bediscussieerd. De studies in dit proefschrift laten zien dat het ontwikkelde COPD-model beleidsmakers kan voorzien van nuttige informatie over de kosten en effecten van een breed scala aan COPD-behandelingen. De kosteneffectiviteitsberekeningen die voor dit proefschrift gedaan zijn, laten zien dat stop-roken interventies en in het bijzonder intensieve ondersteuning in combinatie met stop-roken medicatie voor COPD-patiënten kosteneffectief zijn. Op basis van de gevonden kosten per gewonnen QALY kan het INTEROM programma als matig kosteneffectief worden beschouwd. De uitkomsten kunnen gebruikt worden voor het wetenschappelijk onderbouwen van de richtlijnontwikkeling voor de behandeling van COPD.

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Groot is Uw trouw, o Heer,
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Al wat ik nodig had, hebt U gegeven.
Groot is Uw trouw, o Heer,
aan mij betoond.

Curriculum vitae

Martine Hoogendoorn-Lips was born in Gouda on March 14, 1979. She graduated from secondary school (Gymnasium) at the Driestar College in Gouda. From 1997 to 2002 she studied Human Nutrition at Wageningen University, where she graduated (cum laude) with specializations in Epidemiology and Public Health. As part of her study she did a four month internship at the University of British Columbia in Vancouver, Canada. Since 2002 she has been working as a researcher at the institute for Medical Technology Assessment (iMTA) of the Erasmus University in Rotterdam. Her first project focused on the development of the COPD progression model described in this thesis. Between 2006 and 2010 she worked on the two other projects included in this thesis, the cost-effectiveness study of the INTERCOM trial and the extension and update of the COPD model. During her time at iMTA she also performed cost of illness studies on asthma, COPD and metabolic syndrome, a study on the measurement of utilities for COPD and cost-effectiveness studies of a new drug for smoking cessation and pharmacological agents for COPD. In 2011 she participated in one of the organizing boards of the fifth European Conference on Tobacco or Health. Currently she continues her research at iBMG/iMTA on modelling and economic evaluations in COPD care. Martine is married with Wim and they have two children, Steven (2007) en Nienke (2009).