Comparing the cost-effectiveness of a wide range of COPD interventions using a stochastic, dynamic, population model for COPD

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Abstract

Modeling a chronic disease like COPD is useful to extrapolate treatment effects observed in short-term randomized trials to the medium or long term. A model is also a tool to synthesize knowledge from various different sources of information in a consistent way. The previous IMTA/RIVM COPD severity stage model relates COPD incidence to age, gender and smoking status and COPD progression to age, gender, FEV_1% predicted at model-start and smoking status. The current project extended this model by adding exacerbations and making it stochastic through the specification of probability distributions around all important model parameters. The structure was adjusted to allow for moderate and severe exacerbations and the following additional input parameters were estimated: frequency of exacerbations by COPD severity, case-fatality due to a severe exacerbation, additional decline in lung function because of an exacerbation, loss of quality of life and increased costs during an exacerbation. These parameters were estimated by quantitative meta-analyses. In addition, long term costs and effects were projected for a variety of COPD interventions to illustrate the potential use of the model in cost-effectiveness analysis.

The number of COPD patients above 45 years of age in 2007, the starting year of the simulation, was 320,000, 46% females and 30% current smokers.

Compared to the reference scenario which represented minimal treatment, the cost-effectiveness of ten years maintenance treatment with a combination of a long-acting bronchodilator (LABA) with an inhaled corticosteroid (ICS) or a LABA alone for all moderate and severe COPD patients was estimated to be €10,100 and €7,100 per QALY gained, respectively. The cost per QALY of a stop-smoking program consisting of intensive counseling plus pharmacotherapy which was provided to all smoking COPD patients during one-year was €6,100 using a time horizon of twenty years. Two year implementation of an interdisciplinary pulmonary rehabilitation program for all patients with moderate and severe COPD resulted in an estimate of €12,200 per QALY gained based on a five year time horizon. The probability of the interventions to be cost-effective at a ceiling ratio of €20,000 was 100% for the combination ICS/LABA, 100% for LABA alone, 98% for the smoking cessation intervention and 76% for the pulmonary rehabilitation program.

The new model can be used to assess the costs and health effects of interventions that aim to reduce disease progression, the frequency and/or severity of exacerbations or mortality or that aim to improve quality of life or combinations of these effects. Interventions that affect other outcomes cannot be evaluated. Projections for the intervention scenarios are compared to projections for the reference case, representing minimal intervention, to estimate the gain in life expectancy, the gain in QALYs, the

number of exacerbations avoided, the difference in intervention costs and the savings in COPD-related health care cots. The new model presents the uncertainty around the outcomes using probabilistic sensitivity analysis, which is the current state of the art for cost effectiveness analyses of interventions.

The extended COPD model now is a tool allowing policy makers to get an overview of short term and long term costs and effects of interventions over the entire chain, from primary prevention to care for very severe COPD. Furthermore, being stochastic, the model enables to estimate the added value of doing additional research for specific model-parameters in a value of information analysis.

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1. Introduction

In 2005 we have published a decision analytic cost-effectiveness model of Chronic Obstructive Pulmonary Disease (COPD) which was used for two distinct purposes [1]. One purpose was to simulate the future burden and costs of COPD in the Netherlands [2] and the other purpose was to calculate the cost-effectiveness of interventions to prevent and treat COPD [2]. The importance of models such as the COPD model is increasingly recognized because they not only provide decision makers with insight in the future health care needs but they also provide them with information on the returns of their investments in terms of health benefits [3]. Hence, these models can raise the awareness about the future burden of COPD, support capacity planning decisions and help policy makers to prioritize the investment of scarce resources.

The 2005 COPD model [1] is a multistate transition model that calculates the incidence, prevalence, mortality, progression, and health care costs of COPD per GOLD severity stage [4]. The COPD model is based on the life table method. It starts from the age-, gender- and smoking-class distribution in the general population and models the annual incidence of COPD depending on this distribution. The dynamics of the Dutch general population are taken into account using prognosis of birth and mortality and estimates of the start, stop, and restart rates of smoking. The *life table method* means that the model follows birth cohorts over time. Each year a new birth cohort is added, while the existing cohorts age with one year. The model is a *multistate model*, which, for COPD, implies that we distinguish between the following states: no COPD, mild, moderate, severe and very severe COPD and death. The model follows COPD patients over their course of disease, from incidence until death. Incidence depends on age, gender and smoking status. Disease progression is modelled as annual decline in FEV_1% predicted, depending on age, gender, smoking status and FEV_1% predicted. COPD mortality rates depend on age, gender, FEV_1% predicted, and smoking status. 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 2005 version of the COPD model had two important shortcomings. It did not include exacerbations and all parameters were fixed. With respect to the first shortcoming, the model could only assess the impact of interventions that affected the decline in lung function and/or the survival. An example of such an intervention is smoking cessation support. However, many COPD interventions, such as most medications, exercise training, education, multidisciplinary rehabilitation, and self-management, have not (yet)

been shown to influence COPD progression. These interventions rather reduce the frequency, severity and/or duration of COPD exacerbations, improve exercise capacity, symptoms and/or quality of life. With respect to the second shortcoming, a deterministic model only gives point estimates of the burden and costs of COPD and the cost-effectiveness of interventions without information about the uncertainty of these estimates. This uncertainty results from the model input parameters being obtained from sampled data.

The current project aimed at improving the Dutch COPD model and addressing these two major shortcomings by including the exacerbations and making the model stochastic. Adding exacerbations is important because they are common and contribute to poor health-related quality of life [5-7] and high costs [8-10]. Moreover, there is some evidence that frequent exacerbations accelerate the progression of the disease [11,12][13]. The frequency of these exacerbations increases with the severity of COPD [14,15]. In patients with mild to moderate COPD an exacerbation often requires medical attention by a general practitioner or specialist. When the severity of COPD increases, exacerbations may become major life events that require hospital admission. Hospital mortality of patients admitted for an exacerbation of COPD is high and the long-term outcome is poor [4]. Hence, these severe exacerbations represent a significant burden on patients as well as on the healthcare system. This makes it very important to include them in the model. Taking account of the uncertainty in the input parameters by making the model stochastic is also important because it enables us to demonstrate the likelihood of certain outcomes to occur and the likelihood of interventions being cost-effective. Crucial model parameters were no longer entered as point estimates but as distributions from which values were randomly drawn. The uncertainty was then quantified using Monte Carlo simulation, where the model is run a large number of times, and iterations involve random draws from the distributions of the input parameters. Each iteration results in an estimate of the outcomes (e.g. prevalence, costs, and health outcomes) and the mean and 95% uncertainty interval across these iterations represent the expected outcome values and the uncertainty intervals. This process is referred to as a probabilistic sensitivity analysis, and is currently regarded as the state of the art in cost-effectiveness analysis [16].

The revised version of the COPD model can be used to evaluate a series of interventions for COPD that can be applied during various stages of the disease progression. In the current project this was illustrated by estimating the cost-effectiveness of interventions that either reduce the decline in lung function, reduce the exacerbation rate, improve the quality of life, reduce mortality or combinations of these effects. More specifically, the

model was used to address how the cost-effectiveness of two pharmaceutical interventions (i.e. a fixed combination of a long-acting bronchodilator with an inhaled corticosteroid or a long-acting bronchodilator alone) compares with the cost-effectiveness of a smoking cessation intervention (i.e. intensive counselling plus pharmaceutical support) and the cost-effectiveness of pulmonary rehabilitation?

To summarize, this project aimed to:

1. revise the 2005 COPD model by building exacerbations into the model
2. making the model stochastic in order to allow calculating uncertainty
3. to illustrate the potential of the model by calculating the cost-effectiveness of a number of different COPD interventions.

In chapter two a description of the revised model will be given along with a description of how the new model input parameters were obtained and existing model parameters were updated. Chapter three describes the scenario analyses that were done and chapter four describes the one-way sensitivity analysis and the probabilistic sensitivity analyses. In chapter five the results of the cost-effectiveness analyses will be presented, including cost-effectiveness planes and cost-effectiveness acceptability curves. The analyses were done to illustrate the potential use of the model. Chapter six contains the discussion and chapter seven the conclusions.

2. Model and input data for the reference scenario

2.1 General description of the COPD model

Figure 1 shows the revised version of the Markov model. The length of a Markov cycle is one year and the future projections start in the year 2007. The time horizon of the projections can vary between one year and lifetime.

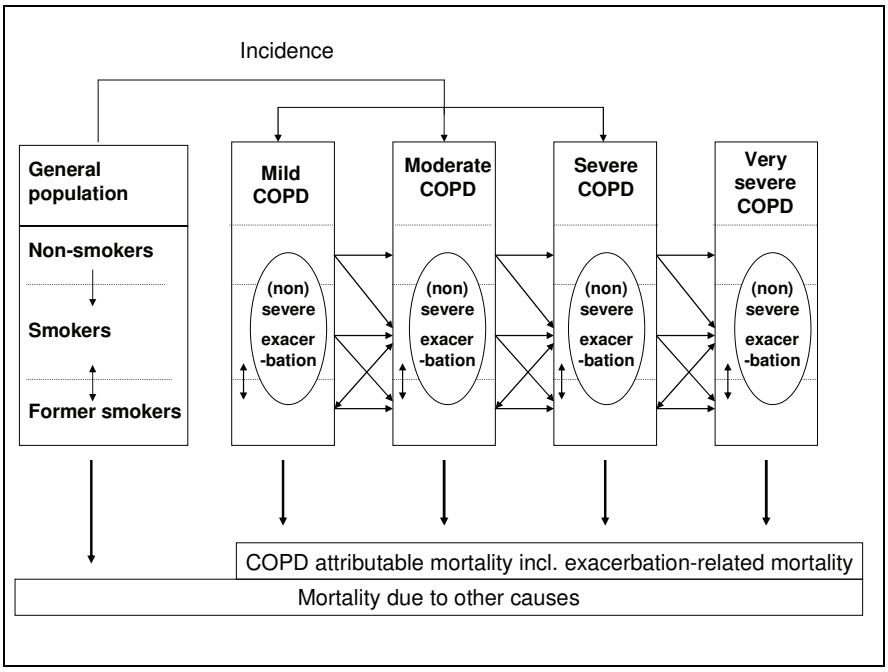

Figure 2.1 Description of the Dutch COPD population model

Starting point of the model simulation is a description of the Dutch general population in terms of age, gender (Table A.1) and smoking status (smokers, former-smokers and never-smokers) (Table A.2) and the incidence and prevalence of COPD by gender and one-year age classes starting at age 45 and ending with age 100 (Table A.3).

The *prevalence of COPD* in each age and gender class is distributed over the three smoking classes using the number of smokers in each smoking class and the relative risks of smokers and former smokers to have COPD [17,18] (Table A.4). It assumed that the RR of smokers and former smokers to get COPD is equal to the relative risk to have COPD, which is assumed to be equal to the RR to die of COPD. The prevalence of COPD in each age, gender and smoking class is further distributed over the four GOLD stages of

COPD severity using the frequency distribution of FEV_1% predicted over all COPD classes that was obtained from Dutch GP data [19]. Based on a normal distribution with a mean FEV_1% predicted of 68.3% (SD 19.9%) we estimated that 27% has mild COPD, 55% has moderate COPD, 15% has severe COPD and 3% has very severe COPD. The distribution of the FEV_1% predicted within each COPD severity stage is modelled as a linear function that is obtained from the continuous normal distribution (Appendix D).

Like the prevalence, the *incidence of COPD* in each age and gender class is distributed over the three smoking classes using the number of smokers in each smoking class and the relative risks of smokers and former smokers to have COPD. The frequency distribution of the FEV_1% predicted among the incident cases 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 normal distribution with a mean FEV_1% predicted of 76.4% (SD 15.6%) it was estimated that 40% of the newly diagnosed COPD patients has mild COPD, 55% has moderate COPD, 4% has severe COPD and 0.1% has very severe COPD.

Each year transitions between smoking stages occur. Non-smoking patients can start smoking, smoking patients can stop smoking and former smoking patients have a certain probability to restart smoking (Table A5).

Once having COPD, there is a probability to progress to the next level of COPD severity. This *disease progression* is modelled as the annual decline in FEV_1% predicted, depending on gender, age, smoking status and FEV_1% predicted (Table A.6). Each exacerbation accelerates this decline.

Each stage of COPD is associated with an annual exacerbation rate, which increases as the severity of COPD increases. Using an event-based definition of exacerbation-severity, a distinction is made between the rate of moderate exacerbations and the rate of severe exacerbations, where a severe exacerbation is defined as an exacerbation leading to hospital admission and a moderate exacerbation as an exacerbation leading to a prescription of systemic corticosteroids and/or antibiotics.

Each COPD stage is associated with costs of maintenance therapy and utility values (i.e. generic quality of life values). Costs of maintenance therapy increase with age and COPD severity and are higher for females than males (Table A.7). Utility values decrease as COPD severity increases (Table A.8).

Each exacerbation is associated with costs and a utility decrement. The costs and the reduction in utility value are higher for severe exacerbations than for moderate exacerbations. The utility decrement is modelled as a proportional reduction from the utility value of the COPD stage.

All-cause mortality consists of the mortality attributable to COPD and the mortality from other causes (Table A.9). The latter depends on age, gender and smoking status. The COPD attributable mortality depends on age, gender and FEV_1% predicted, but not on smoking 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. The mortality attributable to COPD is further divided into the mortality that is due to severe COPD exacerbations and the remaining COPD attributable mortality.

To adapt the 2005 COPD model to the new version shown in figure 1, the following new input parameters were estimated:

- rate of moderate and severe COPD exacerbations by GOLD stage of COPD severity (section 2.2)
- case-fatality rate of a severe COPD exacerbation (section 2.3)
- decline in FEV_1% predicted due to an exacerbation (section 2.4)
- utility decrement due to a moderate and a severe exacerbation (section 2.5)
- costs of a moderate and a severe exacerbation (section 2.6).

How these estimates were obtained is described in the next sections. A description of the existing input parameters that were updated to more recent values is given in section 2.7.

2.2. Exacerbation frequency by GOLD stage

We aimed to quantify the relation between lung function expressed as FEV_1% predicted and the annual exacerbation frequency in patients with COPD to be able to calculate the exacerbation rates per GOLD stage. First we performed a systematic literature review for randomized controlled trials and cohort studies reporting the exacerbation frequency in patients receiving care as usual or placebo. Details of the search strategy and the selection criteria can be found in a separate paper, added to this report as appendix B. Annual frequencies were obtained for the following two outcomes: total exacerbations defined by an increased use of health care (event-based) and severe exacerbations defined by a hospitalization. The literature search resulted in 19 reports of the total exacerbation frequency using an event-based definition and 14 reports of the frequency of

severe exacerbations defined by a hospitalization. The association between the mean FEV_1% predicted of study populations in the selected studies and the annual exacerbation frequencies was estimated using weighted log linear regression with random effects. The resulting regression equations for total exacerbations using an event-based definition and severe exacerbations as reported below were built into the model.

Annual total exacerbation rate (event-based definition):
Rate=0.893*exp[1.181-0.014*FEV_1%predicted]

- 0.893 (se=0.093)
- 1.181 (se=0.351)
- -0.014 (se=0.007)
- Covariance between intercept 1.181 and coefficient -0.014 = -0.00227

Annual severe exacerbation rate:
Rate=1.072*exp[-1.043-0.013* FEV_1%predicted]

- 1.072 (se=0.154)
- -1.043 (se=0.904)
- -0.013 (se=0.020)
- Covariance between intercept -1.043 and coefficient -0.013 = -0.00176

Each year the mean exacerbation rate per GOLD severity stage was calculated by applying the mean FEV_1% predicted for each GOLD stage at that time to the estimated equations. In the table below (Table 2.1) the mean exacerbation rates per GOLD stage for the starting year of the simulation are shown. As a result of changes in the mean FEV_1%predicted per GOLD stage over time the mean exacerbation rate per stage did change.

Table 2.1: Estimated annual exacerbation frequency per GOLD stage based on the regression equations for the starting year of the simulation

GOLD stage	Mean FEV_1% predicted at start	Total exacerbations: event-based definition	Severe exacerbations
I, Mild COPD	90	0.82 (0.46-1.49)	0.11 (0.02-0.56)
II, Moderate COPD	65	1.17 (0.93-1.50)	0.16 (0.07-0.33)
III, Severe COPD	42	1.61 (1.51-1.74)	0.22 (0.20-0.23)
IV, Very severe COPD	23	2.10 (1.51-2.94)	0.28 (0.14-0.63)

2.3 Case fatality

The methods and results of the estimation of the case fatality of a severe COPD exacerbation have been reported in detail in a separate manuscript (see Appendix C). A short summary is given below. We assumed mortality to be increased after a severe exacerbation for COPD defined as a hospitalization for COPD. We performed a literature search for studies reporting at least 1.5 year survival after a severe exacerbation resulting in hospitalization. For each study, we extracted the presented or estimated survival curve and 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. Mortality during the stable period was then estimated by extrapolating the survival curve during the stable period back to the time of exacerbation onset (see Figure 2.2). The case fatality was defined as the additional 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. Based on six studies that fulfilled the inclusion criteria the weighted average case-fatality rate was estimated to be 15.6% (95% CI: 10-9%-20.3%).

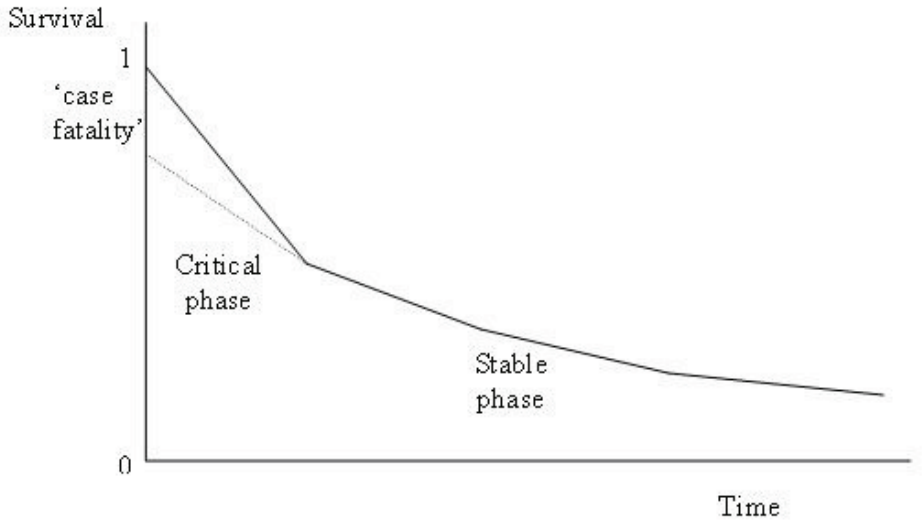

Figure 2.2: Survival curve after hospitalization for an exacerbation of COPD. The dotted line represents the extrapolated curve during the stable phase (Schematic figure not based on real data).

As age is a significant predictor of mortality [20], we also investigated the association between age and mortality after a severe exacerbation in the six studies selected for the calculation of the case fatality. On average the probability to die after a hospitalization for an exacerbation increased with 4.1% per year increase in age (RR=1.041 95%CI: 1.037-1.045). With the use of this relative risk we made the case fatality of a COPD exacerbation in the model dependent on age. We applied the mean case fatality of 15.6% to the mean age of the COPD population in the papers selected from the literature, i.e. 69 years. For each year below 69 years, the case fatality decreased with 4.1%, for each year above 69 years, it increased with 4.1%.

2.4 Exacerbations and lung function decline

To estimate the relation between exacerbations and lung function decline we performed a search in Medline to find papers published after 1990 reporting this association. We used the following search query:

COPD or “chronic obstructive pulmonary disease” or “chronic bronchitis” in the title
AND
FEV* or lung function in the title
AND
Decline or progression in the title
AND
Exacerbat* or inflammation* or virus* or illness* in the title or abstract

This search resulted in eleven studies of which five reported the relation between exacerbations and decline in lung function. Results are shown in table 2.2.

The largest study, the study of Kanner et al did not provide information about the uncertainty around their estimate [11]. If the standard error around the estimate obtained from Kanner was assumed to be 0.05, which seems reasonable given the standard errors of the other, though smaller, studies, the final weighted average decline per exacerbation was estimated to be 0.19% predicted (SE of 0.03). However, due to the large number of assumptions we needed to make in the calculations we used an SE of 0.05 in the model. Due to the low number of studies, the weighted average decline per exacerbation could not be specified for subgroups, such as COPD disease severity.

Table 2.2: Decline in lung function in FEV_1% predicted in relation to exacerbations

Study	**N**	**Data extracted from the study**	**Decline in FEV_1% predicted due to an exacerbation**	
			Mean	Estimated SE#
Donaldson, 2002[12]	32	Difference between patients with infrequent and frequent exacerbations: 2.3 exacerbations, difference in lung function decline -0.28%/yr*	-0.12%	0.06
Makris, 2007[21]	102	Difference between patients with infrequent and frequent exacerbations: 2.9 exacerbations, difference in lung function decline -1.56%/yr	-0.54%	0.08
Kanner, 2001[11]	5887	-0.212%/additional lower respiratory illness per year	-0.21%	-
Spencer, 2004[22]	577	Difference between patients with infrequent and frequent exacerbations: 1.9 exacerbations, difference in lung function decline 0.04%/yr	+0.02%$^{\$}$	0.07
Celli, 2008[23]	1137	Placebo group: difference between patients with and without exacerbations: 1.52 exacerbations, difference in lung function decline -0.22%/yr	-0.14%	0.1
Weighted average decline per exacerbation (with SE Kanner assumed to be 0.05)			-0.19%/exacerbation	0.03
Weighted average decline per exacerbation (with SE Kanner assumed to be 0.1)			-0.18%/exacerbation	0.04
Final estimate used in the model			-0.19%/exacerbation	0.05

*Calculated from the values in liters, the mean FEV1 in liters and the mean FEV1 as predicted

The calculations needed to calculate the decline per exacerbation in the various studies were applied to 1000 random draws from the normal distribution of the decline in lung function and 1000 random draws from the distribution of the exacerbation rate from that specific study if available. This resulted per study in 1000 estimates of the decline per exacerbation. The presented figure is the SE of these 1000 estimates.

$ Estimates using data from Spencer, 2004 [22] did not indicate an additional lung function decline due to an exacerbation

2.5 Exacerbations and quality of life

We did not change the utility values for the different COPD severity stages. These were kept the same as in the publication of the former version of the model[1], which were based on EQ-5D and obtained from the study of Borg et al.[24]

Table 2.3: Mean utility scores by COPD severity stage according to GOLD

GOLD stage:	Mean utility score (SD)
Mild COPD	0.8971 (0.1117)
Moderate COPD	0.7551 (0.2747)
Severe COPD	0.7481 (0.2991)
Very severe COPD	0.5493 (0.3129)

To estimate the impact of exacerbations on the number of quality-adjusted life years (QALYs), data about the relation between exacerbations and utility values, as measured by generic quality of life instruments, such as the EQ-5D were needed. Therefore we performed a literature search in Medline for studies published after 1990 using the following search query:

COPD or “chronic obstructive pulmonary disease” or “chronic bronchitis” in the title
AND
Exacerbation* in the title
AND
“Health status” or “quality of life” in the title/abstract
AND
Utility or EQ-5D in the title/abstract

The search resulted in four studies of which two reported the relation between exacerbations and quality of life using the EuroQol (EQ-5D), one for severe exacerbations[10] and one for moderate exacerbations[25].

Severe exacerbations

The study of O’Reilly et al [10] provided data on the utility scores during a hospitalization for an exacerbation valued with the UK tariff [26]. The EQ-5D was measured both at admission and at discharge. The mean length of hospitalization was 11 days. We assumed the utility scores after a severe exacerbation to be reduced for a period equal to

the period in which the mortality due to a severe exacerbation was increased, about 4.5 months. We further assumed that the utility score of a patient admitted with a severe COPD exacerbation had returned back to the baseline level 4.5 months after admission. Because the baseline utility before the hospitalization was unknown the mean EQ-5D utility of the patients in the study of O'Reilly at baseline was approximated using the severity distribution of the patients in the study and the utility scores per COPD severity stage from the study of Borg et al [24]. Based on the mean utility scores at admission (-0.077 se 0.027), at discharge (0.576 se 0.021) and at baseline (0.689 se 0.028), the utility loss due to a severe exacerbation was calculated as the area above the curve in figure 2.3 (grey area in the Figure)

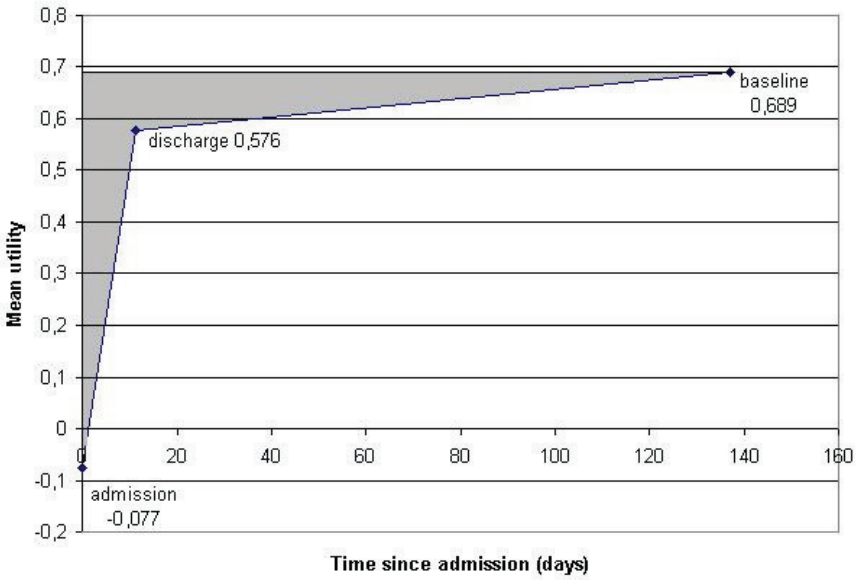

Figure 2.3: Mean utility scores after hospitalization for a severe COPD exacerbation over time

To obtain uncertainty around this estimate, the above mentioned calculation was applied to 2500 random draws from the normal distributions of the utility scores at the three different time points. This resulted in 2500 estimates of utility loss due to a severe exacerbation. The presented figure is the SE of these 2500 estimates. The mean annual utility loss due to a severe exacerbation was estimated to be 0.0332 (se 0.007). Expressed as percentage of the mean baseline utility value, 0.689, the annual utility loss due to a severe exacerbation was estimated to be 4.82% (se 0.87) of the baseline value.

Moderate exacerbations

The second study found in our literature search, the study of Patterson et al, reported about the utility scores during a moderate exacerbation. In this study patients with chronic bronchitis visiting their GP for an acute exacerbation, defined as an increase in symptoms, were included. The EQ-5D was measured at the first visit and at a follow-up visit one week after completing treatment. Because it was unclear what the time between the two measurements was and whether the first measurement was at the start of the exacerbation and the last measurement was after the exacerbation, this study was less suitable for our purpose [25].

We also had access to a submitted paper by Goossens et al [27], who measured utility scores during a moderate exacerbation at four different time points over a period of six weeks: i.e. within 48 hours after onset of the exacerbation and 7, 14 and 42 days thereafter. In this study which included 59 patients a moderate exacerbation was defined as the prescription of antibiotics or systemic steroids but no hospital admission. Utility scores were based on the EQ-5D and valued using the UK tariff. The number of QALYs lost due to a moderate exacerbation was estimated to be 0.013 (SE 0.0017). Expressed as percentage of the mean baseline utility value, 0.783, the annual utility loss due to a moderate exacerbation was estimated to be 1.66% (SE 0.22) of the baseline value.

The calculated mean annual utility loss due to a severe and a moderate exacerbation as percentage of the baseline utility value, 4.82% and 1.66%, respectively were used in the model. We applied these percentages to the baseline utilities of the different COPD severity stages. As a result the absolute disutility for respectively a moderate or a severe exacerbation varied over the severity stages (see table 2.4).

Table 2.4: Absolute disutilities for a moderate and severe exacerbation according to GOLD

GOLD stage:	Absolute disutility moderate exacerbation	Absolute disutility severe exacerbation
Mild COPD	0.0149	0.0432
Moderate COPD	0.0125	0.0364
Severe COPD	0.0124	0.0360
Very severe COPD	0.0091	0.0265

2.6 Exacerbations and costs

Total direct medical costs for COPD in the Netherlands for the year 2000 specified by age and gender were obtained from a previous cost of illness study [28]. Based on a prevalence estimate of 305,000 patients in 2000, the total costs for COPD in 2000 were estimated to 279.7 million euro. These costs were updated to the year 2007 using consumer price indices [29]. For the current study the total direct medical costs needed to be divided in exacerbation-related costs and maintenance costs.

To calculate the total exacerbation-related costs the cost per moderate and severe exacerbation was calculated using resource use and unit costs for a moderate and severe exacerbation from Oostenbrink et al [8]. Because that study used different definitions of exacerbations we slightly modified the cost estimate of a moderate exacerbation as follows: we used mean resource use as observed during a non-severe exacerbation in the paper of Oostenbrink, after deleting the inpatient hospital costs. Resource use as observed during a severe exacerbation was kept unchanged and assumed to reflect the healthcare use during a severe exacerbation defined as a hospitalization. The final costs estimates were updated to the year 2007. This resulted in a cost estimate of 94 euro (se 7) for a moderate exacerbation and 4100 euro (se 894) for a severe exacerbation.

Total exacerbation-related costs were calculated as the sum of the costs of moderate and severe exacerbations in all four severity stage and calculated as follows: $\Sigma_{\text{mild-very severe}}$ number of patients per GOLD severity stage * (moderate exacerbation rate * costs moderate exacerbation + severe exacerbation rate * costs severe exacerbation).

COPD-related maintenance costs were calculated as the total direct medical cost per gender and age class minus the exacerbation-related costs per gender and age class. The maintenance costs within each gender and age class were divided over the four COPD 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). The ratio for costs of a moderate patient compared to costs of a mild patient were obtained from a study of Steuten et al [30]. Ratios of the costs for a severe patient and a very severe patient compared to a moderate patient were obtained from Oostenbrink et al [31]. As no data about uncertainty around the maintenance costs were available, we assumed a standard error of 15% of the mean cost per patient in each subclass.

Main input parameters used in the model were the gender, age and severity stage-specific maintenance costs per patient (see Appendix A7) and the costs for a moderate and severe exacerbation, 94 (se 7) and 4100 (se 894) respectively.

2.7 Other parameters that were updated

The incidence, prevalence and mortality input data in our COPD model are linked to the RIVM Chronic Disease Model (CDM). These input data have been updated in 2009, adding estimates of standard errors. The new version of the CDM was published in VTV2010 [32], and includes a description of data sources used. The new values of the most relevant input data for our COPD model, demography, smoking prevalence, smoking transition rates and relative risks for smokers and former smokers to develop COPD are presented in appendix A. Demography data for the year 2007 were obtained from Statistics Netherlands [29]. Updated information on smoking prevalence and smoking transition rates were obtained from STIVORO [33,34] Relative risks for smokers and former smokers to get COPD were based on the same data source as the 2005 model [17,18].

Appendix A also shows the new incidence, prevalence and attributable mortality for COPD adapted from VTV-2010 [32]. Prevalence and incidence data in VTV 2010 are based on five general practice data bases, Continue Morbiditeits Registratie (CMR) Nijmegen, Landelijk Informatie Netwerk Huisartsenzorg (LINH), Registratienet Huisartsenpraktijken (RNH), Registratie Netwerk Universitaire Huisartspraktijken Leiden en omstreken (RNUH-LEO) and Transitieproject. For the Chronic Disease Model and therefore also for our COPD model, the prevalence and incidence estimates used are based on three data bases (CMR, RNH, RNUH-LEO), because RNH and Transitieproject were suspected to overestimate COPD incidence. The data on COPD related mortality are the data used in the DYNAMO-HIA project, which are originally based on the General Practice Research Database (GPRD) from the UK (www.gprd.com). More details about the new method used to calculate COPD-related mortality can be found in Appendix D.

Uncertainty around the estimates of COPD incidence, prevalence and mortality was estimated using the approach that was used for the RIVM Chronic Disease Model [32], and based on the observed variation between the different GP registries as well as the uncertainty within these registries. We varied the three disease parameters jointly to account for the association between them. First, for incidence and prevalence, random effects models with polynomials of age as an explanatory variable were simultaneously estimated. We constructed uncertainty intervals by taking random draws from the joint distribution of the model parameters. Likewise a model with polynomials of age was estimated for the estimates of the COPD-related mortality. We again constructed uncertainty intervals by taking random draws from the joint parameter distribution. For the PSA, for each model run a random draw of the joint parameter distribution of COPD incidence and prevalence was taken, that was used to calculate the age-dependent

incidence rate and prevalence probability. Likewise, a random draw was taken from the parameter distribution of the COPD-related mortality rate.

2.8 Model implementation and internal validation

A detailed mathematical description of the model and its implementation in *Mathematica* [35] is given in Appendix D. During the development of the model, the internal validity of the model was secured by performing fifteen different model checks to prevent internal inconsistencies. The performed model checks, results and possible actions to resolve the problem are shown in Appendix E.

3. Reference and intervention scenarios

With the extended model it is possible to estimate the long-term effectiveness and cost-effectiveness of pharmaceutical and non-pharmaceutical COPD interventions that have an effect on disease progression, quality of life, mortality and/or the frequency and severity of exacerbations. Thus consistent and long-term cost-effectiveness outcomes can be obtained for a range of interventions.
The effect of interventions is modeled by means of multiplicators. These multiplicators are applied to the parameters that change in an intervention scenario. The intervention therefore needs to be specified in terms of the relative change in disease progression, quality of life, all-cause mortality or exacerbation frequency compared to the reference scenario.
To illustrate the potential use of the model three different types of interventions for COPD are simulated. All scenario analyses were performed using a cohort of COPD patients, thus assuming no newborns and no new incidence of COPD.

3.1 Reference scenario

Chapter two described the input parameters for the reference scenario. Because input parameters are as far as possible based on data sources in which patients received minimal treatment, the reference scenario in our model represents the COPD population in the Netherlands receiving minimal intervention. A change in certain model parameters due to an intervention can be evaluated in so-called scenario analyses. Comparison of these scenarios with the projections for the reference scenario, gives an estimate of the impact of the intervention compared to minimal intervention.

3.2 Scenario one and two: pharmacotherapy

The first two scenarios assumed implementation of a combination of a long-acting beta-agonist and inhaled corticosteroid (ICS/LABA=salmeterol/fluticasone) or implementation of a long-acting beta-agonist alone (LABA=salmeterol) for all COPD patients in the GOLD stages moderate and severe COPD. Both pharmacotherapies were assumed to affect lung function decline, exacerbation frequency and mortality. Data on short-term effectiveness, i.e. three years, were obtained from the TORCH trial [36]. The relative risks or the calculated ratio of the effect for lung function decline, exacerbation frequency and all-cause mortality compared to placebo are shown in table 3.1.

Table 3.1: Short-term effectiveness of a long-acting beta-agonist or a combined long-acting beta-agonist and inhaled corticosteroid based on the TORCH trial[36], relative risks or ratios of the effect in the active treatment group compared to placebo (95% confidence interval)

	Salmeterol (n=1521)	Combination Salmeterol/fluticasone (n=1533)
Annual decline in lung function	0.67 (0.51-0.82)	0.60 (0.45-0.76)
Total exacerbations	0.85 (0.78-0.93)	0.75 (0.69-0.81)
All-cause mortality at 3 yr	0.879 (0.729-1.061)	0.825 (0.681-1.002)

As the three parameters are related, i.e. a reduction in lung function decline has an effect on exacerbation frequency and mortality, we modeled the effectiveness of the interventions in three steps. We first applied the effect of the treatment options on lung function decline. We then studied what effect this had on the annual exacerbation rate over three years, the duration of the trial. If the effect was smaller than the effect on exacerbations given in the table, we moved to step 2 and adjusted the effect of the treatment options on exacerbation frequency till the magnitude of the effect seen in the trial. After that the effect of the first two steps on all-cause mortality was determined. In step 3 we adjusted the effect on mortality till the effect seen in the trial.
Costs of the two pharmacotherapies were obtained from the Dutch Pharmacotherapeutic Compass [37]. Based on the assumption that patients receive four prescriptions per year, the total annual costs for salmeterol/fluctisone and salmeterol were estimated to be €773 and €397, respectively (including VAT and four times the mark-up to cover pharmacy expenses of on average €7,00). For scenario one and two we assumed continuous implementation, i.e. the effects and the intervention costs are applied each year. The chosen time horizon was 10 years.

3.3 Scenario three: smoking cessation

The third scenario assumed increased use of smoking cessation support by smoking COPD patients. As the current guidelines recommend that all smoking COPD patients should be offered the most intensive smoking cessation intervention feasible, we choose to model the implementation of intensive counseling (>90 minutes) in combination with pharmacotherapy (NRT, bupropion or nortriptyline).

The 12 month continuous abstinence rate for intensive counseling plus pharmacotherapy was estimated to be 10.9% (95%: 6.9-15.0) higher than the abstinence rate for usual care [38]. Intervention costs of intensive counseling plus pharmacotherapy were estimated to be €305 (price level 2007) [38]. The implementation of smoking cessation interventions for COPD patients was modelled by replacing the smoking cessation rates of usual care with the higher smoking cessation rates of the intervention for one year, for all smoking COPD patients. 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 (see Table A6 in Appendix A)[39] and reduced mortality due to COPD and other smoking-related diseases. The effects of one-year implementation of intensive counselling plus pharmacotherapy were evaluated over a time horizon of 20 years.

3.4 Scenario four: pulmonary rehabilitation

In scenario four we simulated implementation of a pulmonary rehabilitation program, which was assumed to affect quality of life. We modeled implementation of a two-year interdisciplinary community-based pulmonary rehabilitation program for all patients with moderate and severe COPD. The gain in QALYs for the intervention group over two years was assumed to be 0.08 (95% CI: -0.01-0.18) based on the INTERCOM trial. Two-year costs of the program were €1,490 [40]. Effects of the program were assumed to remain present one year after the intervention period. This means that effects were implemented for three years, intervention costs for two years. The time horizon for the evaluation of pulmonary rehabilitation was shorter than for the other scenarios, 5 years.

Results of the model simulations for the four different scenarios were compared to the reference scenario, representing minimal intervention, to estimate the number of (quality-adjusted) life years gained, the number of exacerbations avoided, the incremental intervention costs and the savings in COPD-related health care costs. Health outcomes were discounted by 1.5%, costs by 4% as recommended by Dutch guidelines [41]. The cost per quality-adjusted life year gained was calculated as the ratio of total intervention costs minus savings in COPD-related healthcare costs due to the intervention compared to the reference scenario divided by the cumulative quality-adjusted life years gained compared to the reference scenario. The cost per exacerbation avoided was calculated as the ratio of total intervention costs minus savings in COPD-related healthcare costs compared to the reference scenario divided by the cumulative exacerbations avoided compared to the reference scenario representing minimal intervention.

4. Sensitivity analyses

For all scenario analyses two types of sensitivity analyses were performed. First, one-way sensitivity analyses were performed for a number of key model assumptions and key parameter values including the values of parameters for which a probabilistic approach was not appropriate, for instance the discount rates. If possible, the input parameters evaluated were varied using the lower and upper limit of their 95% confidence interval. Second, probabilistic sensitivity analysis was performed for most input parameters simultaneously, using Monte Carlo simulation and drawing from probability distributions for each parameter in each simulation to result in confidence intervals around the outcome parameters. This required building a shell for Monte Carlo simulation around the model. The probability distributions on input parameters are described in section 4.2. To estimate the uncertainty around the cost-effectiveness of the scenarios we used 1000 model simulations in the probabilistic sensitivity analysis.

4.1 One-way sensitivity analyses

One-way sensitivity analyses were performed on the following parameters.

a. Change of lung function over time, annual decline in FEV_1% predicted.

We investigated the effect of a 50% higher or lower annual decline in FEV_1% predicted.

1. 50% lower annual decline in FEV_1% predicted
2. 50% higher annual decline in FEV_1% predicted

b. The baseline exacerbation frequencies per COPD severity stage

We performed two sensitivity analyses using the lower and upper limit of the 95% uncertainty interval around the estimated mean exacerbation frequency per GOLD stage.

1. Lower 95% CI limits for each GOLD stage from the table below (or paragraph 2.2)
2. Upper 95% CI limits for each GOLD stage from the table below (or paragraph 2.2)

Table 4.1: Exacerbation frequencies per GOLD stage with 95% uncertainty limits

GOLD stage	Total exacerbations			Severe exacerbations		
	Mean	95% lower limit	95% upper limit	Mean	95% lower limit	95% upper limit
I, Mild COPD	0.82	0.46	1.49	0.11	0.02	0.56
II, Moderate COPD	1.17	0.93	1.50	0.16	0.07	0.33
III, Severe COPD	1.61	1.51	1.74	0.22	0.20	0.23
IV, Very severe COPD	2.10	1.51	2.94	0.28	0.14	0.63

c. The case-fatality of a COPD exacerbation

We investigated the effect of no case-fatality of a COPD exacerbation or using the lower and upper limit of the 95% confidence interval of the estimated mean case fatality of a COPD exacerbation of 15.6%.

1 Lower 95% CI limit: 10.9%

2 Upper 95% CI limit: 20.3%

d. Decline in lung function due to an exacerbation

We performed three additional analyses using no decline in lung function due to an exacerbation and using the lower and upper limit of the 95% confidence interval of the estimated mean decline in lung function due an exacerbation of -0.19% predicted.

1 Lower 95% CI limit: -0.092% predicted

2 Upper 95% CI limit: -0.288% predicted

e. Utility decrement due to an exacerbation

We investigated the effect of using the lower and upper limits of the 95% confidence intervals of the estimated mean utility decrement due to an moderate exacerbation, 1.66% (95% CI: 1.23-2.09) of the baseline utility value in a particular COPD severity stage and the calculated mean utility decrement for a severe exacerbation, 4,82% (95% CI: 3.11-6.53), which resulted in the absolute utility decrements as shown in the table below.

Table 4.2: Absolute disutilities for a moderate and severe exacerbation according to GOLD including uncertainty

GOLD stage	Moderate exacerbation			Severe exacerbation		
	Mean	95% lower limit	95% upper limit	Mean	95% lower limit	95% upper limit
I, Mild COPD	0.0149	0.0110	0.0188	0.0432	0.0279	0.0585
II, Moderate COPD	0.0125	0.0093	0.0158	0.0364	0.0235	0.0493
III, Severe COPD	0.0124	0.0092	0.0156	0.0361	0.0233	0.0488
IV, Very severe COPD	0.0091	0.0068	0.0115	0.0265	0.0171	0.0358

1. Lower 95% CI limits: 1.23% from the baseline utility value in a particular COPD severity stage for a moderate and 3.11% for a severe COPD exacerbation
2. Lower 95% CI limits: 2.09% from the baseline utility value in a particular COPD severity stage for a moderate and 6.53% for a severe COPD exacerbation

f. Costs of a COPD exacerbation

We performed additional analyses using the lower and upper limit of the 95% confidence intervals of the estimates of the costs of a moderate exacerbation, €94 (95% CI: 86-102) and a severe exacerbation, €4100 (95% CI: 2348-5852)

1. Lower 95% CI limits: €86 for a moderate and €2348 for a severe exacerbation
2. Upper 95% CI limits: €102 for a moderate and €5852 for a severe exacerbation

g. Mean utility scores by COPD severity stage according to GOLD

We performed two sensitivity analyses using 10% lower and 10% higher utility values per GOLD stage.

1. 10% lower utility values in each GOLD stage
2. 10% higher utility values in each GOLD stage

h. Usual care stop rate for smoking COPD patients

In the model, the stop rate among smoking COPD patients in the reference scenario is equal to the stop rate for smokers in the general population. Based on the gender- and age distribution of the COPD population, the mean stop rate for COPD patients receiving usual care is 7.6%. Based on an earlier performed meta-analysis on smoking cessation interventions in COPD patients, we feel that the stop rate for usual care in smoking COPD

patients may be lower. However, there are virtually no studies on stop rates in usual care in the Netherlands. There is one study, the SMOCC study that reported 1.4% [38]. In this sensitivity analysis we investigated the impact of using the lower stop rate for smoking COPD patients.

1. Using a usual care stop rate for smoking COPD patients of 1.4%

i. Costs of the intervention

For this sensitivity analysis we investigated the impact of a 10% reduction or increase in intervention costs.

1. 10% reduction in intervention costs
2. 10% increase in intervention costs

j. Discount rates

We performed additional analyses using different discount rates than in the reference scenario analyses in which we used 1.5% for effects and 4% for costs, which are the Dutch standard rates[41].

1. 0% for effects and 0% for costs
2. 4% for effects and 4% for costs

k. Time horizon

The analysis for the reference scenario was performed using a time horizon of ten years for the scenarios on salmeterol/fluticasone and salmeterol, twenty years for smoking cessation and five years for pulmonary rehabilitation. We performed additional analyses using a shorter time horizon or a longer time horizon.

1. Time horizon of 5, 10 or 2 years, respectively
2. Time horizon of 20, 30 or 10 years, respectively

4.2 Probabilistic sensitivity analyses.

In order to assess the impact of uncertainty around the different input parameters on the outcomes, a probabilisitic sensitivity analysis (PSA) was performed. A probabilistic sensitivity analysis considers the uncertainty around the input parameters simultaneously by using pre-specified distributions for these parameters instead of point estimates. Table 4.3 lists all model parameters that were varied in the probabilistic sensitivity analyses, as well as the variances used for this parameter. All parameters were assumed to be Normally distributed. The uncertainty around the probabilistic input parameters is propagated through the model simultaneously by conducting second-order Monte Carlo

simulations. This means that for the uncertain parameters random draws are made from their probability distribution. The model is run for each set of parameters that is drawn and the outputs from each run are collected. The current analyses were based on 1000 iterations. The results of all iterations are plotted on a cost-effectiveness plane (CE-plane) to display the uncertainty around costs and effects. The information in the CE-plane is summarized in a cost-effectiveness acceptability curve (CEAC), which shows the probability that an intervention has a cost-effectiveness ratio below various threshold values of the willingness to pay for a quality-adjusted life year gained.

Table 4.3: Details about the distribution and parameter values of variables including in the probabilistic sensitivity analysis.

Type of data	**Parameters**	**Distribution**	**Remarks**
Severity distribution of the COPD population in the starting year	Mean and SD of the normal distribution of the FEV1% pred. at baseline	Normal distribution: Mean: 68.3 (SE 0.91) SD: 19.93 (SE 0.644)	
Annual change of lung function	Annual decrease in FEV_1% predicted	Normal, with parameters see Appendix A, table A6	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 Appendix A, table A6	Idem
Annual probability of total exacerbations	Coefficients of the regression equation (see paragraph 2.2)	Normal, with parameters: Intercept: 1.181 (SE 0.351) Coefficient: -0.014 (SE 0.007)	
Annual probability of severe exacerbations	Coefficients of the regression equation (see paragraph 2.2)	Normal, with parameters: Intercept: -1.043 (SE 0.904) Coefficient: -0.013 (SE 0.020)	
Case fatality of an exacerbation	m(E)	Normal, with parameters: 15.6 (SE 0.0235)	
	$RR_{tot}^{E}(a)$	1.041 (SE 0.002)	Constant in the PSA, SE was very low

Type of data	Parameters	Distribution	Remarks
QALY-weights for 4 COPD severity classes		Normal, with parameters: Mild: 0.8971 (se 0.0194) Moderate: 0.7551 (SE 0.0309) Severe: 0.7481 (SE 0.0352) Very Severe: 0.5493 (SE 0.0591)	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 (SE 0.0022)	
	Severe exacerbation	Normal, with parameters: 0.0482 (SE 0.0087)	
Effect of lung function on mortality	RRFEVtot	Logarithm of RRFEVtot is normal distributed, with parameters 0.0182 (SE 0.0015) / % decline	
Effect exacerbations on lung function decline.		Normal, with parameters: 0.19 (SE 0.05)	
COPD-related healthcare costs	Maintenance costs	Normal, with parameters: (zie appendix B (SE 15% of mean value)	Monotonicity was enforced: Costs_severity stage < Costs_severity stage+1
	Costs of exacerbations	Normal, with parameters: Moderate exac: 94 (SE 7) Severe exacerbation: 4100 (SE 894)	

Type of data	Parameters	Distribution	Remarks
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 gender Cf

5. Results

5.1 Description of the reference scenario of the model

The COPD population in 2007, the starting year of the simulation consisted of 321,300 patients above 45 years, 172,200 males and 149,100 females (Table 5.1). Thirty percent was smoker, while 64% was former smoker. The majority of patients had moderate COPD.

Table 5.1: Description of the Dutch COPD population of 45 years and older in 2007, the starting year of the simulation.

	Absolute number	Percentage
Total COPD population	321,300	
Males	172,200	53.6%
Females	149,100	46.4%
Never smokers	19,000	5.9%
Current smokers	97,100	30.2%
Former smokers	205,200	63.9%
Mild COPD	85,400	26.6%
Moderate COPD	177,800	55.3%
Severe COPD	49,800	15.5%
Very severe COPD	8,400	2.6%
Total COPD-related health care costs	€352.8 million	
- Exacerbation-related costs	€238.1 million	67.5%
- Costs for maintenance	€114.8 million	32.5%

5.2 Cost-effectiveness results for the scenario's

In table 5.2 results of the cost-effectiveness analyses for the four different scenarios are shown for the most realistic time horizons for each intervention, ten years for ICS/LABA and LABA, twenty years for smoking cessation and five years for pulmonary rehabilitation. Table 5.3 shows the cost-effectiveness of the four different scenarios for each of the three different time horizons, i.e. five, ten and twenty years, to be able to compare the interventions with each other using the same time horizon.

Cost per QALY gained

Of the two types of medications LABA or the combination of ICS/LABA, the combination resulted in the highest gain in QALYs and exacerbations avoided, but also in the highest intervention costs. Given a time horizon of ten years the cost-effectiveness ratios of both pharmacotherapies were relatively low, around or below €10,000 (Table 5.2). The cost per QALY gained for smoking cessation and pulmonary rehabilitation for a ten-year time horizon were €9,900 and €12,200, respectively (Table 5.3).

A time horizon of ten years to evaluate smoking cessation interventions is however relatively short as the annual gain in QALYs is maximal around ten years. Based on a more realistic time horizon of twenty years, the cost-effectiveness ratio for implementation of intensive counseling plus pharmacotherapy was €6,100 per QALY gained (Table 5.2), compared to €6,400, €4,500 and €12,200 for ICS/LABA, LABA and pulmonary rehabilitation, respectively, using the same time horizon (Table 5.3).

The 5-year cost-effectiveness ratio for pulmonary rehabilitation was estimated to be €12,200 for two-year implementation of an interdisciplinary, community-based program for all patients with moderate and severe COPD. Using a five year time horizon, the cost per QALY gained for the other interventions were higher, especially for the smoking cessation intervention (Table 5.3).

Cost per exacerbation avoided

For both scenarios on increased implementation of pharmacotherapy, i.e. LABA or ICS/LABA, the cost per exacerbation avoided was around €2,000, irrespective of the time horizon. For the smoking cessation scenario only a time horizon of five years resulted in exacerbations avoided. For longer time horizons, the number of exacerbations in the smoking cessation arm was higher as patients live longer and are therefore longer at risk to get an exacerbation. As pulmonary rehabilitation was assumed to affect quality of life only, the scenarios on pulmonary rehabilitation did not result in a difference in exacerbations compared to the reference scenario and therefore the cost per exacerbation avoided could not be calculated.

Table 5.2: Cost-effectiveness of four different interventions offered to the cohort of Dutch COPD patients in 2007 compared to the reference scenario (=minimal intervention), using the most realistic time horizon for each intervention, 10, 20 or 5 yrs, discount rates 1.5% for effect, 4% for costs, data are mean (95% confidence intervals)

	Total exac. avoided	**QALYs gained**	**Difference in intervention costs (*10^6)**	**Savings in COPD-related health costs (*10^6)**	**Cost per exac. avoided**	**Costs per QALY gained**	**Gain in life expectancy in years**
1. Ten yrs implementation of combination of ICS/LABA (=salmeterol/fluticasone) for all patients with moderate and severe COPD (n=227,566, time horizon 10 yrs)	422,100 (270,300-637,800)	88,700 (55,500-137,000)	1101.0 (791.2-1540.5)	205.3 (91.8-373.9)	2,100	10,100	0.48
2. Ten yrs implementation of LABA (=salmeterol) for all patients with moderate and severe COPD (n=227,566, time horizon 10 yrs	247,400 (148,800-383,700)	61,500 (34,900-96,200)	554.7 (390.3-769.6)	117.0 (48.4-234.1)	1,800	7,100	0.33
3. One yr implementation of pharmacotherapy plus intensive counselling for all smoking COPD patients (n=97,081, time horizon 20 yrs)	-2,700 (-8,900-2,100)	5,400 (2,400-8,200)	29.6 (21.9-40.4)	3.2 (-1.4-11.9)	Dominated	6,100	0.021
4. Two-yr implementation of an interdisciplinary, community-based pulmonary rehabilitation program for all patients with moderate and severe COPD (n=227,566, time horizon 5 yrs, assuming 3 yrs effectiveness and 2 yrs costs)	0	26,000 (-4,000-56,000)	318.0 (232.9-433.1)	0	-	12,200	0

Table 5.3: Cost-effectiveness of four different interventions offered to the cohort of Dutch COPD patients in 2007 compared to the reference scenario (=minimal intervention) for different time horizons, discount rates 1.5% for effect, 4% for costs

	Time horizon	Cost per exacerbation avoided	Cost per QALY
1. Continuous implementation of combination of ICS/LABA (=salmeterol/fluticasone) for all patients with moderate and severe COPD	5 years	2,000	18,600
	10 years	2,100	10,100
	20 years	2,400	6,400
2. Continuous implementation of LABA (=salmeterol) for all patients with moderate and severe COPD	5 years	1,600	13,200
	10 years	1,800	7,100
	20 years	2,100	4,500
3. One yr implementation of pharmacotherapy plus intensive counselling for all smoking COPD patients	5 years	31,900	26,800
	10 years	Dominated	9,900
	20 years	Dominated	6,100
4. Implementation of a 2-yr interdisciplinary, community-based pulmonary rehabilitation program for all patients with moderate and severe COPD assuming 3 yrs effectiveness and 2 yrs costs)	5 years	-	12,200
	10 years	-	12,200
	20 years	-	12,200

5.3 Results for the one way sensitivity analysis for the four different scenario's

Results for the one way sensitivity analyses for each of the four scenarios are shown in Table 5.4 to Table 5.7.

Cost per QALY gained

For the scenarios on ICS/LABA and LABA, costs per QALY gained were most sensitive to the time horizon chosen. Of all sensitivity analyses on exacerbation-related input parameters changes in the baseline exacerbation frequencies had the highest influence on the cost per QALY gained. For the scenario on pharmacotherapy for smoking cessation the time horizon chosen also had the highest impact on the cost per QALY gained. Of the other sensitivity analyses the baseline exacerbation frequencies and a lower usual care stop rate for smoking COPD patients had the highest influence on the cost-effectiveness ratio.

For the scenario on pulmonary rehabilitation a 10% reduction or increase in the intervention costs and a 10% reduction or increase in the utility values for the COPD GOLD stages had the largest influence, while a two-year time horizon increased the costs per QALY for implementation of an interdisciplinary community-based program from €12,200 to €17,400.

Cost per exacerbation avoided

For the two medication scenarios the cost per exacerbation avoided were rather stable and remained below €5,000 per exacerbation avoided in all sensitivity analyses.

For the smoking cessation scenario cost per exacerbation avoided were negative due to a higher number of exacerbations in the intervention scenario compared to the reference scenario for all sensitivity analyses. As mentioned the cost per exacerbation avoided could not be calculated for the pulmonary rehabilitation program as no exacerbations were avoided.

Table 5.4: Sensitivity analyses for 10 year implementation of a combination of ICS/LABA, i.e. salmeterol/ fluticasone, for the cohort of Dutch COPD patients with moderate or severe COPD in 2007, time horizon 10 years, €

	Cost per exacerbation avoided	**Costs per QALY gained**
Standard comparison of the intervention scenario with the reference scenario	2,100	10,100
a. Annual decline in FEV_1% predicted		
1. 50% lower annual decline	2,300	11,300
2. 50% higher annual decline	1,900	8,900
b. Baseline exacerbation frequencies		
1. lower 95% CI limits for all four GOLD stages	2,700	12,900
2. upper 95% CI limits for all four GOLD stages	1,700	6,900
c. Case fatality of a COPD exacerbation		
1. lower 95% CI limit: 10.9%	2,000	10,900
2. upper 95% CI limit: 20.3%	2,200	9,400
d. Decline in lung function due to an exacerbation		
1. lower 95% CI limit: -0.092% predicted	2,200	10,400
2. upper 95% CI limit: -0.288% predicted	2,100	9,900
e. Utility decrement due to an exacerbation		
1. lower 95% CI limit: 1.23% for moderate, 3.11% for severe exacerbation	2,100	10,300
2. upper 95% CI limit: 2.09% for moderate, 6.53% for severe exacerbation	2,100	9,900
f. Costs of an exacerbation		
1. Lower 95% CI limit: €86 for moderate, €2348 for severe exacerbation	2,300	11,200
2. Upper 95% CI limit: €102 for moderate, €5852 for severe exacerbation	1,900	9,000
g. Utility scores for the COPD GOLD stages		
1. 10% reduction in utility score in each GOLD stage	2,100	11,200
2. 10% increase in utility score in each GOLD stage	2,100	9,200
h. Lower usual care stop rate for smoking COPD patients		
1. Using a stop rate of 1.4%	2,100	10,100
i. Costs of the intervention		
1. 10% reduction in intervention costs	1,900	8,900
2. 10% increase in intervention costs	2,400	11,300

	Cost per exacerbation avoided	Costs per QALY gained
j. Other discount rates		
1. 0% effects, 0% costs	2,300	10,800
2. 4% effects, 4% costs	2,300	11,600
k. Different time horizon		
1. Two times shorter time horizon than base case (=5 years)	2,000	18,600
2. Two times longer time horizon than base case (=20 years)	2,400	6,400

Table 5.5: Sensitivity analyses for 10 year implementation of LABA, i.e. salmeterol for the cohort of Dutch COPD patients with moderate or severe COPD in 2007, time horizon ten years, €

	Cost per exacerbation avoided	**Costs per QALY gained**
Standard comparison of the intervention scenario with the reference scenario	1,800	7,100
a. Annual decline in FEV_1% predicted		
1. 50% lower annual decline	2,000	8,200
2. 50% higher annual decline	1,600	6,100
b. Baseline exacerbation frequencies		
1. lower 95% CI limits for all four GOLD stages	2,300	9,000
2. upper 95% CI limits for all four GOLD stages	1,400	4,900
c. Case fatality of a COPD exacerbation		
1. lower 95% CI limit: 10.9%	1,700	7,600
2. upper 95% CI limit: 20.3%	1,900	6,700
d. Decline in lung function due to an exacerbation		
1. lower 95% CI limit: -0.092% predicted	1,800	7,300
2. upper 95% CI limit: -0.288% predicted	1,700	6,900
e. Utility decrement due to an exacerbation		
1. lower 95% CI limit: 1.23% for moderate, 3.11% for severe exacerbation	1,800	7,200
2. upper 95% CI limit: 2.09% for moderate, 6.53% for severe exacerbation	1,800	7,000
f. Costs of an exacerbation		
1. Lower 95% CI limit: €86 for moderate, €2348 for severe exacerbation	2,000	8,000
2. Upper 95% CI limit: €102 for moderate, €5852 for severe exacerbation	1,500	6,200
g. Utility scores for the COPD GOLD stages		
1. 10% reduction in utility score in each GOLD stage	1,800	7,900
2. 10% increase in utility score in each GOLD stage	1,800	6,500
h. Lower usual care stop rate for smoking COPD patients		
1. Using a stop rate of 1.4%	1,800	7,100
i. Costs of the intervention		
1. 10% reduction in intervention costs	1,500	6,200
2. 10% increase in intervention costs	2,000	8,000

	Cost per exacerbation avoided	Costs per QALY gained
j. Other discount rates		
1. 0% effects, 0% costs	2,000	7,600
2. 4% effects, 4% costs	1,900	8,100
k. Different time horizon		
1. Two times shorter time horizon than base case (=5 years)	1,600	13,200
2. Two times longer time horizon than base case (=20 years)	2,100	4,500

Table 5.6: Sensitivity analyses for 1 year implementation of intensive counseling plus pharmacotherapy for smoking cessation for all Dutch smoking COPD patients in 2007, time horizon 20 years, €

	Cost per exacerbation avoided	**Costs per QALY gained**
Standard comparison of the intervention scenario with the reference scenario	Dominated	6,100
a. Annual decline in FEV_1% predicted		
1. 50% lower annual decline	Dominated	6,300
2. 50% higher annual decline	Dominated	5,800
b. Baseline exacerbation frequencies		
1. lower 95% CI limits for all four GOLD stages	Dominated	5,700
2. upper 95% CI limits for all four GOLD stages	Dominated	10,100
c. Case fatality of a COPD exacerbation		
1. lower 95% CI limit: 10.9%	Dominated	6,000
2. upper 95% CI limit: 20.3%	Dominated	6,100
d. Decline in lung function due to an exacerbation		
1. lower 95% CI limit: -0.092% predicted	Dominated	6,000
2. upper 95% CI limit: -0.288% predicted	Dominated	6,100
e. Utility decrement due to an exacerbation		
1. lower 95% CI limit: 1.23% for moderate, 3.11% for severe exacerbation	Dominated	6,100
2. upper 95% CI limit: 2.09% for moderate, 6.53% for severe exacerbation	Dominated	6,100
f. Costs of an exacerbation		
1. Lower 95% CI limit: €86 for moderate, €2348 for severe exacerbation	Dominated	6,000
2. Upper 95% CI limit: €102 for moderate, €5852 for severe exacerbation	Dominated	6,200
g. Utility scores for the COPD GOLD stages		
1. 10% reduction in utility score in each GOLD stage	Dominated	6,700
2. 10% increase in utility score in each GOLD stage	Dominated	5,500
h. Lower usual care stop rate for smoking COPD patients		
1. Using a stop rate of 1.4%	Dominated	4,700
i. Costs of the intervention		
1. 10% reduction in intervention costs	Dominated	5,500
2. 10% increase in intervention costs	Dominated	6,600

	Cost per exacerbation avoided	Costs per QALY gained
j. Other discount rates		
1. 0% effects, 0% costs	Dominated	5,600
2. 4% effects, 4% costs	Dominated	7,500
k. Different time horizon		
1. Two times shorter time horizon than base case (=10 years)	Dominated	9,900
2. Longer time horizon than base case (=30 years)	Dominated	5,500

Table 5.7: Sensitivity analyses for 2 year implementation of an interdisciplinary, community-based pulmonary rehabilitation program for all Dutch COPD patients with moderate and severe COPD in 2007, time horizon of five years, €

	Cost per exacerbation avoided	**Costs per QALY gained**
Standard comparison of the intervention scenario with the reference scenario	-	12,200
b. Baseline exacerbation frequencies		
1. lower 95% CI limits for all four GOLD stages	-	12,100
2. upper 95% CI limits for all four GOLD stages	-	12,400
e. Utility decrement due to an exacerbation		
1. lower 95% CI limit: 1.23% for moderate, 3.11% for severe exacerbation	-	12,100
2. upper 95% CI limit: 2.09% for moderate, 6.53% for severe exacerbation	-	12,300
g. Utility scores for the COPD GOLD stages		
1. 10% reduction in utility score in each GOLD stage		13,600
2. 10% increase in utility score in each GOLD stage		11,100
i. Costs of the intervention		
1. 10% reduction in intervention costs	-	11,000
2. 10% increase in intervention costs	-	13,400
j. Other discount rates		
1. 0% effects, 0% costs	-	12,300
2. 4% effects, 4% costs	-	12,500
k. Different time horizon		
1. Two times shorter time horizon than base case (=2 years)	-	17,400
2. Two times longer time horizon than base case (=10 years)	-	12,200

*****Sensitivity analyses a, c, d, f and h are not shown as pulmonary rehabilitation did not influence these parameters and the cost per QALY remained €12,200 in these analyses

5.4 Results for the probabilistic sensitivity analysis for the four different scenario's

Scenario 1: Implementation of a combination of ICS/LABA

Figure 5.1 shows the cost-effectiveness plane for 10 year implementation of a combination of ICS/LABA to all Dutch COPD patients with moderate and severe COPD evaluated over a ten year time horizon. All 1000 model simulations felt in the upper right quadrant indicating more QALYs and higher costs compared to the reference scenario.

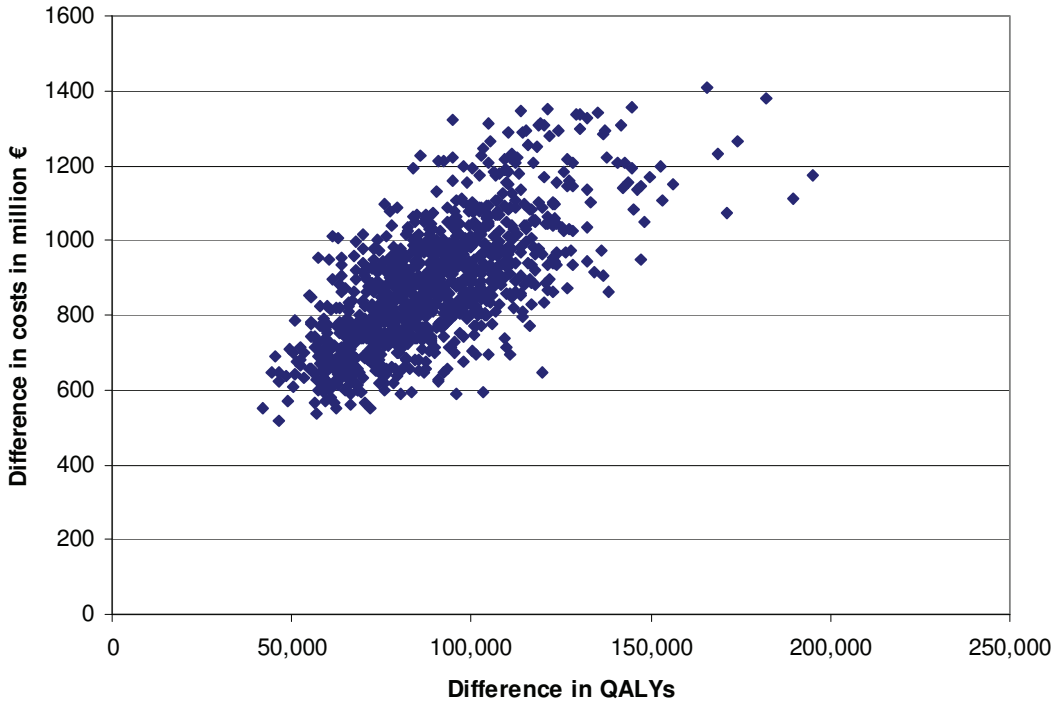

Figure 5.1: Cost-effectiveness plane for ten year implementation of a combination of ICS/LABA to all Dutch COPD patients with moderate and severe COPD, time horizon ten years, discount rates 1.5% effects, 4% costs

The accompanying acceptability curve (Figure 5.2) showed that the probability of a combination of ICS/LABA to be cost-effective was 52% for a maximum willingness-to-pay of €10,000 and 100% for a ceiling ratio of €20,000.

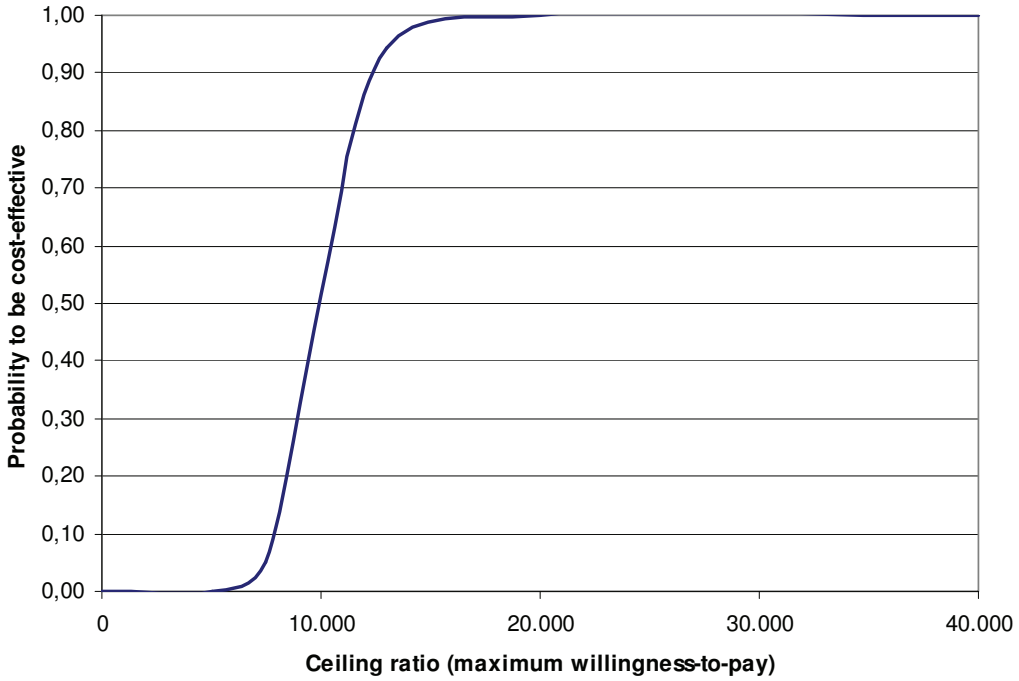

Figure 5.2: Acceptability curve for ten year implementation of a combination of ICS/LABA for all Dutch COPD patients with moderate and severe COPD, time horizon 10 years, discount rates, 1.5% effects, 4% costs.

Scenario two: Implementation of LABA

Figure 5.3 shows the cost-effectiveness plane for 10 year implementation of a LABA to all Dutch COPD patients with moderate and severe COPD evaluated over a ten year time horizon. Again, all 1000 model simulations felt in the upper right quadrant indicating more QALYs and higher costs compared to the reference scenario.

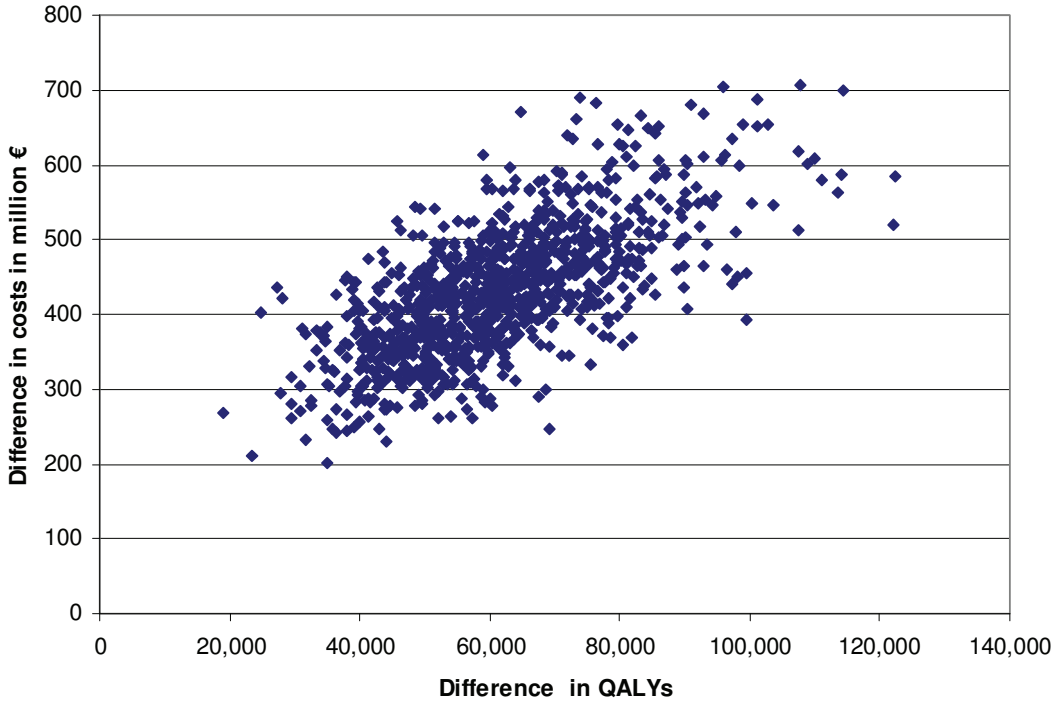

Figure 5.3: Cost-effectiveness plane for ten year implementation of a LABA to all Dutch COPD patients with moderate and severe COPD, time horizon ten years, discount rates 1.5% effects, 4% costs

The acceptability curve showed that the probability of the LABA salmeterol to be cost-effective was 96% and 100% for a maximum willingness-to-pay of €10,000 and €20,000, respectively (Figure 5.4).

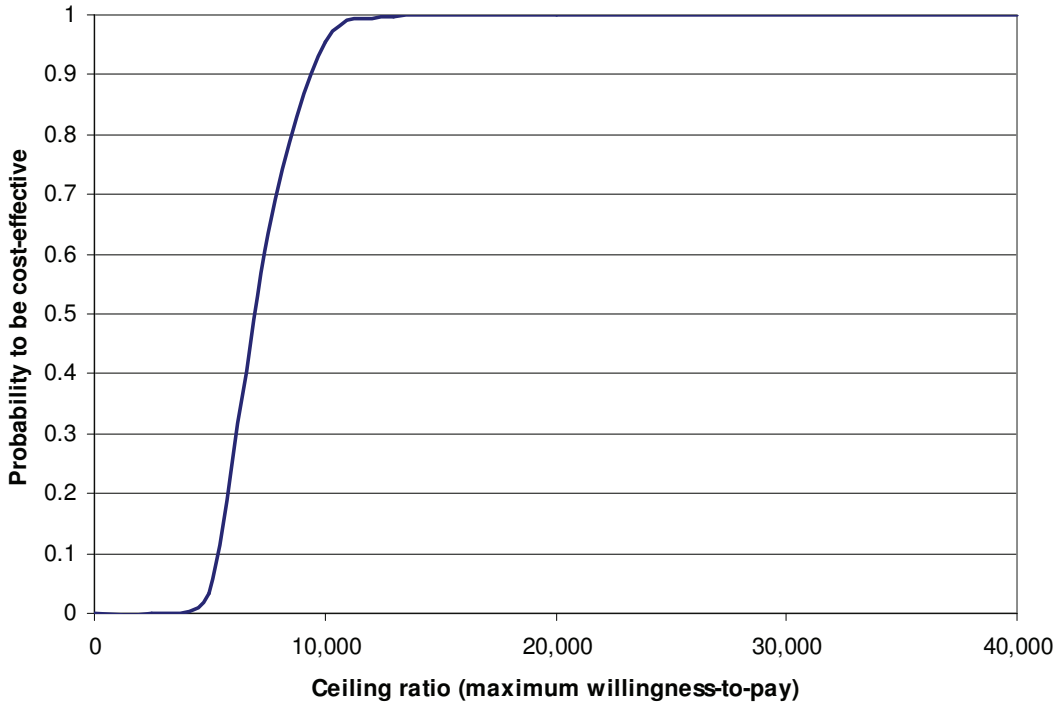

Figure 5.4: Acceptability curve for ten year implementation of a LABA (=salmeterol) for all Dutch COPD patients with moderate and severe COPD, time horizon 10 years, discount rates, 1.5% effects, 4% costs.

Scenario three: implementation of pharmacotherapy for smoking cessation

Figure 5.5 shows the cost-effectiveness plane for 1 year implementation of intensive counseling plus pharmacotherapy for smoking cessation for all smoking COPD patients evaluated over a twenty year time horizon. Of the 1000 model replications 99.9% felt in the upper right quadrant indicating more QALYs and higher costs compared to the reference scenario, while in 0.1% of the simulations the scenario had lower QALYs, but higher costs than the reference scenario.

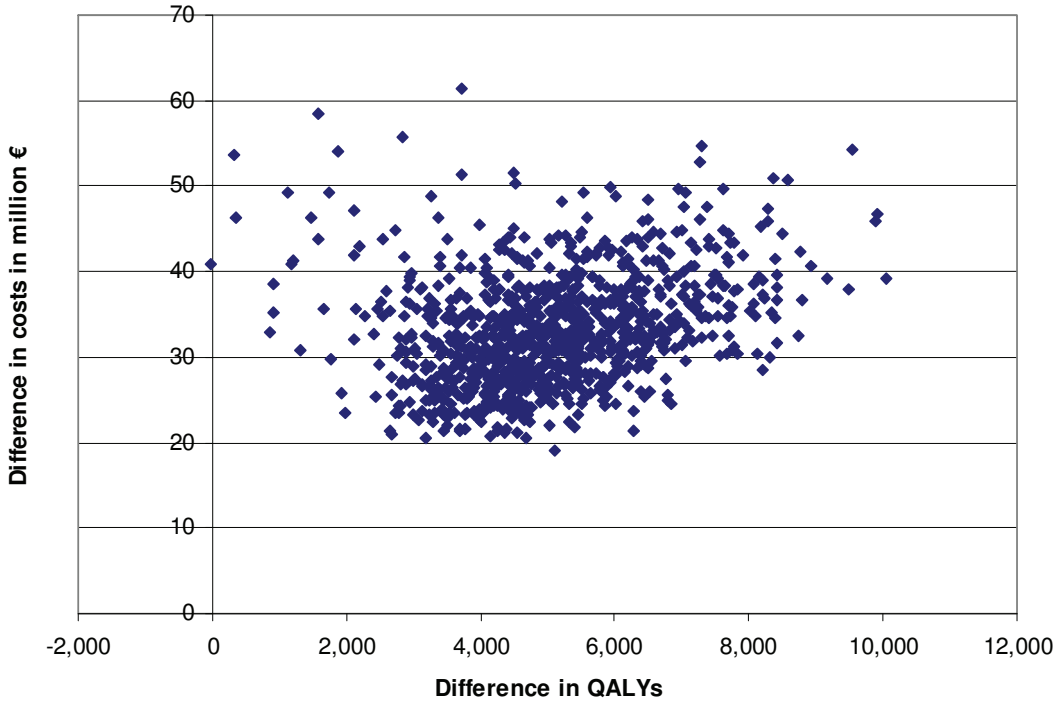

Figure 5.5: Cost-effectiveness plane for one year implementation of intensive counseling plus pharmacotherapy for smoking cessation for all smoking COPD patients, time horizon twenty years, discount rates 1.5% effects, 4% costs

The acceptability curve showed that the probability of the smoking cessation intervention to be cost-effective was 91% for a maximum willingness-to-pay of €10,000 and 98% for a ceiling ratio of €20,000.

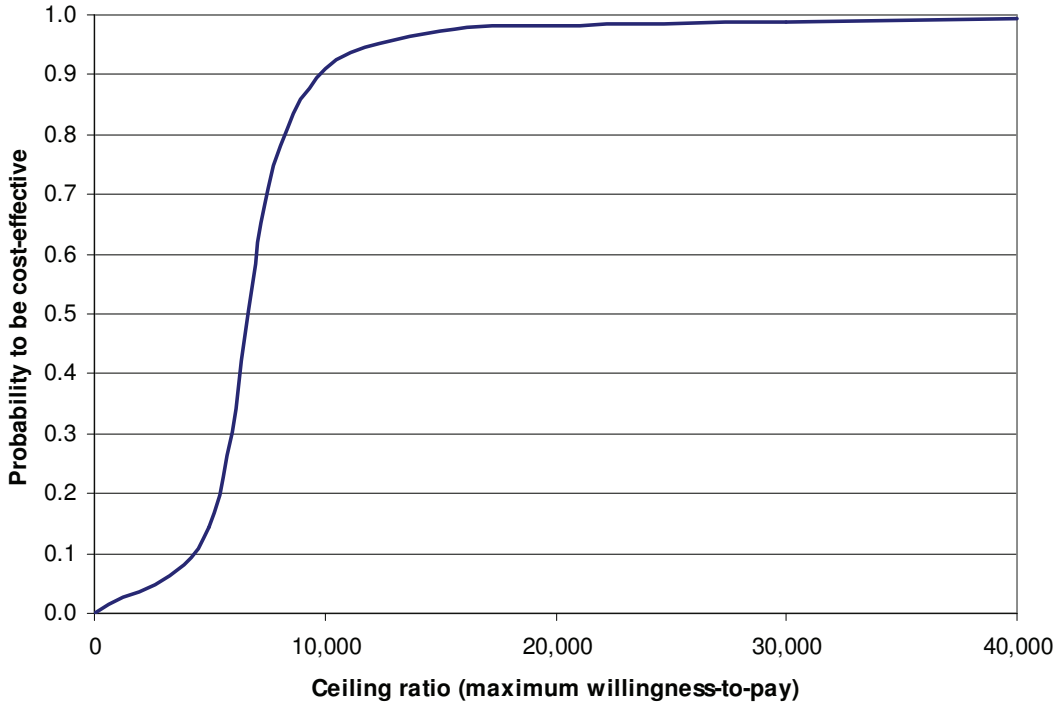

Figure 5.6: Acceptability curve for one year implementation of intensive counseling plus pharmacotherapy for smoking cessation for all smoking COPD patients, time horizon twenty years, discount rates 1.5% effects, 4% costs

Scenario four: implementation of community-based pulmonary rehabilitation program

Figure 5.7 shows the cost-effectiveness plane for two year implementation of an interdisciplinary community-based pulmonary rehabilitation program for all patients with moderate and severe COPD evaluated over a five year time horizon. 96% of the model simulations felt in the upper right quadrant indicating more QALYs and higher costs compared to the reference scenario.

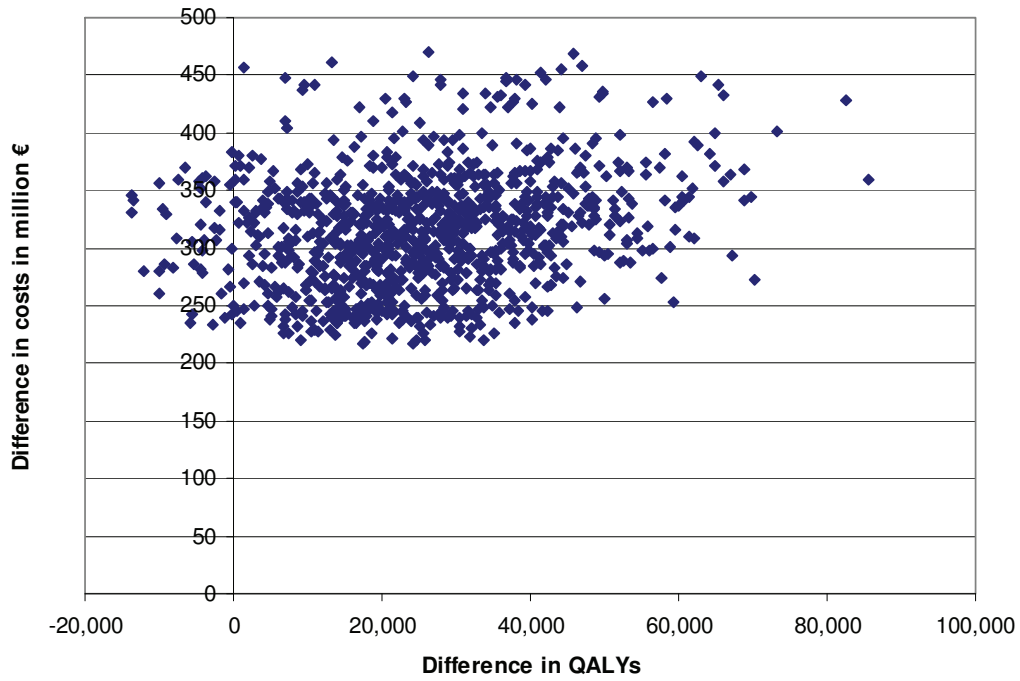

Figure 5.7: Cost-effectiveness plane for two year implementation of interdisciplinary community-based pulmonary rehabilitation to all Dutch COPD patients with moderate and severe COPD, time horizon five years, discount rates 1.5% effects, 4% costs

The acceptability curve showed that the probability of an interdisciplinary community-based pulmonary rehabilitation program to be cost-effective was 33% for a maximum willingness-to-pay of €10,000 and 76% for a ceiling ratio of €20,000.

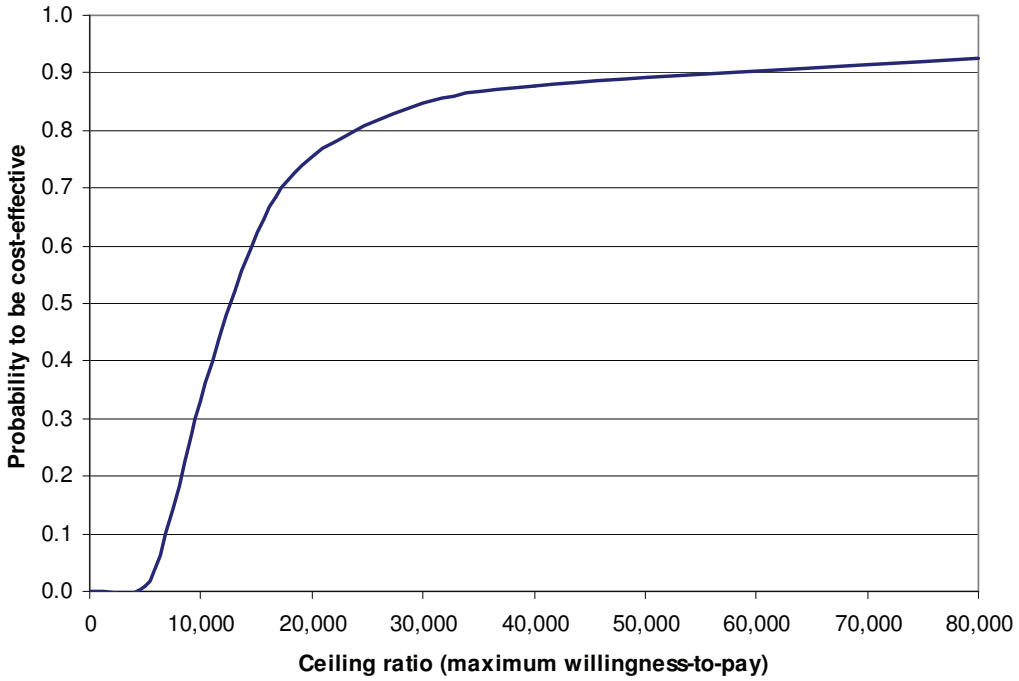

Figure 5.8: Acceptability curve for two year implementation of interdisciplinary community-based pulmonary rehabilitation for all patients with moderate and severe COPD, time horizon five years, discount rates 1.5% effects, 4% costs

6. Discussion

This study aimed at improving our previously published COPD model by including exacerbations and making the model stochastic. To illustrate the potential of the model four different COPD interventions were evaluated. The outcomes of these so-called scenario analyses were only illustrative and no definite conclusions can be drawn from the results for the following two reasons. For three scenario analyses short-term effectiveness used to fill the model was based on one study, i.e. the TORCH trial [36] or the INTERCOM trial [42]. To obtain more representative results effectiveness should be based on systematic reviews as for the smoking cessation scenario [38]. Second, we did not take into account realistic percentages of patients receiving the interventions, but applied the effects to all Dutch moderate or severe COPD patients or all smoking COPD patients. This is not realistic as for instance in the smoking cessation intervention, not all smoking COPD patients are willing to participate in a smoking cessation intervention. The percentage of smoking COPD patients reporting a willingness to stop smoking within six months is about fifty percent [43,44]. The same applies to the pulmonary rehabilitation scenario as not all moderate and severe COPD patients are eligible for such a program. For example, the INTERCOM program was indicated for patients with an impaired exercise capacity, only. To give more realistic estimates of the results in absolute numbers, reliable estimates of the percentage of patients using the interventions would be needed. These percentages however, do not substantially affect the estimates of the cost per QALY gained or the cost per exacerbation avoided. A different indication however, does affect the cost-effectiveness.

By choosing four completely different scenarios we tried to emphasize that the extended model can be used to evaluate a wide range of interventions. The model can be used to evaluate interventions that have an effect on lung function decline, quality of life, mortality and/or the frequency and severity of exacerbations. In our scenario analyses, both pharmacotherapies are assumed to affect disease progression, exacerbation frequency and all-cause mortality. The smoking cessation intervention is assumed to affect disease progression only. Indirectly, this affects mortality as patients reach the more severe stages of COPD later than they would if they would not have stopped smoking. Mortality is also directly reduced because within each severity stage smokers who quit get the lower mortality risk of former smokers. A possible positive effect of smoking cessation on exacerbation frequency could have been included in the scenario analysis, but no data are available which could be used as input for the model. The third type of scenario analysis, implementation of a pulmonary rehabilitation program, was assumed to have an

effect on quality of life. The model can also assess the impact of smoking cessation in the general population on COPD incidence. However, the current analysis was restricted to a cohort analysis among COPD patients already diagnosed.

Three different aspects with respect to the intervention scenarios should be kept in mind when comparing the cost-effectiveness outcomes of the four scenario analyses with each other. These aspects have a substantial impact on the absolute numbers of exacerbations avoided, QALYs gained, intervention costs and savings in COPD-related healthcare costs but also on the cost-effectiveness ratios. First, due to the different types of interventions used, the most realistic time horizon to use was different for each intervention. For pharmacotherapies ten years seemed a realistic time horizon, while for smoking cessation a ten-year time horizon was relatively short as the annual gain in QALYs was maximal around ten years. For pulmonary rehabilitation a ten-year time horizon is too long and a five-year time horizon seemed more appropriate. Second, the duration of implementation was different for all interventions. For pharmacotherapies we assumed that both ICS and LABA/ICS were used as maintenance therapy for the whole time horizon, i.e. continuous implementation. For the smoking cessation scenario however, we only used an implementation period of one year because it is not realistic to assume that all COPD patients receive smoking cessation interventions repeatedly each year. The scenario on pulmonary rehabilitation was based on a two-year trial, but we assumed the quality of life to be improved for three years. Finally, the patient population to which the intervention was offered was different for the smoking cessation scenario. Both scenarios on pharmacotherapies and pulmonary rehabilitation are assumed to be implemented for all moderate and severe patients (n=227,600), while the smoking cessation intervention was assumed to be given to all smoking patients, regardless of their disease severity (n=97,100). The shorter duration of the implementation period and the smaller patient population to which the intervention was offered explains why for example the absolute gain in QALYs in the smoking cessation scenario was substantially lower.

For all four scenario analyses we performed extensive one-way sensitivity analyses on the new exacerbation-related model parameters and on parameters for which a probabilistic sensitivity analysis is not appropriate, such as discount rates. One-way sensitivity analyses on the model parameters that were already included in the 2005 version of the model, such as the estimated severity distribution of the COPD population at baseline, the decline in lung function and mortality were performed previously [1]. In the 2005 version the distribution of the incidence over the severity stages had the largest influence on the projections but as the current scenario analyses are based on a cohort assuming no new

incidence, the distribution of the incidence plays no role in the current analyses. As the decline in FEV_1% predicted is the parameter defining disease progression, a very important parameter in our model, we also included a one-way sensitivity analysis on this parameter. In the 2005 version of the model, a 10% lower or higher annual decline in FEV_1% predicted had a moderate influence on the projections of the prevalence and costs over twenty five years. In the current version comparing intervention scenarios with the reference scenario the sensitivity analyses on decline did not have a large influence. For all four scenarios the time horizon chosen had the largest influence on the results. For the scenarios on pharmacotherapy and smoking cessation baseline exacerbation frequencies also influenced the results substantially. The latter however are well-based estimates obtained from a systemic review (see Appendix B). For the smoking cessation intervention, a lower stop rate for usual care also influenced the cost per QALY. However, because of the lack of studies reflecting usual care with respect to smoking cessation in COPD, the abstinence rate of usual care used in the sensitivity analyses was based on only one study.

Compared to the 2005 model, the extended model can generate uncertainty around the estimated results using probabilistic sensitivity analyses. The overall uncertainty around the estimates of the outcomes was relatively limited as in almost all cost-effectiveness planes all model iterations fell in one single quadrant, the north-east quadrant, indicating more effect but higher costs. Although the individual uncertainty around the gain in QALYs and the costs was substantial, the positive correlation between effects and costs led to a smaller uncertainty around the incremental cost-effectiveness ratio than would be expected based on the uncertainty around the costs and effects alone. The uncertainty may also be reduced by the assumption of monotonicity that was applied to the utility values per GOLD stage and the costs per GOLD stage. For utility values for example this means that in each simulation the randomly drawn value for the utility weight for mild COPD needed to be higher than the randomly random drawn values for the utility weights for moderate and the value for moderate COPD needs to be higher then the value for severe COPD etc. Monotonicity was also indirectly included for the exacerbation frequencies as these were based on a regression equation. The impact of the assumption of monotonicity on the uncertainty needs to be explored in a future probabilistic sensitivity analysis without this assumption. However, this requires an adjustment of the structure of the model. Finally uncertainty is also influenced by the fact that we did not consider structural model uncertainty. A decrease in number of severe exacerbations for example always results in a reduction of the case fatality. The same is true for a reduction in

exacerbation frequency which always results in a gain in utility. However, assumptions like this are medically very plausible.

A limitation of our model is of course that the severity and the progression of COPD are only defined by lung function, i.e. FEV_1% predicted. In real life, the severity of COPD is not only determined by the degree of airflow limitation, but also by the severity of symptoms, especially breathlessness, the level of exercise impairment and the existence of co-morbidities [4]. Celli et al showed that the BODE index, a simple multidimensional grading system using BMI, degree of airflow obstruction, dyspnea and exercise as parameters, was a better predictor of mortality in COPD patients than FEV_1 alone [45]. But also other composite measures, such as the DOSE (=Dyspnea, airflow Obstruction, Smoking status, Exacerbation frequency) and the ADO (=Age, Dyspnea, airflow Obstruction) seem to be better predictors of disease severity [46,47]. The same is true for disease progression. Other factors than the decline in lung function also influence the progression of the COPD [48]. However, parameters used in the BODE index for example are not all registered at general practices and in hospitals and therefore input data representative for the Dutch COPD population specified by BODE score are very difficult or impossible to obtain. For reasons of availability and simplicity the progression of COPD in the model is therefore only assumed to be dependent on the decline in FEV_1% predicted, which in turn depends on gender, age, smoking status and FEV_1% predicted.

Up to now, six different COPD models, including our 2005 COPD model have been published [1,24,31,49-51]. All existing models are Markov models and comparable with respect to COPD severity based on FEV_1% predicted, progression based on lung function decline, inclusion of exacerbations, distinction between at least severe and non-severe exacerbations and costs and utilities depending on severity stage and exacerbation frequency. Differences between the models are among others the number of COPD severity stages, inclusion of incidence and the allowance of backward transitions. Furthermore, some of the models are probabilistic [1,31,50], while others are not. Only the BOLD model described by Nielsen et al [51] and our model [1] are population-based models, representative for a total nationwide COPD population. However, the model of Nielsen et al is not stochastic. As our model is a probabilistic population-based model that includes new incidence, but can also be used for cohort analysis, it can be used to evaluate a wide range of interventions and assess the uncertainty around the results.

7. Conclusions

The updated and adapted model described in this report is now well equipped to provide decision support with information about long-term health effects, costs and cost-effectiveness of policy scenarios. Moreover it provides insight into the uncertainty of the outcomes.

The model is innovative in that it combines modelling the incidence of COPD with the course of disease. This allows the identification of the most cost-effective interventions within the whole spectrum from prevention to care. Up to now this was impossible, because only fragmented information exists on the cost-effectiveness of COPD interventions. Moreover the information available is usually incomparable because of methodological differences. The current model also allows comparing interventions of different intensity and target group. It may stress the need for integrated approaches, since single programs will probably not reduce the burden of COPD sufficiently on a nationwide scale.

The model has been developed without any industry support (funded by the RIVM, the Netherlands Asthma Foundation, the Dutch Ministry of Health, Welfare and Sports and the Erasmus University), and hence provides an independent tool for evaluation.

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APPENDIX A: Input parameters

Table A1: Dutch general population by gender and age*

	Dutch population 2007		All-cause mortality as fraction of the total population 2006	
	Males	Females	Males	Females
0-4	494914	471967	0.0011	0.0009
5-9	514058	491939	0.0001	0.0001
10-14	504748	480989	0.0001	0.0001
15-19	510433	488055	0.0003	0.0002
20-24	488388	477647	0.0005	0.0002
25-29	495146	494331	0.0005	0.0002
30-34	534023	534125	0.0006	0.0004
35-39	653937	641539	0.0008	0.0006
40-44	663663	646161	0.0013	0.0010
45-49	622404	613365	0.0021	0.0018
50-54	569839	562389	0.0038	0.0030
55-59	560626	550416	0.0061	0.0044
60-64	464275	460263	0.0103	0.0064
65-69	345852	361640	0.0168	0.0097
70-74	270832	314133	0.0296	0.0162
75-79	200533	274520	0.0515	0.0301
80-84	123040	216114	0.0898	0.0560
85+	71803	189885	0.1780	0.1417

* Aggregated into five years age classes

Data source:

Statistics Netherlands (CBS, 2006/2007)

Table A2: Proportion of never smokers, smokers and former smokers*

	Males			Females		
	Never smoker	Current smoker	Former smoker	Never smoker	Current smoker	Former smoker
0-4	1.00	0.00	0.00	1.00	0.00	0.00
5-9	1.00	0.00	0.00	1.00	0.00	0.00
10-14	0.93	0.06	0.00	0.94	0.06	0.00
15-19	0.77	0.20	0.03	0.79	0.18	0.03
20-24	0.60	0.31	0.09	0.64	0.27	0.09
25-29	0.49	0.35	0.16	0.54	0.30	0.16
30-34	0.45	0.35	0.20	0.52	0.29	0.19
35-39	0.43	0.36	0.21	0.50	0.28	0.22
40-44	0.38	0.36	0.26	0.39	0.31	0.30
45-49	0.28	0.37	0.35	0.31	0.32	0.38
50-54	0.21	0.35	0.44	0.29	0.31	0.40
55-59	0.18	0.31	0.51	0.34	0.27	0.39
60-64	0.17	0.25	0.58	0.41	0.21	0.38
65-69	0.14	0.18	0.68	0.45	0.15	0.40
70-74	0.12	0.14	0.73	0.46	0.13	0.41
75-79	0.11	0.14	0.75	0.49	0.12	0.39
80-84	0.10	0.15	0.75	0.53	0.10	0.37
85+	0.10	0.16	0.74	0.56	0.09	0.35

* Aggregated into five years age classes

Data source:

STIVORO. Roken, de harde feiten: Volwassenen 2007. STIVORO, Den Haag

Table A3: Age-and gender specific COPD prevalence and incidence*

	Prevalence as fraction of the general population		Incidence as fraction of the general population	
	Males	Females	Males	Females
0-4	0.001	0.001	0.000	0.000
5-9	0.001	0.001	0.000	0.000
10-14	0.002	0.001	0.000	0.000
15-19	0.003	0.002	0.000	0.000
20-24	0.004	0.002	0.000	0.000
25-29	0.005	0.003	0.000	0.000
30-34	0.006	0.005	0.000	0.000
35-39	0.007	0.007	0.001	0.001
40-44	0.009	0.011	0.001	0.001
45-49	0.013	0.016	0.002	0.002
50-54	0.019	0.023	0.003	0.004
55-59	0.029	0.032	0.005	0.005
60-64	0.045	0.042	0.007	0.006
65-69	0.071	0.053	0.009	0.007
70-74	0.107	0.064	0.012	0.007
75-79	0.146	0.072	0.013	0.006
80-84	0.173	0.076	0.014	0.006
85+	0.174	0.074	0.014	0.005

* Aggregated into five years age classes

Adapted from data source:
Van der Lucht F, Polder JJ. Van gezond naar beter. Kernrapport van de Volksgezondheid Toekomst Verkenning VTV-2010, versie 1.0, 25 maart 2010, RIVM, Bilthoven

* Prevalence and incidence data in VTV 2010 are based on five general practice data bases, Continue Morbiditeits Registratie (CMR) Nijmegen, Landelijk Informatie Netwerk Huisartsenzorg (LINH), Registratienet Huisartsenpraktijken (RNH), Registratie Netwerk Universitaire Huisartspraktijken Leiden en omstreken (RNUH-LEO) and Transitieproject. For the Chronic Disease Model and therefore also for our COPD model, the prevalence and incidence estimates used are based on three data bases (CMR, RNH, RNUH-LEO).

Table A4: Relative risks of smokers and former smokers to get COPD*

	Males			Females		
	Never smoker	Current smoker	Former smoker	Never smoker	Current smoker	Former smoker
0-4	1	1.9	1.7	1	1.7	1.5
5-9	1	1.9	1.7	1	1.7	1.5
10-14	1	1.9	1.7	1	1.7	1.5
15-19	1	1.9	1.7	1	1.7	1.5
20-24	1	1.9	1.7	1	1.7	1.5
25-29	1	1.8	1.6	1	1.6	1.4
30-34	1	2.0	1.8	1	1.8	1.6
35-39	1	3.2	2.7	1	2.6	2.3
40-44	1	5.1	4.1	1	4.0	3.4
45-49	1	7.5	5.9	1	5.6	4.8
50-54	1	9.8	7.9	1	7.7	6.4
55-59	1	11.0	9.6	1	9.9	7.7
60-64	1	11.7	10.3	1	11.3	8.3
65-69	1	12.2	9.5	1	11.2	8.2
70-74	1	12.5	8.5	1	10.0	7.4
75-79	1	12.2	7.7	1	8.1	6.5
80-84	1	11.0	7.0	1	6.1	5.4
85+	1	9.1	6.4	1	4.5	4.1

* Aggregated into five years age classes

Data source:

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Table A5: Age- and gender specific start, stop and restart probabilities for smoking, no uncertainty available*

	Males			Females		
	Start	Stop	Restart	Start	Stop	Restart
0-4	0	0	0	0	0	0
5-9	0.005	0	0	0	0	0
10-14	0.033	0.010	0.224	0.038	0.021	0.191
15-19	0.052	0.042	0.401	0.052	0.078	0.369
20-24	0.031	0.067	0.203	0.028	0.101	0.239
25-29	0.009	0.077	0.081	0.007	0.104	0.098
30-34	0.002	0.072	0.077	0.001	0.092	0.062
35-39	0.003	0.060	0.073	0.001	0.067	0.060
40-44	0.004	0.053	0.048	0.003	0.049	0.048
45-49	0.005	0.056	0.028	0.004	0.048	0.032
50-54	0.007	0.062	0.021	0.003	0.056	0.020
55-59	0.006	0.068	0.012	0.002	0.064	0.013
60-64	0.004	0.073	0.011	0.001	0.072	0.010
65-69	0.003	0.072	0.010	0	0.080	0.009
70-74	0.002	0.070	0.006	0	0.088	0.006
75-79	0.001	0.073	0.003	0	0.096	0.004
80-84	0	0.080	0.003	0	0.104	0.002
85+	0	0.086	0.003	0	0.109	0

* Aggregated into five years age classes

Data source:

STIVORO. Roken, de harde feiten: Volwassenen 2003. STIVORO, Den Haag

Table A6: Regression coefficients of the random effect model to predict lung function decline

	β-Coefficient	SE
Intercept	-20.9546	18.4636
Year	0.2394	0.2473
Smoking cessation	14.3188	1.0216
Gender	7.3174	4.44
Age	1.1132	0.7312
Baseline FEV_1% predicted	1.3646	0.2282
Year*smoking cessation	0.4556	0.05597
Year*gender	-0.1562	0.03543
Year*age	-0.03144	0.00332
Year*baseline FEV_1% predicted	0.006027	0.001933
Smoking cessation*gender	1.7297	0.2029
Smoking cessation*baseline FEV_1% predicted	-0.1242	0.01092
Gender*age	-0.4038	0.1694
Gender*baseline FEV_1% predicted	0.02723	0.01347
Age*baseline FEV_1% predicted	-0.01818	0.009069
Age^2	-0.01213	0.007189
Age^2*smoking cessation	-0.00086	0.000143
Age^2*gender	0.004299	0.001674
Age^2*baseline FEV_1% predicted	0.000197	0.000089

Data source:

Hoogendoorn M, et al. A dynamic population model of disease progression in COPD. 2005, Eur Respir J, 26(2): 223-233

Table A7: COPD-related maintenance costs per patient by gender, age and disease severity

	Mild COPD	Moderate COPD	Severe COPD	Very severe COPD
Males:				
45-49	47	58	65	96
50-54	32	39	44	65
55-59	31	39	43	65
60-64	72	89	99	148
65-69	135	167	187	277
70-74	197	245	273	406
75-79	346	430	480	712
80-84	344	428	477	708
85+	659	820	913	1356
Females:				
45-49	220	273	305	452
50-54	270	335	374	555
55-59	261	324	361	536
60-64	263	327	364	541
65-69	326	405	452	671
70-74	292	364	405	602
75-79	371	462	514	764
80-84	407	507	564	838
85+	831	1034	1152	1711

Table A8: Mean utility scores by COPD severity stage according to GOLD

GOLD stage:	Mean utility score (SD)
Mild COPD	0.8971 (0.1117)
Moderate COPD	0.7551 (0.2747)
Severe COPD	0.7481 (0.2991)
Very severe COPD	0.5493 (0.3129)

Table A9: All-cause mortality, mortality attributable to COPD and mortality from other causes, specified by gender and age (per 1000 COPD patients)*

	All-cause mortality		Mortality attributable to COPD		Mortality from other causes	
	Males	Females	Males	Females	Males	Females
0-4	90.9	102.6	90.9	102.6	0	0
5-9	0	0	0	0	0	0
10-14	1.9	0	1.9	0	0	0
15-19	8.3	2.6	8.3	2.6	0	0
20-24	9.2	1.8	9.2	1.8	0	0
25-29	5.8	5.3	5.8	5.3	0	0
30-34	5.8	5.2	5.8	5.2	0	0
35-39	7.7	7.1	6.8	6.9	0.9	0.2
40-44	9.9	9.2	8.6	8.4	1.3	0.8
45-49	14.7	13.7	12.5	12.0	2.1	1.7
50-54	21.8	18.7	18.0	15.9	3.8	2.8
55-59	32.1	24.6	25.9	20.1	6.2	4.5
60-64	44.4	30.7	34.7	24.4	9.8	6.3
65-69	61.0	39.8	45.6	30.4	15.4	9.4
70-74	84.2	55.7	58.9	40.3	25.3	15.5
75-79	119.2	84.0	75.2	56.1	44.0	27.9
80-84	171.2	129.1	90.9	75.7	80.2	53.5
85+	281.2	254.1	110.3	117.2	170.9	136.9

* Aggregated into five years age classes

Adapted from data source:
DYNAMO-HIA project originally based on the General Practice Research Database (GPRD) from the UK (www.gprd.com).

APPENDIX B: The association between lung function and exacerbation frequency in patients with COPD (working paper)

Running title: Exacerbation frequency specified by COPD severity

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Abstract

Objectives: To quantify the relation between severity of COPD as expressed by GOLD stage and the annual exacerbation frequency in patients with COPD.

Methods: We performed a systematic literature review for randomized controlled trials and cohort studies reporting the exacerbation frequency in patients receiving usual care or placebo. Annual frequencies were determined for the following outcomes: total exacerbations defined by an increase use of health care (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.

Results: 37 unique studies were found with 43 reports of the total exacerbation frequency (event-based: 19, symptom-based: 24) and 14 reports of the frequency of severe exacerbations. Annual event-based exacerbation frequencies per GOLD stage were estimated at 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. Annual symptom-based frequencies were 1.15 (95%CI: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%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. Study duration or type of study (cohort versus trial) did not significantly affect the outcomes.

Conclusions: This study provides an estimate of the exacerbation frequency per GOLD stage, which can be used for health economic and modeling purposes.

Key words: COPD, exacerbations, disease severity, GOLD, review, regression

Introduction:

The progression of chronic obstructive pulmonary disease (COPD) is often accompanied by periods of increasing symptoms, such as dyspnea, cough and sputum production, named exacerbations. Exacerbations are associated with an increase in mortality (1, 2) and have a high impact on health-related quality of life as the number and severity of exacerbations impairs the health status of a patient significantly (3-5). Exacerbations are also associated with an increase in healthcare use and associated costs (6, 7), especially in case of a hospitalization (8). Exacerbation frequency is therefore an important outcome parameter for patients with COPD (9, 10).

Quantification of the average exacerbation frequency however, is difficult. Many studies report the exacerbation frequency but results can not be compared directly as 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). Especially the use of different definitions seems to have a large influence. These definitions can roughly be divided in two groups: the symptom-based definitions and the 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, since the estimates also include the exacerbations which are not presented 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 doctor’s visit, the use of antibiotics and/or systemic steroids or hospitalization. However, event-based definitions are sensitive to differences in treatment patterns between settings. Besides the different criteria used to define an exacerbation, there is also no general agreement on how to classify the severity of an exacerbation. Most studies classify exacerbations based on the treatment required, increase of regular medication, 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 quantified this relationship. The present study aimed to quantify the relationship between the 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 the two most important types of definitions used, symptom-based and event-based and for total and severe exacerbations. We also 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 GOLD that

were used as input parameters in a dynamic multistate, life table model (14, 15). As this model aims to simulate the long-term cost-effectiveness of interventions which successfully prevent exacerbations, the exacerbation frequency in patients receiving care as usual was essential.

Methods

A systematic literature review was performed for 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 1) were published after 1990, 2) had a follow-up of at least three months, 3) used an event- or symptom-based definition for an exacerbation and 4) 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 other criteria than lung function were excluded (e.g. studies only including patients admitted to hospital, studies on 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 cross-references of the studies that met the in- 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 by GOLD stage.

Data extraction

Because the comparator arm in our model needs to reflect minimal care, we only extracted exacerbation data of the groups of patients that received either usual care or placebo. The following data were extracted: percentage males, mean age, and mean lung function in FEV_1% predicted of the study population, follow-up time, definition of

exacerbation used (symptom- or event-based) and the annual exacerbation frequency. If the mean FEV1 was only given in liters, the mean FEV_1% predicted of the study population was calculated based on other studies reporting both liters and percentages predicted. If the exacerbation frequency was presented for different classes of the FEV_1% predicted and the within-class mean 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 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 using the assumption that drop-outs count for half of the follow-up time.

Data analysis
As almost all studies only provided point estimates of exacerbation rates, uncertainty around the exacerbation rates was estimated assuming the exacerbations being Poisson distributed within each study. To quantify the relationship between the FEV_1% predicted and the annual exacerbation frequency, log linear random effect regression analysis was performed using the logarithm of the annual exacerbation frequency as dependent variable and the mean FEV_1% predicted of the study as independent variable. This regression analysis was performed using the S-plus routine glm for mixed-effects models (16). Analyses were performed separately for total event-based, total symptom-based and severe exacerbations. Retransformation of the logarithm of the exacerbations rates to exacerbation rates was performed using a smearing factor, which was calculated using the model fit residuals following the method of Duan et al (17, 18):

Smearing factor $\varphi = 1/n \; \Sigma 1\text{-}n \exp[\text{exacerbationrate\_observed} - \text{exacerbationrate\_predicted}]$

where n was the number of data points in the regression analysis. The relationship between the annual exacerbation frequency and the FEV_1% predicted was then:

Annual exacerbation frequency = $\varphi * \exp[a + b * FEV_1\%\ \text{predicted}]$
φ = smearing factor
a = intercept (estimated in the regression analysis)
b= coefficient for FEV1% 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). Uncertainty around the exacerbation rates per GOLD stage was estimated by Monte Carlo simulation. That is, 1000 random draws were taken from the distribution of the intercept and the coefficient for FEV_1% predicted. Covariance between the two parameters was taken into account by drawing random values for the coefficient for FEV_1% predicted that were dependent on the values drawn for the intercept. 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 time (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 resulted in 86 references of 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 9 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 B1.

Figure B1 shows the logarithm of the annual total and severe exacerbation frequency plotted against the mean FEV_1% predicted of the study with the estimated relation between the two obtained from the regression analyses. Parameters of the relationship between the mean FEV_1% predicted of the study and the exacerbation frequency are shown in Table B2. Lung function was a predictor of borderline significance for event-

based exacerbations only (p=0.053). Results for the mean exacerbation frequencies for the different GOLD stages based on the regression equations are presented in Table B3. Using an event-based definition the total exacerbation frequency was significantly higher in patients with an FEV_1% predicted below 50% compared to patients with an FEV_1% predicted above 50%.
Regression analyses with additional covariates showed that in general, no significant effect of the duration of follow-up of the study or the type of study (cohort versus trial) was found. Only for total exacerbations using the symptom-based definition the duration of follow-up was of borderline significance with longer follow-up resulting in lower rates (Table B4).

Discussion

Although many trials and cohort studies report on the important outcome, exacerbation frequency, the association between lung function and exacerbation frequency is less often investigated. The current study gathered the information contained in the literature and combined it to an estimate of exacerbation frequency as a function of the FEV_1% predicted. 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. The coefficient for lung function was of borderline significance.
The reason we have not found a strong relation between lung function and exacerbation frequency may be that regression on study summary estimates, as we did in this study, has substantially less power than regression on patient-level data (56). There is likely to be less variation in lung function across studies than in the 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 is not accounted for. 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 especially studies with a very low (<30%) and a very high mean FEV_1% predicted (>80%) were scarce or completely lacking.
In patient-level data the association of a lower FEV_1% predicted resulting in higher exacerbation frequencies is seen more clearly (6, 13, 54). Patient-level data on the exacerbation frequency specified by subgroup of lung function are however limited. 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 were lower than our estimates, except for very severe COPD. Vestbo et al reported about 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 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 2 or more exacerbations per year. The results of our study showed the same picture.

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 to 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 time. The mean follow-up in the studies in the review was 14 months, ranging from 3 to 36 months. Exacerbations depend on the season and are more likely to occur in the winter (3). According to recommendations 12, studies therefore need to have a follow-up of at least twelve months to give reliable estimates of the exacerbation frequency. Although we choose for a minimal follow-up of three months to have more data points for especially the lowest and highest values of the mean FEV_1% predicted, 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, although we did not find a significant difference between studies with a follow-up shorter and longer than 12 months. No systematic difference was found between the cohort studies and trials. This indicates that these selected trial populations seemed to be sufficiently representative for the COPD population as seen in daily practice with regard to the exacerbation frequency.

In conclusion, the current study provided a well based estimate for the average relation between the annual total and severe exacerbation frequency and FEV_1% predicted in

COPD. Results were in line with the few studies reporting about this relation in patient-level data. However, the general assumption that a lower FEV_1% predicted is indeed associated with a higher annual number of exacerbations was only true for total exacerbations using an event-based definition.

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Figure legends

Figure B1: Logarithm of the annual total or severe exacerbation frequency plotted against the mean FEV_1% predicted of the study

Table B1: 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	121	84	65	58	12	Event-based	1.51	0.14
Trial	Coultas, 2005	51	54	69	46	6	-	-	0.20
Trial	Rea, 2004	52	41	68	50	12	-	-	0.67
Trial	Littlejohns, 1991	65	63	63	50	12	-	-	0.31
Trial	Gallefoss, 1999	31	52	58	56	12	-	-	0.14
Trial	Brusasco, 2003	400	76	65	39	6	Symptom-based	1.49	0.15
Trial	Casaburi, 2002	371	63	65	38	12	Symptom-based	0.95	0.16
Trial	Niewoehner, 2005	915	99	68	36	6	Symptom-based	1.05	0.25
Trial	Vincken, 2002	179	86	65	39	12	Symptom-based	0.96	0.16
Trial	Dusser, 2006	510	87	65	48	12	-	-	0.15
		280	-	-	67	12	Event-based	1.97	-
		230	-	-	31	12	Event-based	2.70	-
Trial	Calverley, 2003a	361	75	63	44	12	Event-based	1.30	-
Trial	Calverley, 2003b	256	75	65	36	12	Event-based	1.80	-
Trial	Szafranski, 2003	205	83	65	36	12	Event-based	1.87	-
Trial	Calverley, 2007	1524	76	65	44	36	Event-based	1.13	0.19
Trial	Dal Negro, 2003	6	83	40-76	50	12	Event-based	4.17	-
Trial	Wonsurakiat, 2004	125	95	68	60	12	Symptom-based	1.35	0.06
Trial	Allegra, 1996	218	71	59	70	6	Symptom-based	1.32	-

Trial	Bontognali, 1991	30	57	59	75	3	Event-based	1.27	-
Trial	Decramer, 2005	258	79	62	57	36	Event-based	1.31	-
Trial	Grassi, 1994	41	79	62	57	3	Symptom-based	5.37	-
Trial	Hansen, 1994	70	46	52	85	5	Symptom-based	1.95	-
Trial	Malerba, 2004	119	76	61	70	12	Symptom-based	0.87	-
Trial	Meister, 1999	124	41	58	79	6	Symptom-based	1.20	-
Trial	Moretti, 2004	61	75	68	59	8	Symptom-based	2.07	-
Trial	Pela, 1999	84	71	66	59	6	Symptom-based	3.50	-
Trial	Burge, 2000	370	74	64	50	36	Event-based	1.90	-
Trial	Van Grunsven, 1999	88	90	61	44	24	Event-based	1.00	-
Trial	Vestbo, 1999	145	62	59	87	36	Symptom-based	0.45	-
Cohort	Llor, 2008	136	96	70	49	24	Symptom-based	0.93	
Cohort	Mittmann, 2008	609	58	69	44	12	Symptom-based	1.39	0.27
		609	58	69	44	12	Event-based	1.13	
Cohort	Langsetmo, 2008	421	57	67	46	6	Symptom-based	2.70	
Cohort	Hutchinson, 2007	92	63	72	40	Median 10.8	Symptom-based	1.79	
Cohort	O'Reilly, 2006	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	441	98	66	33	24	Symptom-based	1.50	
Cohort	Donaldson, 2003	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	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	30	43	67	68	Mean 26	Symptom-based	1.80	-
		32	41	64	36	Mean 26	Symptom-based	3.0	-

Table B2: Estimates 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)	0.981 (0.364)	-1.043 (0.904)
Coefficient FEV_1% predicted: b	-0.014 (0.007)	-0.009 (0.007)	-0.013 (0.020)
Covariance intercept and coefficient	-0.00227	-0.00227	-0.0176
Smearing factor: φ	0.893 (0.093)	0.960 (0.113)	1.072 (0.154)

[#] Values are mean (SE)

Table B3: 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 (1.51-1.74))	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)

Table B4: Random effect regression analysis of FEV1%predicted and annual exacerbation frequency: significance of the covariates, type of study and duration of follow-up

	P-value for type of study (cohort vs 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

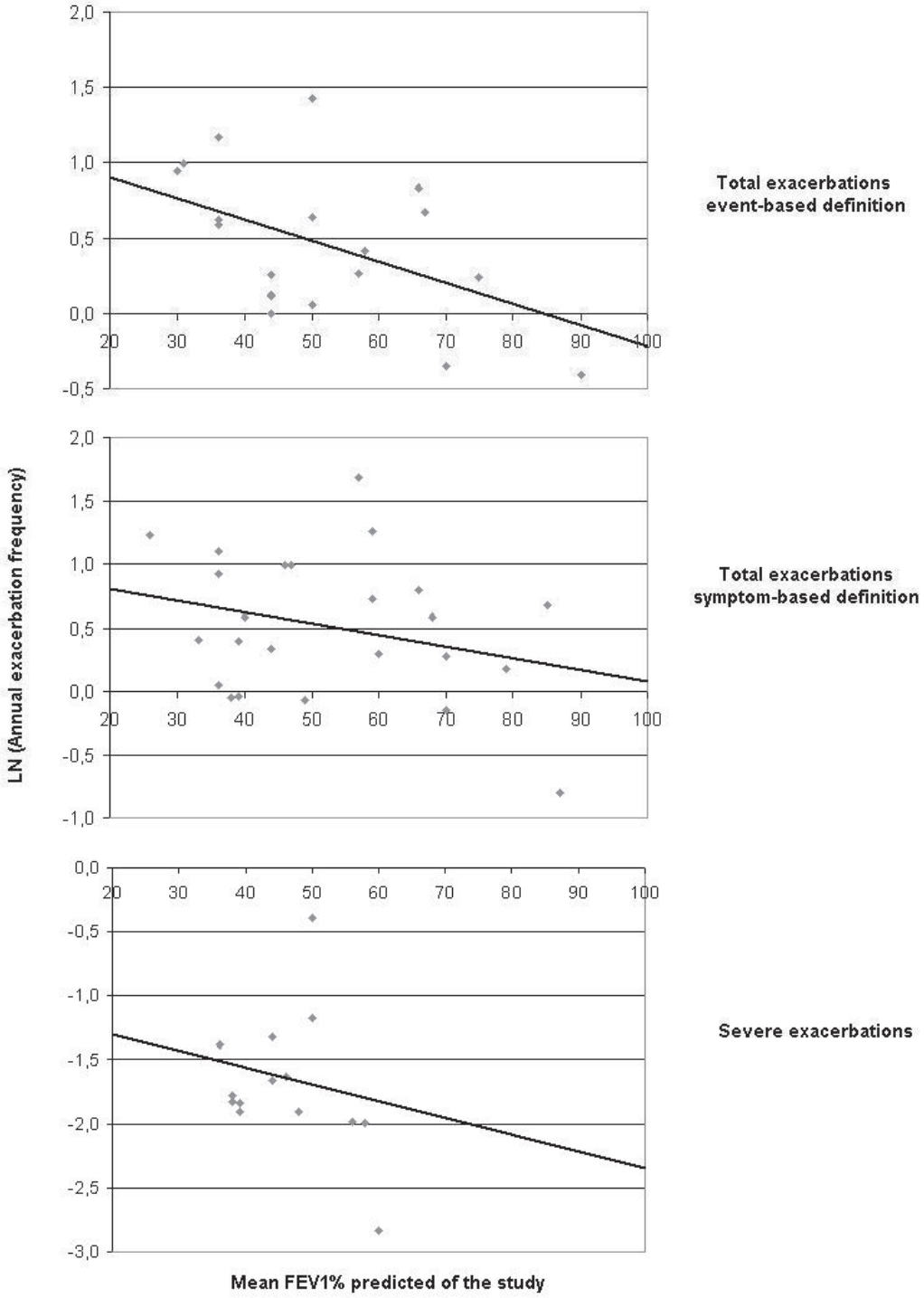

Figure B1: Logarithm of the annual total or severe exacerbation frequency plotted against the mean FEV_1% predicted of the study

APPENDIX C: Case-fatality of COPD exacerbations: a meta-analysis and statistical modeling approach (working paper)

Note: Submitted to Eur Resp J, Accepted for first revision (May 2010)
Short title: Case-fatality of COPD exacerbations

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Abstract

Objective of the 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 at least 1.5 year survival after a severe COPD exacerbation resulting in hospitalization. Each study's 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. 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 of the estimated case-fatalities were obtained by bootstrapping. A random effect model was used to combine all estimates into in a weighted average with 95%-confidence interval.

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 resulting in 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.

Word count abstract: 200

Keywords: case-fatality, chronic obstructive pulmonary disease, exacerbation, hospitalization, meta-analysis

Introduction

Worldwide, mortality due to COPD is high. According to the WHO, at least 2.7 million deaths are due to COPD every year [1]. The 30-year 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 women - and aging 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), dyspnea, co-morbidity, body mass index (BMI), fat-free mass, exercise capacity, PaO2, C-reactive protein, the BODE-index, incorporating BMI, airflow obstruction, dyspnea, 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 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, the present 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, multistate, life-table 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 and age 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 at least 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 obtain 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.

Our general approach was as follows (see figure C1). For each study, we extracted the presented or estimated survival curve and 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:

$$S(t) = (1-g)\,\mathrm{Exp}[-\alpha t - \beta t2]$$

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. Then we 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). Confidence intervals for each parameter were obtained from bootstrapping. Conditional 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 one study was investigated, as 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 (see figure C2). Entire review of these remaining publications resulted in exclusion of another 44 studies for different reasons (figure C2). The main reasons for exclusion were that the association between hospitalization for COPD and mortality was not reported (13 studies) and that the study 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 other diagnoses 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; 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 as presented in the article. Characteristics of the studies included are shown in Table C1.

Case-fatality

Table C2 presents the results of the curve fitting procedure for each of the six studies selected. Details about the parameter values for each study are presented in the online data supplement. 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%).

Association between mortality and age

All of the six studies reported about 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 to die after a hospitalization for an exacerbation increased with 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 C3 [9,10,21-28]. Table C4 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 weighted mean in-hospital mortality rate was 4.4%. The average mortality rates at three and six months were 16% and 29%, respectively.

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%. Comparing our results of the case-fatality with mortality probabilities at specific time points (table C4) showed that the weighted average in-hospital mortality rate was 4.4%, which strongly supports the notion that the critical period indeed exceeds the duration of the hospitalization.

The exact distinction between the critical and stable period after exacerbation onset however, could not be determined. The critical period was defined as the period in which mortality is increased compared to the stable situation. This period therefore ranges from the hospital admission till the point were the estimated survival curve during the stable period approaches the actual observed survival curve (see 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 of 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, gender 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 gender was less clear. Mortality after a hospitalization for an exacerbation was however highly dependant 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 seen 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 are for example 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. The mean in-hospital mortality rate however, did not differ, so possible differences in the characteristics of the study population do not seem to have an important effect on the results.

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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Figure legends

Figure C1: Survival curve after hospitalization for an exacerbation of COPD. The dotted line represents the extrapolated curve during the stable phase

Figure C2: Results of the systemic literature search

Table C1: 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	Mean age	Patient selection	Definition exacerbation	Country
Connors, 1996	1016	70	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	USA
Vestbo, 1998	487	67	Patients (age>20yr) admitted for COPD (Copenhagen City Heart Study)	Hospitalization (>24 hours) with primary diagnosis ICD-8:491-492	Denmark
Groenewegen, 2003	171	70	Patients with COPD (ATS criteria), with a FEV1<70% and reversibility<11% who were admitted	Increase of two of three symptoms: dyspnea, cough, sputum severe enough to warrant hospitalization	Netherlands
Gunen, 2005	205	65	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	Turkey
McGhan, 2007	54269	69	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	USA
Brekke, 2008	996	71	Patients (age>40 yr) admitted for COPD	Hospitalization with primary discharge diagnosis ICD-10:J44.0, J44.1, J44.x with J13-J18.9	Norway

Table C2: 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	1016	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	53,249	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.

Table C3: 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	Mean age	Patient selection	Definition exacerbation	Country
Fuso, 1995	590	68	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	Italy
Cydulka, 1997	131974	75	Patients (age>65yr) admitted for COPD	Hospitalization with first diagnosis ICD-9: 490-492, 496	USA
Eriksen, 2003	300	71	Patients admitted for COPD	Hospitalization for COPD exacerbation	Denmark
Patil, 2003	71130	70	Patients (age>40 yr) admitted for COPD	Hospitalization with discharge code ICD-9: 491.21	USA
Yohannes, 2005	104	73	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	UK
Wang, 2005	282	71	Patients (>40yr), smoker/former smoker, FEV1<80%, FEV1/FVC<70% , no other lung disease who were admitted	Hospital admission for an acute exacerbation of COPD	Canada
Price, 2006	7529	Unknown	Patients with physician-diagnosed COPD who were admitted	Acute hospital admission for COPD	UK
Bustamente, 2007	763	76	Patients (age>45yr) with COPD according to GOLD who were admitted	Hospitalization with diagnosis: ICD-9: 491.21	Spain
Kinnunen, 2007	72896#	72	Patients (age>44yr) admitted for COPD	Hospital admission with primary diagnosis ICD-8,9: 491, 942, 496 ICD-10: J41, 42, 43, 44	Finland
Dransfield, 2008	825	66	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	USA

Number of admissions instead of number of patients

Table C4: Mortality rates after hospitalization for a COPD exacerbation at different time points for the seven 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	1016	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	54269	3.6%	-	-	-	-	57%
Brekke, 2008	897	9.9%	22%	27%	32%	41%	-
Studies (follow-up<1.5 years) excluded from the meta-analysis							
Fuso, 1995	590	14%	-	-	-	-	-
Cydulka*, 1997	131974	6%	-	-	-	-	-
Eriksen, 2003	300	8.6%	19%	-	36%	-	-
Patil, 2003	71130	2.5%	-	-	-	-	-
Yohannes, 2005	104	3.8%	-	-	38%	-	-
Wang, 2005	282	9.9%	-	-	-	-	-
Price, 2006	7529	7.4%	15%	-	-	-	-
Bustamente, 2007	763	6.4%	-	-	-	-	-
Kinnunen, 2007	72896#	3.2%	-	-	-	-	-
Dransfield, 2008	825	5.2%	-	-	-	-	-
Weighted average rate based on all 16 studies		**4.4%**	**16%**	**29%**	**36%**	**44%**	**57%**

* Results year 1991
# Number of admissions instead of number of patients
- Not reported

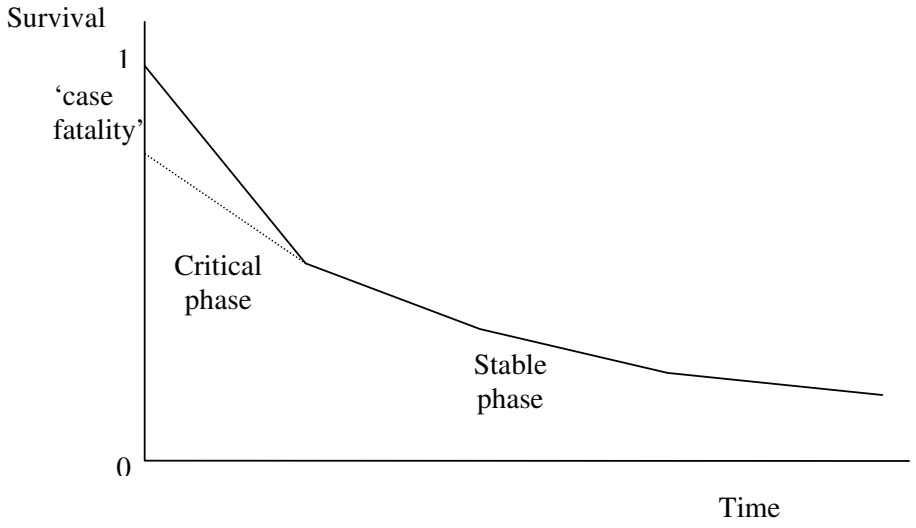

Figure C1: Survival curve after hospitalization for an exacerbation of COPD. The dotted line represents the extrapolated curve during the stable phase.

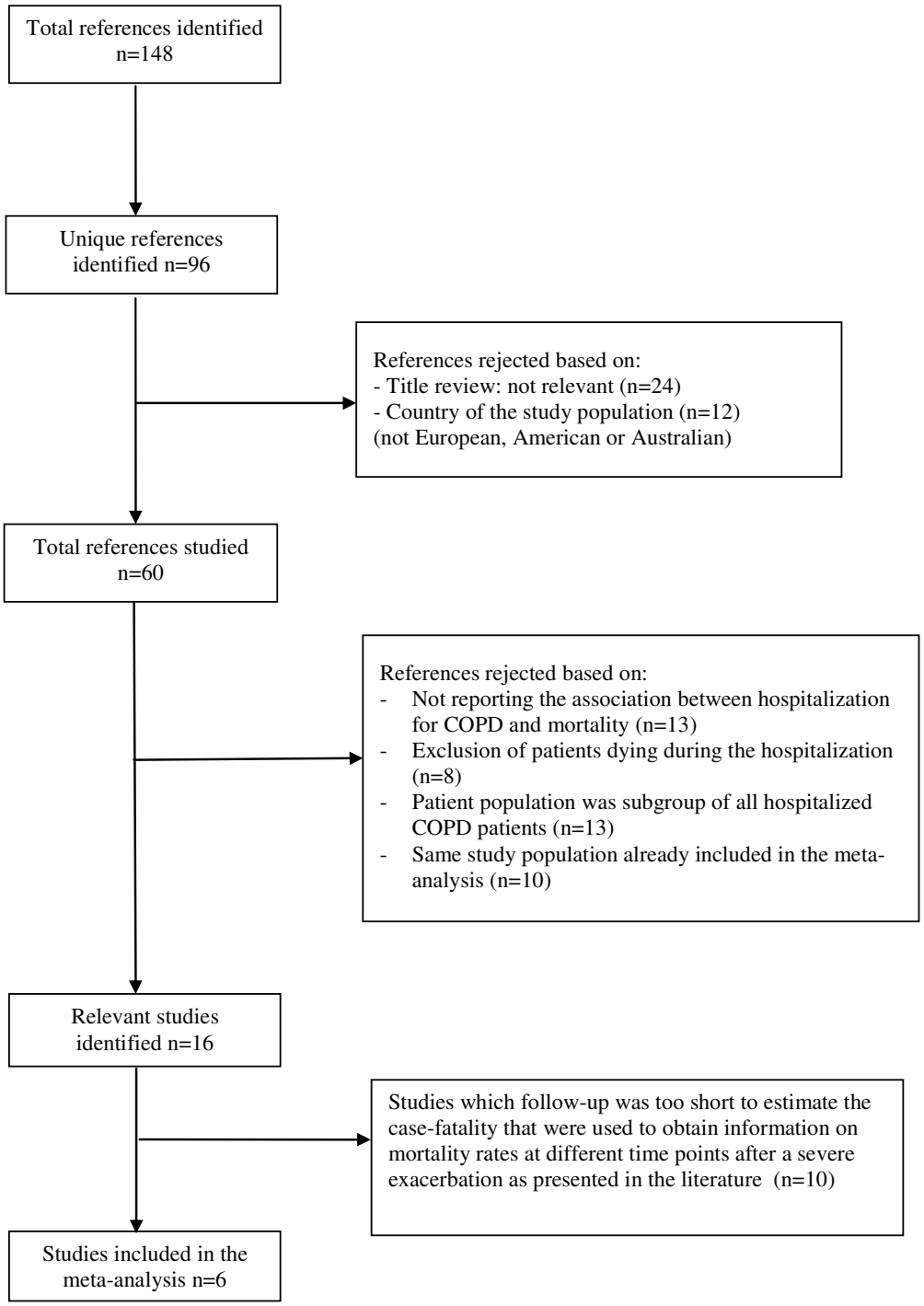

Figure C2: Results of the systematic literature search

ONLINE DATA SUPPLEMENT

of manuscript

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

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

$S(t) = (1-g)\ Exp[- \alpha\ t - \beta\ t2]$

with t time, with x=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 Suppl. C1: Median parameter values (95% uncertainty interval) of the survival function

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

Based on patient-level data

References:

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APPENDIX D: Mathematical description of the COPD model with exacerbations

D1. Introduction

This appendix contains a formal, mathematical description of the COPD model, in addition to the short verbal description in section 2.1. An earlier version of the model has been published [1]. However, for the sake of clarity the current appendix describes the entire new model.

After this introduction, the appendix contains three sections. The first presents the general formal model structure. The formulas given summarize the Mathematica code that forms the model used in the calculations. The model will be described as a deterministic model first, followed by a description of how probabilistic sensitivity analysis of model results can be performed by taking random draws for a range of parameters values. The section starts with an overview of the symbols used throughout this whole section.

In the second section, for specific elements in the model, the approach taken is further elaborated and mathematical background for the equations used is given.

Finally a third section contains a description of the methods used to find the input values for COPD excess mortality.

D2. Description of the general model structure.

D2.1 Overview of symbols used in appendix D2

Tables D1 to D3 list the symbols used in the current section and the corresponding variable name in the MMA code.

Table D1: Definition of index-symbols used in model formulas

a	age
r,r'	indexes over smoking classes, r=1,2,3 (never, current, former smoker)
c	index over COPD severity classes, c=1 (no COPD), 2,3,4,5,6 (very severe, severe, moderate B, moderate A and mild COPD)
D, $\overline{D}$	with (= conditional on having) and without (= conditional on not having) COPD respectively
a(t)	age on time t
x	value of continuous lung function
E	exacerbation (as an event)
j	Index indicating a decrease (1), or increase in lung function (2)

Table D2: Definition of model input parameters, for values see appendix A.

Category	Symbol	MMA code variable names	Explanation
general demography	$m_{tot}(a)$	morttot	All cause mortality
	P(a)	npop0	Population size
smoking	P(r;a)	prisk1	Initial proportion in smoking class r at age a.
	$\lambda^R_{+1}(r;a(t))$	transriskscen	transition rate from smoking class r to class r+1 (that is: start rate, quit rate or zero)
	$\lambda^R_{-1}(r;a(t))$	transriskscen	transition rate from smoking class r to class r-1 (that is: zero, zero, or relapse rate)
COPD:	P(D;a)	COPDprev	Probability of having COPD at age a
	em(D;a)	COPDexcessmort	COPD excess mortality
	$i_D(a)$	COPDinc	COPD incidence rates
	$P_{inc}(c\|D;a)$		initial distribution over severity classes for new COPD patients
	$P_{prev}(c\|D;a)$		initial distribution over severity classes for current COPD patients
exacerbations:	P(E;x)	Makeprobexacerbsev, resp Makeprobexacerbtot	exacerbation frequency that depends on lung function x
	m(E;a)	mortexacerb	case fatality of a severe exacerbation at age a.
	FE	FEV1exacerb	Lung function decrease as a result of a severe exacerbation
smoking and COPD:	$P(r \mid D;a)$	prokenCOPD0	Percentage of never, current and former smokers, conditional on having COPD
	$P(r \mid \overline{D};a)$	prokennonCOPD0	idem conditional on not having COPD
	$P(r,\overline{D};a)$		initial joint probability for smoking class r and being COPD-free
risk ratios:			
	$RR^E_{tot}(a)$		case fatality relative risk for an exacerbation
	$RR^F_{tot}(x)$	RRFEVtot/HRFEV	all-cause mortality relative risk for lung function x
		RRrisk	relative COPD risk for smoking class r
lung function:	x'(r,x;t)	dFEVdown	autonomous decrease
		dFEVup	increase as a result of smoking cessation

	$\mu_F(c)$	meanFEV0	mean lung function values
	P(E|x), $P_{all}(E|x)$		annual probability of a severe or any exacerbation respectively(1)
	$f_{sev}(x)$		proportion of exacerbations that is severe(1)
	$f_{mod}(x)$		idem, moderate
Costs	$K_{exacerb,sev}(c;a)$	costsexacerbsev	costs related to severe exacerbations
	$K_{exacerb,\mathrm{mod}}(c;a)$	costsexacerbmod	costs related to moderate exacerbations
	$K_{COPD}(c;a)$	costsCOPDpatient	maintenance costs for COPD patients
Health benefits	$QALY_{COPD}(c;a)$	QALYCOPD	QALY weight related to COPDstage
	$QALY_{exaxc,sev}$	QALYexacerbsev	loss of QALY weight because of severe exacerbation, as a factor relative to QALY-weight for COPD severity class
	$QALY_{exaxc,mod}$	QALYexacerbmod	Idem for moderate exacerbation

(1) we distinguished moderate and severe exacerbations, and both combined. Only severe exacerbations result in increased mortality risks, all exacerbations combined result in lung function decrease, and both have different costs. As a result we have the relation $P(E|x) = P_{all}(E|x)\ f_{sev}(x)$.

Table D3: Definition of model variables, values determined during model initialization or model simulation

Category	Symbol	MMA code variable names	Explanation
general demography	P(S;t)		survival probability
	$m_{oth}(a)$	mortothCOPD	other causes mortality rate
smoking	P(r|S;t)		smoking class r probability value on time t, conditional on survival
COPD:	am(D;a)	COPDexcessmortadj	COPD attributable mortality
	$i_{D0}(a)$	incCOPDbase	baseline COPD incidence rate, that is, incidence rate for a never smoking COPD free individual
	$\lambda^{D}_{+1}(c,r;t)$	ptransCOPDup	transition rate to less severe GOLD stage (from c to c+1)
	$\lambda^{D}_{-1}(c,r;t)$	ptransCOPDdown	transition to more severe GOLD stage (from c to c-1)
	$em_{oth}(c;a)$	mortnonexacerb	excess mortality rate that cannot be attributed to exacerbation
smoking and COPD:	P(r,c;t)	nrokenCOPD, nrokenCOPD1	joint distribution function over smoking class r and COPD stage c
	P(r,c;a)		joint probability for smoking class r and COPD severity class c
risk ratios:	$RM^{R}_{oth}(r;a)$	RMothriskCOPD	calculated other causes mortality risk multiplier for smoking class r
	$RR^{R}_{oth}(r;a)$		Idem Relative risk
lung function:	x'(r,x;t)	dFEVdown	autonomous decrease
		dFEVup	increase as a result of smoking cessation
	f(r,x;t); α,β	distFEV, distFEV1, distFEV2, distFEV3	new distribution functions of lung function as a result of different events, coefficients of the distribution function
	$\mu_F(r,c;t)$	meanFEV	mean lung function values
	f(r,x;t)	distFEV,	joint distribution function of lung function and smoking
	f(x|r,c;t)		distribution function of lung function within (= conditional on) smoking class r and COPD severity class c
Costs	$K_{totyr}(t)$		calculated expected costs for year t
Health benefits	$QALY_{totyr}(t)$		calculated QALYs for year t

D2.2 Introduction to model structure.

The model describes the life course of any individual in terms of changes of smoking class, COPD severity class, and lung function value. It is mathematically built in the form of a Markov-type state-transition model. Difference equations describe the change of the state variables over time, as a result of transitions from one state to the other. The cycle length is one year. The two most important state variables in the COPD model are: 1) probability values per COPD severity stage (this includes not having COPD as a special stage), per smoking class, per age class, and gender, and 2) coefficients characterizing the distribution of FEV1%pred within each COPD severity stage per smoking class. The latter distribution has to be interpreted as the mean distribution over both genders and all ages. Finally, the number of exacerbations in each COPD severity stage is important. Basically the model describes how these variables evolve over time and how they are related.

For instance, the number of current smokers with mild COPD in year t+1 is defined by the number of current smokers with mild COPD in year t, adding new mild COPD incidence among smokers, adding new as well as restarted ex-smokers among mild COPD patients, subtracting smoking cessation in mild COPD patients, subtracting decrease in health status to moderate COPD and correcting for mortality. To each state the model attaches estimates of annual costs and a quality of life weight.

Exacerbations are considered as events, not as specific states. In each COPD state, the total number of exacerbations per year is estimated, as well as the number of severe and moderate exacerbations. These numbers affect several transition rates (mortality, and lung function decline) and state specific costs and quality of life.

Lung function is modeled as a continuous variable. A normal distribution function over the entire FEV1% range was used as input and approximated by a linear function within each severity class, characterized by two parameters. These parameters change as a result of transitions between COPD states, smoking classes, and mortality. In this way, the parameters of the distribution function within each severity class also have the Markov-property: annual changes do not depend on past values, conditional on the current values.

Almost all model variables are specific to age and gender. To increase the stability of the model, a few variables were defined as being constant over gender and age. This refers to the parameters of the linear distribution functions of the lung function, and the resulting mean lung function values for each COPD severity class.

Important other smoking-related chronic diseases were included in the model, namely myocardial infarction (AMI), stroke (CVA) and lung cancer (LC).

This section follows the computational order in the model-code. First all input parameters are defined or read from data files and some help variables are computed. The following

model parameters are calculated based on input data: mortality rates from other causes than COPD, case fatality of an exacerbation, the remaining COPD related mortality rates, and the COPD incidence rates. Values of the model variables for the start year are defined. These include the initial joint probability values for all smoking and COPD severity classes and the initial values of parameters of linear distribution function of lung function within each COPD severity class.
Second, for each year in the simulation, three calculation steps are set.
The 1st step is the calculation of the transition numbers between the smoking classes and COPD severity stages. The smoking class transition rates are model input. The COPD severity class transition rates are calculated based on lung function decrease and increase, the distribution of FEV1%pred in each COPD stage and the number of exacerbations in each state.
The 2nd step is the calculation of new COPD and smoking prevalence probabilities using these transition rates and accounting for mortality. Mortality may be due to several causes: case fatality of exacerbations, remaining COPD-related mortality, and other causes of death.
The 3rd step is the calculation of the new FEV1%pred distributions in each COPD stage using lung function decrease and increase. The effect of exacerbations was included in the decrease and increase of lung function.

D2.3 Initialisation.

The model initialization part consists of calculating all transition rate vales (including mortality and incidence) and the initial joint probability values for all smoking and COPD severity classes, for both genders and all ages. Moreover, the lung function distribution within each COPD severity class is initialized.

a. Prevalence of smoking and COPD severity in base year:

Initial values of the joint probability of all smoking and COPD severity classes were calculated in two steps.
First, the initial smoking class probability values were calculated conditional on having COPD. The relative risk values used to estimate smoking class specific COPD incidence numbers were assumed to approximate the relative risk of smoking class for prevalent COPD cases for the start year. The initial smoking class probability value conditional on not having COPD is the complement.

Hence: Prevalence of smoking classes:

Conditional on having COPD: $P(r \mid D;a) = \frac{RR_D^R(r;a)}{\sum_{r'} RR_D^R(r';a) \cdot P(r';a)} \cdot P(r;a)$

Conditional on not having COPD: $P(r \mid \overline{D};a) = \frac{P(r;a) - P(D;a) \cdot P(r \mid D;a)}{1 - P(D;a)}$

Second, initial joint probability values were derived from the conditional ones. Initial smoking class probability values were assumed equal for all COPD severity classes.

Smoking class joint with COPD severity class:

$P(r,c;a) = P(D;a) \cdot P_{prev}(c \mid D;a) \cdot P(r \mid D;a)$

Smoking class joint with not having COPD: $P(r,\overline{D};a) = P(r;a) - \sum_c P(r,c;a)$

b. Initial values for distributions of lung function.

For the start year, the FEV1%pred-distributions within each COPD and smoking class are approximated using a distribution over all smoking classes. As a result, for the start year, the mean FEV1%pred values within each smoking class are approximated by the mean values over all smoking classes, which are given as input variables:

$$\mu_F(r;c;t)_{t=0} = \mu_F(c)$$

c. Baseline incidence rates

In the model, COPD incidence rates per smoking and severity stage are calculated as a baseline rate multiplied by a relative risk. These baseline rates are to be calculated from the input data, which give overall incidence rates. The input incidence rates are divided by (1-prev), because data incidence rates apply to the general population and model incidence rates apply to the COPD-free population only. They are moreover divided by $\sum_r RR_D^R(r;a) \cdot P(r;a)$ to find the incidence rate for a non smoker.

Baseline disease incidence rate=

$$i_{D0}(a) = \frac{i_D(a)}{p(\overline{D};a) \cdot \sum_r RR_D^R(r;a) \cdot P(r \mid \overline{D};a)}$$

d. Baseline mortality rates

Like the incidence rate, COPD mortality rates per smoking and severity stage are calculated as a baseline rate multiplied by a relative risk. To find this baseline rate, first COPD attributable mortality has to be derived from the difference in all cause mortality between COPD patients and non COPD patients (excess mortality), taking into account the effect of smoking on both COPD prevalence and all-cause mortality. Excess mortality for COPD is adjusted to find the COPD attributable mortality according to the following formula (for details see C3.2):

$$am(D;a) = \frac{(1 - P(D)) \cdot em_D - (E_{r|D}(m_{tot}(r)) - m_{tot})}{1 - E_{r|D}(P(D \mid r))}$$

The $E_{r|D}(m_{tot}(r)) - m_{tot})$ are estimated by using the relative risks for smoking on all-cause mortality and COPD incidence:

$$E_{r|D}(m_{tot}(r)) - m_{tot}) = (\sum_r RM_{tot}(r) \cdot RM_D(r) \cdot P(r) - 1) \cdot m_{tot}$$

with: $RM_{tot}(r) = \frac{RR_{tot}(r)}{\sum_z RR_{tot}(r) \cdot P(r)}$ and $RM_D(r) = \frac{RR_D(r)}{\sum_z RR_D(r) \cdot P(r)}$.

Likewise we have:

$$E_{R|D}(P(D|z)) = \sum_r RM_D(r) \cdot RM_D(r) \cdot P(r)$$

Mortality from other causes than COPD is now found by subtracting COPD attributable mortality from total mortality: $m_{oth}(a) = m_{tot}(a) - P(D;a) \cdot am_D(a)$. If negative other causes mortality rate values result, they are set to value 0.

COPD attributable mortality is then to be divided over severity stages using the relative risk for mortality of lung function, the average lung function in each severity stage and the percentage of patients in each stage. To do so, a baseline value is calculated for persons in mild COPD:

$$am_0(D;a) = \frac{am(D;a)}{\sum_c RR^F_{tot}(\mu_F(c;a)) \cdot P_{prev}(c \mid D;a)}$$

This mortality is then to be split into exacerbation related case fatality and a rest term. The rest term is estimated after definition of policy scenarios that may affect exacerbation frequency in the various COPD stages, but before the simulations. It is found by subtracting exacerbation related mortality from severity specific COPD attributable mortality:

$$am_{oth}(c;a) = RR_{tot}^{F}(\mu_F(c;a)) \cdot am_0(D;a) - P(E \mid \mu_F(c;a)) \cdot m(E;a)$$

To prevent unrealistic values for specific mortality rates to occur the code contains to external limits to the results of this calculation, setting its minimum value to 0 and its maximum value to 0.6

D2.4 Simulation.

a. Apply the distribution of FEV1%pred on the population numbers in each severity stage and smoking class to find the fractions flowing to and from neighboring stages

The fractions flowing from and to each severity stage as a result of the worsening of lung function over time (or the improvement of lung function for recent quitters) are called the COPD stage transition rates (transCOPD(j,r,c)).

These are calculated in the model for each year, using distribution characteristics for the distribution of FEV1%pred within each severity stage, the lung function decrease/increase in that period and changes in the distribution that result from changes in smoking prevalences. The lung function decrease/increase in a period, f(j,r,c,g,a), is defined as a function of lung function at the lower respectively upper boundary of each severity stage and was estimated based on the Lung Health Study data. From the estimated function, the f(j,r,c,g,a) are calculated as a function of age, gender, severity stage (i.e. lung function at the boundary of the severity stage) and smoking class. To find the COPD stage transition rates, the following steps are taken:

First, the mean decrease and increase for each severity and smoking class is found as the weighted average over age and gender. Increases are only defined for ex smokers in the year of quitting.

Mf(1,r,c) = Σg,a (f(1,r,c,g,a) N(r,c,g,a)) / Σg,a N(r,c,g,a), c=2,..6;r=1,..3

And

Mf(2,3,c)= Σg,a (f(2,3,c,g,a) N(2,c,g,a) transsmok(1,2,g,a)) /Σg,a [N(3,c,g,a) + N(2,c,g,a) transsmok(1,2,g,a)] c=2,..6, with *Mf(2,r,c)=0;* r=1,2

Second, new COPD stage transition fractions are calculated for each smoking and severity stage. These depend on the current distribution of lungfunction within the stage (distfev), the stage, and the size of the transitions (mean decrease or increase) as follows:

transdown(distfev, c, down(c,r)) = down / (FEVlength(c)*(1+0.5*down*A) / (1+0.5*A*FEVlength(c))

transup(distfev, c,up)= up / FEVlength(c)*(1+0.5*B*(Fevlength(c)-0.5 up)) / (1+0.5*A*Fevlength(c))

With A=Abs(distfev(1)/distfev(2)+eps)),

B=distfev(1)/(distfev(2)+eps)

down(c,r)= P(E;x)*FE−Mf(1,r,c)

up(c,r)=Mf(2,r,c)

The transition rates are used in step b of the simulation. The mean decreases are used in step c of the simulation.

b. Find new prevalences, i.e. new joint COPD severity and smoking prevalences

The new smoking and COPD stage prevalences are calculated. This uses the transCOPD values from step a as well as the mFEV values.

Prevalence in each smoking and severity stage changes as a result of

1. COPD related mortality
2. Mortality from other causes, dependent on smoking class.
3. Outflow to next smoking class (i.e. from non to current and from current to former smoker)
4. Outflow to previous smoking class (i.e. from former to current smoker)
5. Outflow to next, i.e. more severe COPD stage (equals 0 for very severe COPD)
6. Outflow to previous, i.e. less severe COPD stage (equals 0 for mild COPD)
7. COPD incidence
8. Inflow from previous smoking class (i.e. new smokers and new former smokers)
9. Inflow from next smoking class (i.e. restarting former smokers)
10. Inflow from previous, i.e. less severe COPD stage (equals 0 for mild COPD)
11. Inflow from next, i.e. more severe COPD stage (equals 0 for very severe COPD)

Because the smoking and COPD severity classes are ordered, only transitions to neighbor classes are relevant. Another consequence of the state-transition structure of the model is that each transition works as both an outflow and inflow. The only exception is mortality.

This results in the following formulas for prevalence in the stages without and with COPD respectively:

For c=1, i.e *for being COPD-free, transitions1,5,6,10 and 11 are irrelevant, while transition 7 causes outflow :*

$$
\begin{aligned}
P(r,\overline{D};t+1) &= P(r,\overline{D};t) \\
&- RM^{R}_{oth}(r;a(t)) \cdot m_{oth}(a(t)) \cdot P(r,\overline{D};t) \\
&- (\lambda^{R}_{+1}(r;a(t)) + \lambda^{R}_{+1}(r;a(t))) \cdot P(r,\overline{D};t) \\
&- i_{D0}(a(t)) \cdot RR^{R}_{D}(r;a(t)) \cdot P(r,\overline{D};t) \\
&+ \lambda^{R}_{+1}(r-1;a(t)) \cdot P(r-1,\overline{D};t) \\
&+ \lambda^{R}_{-1}(r+1;a(t)) \cdot P(r+1,\overline{D};t)
\end{aligned}
$$

For c>1, that is for persons with COPD, all transitions are relevant and transition 7 causes inflow. Transition no 1 consists of COPD attributable mortality not through exacerbations and case fatality from exacerbations.

$$
\begin{aligned}
P(r,c;t+1) &= P(r,c;t) \\
&- am_{oth}(c;a(t)) \cdot P(r,c;t) \\
&- P(E \mid \mu_{F}(r,c;t)) \cdot m(E;a(t)) \cdot P(r,c;t) \\
&- RM^{R}_{oth}(r;a(t)) \cdot m_{oth}(a(t)) \cdot P(r,c;t) \\
&- (\lambda^{R}_{+1}(r;a(t)) + \lambda^{R}_{-1}(r;a(t))) \cdot P(r,c;t) \\
&- (\lambda^{D}_{-1}(c,r;t) + \lambda^{D}_{+1}(c,r;t)) \cdot P(r,c;t) \\
&+ i_{D0}(a(t)) \cdot RR^{R}_{D}(r;a(t)) \cdot P_{inc}(c;a(t)) \cdot P(r,\overline{D};t) \\
&+ \lambda^{R}_{+1}(r-1;a(t)) \cdot P(r-1,d;t) \\
&+ \lambda^{R}_{-1}(r+1;a(t)) \cdot P(r+1,d;t) \\
&+ \lambda^{D}_{+1}(c-1,r;t) \cdot P(r,c-1;t) \\
&+ \lambda^{D}_{-1}(c+1,r;t) \cdot P(r,c+1;t)
\end{aligned}
$$

Multiplication with initial population numbers results in current prevalence numbers rather than current probabilities.

Using the above joint smoking and COPD severity class probability values, other probability values may be calculated as follows:

Current smoking class probability values conditional on survival:

$$P(r \mid S;t) = \frac{P(r,\overline{D};t) + \sum_{c} P(r,c;t)}{P(S;t)}$$

with survival probability found as*:* $P(S;t) = \sum_{r} P(r,\overline{D};t) + \sum_{r,c} P(r,c;t)$

c. Calculate new distributions of FEV1%pred and new meanFEV1% pred values specific to smoking and severity stage

The new distributions of the FEV1%pred are calculated from the existing distributions, the lung function decrease and increase for each COPD stage and smoking class (Mf(j,r,c)) found in part 1, as well as from mortality, specified by age, gender, smoking and COPD stage. We described the lung function within each smoking and COPD state, which can be interpreted as conditional on the state. Therefore we also have to take account of the state (class) transitions. Class transitions result from autonomous (due to aging) and intentional (due to smoking cessation) changes of the lung function, COPD incidence, and smoking class transitions.

The sum (integral) of the lung function probability values for each joint smoking and COPD severity class must equal the probability value calculated in the previous section. However, due to the approximations we had to make this equality does not hold exactly. By assumption the new joint smoking and COPD severity class probability values are considered the right ones. As a result, a new lung function probability distribution function over the entire lung function range and for each smoking class is calculated as the product of the joint smoking and COPD class probability value times the distribution function conditional on these classes. After each time step the opposite calculation step is made and lung function distribution functions are calculated conditional on smoking and COPD class. For reason of model robustness the distribution of the lung function was only specified by smoking and COPD severity class, not by gender or age.

Consequently, for each one-year time-step the following calculation steps are set:

1. Un-conditioning the lung function probability distribution function

The distribution function over the entire lung function range and for each smoking class is found by multiplying the class probability value with the conditional distribution function:

$$f(r,x;t) = f(x \mid r,c;t) \cdot P(r,c;t)$$

2a. Finding the mean annual change of the lung function, ignoring effects of smoking cessation:

The annual mean change of the lung function for each smoking and COPD severity class is found as the sum of autonomous decrease, first term, and additional decrease as a result of exacerbations, second term. 'Mean' here refers to averaged over both genders and all ages for a given smoking class.

$x'(r,x;t) - \alpha\ P(E|x)$

The autonomous decrease was based on a regression formula fit on the Lung Health Study data, and the effect of exacerbations was added.

2b. Change of parameters of linear lung function distribution due to autonomous decrease and to incidence of newly diagnosed COPD patients:

The change of the lung function distribution function for each smoking and COPD severity class was found given the autonomous lung function decrease calculated above. The formulas used are described in more detail in section C3.2d below. The new parameters are the result of drawing a new linear distribution function that combines the original linear functions and the linear functions for the parts added from a less severe COPD severity class. Then the effect of incidence is accounted for as follows. The probability mass related to the incidence in the joint smoking class r and COPD class c is the 1-year incidence probability times the proportion of new cases in class c:

. $i_{D0}(a(t)) \cdot RR_D^R(r;a(t)) \cdot P(r,\overline{D};t) \cdot P_{inc}(c \mid d;a(t))$

The parameters of the lung function distribution for each class are updated by multiplying this probability mass with the parameters of the initial lung function distribution within this class.

2c. Change of lung function probability distribution function due to smoking class transitions:

Since the lung function distribution functions are specified by smoking class, we also calculated the effects of transitions between the smoking classes, using the smoking class transition rates $\lambda_{+1}^R(r-1;a)$ and $\lambda_{+1}^R(r-1;a)$. The calculation method is the same as described in 2b.

```
Do[distFEV2[[ri, di]] =
       distFEV1[[ri, di]] (1 - Plus@@ptrsrokenCOPD[[ri, di]])+
       If[(ri == 1), 0, ptrsrokenCOPD[[ri - 1, di, 1]] distFEV1[[ri - 1, di]]] +
       If[(ri == ncr), 0, ptrsrokenCOPD[[ri + 1, di, 2]] distFEV1[[ri + 1, di]]],
       {ri, ncr}, {di, nFEV}];
```

2d. Change of lung function probability distribution function because of increase due to smoking cessation:

Then we calculated the change of the lung function distribution function due to smoking cessation for each COPD severity class. This calculation step is made for the former smokers only, and is analogous to step 2c.

```
Do[distFEV3[[3, di]] =
       newdistup[If[(di == 1),
                             {0, 0},
                             distFEV2[[3, di - 1]]],
                      distFEV2[[3, di]],
                      di,
                      dFEVup[[3, di]],
                      If[(di == 1), 0, 1]],
       {di, nFEV}];
```

2e. Change of lung function probability distribution function due to mortality:

Mortality rates depend on the lung function, so the annual change of the probability density function is not the same over the lung function range. Therefore we calculated the change of the parameters of the distribution function, approximating the log-linear mortality function by a linear one (see C3).

```
prevmean      = Plus@@hnrokenCOPD / Plus@@Flatten[hnrokenCOPD];

emmean        = Plus@@Plus@@Table[COPDexcessmortadj[[g]] *
                                 Plus@@Plus@@nrokenCOPD[[g, All, 1 +
                                Range[nFEV]]],
                                 {g, ng}] /
                      Plus@@Flatten[ nrokenCOPD[[All, All, 1 + Range[nFEV]]]];

mu0           = Exp[HRFEVtot FEVbord[[Range[nFEV]]]] /
                      Plus@@(Exp[HRFEVtot meanFEV0] prevmean) emmean;

Do[    distFEV3[[ri, All, 1]] = (1 - mu0) distFEV3[[ri, All, 1]] -
                                 distFEV3[[ri, All, 2]] mu0 HRFEVtot;
       distFEV3[[ri, All, 2]] *= (1 - mu0),
       {ri, ncr}];
```

3. Conditioning the lung function probability distribution function:

This is applying the first calculation step backwards:

$$f(x \mid r,c;t+1) = \frac{f(r,x;t+1)}{\int_{u \in c} f(r,u;t+1)du}$$

The mean FEV values as well as the new normalized distribution functions are used in the next simulation step.

D2.5 Cost and effect calculations

All calculated model state (smoking and COPD severity class) and event (exacerbations) probability values can be valuated in terms of costs and effects. The expected costs for any year t are the sum of the exacerbation related costs and COPD maintenance costs. Exacerbation related costs are found as the costs per severe or moderate exacerbation multiplied with their model state specific frequencies and the size of each model state and summed over all model states (see section 2.6). Maintenance costs are found as the size of each model state multiplied by the state specific maintenance costs.

$$K_{totyr}(t) =$$
$$\sum_{r,c} P(r,c;t) \cdot P_{all}(E \mid c) \cdot [f_{\mathrm{mod}} \cdot K_{exacerb,\mathrm{mod}}(c;a(t)) + f_{sev} \cdot K_{exacerb,sev}(c;a(t))] +$$
$$\sum_{r,c} P(r,c;t) \cdot K_{COPD}(c;a(t))$$

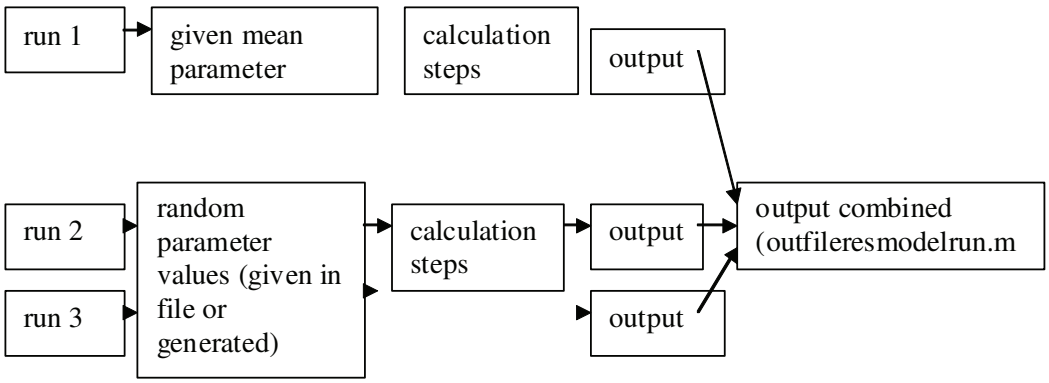
Similarly, the expected quality of life for any year t was calculated from state specific base utilities and exacerbation related utility losses (see section 2.5). The latter were subtracted for each state.

$$QALY_{totyr}(t) =$$
$$\sum_{r,c} P(r,c;t) \cdot QALY_{COPD}(c;a(t)) -$$
$$\sum_{r,c} P(r,c;t) \cdot P_{all}(E \mid c) \cdot QALY_{COPD}(c;a(t)) \cdot [f_{\mathrm{mod}} \cdot QALY_{exacerb,\mathrm{mod}} + f_{sev} \cdot QALY_{exacerb,sev}]$$

Total costs and health benefits are then found by adding costs and benefits over the entire time horizon. Future costs and effects are discounted using discount rates.
Running policy scenarios through the model thus results in net present values of total costs over the entire time horizon for the different scenarios. Comparing these values to the values for the base case scenario, or for a comparator policy scenario, results in incremental costs and incremental health benefits. These were related and presented as cost-effectiveness ratios.

D2.6 Structure of the probabilistic model

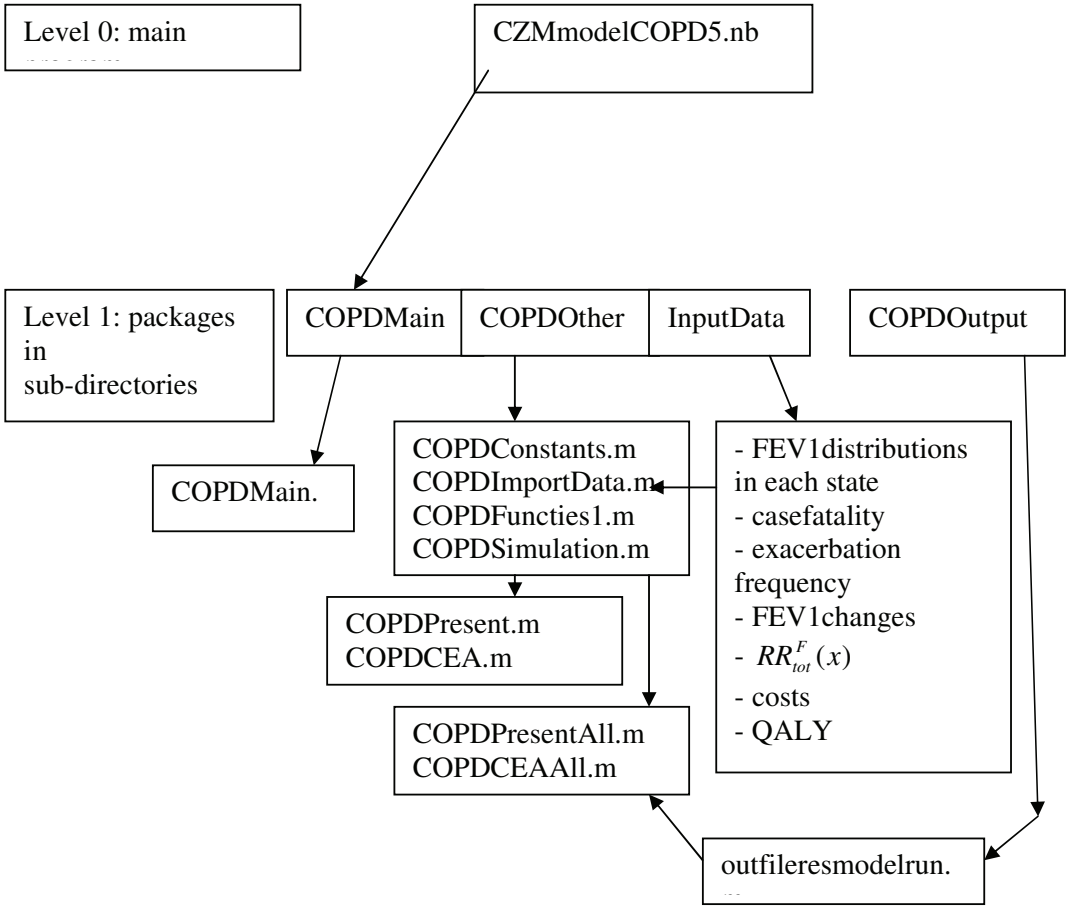
This section describes how the probabilistic sensitivity analysis was carried out in the model and how this was implemented in the model code. Section 4.2 presents the parameters included in the PSA.
The figure below pictures the basic structure for performing Monte Carlo simulations, with different values for the model parameters in each run. In a first deterministic run, the model applies mean parameter values for all variables (run 1). For all runs to follow random parameter values are used. In each run the results of several scenarios can be calculated. The results of each run are stored in working memory, and in backing store (MMA file "outfileresmodelrun.m"). The results of each new model run overwrite the results of the previous run in working memory. In case of multiple runs, at the end the distributions of some model output variables are presented.



D2.7 Implementation in Mathematica

This section is intended as a guide through the software code (obtainable from the authors upon request).

The model is implemented in Mathematica (MMA). The main program is a MMA Notebook (NB) that calls on several MMA Packages as depicted below.



The package COPDMain.m contains the routine COPDProgram that runs the program. In each run the results of all scenarios are calculated. The results of the current run are stored in working memory (MMA variable resultres). All results, including those of the previous runs, are stored in backing store (MMA file "outfileresmodelrun.m"). In case of only one model run the results are presented in graphical form by the packages COPDPresent.m and COPDCEA.m. In case of multiple runs, the distributions of some model output variables are presented by the packages COPDPresentAll.m and COPDCEAAll.m.

The key MMA model characteristics to be selected by the user in the main notebook (CZMmodelCOPD5.nb) are:

nstap the number of one-year time-steps

nscen the number of scenarios

nrun the number of runs (run 1 uses the mean parameter values; all other runs random values)

The scenarios are defined in MMA programming statements that are packed in string format. At the start of each scenario, the string is evaluated, and so the scenario-specific values of all scenario (steering) parameters are assessed.

The MMA variable resultres contains the model results of the current model run, and the MMA file "outfileresmodelrun.m" contains the model results of all model runs. The first element of this file is the number of runs, and the next elements are copies of the variable resultres. This variable is a list of the following outcome variables:

1. prevrokenCOPDres, prevalence numbers in model states with the size nscen*nrun*ng*nr*nd*nage, ie. Number of scenarios times number of runs (time horizon) times 2 (male and female) times number of smoking classes times number of COPD severity stages.
2. incCOPDres, COPD incidence numbers, with the size nscen*nrun*ng*nr*nage, that is only specific to smoking class, not to COPD severity stage.
3. mortrokenCOPDres, mortality numbers in model states with the size nscen*nrun* ng*nr*(nd-1)*3*nage. Only COPDmortality in COPD stages. Three different types of mortality are distinguished: mortality from other causes than COPD, COPD-attributable mortality other than from exacerbations, and COPD-attributable mortality from exacerbations.
4. incres, incidence numbers for other diseases, with the size nscen*nrun*ndis*ng*nage, with ndis the number of other diseases distinguished.
5. prevres, prevalence numbers for other diseases, with the same size
6. mortcausres, mortality numbers for other diseases, with the same size
7. distFEVres, parameters of linear distribution of lung function within COPD severity classes, with the size nscen*nrun*nr*nd-1*2, since 2 parameters for each distribution function are estimated (a and b)
8. exacerbres, severe and total exacerbation numbers, with the size nscen*nrun*2*nd-1: exacerbation numbers in each COPD severity stage, for severe exacerbations only and for total exacerbations.
9. all kea outcomes.

{QALYCOPD, QALYexacerbsev, QALYexacerbmod, costsCOPDpatient, costsexacerbsev, costsexacerbmod},

This element of the list is a compound Mathematica list that has 6 fields. The first field has 5 fields itself, one for each COPD severity stage. The second and third fields are single figures reflecting the relative utility decrement for a severe and a moderate exacerbation,

respectively. The 4th field is a list of size ng*nd-1*nage, containing costs per patient, specific to gender and age and COPD severity stage. The 5th and 6th fields are single figures again.

For model verification and debugging several options are available. In the package COPDMain the MMA variable bugind is defined. In case of value 1 labels are printed on screen that enables the model user to locate program errors. In case of multiple runs (nrun>1), no labels are printed because that would slow down the program too much. In the package COPDSimulation.m the MMA variable plotind is defined. In case of value 1 the calculated lung function distribution functions are presented graphically.
The file maakprint.bat generates a listing in ASCII-format of all MMA packages used.

D3. Mathematical background for specific model elements.

This section provides further elaboration on specific model elements. The mathematical model was defined in continuous time. We have made this model time-discrete using 1-year time-steps using the Euler-method of order 1. In section C2 the description hence was as much as possible in terms of 1 year time steps, but this section will describe the original mathematical structure in continuous time.

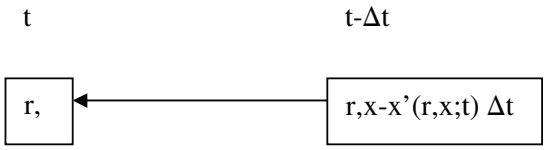
Section C3.1 describes the linear approximation of the distribution function of the lung function within each severity class. We work out the formulas for several aspects: the calculation of the annual COPD severity class transition probability, the annual update of the parameters of the linear distribution function, and the effect of mortality on these parameters.
Section C3.2 discusses all parameters that are related to mortality. We start in C3.2a with the excess mortality rate and adjust to a mortality rate that uniquely can be attributed to COPD. The calculation method is part of the standard methodology of the RIVM Chronic Disease Model. We proceed in C3.2b with the case fatality of an exacerbation. Then in C3.2c, the proportion of the COPD-related excess mortality that does not result from the case fatality of exacerbations is found. Finally mortality from other causes is defined in C3.2d.

D3.1 Issues related to lung function

a. The joint distribution over smoking class and lung function

Essentially, our model describes the joint probability distribution function over smoking and lung function of any COPD-patient, and its change over time. Because the lung function is a continuous variable and we did not want to fix the form of the lung function distribution function, we chose a semi-parametric form. I.e., we distinguished several COPD severity classes using lung function cut-off points, and we approximated the distribution function within each COPD severity class by a linear function. The result is a so-called non-continuous piecewise linear function, with the severity class cut-off points being the break-points.

We start with the general joint probability distribution function over smoking and lung function of any COPD-patient. We describe how the value for time t depends on the values for time t-Δt, for any lung function value f and smoking class r. At first we assume the smoking class r being fixed, and thus allow no smoking class transitions, and assume no mortality. The mathematics to describe the change over time of the lung function probability distribution function is similar to the mathematics of water flows. We have to relate the change of the probability distribution function to the change of the lung function itself. We start with any time point t, and describe the change of the cumulative probability distribution function as a function of the cumulative probability distribution function on time point t-Δt, with Δt being sufficiently small.



The mathematical equation that describes the change of the cumulative probability distribution function is:

$$
\begin{aligned}
&F(r,x+\Delta x;t)-F(r,x;t)=\\
&\quad F(r,x+\Delta x-x'(r,x+\Delta x;t)\cdot\Delta t;t)-F(r,x-x'(r,x;t)\cdot\Delta t;t)=\\
&\quad F(r,x+\Delta x;t)-f(r,x+\Delta x;t)\cdot x'(r,x+\Delta x;t)\cdot\Delta t-F(r,x;t)+f(r,x;t)\cdot x'(r,x;t)\Delta t=\\
&\quad f(r,x;t)\cdot\Delta x-[f(r,x;t)+\frac{\delta f}{\delta x}(r,x;t)\cdot\Delta x][x'(r,x;t)+x''(r,x;t)\cdot\Delta x]\cdot\Delta t+\\
&\quad\quad f(r,x;t)\cdot x'(r,x;t)\cdot\Delta t=\\
&\quad f(r,x;t)\cdot\Delta x-f(r,x;t)\cdot x''(r,x;t)\cdot\Delta x\cdot\Delta t-\frac{\delta f}{\delta x}(r,x;t)\cdot x'(r,x;t)\cdot\Delta x\cdot\Delta t
\end{aligned}
$$

Moreover we find:

$$
\begin{aligned}
&F(r,x+\Delta x;t+\Delta t)-F(r,x;t+\Delta t)=\\
&\quad f(r,x;t+\Delta t)\cdot\Delta x=\\
&\quad [f(r,x;t)+\frac{\delta f}{\delta t}(r,x;t)\cdot\Delta t]\cdot\Delta x
\end{aligned}
$$

Combining both equations results in:

$$
\frac{\delta f}{\delta t}(r,x;t)=-f(r,x;t)\cdot x''(r,x;t)\cdot\Delta x\cdot\Delta t-\frac{\delta f}{\delta x}(r,x;t)\cdot x'(r,x;t)
$$

x, Δx continuous lung function, small change of lung function respectively

r smoking class

t, Δt time, small time interval respectively

x'(r,x;t) rate of change of lung function over time

x"(r,x;t) rate of rate of change of lung function over time

F(r,x;t) cumulative probability function over lung function x for fixed smoking class r on time t

f(r,x;t) probability density function over lung function x

The equation we derived is an example of a so-called partial differential equation: it relates the changes over both arguments time t and lung function value x. E.g., take the last term of the equation: if the lung function increases over time t (x'(r,x;t)>0) and if the probability density function increases over lung function value x for fixed time t ($\frac{\delta f}{\delta x}(r,x;t)$ >0), then the probability density function decreases over time t for fixed lung function value x.

This mathematical equation becomes much more complex by introducing transitions between smoking classes. A formal analytical solution is far too complex. That's why we have approximated both the solution to the effects of the simultaneous smoking class and lung function value changes, and the solution to the time-continuous change of the lung function itself (see equation above). This approximation consists of the following successive calculation steps, i.e. we calculate how the probability distribution function changes for all joint smoking and COPD severity classes:

1 due to the autonomous time-continuous decrease, including the effect of exacerbations and incidence
2 because of the smoking class transitions using the smoking class transition rates
3 due to the increase of the lung function because of smoking cessation
4 due to mortality

In the 3rd calculation step we again (see step 1) fixed the smoking classes, so the lung function effect of smoking cessation is diluted over all former smokers.

b. The piecewise-linear distribution function of the lung function

We approximated the probability distribution of the lung function by a linear function within each COPD severity class:

$$f(x \mid c) = \alpha + \beta \cdot x$$

x continuous lung function; x=0 corresponds with the left cut-off value of the COPD severity class
α intercept
β regression coefficient
c index over COPD severity classes

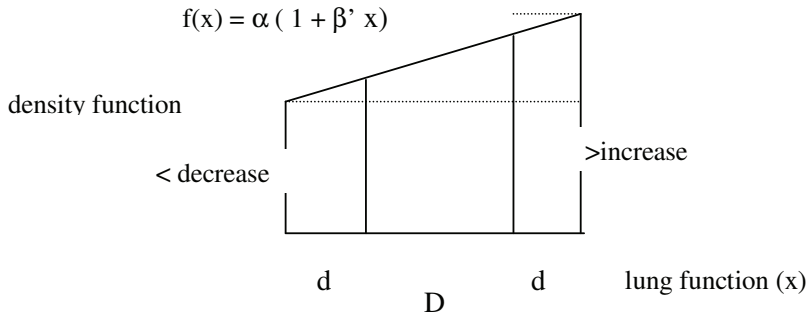
The parameters α and β also depend on c formally.

The probability of being in a smoking and COPD severity class is defined elsewhere in the model (C2.4c). At the start and end of each one-year time-step we un-condition and condition the probability distribution function on the COPD severity class respectively (see also C2.4c). The resulting distribution function is called a piecewise-linear function, although the function is not continuous in the lung function cut-off points.

c. COPD severity class transition probability

The problem addressed here is: given the linear distribution of the lung function within a COPD severity class, and the annual change of the lung function, what is the proportion

that leaves the state? We distinguish an increase of the lung function that results in a transition to the severity class on the right, and a decrease of the lung function that results in a transition to the severity class on the left. (See figure x)



β' transformed regression coefficient, $\beta' = \beta/\alpha$

D length of COPD severity class

d annual change of lung function

x continuous lung function value

$\lambda_{+1}(d, D, \beta')$ annual transition probability due to increase of lung function

$\lambda_{-1}(d, D, \beta')$ idem, due to decrease

Case of increase of lung function:

Probability mass that moves out: $\alpha \cdot d \cdot (1 + \beta' \cdot D - \frac{1}{2} \cdot \beta' \cdot d)$

Current probability mass: $\alpha \cdot D \cdot (1 + \frac{1}{2} \cdot \beta' \cdot D)$

Proportion moving out: $$\lambda_{+1}(d, D, \beta') = \frac{d}{D} \cdot \frac{1 + \beta' \cdot (D - \frac{1}{2} \cdot d)}{1 + \frac{1}{2} \cdot \beta' \cdot D}$$

Case of decrease of lung function:

Probability mass that moves out: $\alpha d (1 + \frac{1}{2} \beta' d)$

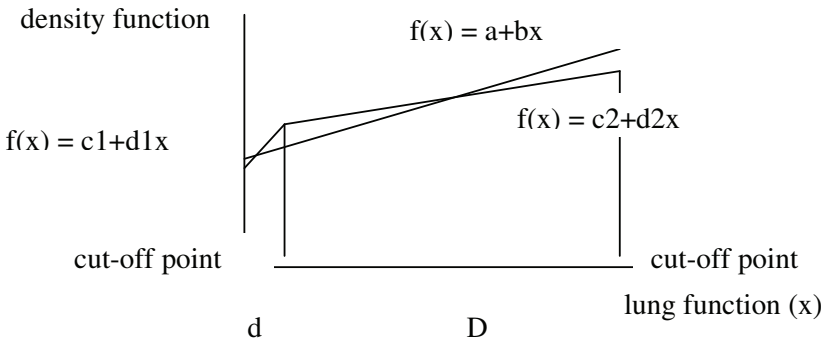
Proportion moving out: $$\lambda_{-1}(d, D, \beta') = \frac{d}{D} \cdot \frac{1 + \frac{1}{2} \cdot \beta' \cdot d}{1 + \frac{1}{2} \cdot \beta' \cdot D}$$

NB: the severity class transition probability values only depend on $\beta' = \beta/\alpha$, not on the absolute values. The proportions moving out correspond with the model transition probabilities (increase) $\lambda_{+1}^{D}(c;t)$ and (decrease) $\lambda_{-1}^{D}(c;t)$ for any COPD severity class c on time t (see C2.4).

d. New linear lung function probability distribution

The problem addressed here is: what is the best approximation of the linear lung function distribution function that is constructed from two successive linear distribution functions. We distinguish between an increase and decrease of the lung function.

Case of increase of lung function:



d lung function values (interval) that crosses the cut-off point on the left
D lung function values (interval) that stay within class during one year, i.e. do not cross the cut-off point on the right during the year

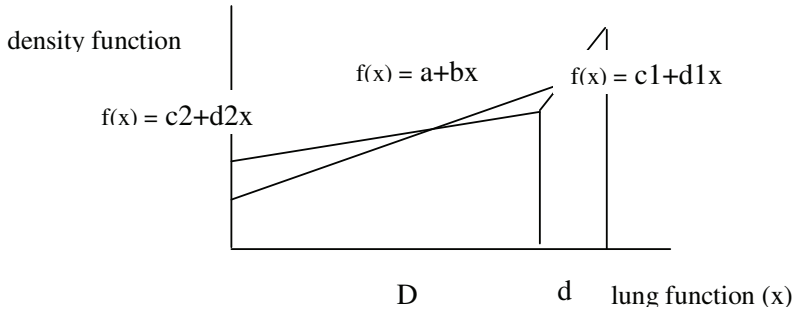
d is the lung function interval in the COPD severity class on the left that crosses the cut-off point on the left. The related probability mass describes the transition number. Likewise, D is the lung function interval that does not cross the cut-off point on the right. The linear distribution function for the part coming from the severity class on the left is f(x) = c1 + d1 x, and the one for the part staying in the class is f(x) = c2 + d2 x. The new linear distribution function is f(x) = a + b x, and minimizes the following sum of squares (Mathematica format):

```
f[a_,b_]:=
     Integrate[((a+b x)-(c1 +d1 x))^2,{x,0,d}]+
     Integrate[(a+b ( x+d)-(c2+d2 x))^2,{x,0,D}]
```

The solution is found by setting the derivatives of f to parameters a and b to 0. Then:

$a\to(c1\ d\ (d+4\ D)+D\ (c2\ (-2\ d+D)+d\ (2\ d\ d1-D\ d2)))/(d+D)^2$,
$b\to(-6\ c1\ d\ D+6\ c2\ d\ D+d^3\ d1-3\ d^2\ D\ d1+3\ d\ D^2\ d2+D^3\ d2)/(d+D)^3$

Case of decrease of lung function:



d lung function values (interval) that crosses the cut-off point on the right
D lung function values (interval) that stays within class during one year, i.e. do not cross the cut-off point on the left during the year

The linear distribution function for the part coming from the severity class on the right is f(x) = c1 + d1 x, and the one for the part staying in the class is f(x) = c2 + d2 x. The new linear distribution function is f(x) = a + b x, and minimizes the following sum of squares (Mathematica format):

```
g[a_,b_]:=
     Integrate[((a+b x)-(c1+ d1 x))^2,{x,0,D}]+
     Integrate[((a+b (x+D))-(c2+d2 x))^2,{x,0,d}]
```

The solution is found by setting the derivatives of g to parameters a and b to 0. Then:

$$a\to(c2\ d\ (d-2\ D)+D\ (c1\ (4\ d+D)+d\ (2\ D\ d1-d\ d2)))/(d+D)^2,$$
$$b\to(-6\ c1\ d\ D+6\ c2\ d\ D-3\ d\ D^2\ d1+D^3\ d1+d^3\ d2+3\ d^2\ D\ d2)/(d+D)^3$$

In case of increase of the lung function no inflow into the first (very severe) COPD severity class exists, while in case of decrease no inflow into the last (mild) severity class exists. Therefore, we introduced a weight parameter w in the two sums of squares defined above. Weight w describes the weight of the lung function interval that crosses the cut-off point. In the two cases described above, the weight w has value 0, otherwise value 1.

e. Effect of mortality on linear distribution function

The mortality rate depends log-linearly on the lung function. We approximated this by a linear function: $m(x) = m_0 \cdot e^{\delta x} \approx m_0 \cdot (1 + \delta \cdot x)$

m	mortality rate
m_0	intercept
δ	regression parameter

Then the new linear lung function distribution function can be approximated by:

$$f(x \mid c) \approx (\alpha + \beta \cdot x) \cdot (1 - m_0 \cdot (1 + \delta \cdot x)) \approx (1 - m_0) \cdot \alpha + [(1 - m_0) \cdot \beta - \alpha \cdot m_0 \cdot \delta] \cdot x$$

C3.2 Issues related to mortality

a. Definition of excess mortality and attributable mortality

The COPD-related excess mortality rates are defined as: $em(D;a) = m(D;a) - m(\overline{D};a)$

em(D;a) COPD-related excess mortality

$m(D;a)$ mortality rate conditional on having COPD

$m(\overline{D};a)$ mortality rate conditional on not having COPD

That is, it is the additional mortality rate for a person with COPD compared to the rate of a person without COPD. These COPD-related excess mortality can be explained by differences in mortality rates for all co-morbid diseases that are causally related with COPD or that are indirectly related through joint risk factors. Smoking, for instance, is a risk factor for COPD mortality. As a result COPD-patients have higher lung cancer mortality risks compared to COPD-free persons and so part of the COPD-related excess mortality can be explained by lung cancer mortality rates that are different between COPD-patients and COPD-free persons.

b. COPD-related excess mortality adjusted for smoking

The COPD-related excess mortality rate describes the difference between the mortality rate of any person with and without disease, i.e. unadjusted for smoking. In the model we need the excess mortality rate adjusted for smoking. We call the latter the COPD-related attributable mortality rate. We show how the COPD-related attributable mortality rates are calculated from the excess mortality rates. All mathematical equations in this section are formulated in general terms. For our model disease D has to be read as COPD, and frailty variable z has to be read as smoking. The calculation method is based on combining the mortality rates in a homogeneous and heterogeneous population, i.e. unadjusted and adjusted for smoking respectively. For notational convenience the time parameter was omitted here.

Homogeneous population

mortality among patients = mortality rate conditional on having disease D

$$m_{tot}(D) = m_{tot}(\overline{D}) + em_D \qquad (1)$$

mortality in population = unconditional mortality rate

$$m_{tot} = m_{tot}(\overline{D}) + P(D)em_D \qquad (2)$$

=> $$m_{tot}(D) = m_{tot}(\overline{D}) + em_D = m_{tot} + (1 - P(D)) \cdot em_D$$

with D disease index, $\overline{D}$: without disease D (= COPD)

P(D) disease D prevalence rate = proportion with D

m_{tot}	all cause mortality rate
em_D	disease D related excess mortality rate
$m_{tot}(\overline{D})$	mortality rate from other causes of death = mortality of persons without disease D = mortality rate conditional on not having disease D
$m_{tot}(D)$	mortality rate among patients = mortality rate conditional on having disease D

Heterogeneous population

For any frailty variable Z (smoking)

$$m_{tot}(Z) = m_{oc}(Z) + P(D \mid Z) \cdot am_D$$

with: Z,z stochastic frailty variable that describes the population heterogeneity

$m_{tot}(Z), m_{oc}(Z)$	mortality rate for all causes and other causes of death respectively
am_D	disease D related attributable mortality rate

Then:
$$\begin{aligned} m_{tot}(D) &= m_{tot} + (1 - P(D)) \cdot em_D \\ &= E_z(m_{oc}(z \mid D)) + am_D \end{aligned}$$

$$\begin{aligned} & m_{tot}(D) - m_{tot} = \\ & (1 - P(D)) \cdot em_D = \\ & [1 - E_{z|D}(P(D \mid z))] \cdot am_D + \\ & [E_{z|D}(m_{tot}(z)) - m_{tot}] \end{aligned}$$

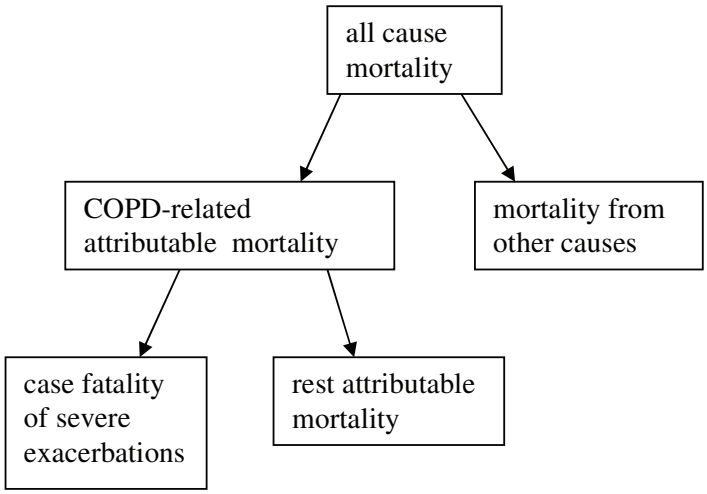
The latter formula results in a formula for calculating the disease related attributable mortality rates from the excess mortality rates:

$$am_D = \frac{(1 - P(D)) \cdot em_D - (E_{z|D}(m_{tot}(z)) - m_{tot})}{1 - E_{z|D}(P(D \mid z))}$$

The all cause mortality rates $E_{z|D}(m_{tot}(z))$ and disease D prevalence rates $E_{z|D}(P(D \mid z))$ are calculated using relative risk values $RR_{tot}(Z)$ and $RR_d(Z)$.

c. Further specifying COPD-related mortality

For the model COPD-related attributable mortality was subdivided in mortality that results from severe exacerbations (case fatality, see d), and rest attributable mortality (see e).



d. Case fatality of severe exacerbation

We calculated the case fatality of a severe exacerbation, i.e. the attributable mortality risk that uniquely can be attributed to a severe exacerbation. The relative risk $RR^{E}_{tot}(a)$ describes the relative change of the case fatality with age.

Case fatality of exacerbation: $m(E;a) = RR^{E}_{tot}(a) \cdot m(E;a_0)$

a_0	reference age value; a_0 = 74
m(E)	given case fatality of severe exacerbation
m(E;a)	calculated case fatality of severe exacerbation on age a
$RR^{E}_{tot}(a)$	relative change of case fatality of severe exacerbation with age; = 1.04

We calculated the reference age value a_0 by assuming that the given empirical value m(E) equals the mean value over all COPD-patients in our model:

$$\frac{\sum_{a,c} m(E;a) \cdot P(E \mid \mu_F(c;a)) \cdot P_{prev}(c \mid D;a) \cdot P(D;a) \cdot P(a)}{\sum_{a,c} P(E \mid \mu_F(c;a)) \cdot P_{prev}(c \mid D;a) \cdot P(D;a) \cdot P(a)} = .157$$

μ_F(c;a)	initial mean lung function in COPD severity class c on age a
P(a)	population frequency according to Statistics Netherlands

e. Rest **attributable** *mortality rate values*

The COPD-related attributable mortality rates are calculated from COPD-related excess mortality rates (see section c.). The larger part of these attributable mortality rates can be explained by the case fatality of severe exacerbations. The rest is called the rest COPD-related attributable mortality rates here. Of course, the rest attributable mortality rates $am_{oth}(c;a)$ must be non-negative.

Baseline COPD-related attributable mortality rate:

$$am_0(D;a) = \frac{am(D;a)}{\sum_c RR_{tot}^F(\mu_F(c;a)) \cdot P_{prev}(c \mid D;a)}$$

Rest COPD-related attributable mortality rate, i.e. not through severe exacerbations:

$$am_{oth}(c;a) = RR_{tot}^F(\mu_F(c;a)) \cdot am_0(D;a) - P(E \mid \mu_F(c;a)) \cdot m(E;a)$$

f	continuous lung function value
$am_0(D;a)$	baseline COPD-related attributable mortality, i.e. for baseline severity class
$RR_{tot}^F(f)$	relative mortality risk for lung function value f
$am_{oth}(c;a)$	COPD-related attributable mortality for severity class s not through severe exacerbations
P(E|f)	annual probability of severe exacerbation conditional on lung function f

f. Other causes mortality rate values

The mortality rate of any person without COPD can be calculated from all cause mortality rates, COPD-related excess mortality rates, and COPD prevalence probabilities. It can be interpreted as the other causes mortality rate (see b). The other causes mortality rate $m_{oth}(a)$ must be non-negative. NB: we have distinguished other causes mortality rates $m_{oth}(a)$ and rest COPD-related attributable mortality rates $am_{oth}(c;a)$ here. The former apply to any person and depend on smoking class, the latter apply to COPD-patients only and depend on COPD severity class.

Mortality rate from other causes than COPD for any individual:

$$m_{oth}(a) = m(\overline{D}; a) = m_{tot}(a) - P(D; a) \cdot am_D(a)$$

Other causes mortality rate multiplier for smoking class r:

$$RM^R_{oth}(r; a) = \frac{m_{oth}(r; a)}{m_{oth}(a)} = \frac{RM^R_{tot}(r; a) \cdot m_{tot}(a) - RM^R_D(r; a) \cdot P(D; a) \cdot am_D(a)}{m_{tot}(a) - P(D; a) \cdot am_D(a)}$$

Other causes mortality risk ratio:

$$RR^R_{oth}(r; a) = \frac{RM^R_{oth}(r; a)}{RM^R_{oth}(1; a)}$$

$m_{tot}(a)$	given all cause mortality rates for any individual
$m_{oth}(a)$	calculated mortality rate from other causes than COPD
$m_{tot}(r;a)$	all cause mortality rate for smoking class r
$m_{oth}(r;a)$	other causes mortality rate for smoking class r
$RM^R_{oth}(r; a)$	other causes mortality rate multiplier for smoking class r
$RR^R_{oth}(r; a)$	other causes mortality risk ratio

Mortality rate multipliers $RM^R_{oth}(r; a)$ and mortality rate ratios $RR^R_{oth}(r; a)$ are similar, but not equal. Risk ratios are defined as the ratio of the mortality rate for any smoking class r to the one for the reference (non-smoking) class. We assume these risk ratios being constant over time, conditional on age. Rate multipliers are defined as the ratio of the mortality rate for any smoking class r to the mean population rate value. As a result, they change over time, but the weighted sum has always value 1 for any time point t.

D4 Data used to find COPD mortality

The input parameters for unadjusted COPD excess-mortality were taken from the RIVM Chronic Disease Model. The following is a short summary description of the COPD specific input data. Further details can be found in publications on the RIVM Chronic Disease Model.

Data used are:

1. the UK GP registration (DYNAMO-HIA project/GPRD) concerning mortality in COPD and non-COPD patients over the period 2000-2008 [2]. The total number of persons in the DYNAMO-HIA/GPRD consists of more than 3,5 million and the number of COPD deaths over the period 2000-2008 was 37000.
2. Dutch GP registrations of COPD incidence and prevalence. [3]

The DYNAMO-HIA/GPRD data were used to estimate a RR for mortality in COPD patients. The RR was estimates using Poisson regression, with as explanatory variables polynomials of age, COPD status, gender and interaction terms. Using the BIC criterion, the best model was selected. Results are presented in figure D4.1 below.
Figure D4.2 then presents the resulting relative risks and excess mortality rates, if the regression model is applied. Confidence intervals were obtained using Monte Carlo simulation.
The RRs were then combined with COPD prevalence estimates based on Dutch GP registrations and Dutch overall mortality rates (statistics Netherlands) to find estimates for COPD mortality in the Netherlands as follows:
Othercause_mortalityNL = total_mortalityNL/{ prev COPD NL*RR_DYNAMO-HIA/GPRD+ (1- prev OCPD NL)}
Exces_mortalityNL= { RR_DYNAMO-HIA/GPRD-1}* Othercause_mortalityNL

Figure D4.3 shows the resulting excess mortality rates and life expectancies for men and women with COPD.

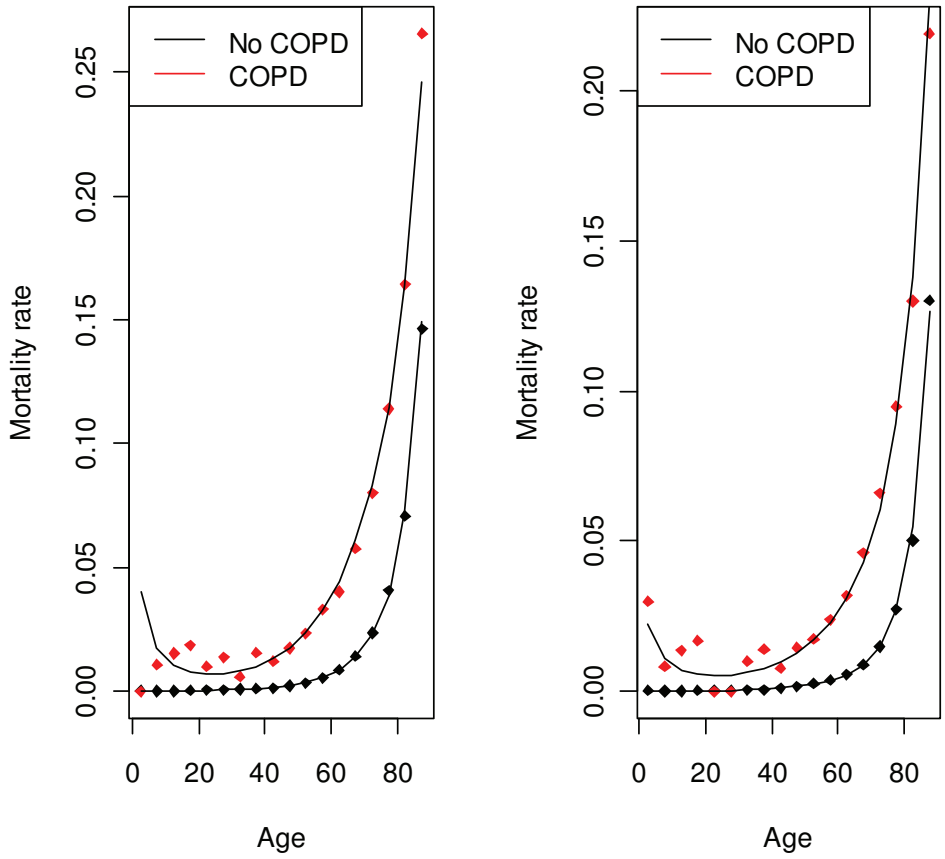


Figure D4.1: Mortality rates in raw DYNAMO-HIA/GPRD data and fitted functions (men and women).

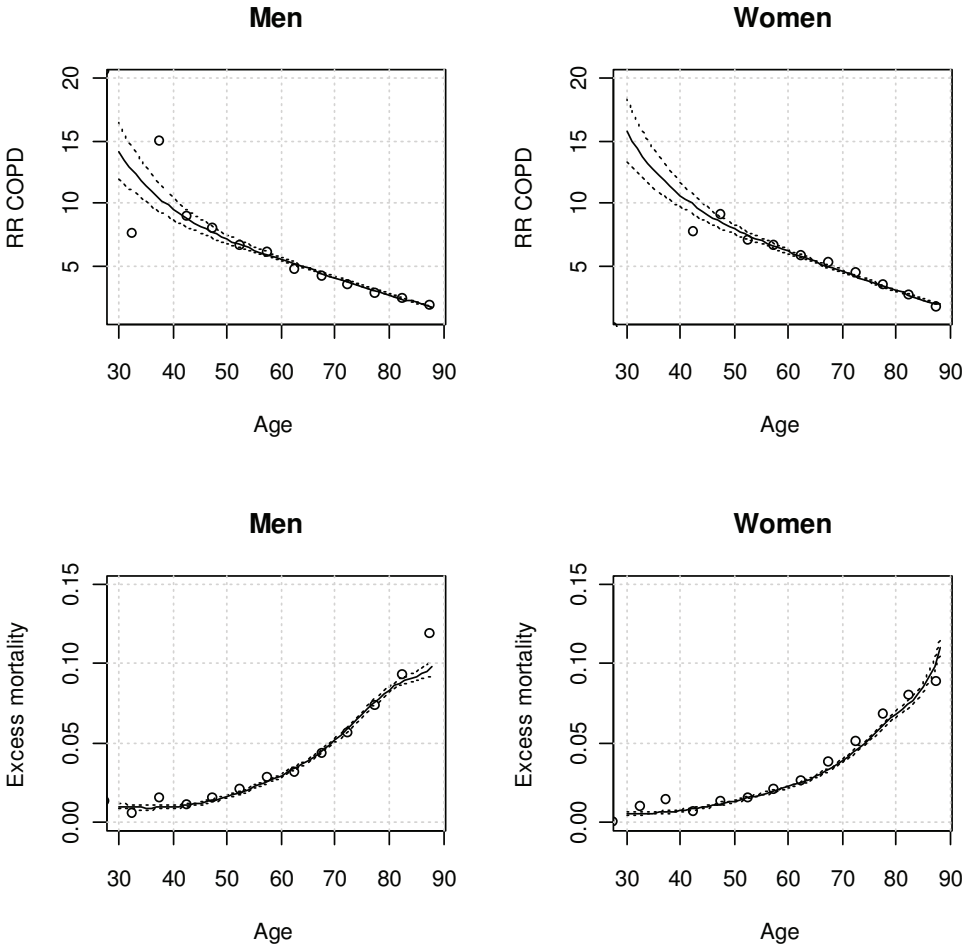


Figure D4.2 : relative risk for mortality (mortality in COPD)/(mortality in persons without COPD) and excess mortality (motrality with COPD) -/- (mortality in persons without COPD)

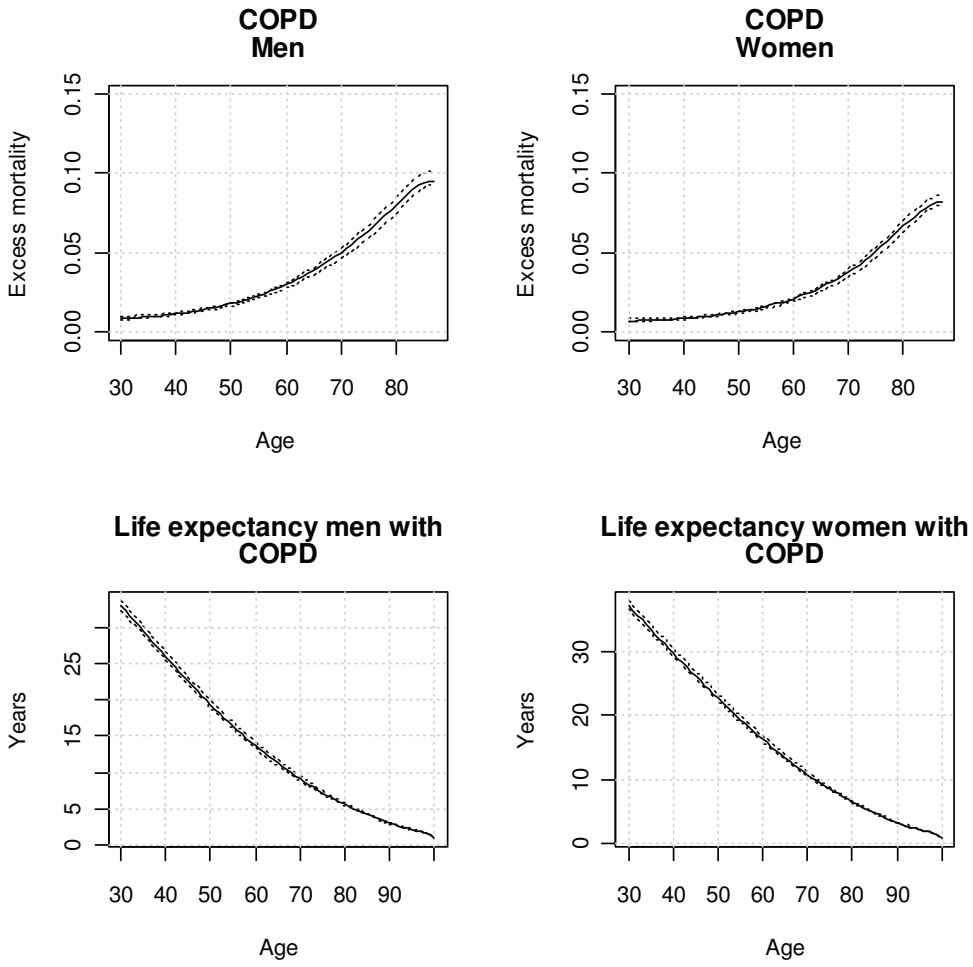


Figure D4.3: excess mortality and life expectancy for COPD patients

References

1. Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT*, et al.* A dynamic population model of disease progression in COPD. *Eur Respir J.* 2005;26 (suppl 2):223-33.

2. DYNAMO-HIA project, originally based on General Practice Research Database (GPRD) from the UK (www.gprd.com).

3. Van der Lucht F, Polder JJ. Van gezond naar beter. Kernrapport van de Volksgezondheid Toekomst Verkenning VTV-2010, versie 1.0, 25 maart 2010, RIVM, Bilthoven

APPENDIX E: Internal validity checks

During the development of the model, the internal validity of the model was secured by performing fifteen different model checks to prevent internal inconsistencies. The performed model checks, results and possible actions to resolve the problem are shown in the Table below.

Table E1: Model checks, all performed for a cohort of patients and a ten year time horizon

NR	Check	Expected outcome	Outcome as expected?	If no, what is done to resolve the problem
1.	Incidence and mortality both set at zero	Prevalence is constant over time	Not completely, prevalence decreased with 2%.	Outflow from very severe below 10% pred and outflow from mild COPD above 110% pred was set to zero*.
2.	Calculate life expectancy	Is the calculated life expectancy plausible? According to data of Van Baal et al, the mean life expectancy for a COPD-patient of with a mean age of 65-70 years is 10 to 12 years	Yes, for all COPD patients above 45 years the mean life expectancy is 10.5 years.	
3.	Model simulation for a 45 year old smoker compared to a 45 year old former smoker	Higher lung function decline, thus increased disease progression, which result in less (QA)LYs and higher mortality compared to a simulation with a 45 year old former smoker	Yes, smokers have a higher mortality	
4.	Model simulation for a 45 year old former smoker compared to a 45 year old smoker	Decreased lung function decline, thus decreased disease progression, which result in more (QA)LYs and a lower mortality compared to a simulation with a 45 year old smoker.	Yes, former smokers have a lower mortality.	

NR	Check	Expected outcome	Outcome as expected?	If no, what is done to resolve the problem
5.	Model simulation only for patients with mild COPD	Compared to a model simulation with only patients with severe COPD, the percentage of people dying is lower and the number of (QA)LYs per patient is higher.	Yes	
6.	Model simulation only for patients with severe COPD	Compared to a model simulation with only patients with mild COPD, the percentage of people dying is higher and the number of (QA)Lys per patient at the start of the simulation is lower.	Yes	
7.	Case fatality of an exacerbation set to zero	COPD attributable mortality is the sum of exacerbation-related mortality and other COPD attributable mortality. If the case fatality of an exacerbation is zero, the exacerbation-related mortality is zero and the other COPD attributable mortality equals the COPD attributable mortality, but total mortality does not change.	Yes, total mortality did not change	
8.	Effect of exacerbations on lung function decline set to zero	Decreased lung function decline, results in less mortality and more (QA)Lys compared to the reference scenario and compared to a simulation with a five times higher effect of exacerbations on lung function .	Yes	

NR	Check	Expected outcome	Outcome as expected?	If no, what is done to resolve the problem
9.	Effect of exacerbations on lung function decline five times higher	Increased lung function decline results in increased mortality and less (QA)LYs compared to the reference scenario and compared to a simulation with the effect of exacerbations on lung function set to zero.	Yes	
10.	Effect on lung function decline set to zero	No annual decline in lung function, results in reduced disease progression, less mortality and more (QA)LYs compared to the reference scenario and compared to a simulation with a five times higher effect on lung function.	Yes	
11.	Effect on lung function decline set five times higher	Increased lung function decline results in increased disease progression, increased mortality and less (QA)LYs compared to the reference scenario and compared to a simulation with the effect on lung function set to zero.	The number of LYs and the number of QALYs are indeed higher. Mortality is only higher in the first four years.	
12.	Effect on exacerbation frequency set to zero.	No exacerbations results in less mortality and more (QA)LYs compared to the reference scenario and compared to a scenario with the three times higher exacerbation frequency.	Number of (QA)LYs is increased, mortality did not change.	Effect on exacerbation frequency was applied to the exacerbation frequency after calculating the baseline parameters in 1st year of the model #

NR	Check	Expected outcome	Outcome as expected?	If no, what is done to resolve the problem
13.	Exacerbation frequency three times higher than the reference scenario	More exacerbations results in increased mortality and less (QA)LYs compared to the reference scenario and compared to a scenario with the exacerbation frequency set to zero.	Yes	
14	All-cause mortality three times higher than the reference scenario	Higher mortality and less (QA)LYs compared to reference scenario	Yes	
15.	All utility values are set to 1.0	The number of QALYs equals the number of life LYs	Yes	

Notes:

*The normal distribution of the FEV_1% predicted of the COPD population is truncated at 10 and 110%. Disease progression in patients with very severe COPD with an FEV_1% predicted around 10% predicted could result in a small percentage crossing the 10%-line. This percentage of patients “disappeared”, which was solved by setting the outflow from very severe below 10% predicted to zero. The same occurred in mild COPD, where as a result of an improvement in lung function due to smoking cessation patients with an FEV_1% predicted around 110% could cross this line. The outflow from mild COPD above 110% was also set to zero.

COPD attributable mortality (fixed as input) was defined as exacerbation-related mortality plus other COPD attributable mortality. Exacerbation-related mortality is calculated as the case fatality of an exacerbation times the exacerbation frequency. If the exacerbation frequency is reduced during the calculation of the baseline parameters in the first year, exacerbation-related mortality is reduced, but the other

COPD attributable mortality is increased, such that the COPD attributable mortality and total mortality did not change. In the scenarios the exacerbation frequency was adjusted after initialization of the baseline parameters and therefore a change in exacerbation frequency in the scenarios does have an effect on the COPD attributable mortality.

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