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A Health Policy Model for COPD:

Effects of Smoking Cessation

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Abstract

Objectives: 1) To improve an existing COPD model by incorporating the distinction between mild, moderate, severe and very severe COPD and by quantifying the progression of COPD over these stages 2) To use the improved model to estimate the potential impact of smoking cessation programs offered to COPD patients and project their effect on the future burden of COPD.

Methods: An existing population model for COPD, which is a module of the RIVM Chronic Disease model, was extended with disease progression over time. Prevalent cases in the starting year were distributed over 4 severity stages mild (28%), moderate (54%), severe (15%) and very severe (3%) (GOLD-classification). The severity distribution was based on data from GP registrations. The COPD incidence was 41% in mild, 55% in moderate and 4% in severe. Disease progression was modelled as annual decline in lung function in FEV_1% predicted. The Lung Health Study was used to estimate gender, age, smoking and baseline FEV_1% predicted dependent values of lung function decline and one-time increase in lung function associated with smoking cessation. A meta-analysis was done to obtain severity stage specific mortality rates. The new model was used to project COPD prevalence, mortality and costs by COPD severity stage over the period 2000-2025 (the base-case scenario). A series of sensitivity analyses was performed to assess the robustness of the results to changes in input data and assumptions.

The new model was used to compare two scenarios on increased implementation of two smoking cessation interventions, minimal counselling by the general practioner (H-MIS) and intensive counselling with bupropion (IC+Bupr). They were compared to the base-case scenario in terms of life-years, QALYs, interventions costs and savings of COPD-related costs. In the scenarios H-MIS or IC+Bupr was implemented for a period of either 1 year, 10 years or 25 years and reached 25% of the smokers. Smoking cessation results in a one-time increase in lung function and a lower annual decline in FEV_1% predicted, which results in less disease progression and less mortality among COPD patients who quit smoking. Future costs and effects of these scenarios were discounted at 4%. Incremental cost-effectiveness ratios were calculated as (additional intervention costs minus the savings in COPD-related health care costs)/ gain in health outcomes.

Results: In the base-case scenario, the total number of COPD patients increases from 300 thousand in 2000 to 490 thousand patients in 2025. Between 2000 and 2025 the prevalence rate of mild COPD increases from 5 to 11 per 1000 inhabitants. The prevalence rate of moderate COPD increases from 11 to 14. For severe COPD the rate increases from 3.0 to 3.9 and for very severe COPD the rate increases from 0.5 to 1.3. In absolute numbers the increase is highest in mild COPD, but the largest relative increase in prevalence rate is seen in very severe COPD. As a result of the increase in COPD prevalence and aging of the COPD population, all-cause mortality rates per 1000 inhabitants increase in all severity stages. In 2000, total COPD-related health care costs are estimated to be 280 million Euros. In 2025 total costs are projected to be 495 million Euros. Costs for very severe COPD have the highest relative increase. The sensitivity analyses show that the model projections were most sensitive to assumptions about the severity distribution of incidence.
Implementation of H-MIS and IC+Bupr results in more mild and moderate and less severe and very severe COPD patients compared to the base-case scenario after 25 years. Costs per additional quitter are 700 for H-MIS and 2700 for IC+Bupr. Irrespective of the duration of implementation, H-MIS generates net savings, which indicates that the intervention costs of H-MIS are offset by the savings in COPD-related costs. For IC+Bupr savings do not outweigh the interventions costs. For the years 2000 to 2025 the costs per life-year gained of implementing IC+Bupr for 10 years are estimated to be 12000 Euros.

Conclusions: Modelling COPD progression over time proves feasible. The model showed that implementation of H-MIS among COPD patients results in better health outcomes and is cost saving. Implementation of IC+Bupr has higher costs than savings, but is still cost-effective with costs per life-year ranging from 10600 to 24500 depending on the duration of implementation.

1. Introduction

In order to plan appropriate allocation of health care resources it is important for decision-makers to be informed about the future burden and costs of disease in their country and the impact of health care interventions on this burden. This is true for COPD in particular, because of the rise in morbidity and mortality that is foreseen for the near future.

Projections of the future burden of COPD for different intervention scenarios can be made through the use of models. In the past the National Institute of Public Health and the Environment (RIVM) and the Institute for Medical Technology Assessment (iMTA) have developed a health policy model for COPD that projects the future incidence and prevalence of COPD by age, gender and smoking class. The model projects the future burden of COPD in terms of mortality, life-years lost, disability adjusted life-years lost (DALYs) and COPD-related health care costs. This model has been published (Feenstra et al., 2001) and has been used to simulate the impact of anti-smoking campaigns directed at the general public on the incidence and burden of COPD in the Netherlands (Rutten-van Molken et al., 1999).

However, this model had a major shortcoming. It did not model the progression of COPD once a person was diagnosed with COPD. Therefore the model could not be used to study the consequences of any intervention that was specifically directed at COPD patients.

The purpose of the current project was to update and improve the model such that it includes the progression of COPD over time, in order to be able to simulate the effects of both preventive and therapeutic interventions upon burden and costs of COPD for an extended time horizon. More specifically the purpose of the project was:

1. To improve the existing COPD model by incorporating the distinction between mild, moderate, severe and very severe COPD and by quantifying the progression of COPD over these states.
2. To use the improved model to estimate the potential impact of smoking cessation programs offered to COPD patients and project their effect on the future burden of COPD.

2. Update of the existing COPD model

The existing COPD model is a module of the chronic disease model developed by the National Institute of Public Health and the Environment (RIVM). This chronic disease model is a dynamic multistate lifetable model that has been used to project the health of the Dutch population (van Oers, 2002), in order to inform policy makers. The model basically consists of a demographic module that is linked to several disease-specific modules, among which is the COPD module.
In contrast to many other models, which follow a cohort of people over time until this cohort has died, the chronic disease model is a dynamic population-based model. This means that it takes account of annual changes in the demography of the Dutch population. These changes are due to ageing, birth, and mortality. It also models epidemiological processes, like changes in the prevalence of risk factors and risk-factor-specific incidence, prevalence and mortality of chronic diseases. When estimating mortality, the model takes account of competing death risks, because otherwise COPD prevalence would be overestimated. In other words, because the incidence of other smoking-related diseases among COPD patients is higher than among the general population, COPD patients run a larger risk to die, not only from COPD, but also from those other smoking-related diseases.

The existing model is populated with demographic data, data on COPD incidence, prevalence and mortality by gender and 5-year age classes, data on smoking prevalence and transition rates between the 3 smoking classes. As part of the project reported here, these data have been updated to the base year 2000. A brief description of the source of these data is given below.

2.1 Demography

Demographic data were obtained from Statistics Netherlands. They comprised data on and prognoses of births and total mortality for each gender and 5-year age class. In table A1 of appendix A the population numbers for the base year 2000 are shown by gender and 5-year age class.

2.2 COPD Incidence, Prevalence and Mortality

Table A2 in appendix A shows COPD incidence, prevalence and excess mortality by gender and 5-year age classes. Incidence data were obtained from 3 GP registration systems that cover different parts of the country: 1) the Continuous Morbidity Registration of the department of General Practice and Social Medicine of the University of Nijmegen (van Weel et al., 2000), 2) the Registration Network Family Practices of the University of Maastricht (Knottnerus et al., 1992) and 3) the Transition project of the department of Family Practice of the University of Amsterdam (Lamberts et al., 1996). Prevalence data were obtained from the first 2 GP registrations.

Data from these GP registrations were combined and smoothed over age to obtain estimates of the incidence and prevalence of COPD in a Dutch general practice in 2000. Incidence and prevalence under the age of 45 years were assumed to be the result of misclassification and were not included. In all projections that were made, the 2000 age- and gender-specific COPD incidence and prevalence rates were used without time trends, other than those caused by changes in smoking patterns.

Mortality rates for COPD patients were estimated as the difference between mortality in the general population and mortality among COPD patients (Hoogenveen et al., 1998). This difference is called COPD excess mortality and includes the additional risk to die from other smoking related diseases.

2.3 Smoking prevalence and transition rates

Smoking is the major risk factor for COPD. The prevalence of non-smokers, smokers and ex-smokers among the Dutch population by gender and 5-year age classes is given in table A3. These rates were based on yearly population monitoring studies of Stivoro for the time period 1997-2000. Table A4 shows the start-, stop-, and restart rates that were used to model changes in smoking prevalence in the Dutch population over time. Start rates were calculated based on the change in age-specific prevalence rates of never smokers. Stop rates were based on a weighted average of Stivoro data (1998-1999) and three Dutch cohort studies (Deeg et al., 1993; Mackenbach et al., 1994; Blokstra et al., 1997). They approximated 12-month continuous abstinence rates. Restart rates were estimated by combining the smoking prevalence rates of the yearly population monitoring studies by Stivoro over the period 1997-2000 with the stop rates mentioned above. In the model, trends in smoking over time are a result of age-specific prevalence, start, restart and stop rates.

2.4 COPD incidence among non-smokers, smokers and ex-smokers

The incidence of COPD in each smoking class was estimated from the observed age- and gender-specific COPD incidence in the GP registrations and the relative risks of smokers and ex-smokers to get COPD (US-DHHS, 1990; van Oers, 2002). These relative risks, stratified by gender and 5-year age class, are shown in table A5.

3. Description of the new COPD model

In order to evaluate the (cost-)effectiveness of interventions specifically directed at COPD patients the existing model was extended with COPD progression over time. The population of COPD patients above 45 years of age and a FEV_1/FVC ratio less than 70% was classified by disease severity according to the lung function values in the GOLD-criteria (GOLD, 2003): mild COPD (FEV_1% predicted ≥80%), moderate COPD (FEV_1% predicted <80% and ≥50%), severe COPD (FEV_1% predicted <50% and ≥30%) or very severe COPD (FEV_1% predicted <30%). The estimated severity distribution based on GP registration data was applied to the COPD prevalence of our base year 2000 and used as a starting point. Figure 3.1 describes the structure of the new model.

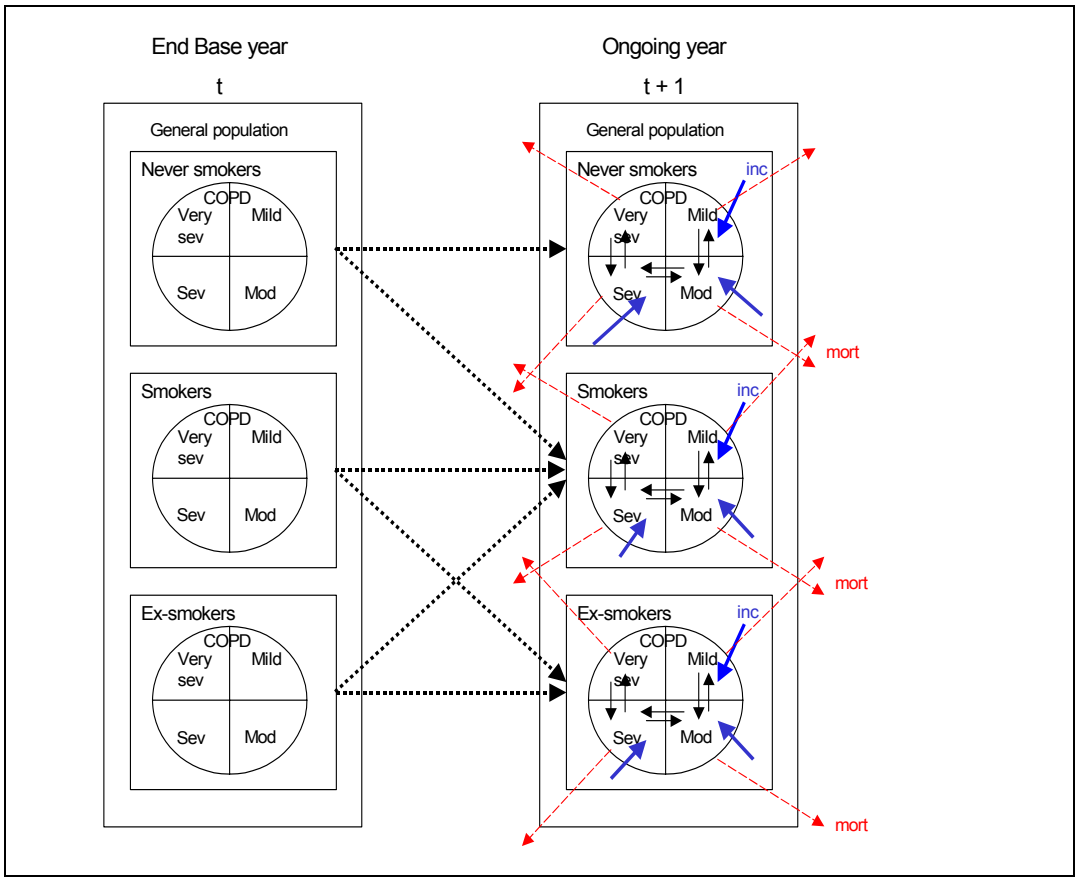

Figure 3.1: Final structure of the COPD model

= transition between smoking classes

= transition between severity stages

= incidence

= mortality

Each year new patients are diagnosed within COPD severity stages. COPD patients can move to a worse severity stage, because of disease progression. Disease progression was modelled as annual decline in lung function. Decline in lung function was assumed to depend on age, gender, smoking and FEV_1% predicted. The annual decline was transformed into a stage transition rate indicating the probability of moving to the next severity stage while being in a specific severity stage. Patients may move backwards into a less severe stage when they stop smoking and their lung function improves, however, the estimated transition rates are very low. Complete recovery from COPD is impossible by assumption. Because worse severity stages are associated with a higher risk of mortality, mortality rates for the different severity stages were estimated. In appendix C the mathematical description of the model is given.

With all these adaptations the new model is able to evaluate interventions in COPD patients, that influence disease progression. For example smoking cessation leads to a one-time increase in FEV_1% predicted and a lower annual decline of FEV_1% predicted. As a result, transition rates for ex-smokers are lower than for smokers. Because mortality is higher in worse COPD severity stages, ex-smokers have a lower COPD mortality than smokers. In the remainder of this chapter the new input data are described. These data were finalized after discussion with and input from an expert panel, which consisted of an epidemiologist, a general practitioner and 2 pulmonologists.[2] Their valuable suggestions and comments gave rise to various adaptations of model parameter values, but the final input data are the full responsibility of the authors. These data concern the distribution of COPD prevalence and incidence by severity, the decline in FEV_1% predicted in each COPD severity stage, the association between FEV_1% predicted and mortality and the COPD related health care costs by severity stage.

3.1 Distribution of prevalence by severity

To estimate the severity distribution of COPD in the Netherlands, we have used two different sources of GP-data: data from the Nijmegen Monitoring Project (NMP) and from the Institute for research in extramural medicine (EMGO). We have chosen GP registrations, because virtually all people in the Netherlands, including those treated by

[2] Members of the expert panel were dr. Jan Schouten (epidemiologist), dr. Ivo Smeele (general practitioner), prof. dr. Emiel Wouters (pulmonologist) and dr. Sonia Buist (pulmonologist)

pulmonologists, are registered with a GP practice. Therefore, these data probably best represent the Dutch COPD population known to the GP. Moreover, the incidence and prevalence data of COPD (see table A2) that go into the model are also based on GP registrations. Classification of COPD-severity was based on post-bronchodilator FEV_1% predicted conform the GOLD-guidelines (GOLD, 2003).

NMP-data

Firstly, we selected all patients with a physician diagnosis of COPD (code R91/R95) and/or asthma (R96) from five general practices in the Nijmegen Monitoring Project (NMP): Lent, Oosterhout, Doesburg, Wychen and Berghem (van Weel et al., 2000). These general practices are unique, because they keep an electronic record of spirometric results. 530 patients had a diagnosis of COPD and 938 had a diagnosis of asthma. Of the 530 COPD-patients, only 25 patients also had a diagnosis of asthma. From 307 of the 530 COPD patients spirometric data were available. Patients with and without spirometry did not differ significantly with respect to age, gender, co-morbidities and number of prescriptions of relevant medication for COPD (Table B1 in Appendix B). Based on the available information we assumed that the groups with and without spirometry were not different.

For each patient, the largest FEV_1 value of the two most recent consecutive years with measurements in the period 1997-2002 was taken. When post-bronchodilator values were not available, pre-bronchodilator values were multiplied by a factor 1.095. This factor was computed from the observed difference between pre- and post-bronchodilator values in the data. The FEV_1% predicted was calculated using the equations of Quanjer (Quanjer et al., 1993). Among the 307 COPD patients with spirometric data, 85 patients who did not have a $FEV_1/FVC < 70\%$ and 6 patients younger than 45 years were excluded for classification. Results of the classification are shown in table 1 below.

EMGO-data

Secondly, we have used a database from the EMGO institute of the Free University of Amsterdam that contained lung function data on asthma and COPD patients from 25 GP practices that participated in a clinical trial (Wijnhoven et al., 2001). All patients with a physician diagnosis of either asthma or COPD were asked to participate in the clinical trial. 2047 patients met the following inclusion criteria: age 16 to 75 years, capable of filling in a Dutch questionnaire, no specific pulmonary disease other than asthma or

COPD and absence of any disease in a terminal phase. 1325 patients were willing to participate in the trial. The 722 patients, who did not enter the trial, were significantly younger and a higher percentage was male (Wijnhoven et al., 2001).

1308 of the 1325 patients had valid lung function measurements at baseline. Of these 1308 patients 701 either had a physician diagnosis of COPD (n=291) or the distinction between asthma and COPD was unknown (n=410). 153 of the 291 patients with a physician diagnosis of COPD also had a diagnosis of asthma, but where included, because the incidence and prevalence data used in the model (see table A2) are also obtained from GP registrations and might also contain some patients which have both diagnoses. FEV_1% predicted values were again calculated with Quanjer's equations (Quanjer et al., 1993). In table B2 in the appendix baseline characteristics of the patients are shown.

Patients were classified using the same criteria that were used for the NMP data, excluding patients with an FEV_1/FVC over 70% and younger than 45 years of age. The results are also shown in table 3.1 below.

Table 3.1: Distribution of disease severity among COPD patients known to the GP

	COPD severity by GOLD criteria, FEV_1/FVC<70% Percentage (number of patients)			
	Mild	Moderate	Severe	Very severe
	FEV_1% predicted >=80%	FEV_1% predicted >=50% and <80%	FEV_1% predicted >=30% and <50%	FEV_1% predicted <30%
NMP	31% (67)	47% (102)	19% (41)	3% (6)
EMGO	28% (75)	55% (146)	15% (39)	2% (5)
Total*	28%	54%	15%	3%

* The final distribution over the four severity stages is based on figure 3.2.

Final severity distribution

In figure 3.2 the frequency distribution of FEV_1% predicted is shown for the combined NMP and EMGO-data. The columns show the empirical data, the continuous line the fitted normal distribution density function. We tested for log normality, but the normal distribution performed better. Therefore we assumed that FEV_1% predicted is normally distributed. Based on this normal distribution with a mean FEV_1% predicted of 68.3% (SD 19.9%) we estimated that 28% had mild COPD, 54% had moderate COPD, 15%

had severe COPD and 3% had very severe COPD. This severity distribution is used in our base-case analysis and applied to each subgroup of COPD patients defined by age, gender and smoking class. Next to that, the normal distribution is used to estimated the distribution of FEV_1% predicted within each COPD stage.

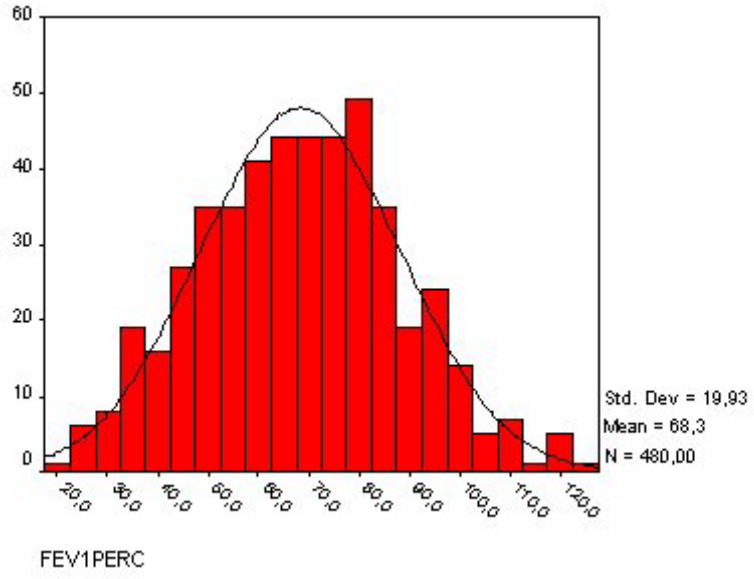

Figure 3.2: Distribution of FEV_1% predicted of prevalent cases of COPD based on both NMP and EMGO data

We assumed that within each COPD stage the distribution function of FEV_1% predicted was linear, i.e. we approximated the normal distribution function by estimating linear functions for each separate severity stage. However, in moderate the curve is not linear, because the top of the curve is in this stage. To describe this top, we divided moderate into two stages (cut-off point of 68 FEV_1% predicted) and fitted linear functions to both the stages of moderate COPD patients.

3.2 Distribution of incidence by severity

Due to small numbers, the distribution of COPD incidence by disease severity could not be estimated reliably from the GP data. Therefore we estimated the distribution of the incidence over the severity stages assuming the prevalence being constant between 2000 and 2001. That is, given the prevalence, disease progression and mortality in 2000, the incidence should be such, that the distribution of FEV_1% predicted in the entire COPD population in the year 2001 should not differ from the distribution in the year 2000, when keeping smoking prevalence rates and population numbers constant. The

estimated severity distribution of the incidence (mean=76.4, sd=15.6) was then applied in each year after 2000. In table 3.2 the estimated distribution of incidence by disease severity is shown. 41% of the newly diagnosed COPD patients has mild COPD, 55% has moderate COPD and 4% has severe COPD. There is no incidence in very severe COPD.

Table 3.2: Distribution of incidence by severity

	Mild FEV_1% predicted >=80%	Moderate FEV_1% predicted >=50% and <80%	Severe FEV_1% predicted >=30% and <50%	Very severe FEV_1% predicted <30%
Incidence	41%	55%	4%	-

This distribution of COPD incidence by severity is used in our base-case and applied to each subgroup of COPD defined by age, gender and smoking class.

3.3 Transition rates between severity stages

In the model disease progression and mortality rates determine the average time spent in a certain severity stage. Estimates of the transition rates were based on estimates of the decline in FEV_1% predicted, which depended on age, gender, smoking class (smokers and ex-smokers) and absolute FEV_1% predicted.

Description of the data

Our primary source of data on FEV_1 decline was the Lung Health Study (LHS), a study that was specifically designed to estimate the effect of smoking and smoking cessation on lung function decline in COPD patients. For this study 5887 smokers with mild to moderate airflow obstruction aged between 35 and 60 years were recruited. Participants were equally randomized into 3 intervention groups, 1 receiving an intensive smoking cessation program, 1 receiving the same program in combination with ipatropium and 1 receiving usual care. In total 66% of the patients followed the smoking cessation program. All patients were followed for 5 years. At baseline and during every annual visit lung function was measured, a questionnaire was filled out and smoking status was

determined by self-report and validated with salivary cotinine assay and exhaled CO measurements (Scanlon et al., 2000).

We have re-analyzed all 5-year follow-up data of the LHS from the 5887 smokers that started the LHS. Baseline characteristics of the study population are shown in table B3. Because no effect of ipatropium on decline in lung function was observed in the LHS, we used data from all three intervention groups.

Statistical procedure

We have re-analized these original data using a random effects model with year, smoking cessation and the interaction between these two variables, year x smoking cessation, as the basic model. Gender, age, age^2 and baseline FEV_1% predicted including all significant interactions were added as explanatory variables. This random effects model was used to predict decline in FEV_1% predicted by age, gender, smoking class (ex-smoker and smoker) and COPD-severity.

The increase in FEV_1% predicted associated with smoking cessation was calculated with the same model. The coefficients of the model are shown in table B4. Table 3.3 shows the decline in FEV_1% predicted and the increase in FEV_1% predicted after smoking cessation, for various subgroups of COPD patients.

Decline outside the range in the observed age and lung function values in the data was based on extrapolation of the same model. As a result, the estimated increase after smoking cessation for very severe patients is probably too high. Therefore we decided to use a maximum of 6.5% for the increase after smoking cessation, which was the 75-percentile of lung function increase among all LHS COPD patients, who quitted smoking in the first year[3]. The increase in lung function associated with smoking cessation can cause remission to a better severity stage. Total remission, i.e. recovery from COPD, is not possible.

[3] The LHS study recruited patients with mild or moderate COPD. Over time some of the moderate patients progressed to severe COPD. For all patients who quitted smoking, while they were in stage severe COPD (n=18), the mean increase in lung function associated with smoking cessation was 4.0 % predicted (median= 3.9%)

Table 3.3: Decline and increase in FEV_1% predicted per year for subgroups

	Age		Decline		Increase after smoking cessation
			Smokers	Ex-smokers	
Men	45 yr	Mild	-0.68	-0.30	-1.09
		Moderate	-0.81	-0.43	3.82
		Severe	-0.94	-0.56	6.50
		Very severe	-1.04	-0.66	6.50
	65 yr	Mild	-1.08	-0.74	-1.23
		Moderate	-1.40	-1.05	1.31
		Severe	-1.71	-1.37	3.85
		Very severe	-1.94	-1.59	5.73
Women	45 yr	Mild	-0.84	-0.47	2.66
		Moderate	-0.97	-0.60	5.38
		Severe	-1.11	-0.73	6.50
		Very severe	-1.21	-0.83	6.50
	65 yr	Mild	-1.08	-0.74	0.50
		Moderate	-1.39	-1.05	3.04
		Severe	-1.71	-1.36	5.59
		Very severe	-1.93	-1.60	6.50

No data were available for never-smoking COPD patients. Therefore we assumed that the decline among never-smoking COPD patients equals the decline among the ex-smokers. We thought this is better than assuming that the decline equals the decline among never-smokers in the general population, because, after all, these patients do have COPD.

Each year the model calculates the new distribution of FEV_1% predicted within each severity stage. The new distribution is calculated as a result of outflow because of disease progression and mortality, inflow because of improvement associated with smoking cessation and COPD incidence. The transition rates to a more severe COPD stage are calculated with the outflow to a more severe stage (surface under the linear curve) as percentage of the total surface under the linear curve in that particular severity

stage. The transition rates to a less severe COPD stage associated with smoking cessation are calculated with the outflow to a less severe stage (surface under the linear curve) as percentage of the total surface under the linear curve in that particular severity stage. Transition rates change every year, because of changes in the distribution of FEV_1% predicted. Transition rates for the first year are shown in table B5.

3.4 Mortality rates by severity

In order to obtain a well-documented estimate of the relative risk (RR) for all-cause mortality per unit change in FEV_1% predicted, we performed a meta-analysis on papers published between 1970 and 2002, which reported the association between FEV_1% predicted and all-cause mortality in a general or COPD population. Papers had to meet the following in- and exclusion criteria

- At least 3 years of follow-up
- Caucasian population
- Correction for at least age and smoking
- No correction for dyspnoea and decline in lung function
- Not in patients hospitalised for a COPD exacerbation
- Reporting standard errors

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

We found 17 studies, 11 directly reporting the RR per unit change in FEV_1% predicted and 6 reporting the RRs by class of FEV_1% predicted (Traver et al., 1979; Beaty et al., 1982; Beaty et al., 1985; Ebi-Kryston, 1988; Postma et al., 1989; Lange et al., 1990; Lange et al., 1990; Gray-Donald et al., 1996; Hole et al., 1996; Neas et al., 1998; Hansen et al., 1999; Knuiman et al., 1999; Landbo et al., 1999; Hospers et al., 2000; Hospers et al., 2000; Pelkonen et al., 2000; Schunemann et al., 2000; Anthonisen et al., 2002; Prescott et al., 2002).

Only 5 of the 17 studies were done in COPD patients. This resulted in an estimate of the RR per 10-unit decline of 1.11 (95% CI 1.10-1.12) for studies in a general population and a RR of 1.20 (95% CI 1.16-1.23) for studies in COPD patients. Thus in COPD patients each 10-unit decrease in FEV_1% predicted increased the mortality risk with 20%. Based on this result the following figure was constructed.

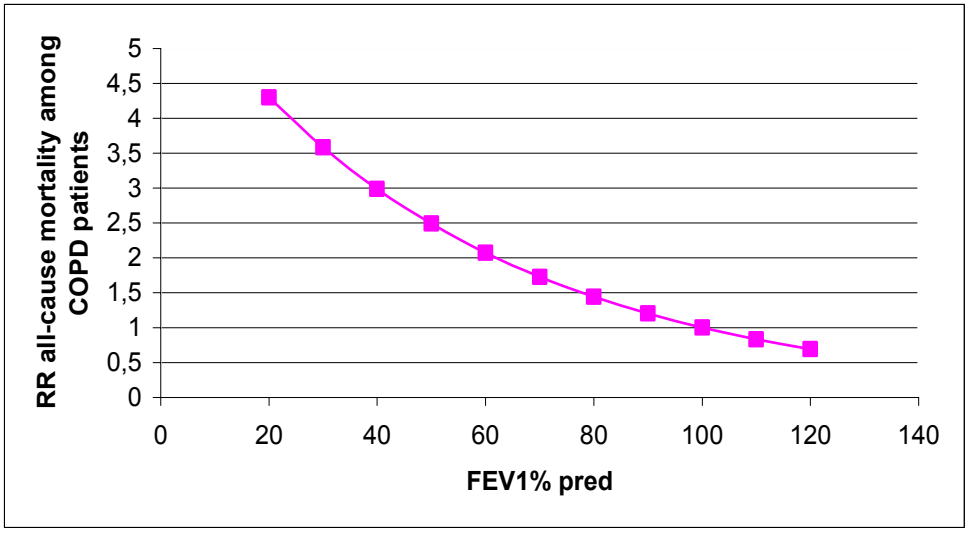

Figure 3.3: Relative Risk of all-cause mortality by FEV_1% predicted in COPD, setting the RR of an FEV1 % predicted of 100 at 1.

The function in figure 3.3 was used to estimate the relative mortality risk of COPD patients by severity stage. All-cause mortality in the model was defined as the sum of COPD excess mortality and mortality from other causes. Excess mortality was defined as the absolute difference in mortality between COPD patients and persons without the disease, given gender and age. Excess mortality includes the mortality due to COPD, but also the higher risk on mortality from other smoking-related diseases. We assumed only excess mortality to be dependent on lung function.

We applied the relative risks from figure 4 to calculate the excess mortality rates for each severity stage. If we assign an RR of 1 to the mean FEV_1% predicted of the mild COPD patients, then the RR of moderate, severe and very severe COPD can be calculated relative to the risk in mild COPD. Total excess mortality in the first year was used to calculate the severity stage specific excess mortality rates as given in table 3.4.

Table 3.4: Severity stage specific excess mortality rates in the first year per 1000 patients in that specific severity stage

	Excess mortality rates
Mild	22.4
Moderate	35.5
Severe	54.1
Very severe	77.4

To calculate excess mortality for a specific severity stage in absolute numbers, the mortality rate for that severity stage was multiplied with the number of patients in that severity stage.

Mortality from other causes was assumed not to depend on COPD severity, but only on age, gender and smoking, which is the same as in the standard model.

3.5 Costs of COPD by severity

We have estimated the direct medical costs of COPD in the Netherlands for the year 2000. Data on health care use were, as much as possible, obtained from representative, national registries to get age- and gender-specific data on costs. Costs per unit of resource use were also estimated. Resource use was multiplied with unit costs to calculate total costs for COPD care in the Netherlands. All costs were valued in Euros (price level 2000). When unit costs for other years than 2000 were available, the consumer price index was used to correct for inflation. Unit costs are shown in table B6 in appendix B. Only costs made by COPD patients aged 45 years and over were taken into account. Total costs were divided by prevalence to find costs per average COPD patient. Finally, these average costs were used to find costs per severity class with the help of severity weights and the prevalences per severity stage.

Primary care and specialist care

The number of times COPD-patients visit their general practitioner during a year was obtained from the Confronting COPD Study (Wouters, 2003). In this study conducted in 8 countries, information on COPD-related health care use and lost productivity was obtained by means of telephone interviews. The patient samples for the survey were identified by systematically screening geographically stratified samples of households, using random digit dialling of telephone numbers (Halpern et al., 2003). Inclusion criteria

for the survey were 45 years of age or older, a smoking history of at least 10 years and previously diagnosed with COPD, emphysema or chronic bronchitis or chronic bronchitis defined by persistent coughing with phlegm or sputum for the last 2 years or more. We have only used the data of the 415 Dutch participants. One-fifth of the participants met the inclusion criterion of persistent cough with phlegm or sputum for the last two years or more, but had not been diagnosed with COPD before.

55% of the 415 COPD patients did visit their general practitioner during one year. The mean number of COPD-related visits was 4.6. This resulted in a mean of 2.56 COPD-related visits for the overall group of COPD-patients. The costs of a visit to the GP were derived from Oostenbrink et al (Oostenbrink et al., 2000).

According to the same data source, 42% of the COPD-patients visited a medical specialist during one year. Mean number of visits was 4.2 (Wouters, 2003). Based on this information we estimated that the average number of COPD-related visits to a specialist was 1.76 for COPD-patients. Unit costs were obtained from (Oostenbrink et al.) . Total costs for primary and specialist care were estimated to be 13 and 26 million Euros respectively.

Home care

Information on use of home care was available from the Patient Panel Chronic Diseases (PPCZ), a group of people with different chronic diseases including COPD (Heijmans et al., 2003). The total Panel of more than 2000 patients includes a group of 310 patients with physician-diagnosed COPD, 46% female with a mean age of 65 years old. The physician-diagnosis was not validated by spirometry.

According to the PPCZ the percentage of COPD-patients using home care (help with household duties) was 17% during one year. In the general population this percentage was 4%. Therefore we assumed that 13% of the use of home care was COPD-related. From the PPCZ no data were available on the number of hours home care. We assumed an average of 3 hours a week, which is the mean number of hours of home care for a 65-year old receiving home care. (Stevens et al., 2001). The unit costs of home care are obtained from Oostenbrink et al (Oostenbrink et al., 2000). Total COPD-related costs for home care were estimated to be 54 million Euros.

Inpatient care

The number of admissions to hospitals, day-care in hospitals and the number of inpatients days for COPD, were obtained from the National Medical Registration (LMR)

(LMR, 2000). This registration covers almost 100% of all Dutch hospitals. It contains information on day-care treatment, hospital admissions, hospital days and clinical procedures. Except for Salem and Davos all Dutch asthma centres are present in this registration. We selected the ICD-9 (International Classification of Disease) codes 490-492, 494 and 496 to represent COPD. Only the admissions with COPD as the main reason for admission were taken into account. In 2000 total number of inpatients days for patients 45 years and older was 959 for day-care treatment and 277663 for clinical days. The mean length of stay per admission was 14.3 days. In the tables B8 and B9 the total number of admissions, days for day-care treatment and hospital days are shown for different age- and gender classes. Unit costs of a hospital day and a day-care treatment day were obtained from Oostenbrink et al (Oostenbrink et al.). Total costs for day-care treatment were estimated to be 170 thousand Euros, while total costs for inpatient hospital days were almost 75.3 million Euros.

Data on costs for COPD related to nursing and residential care facilities were obtained from a cost of illness study from Polder et al. (Polder et al., 2002). Costs were only available for COPD and asthma together. Because we only took into account costs for patients above 45 years old, we assumed that 90% of the costs were due to COPD and 10% to asthma. Total costs for COPD were thus estimated to be 34 million Euros. In table B9 total costs for different age-and gender classes are shown.

Medication

To obtain the percentage of COPD-patients receiving an influenza vaccination annually, we have used data from the evaluation of the national influenza vaccination campaign (Tacken et al., 2000). In 2000 75% of the patients with pulmonary diseases (no further subdivision was given) received an influenza vaccination. We assumed this percentage to be the same for COPD. The costs of an influenza vaccine were obtained from the Pharmacotherapeutic Kompas (Kuy van der et al., 2000). Unit costs for one vaccination were calculated adding half the price of a visit to the general practitioner to the price of the vaccine.

Medication costs included 4 categories of medications: corticosteroids (H02), antibacterials (J01), anti-asthmatics (R03) and cough- and cold-medications (R05). The R03 group contains most of the relevant inhalation medication, such as glucocorticosteroids, anticholergics, ß-sympathicomimetica etc. From the Foundation for Pharmaceutical Statistics (SFK) the total number of prescriptions and total costs for each medicine in the 4 selected groups for the year 2000 in the Netherlands were obtained

(SFK, 2000). Total prescriptions were age- and gender-specific. No information on prescriptions per diagnosis was available in the SFK-data. Therefore we selected the same groups of medications in the LINH, a countrywide registration network of 90 general practices (LINH, 2000), that records both prescriptions and the diagnosis associated with the prescription. For each single medication within the selected groups, the ratio of the number of prescriptions for COPD to the total number of prescriptions was calculated. These ratios from the LINH were used to estimate for each medication in the SFK data, the number of prescriptions in every age-and gender-class in 2000 that was due to COPD. Table B10 shows the total costs for different age- and gender classes. Total costs for medications were 60.4 million of which more than 90% were due to the anti-asthmatics (R03).

The use of oxygen therapy was estimated based on information from the research program “Thuiszorgtechnologie” from the Netherlands Organisation for Health Research and Development (ZonMW, 1999). In this source the number of patients with oxygen therapy at home, irrespective of their diagnosis, was estimated to be 10 000 in 1999. In a study from Kampelmacher et al. 70% of a random sample of clients of an oxygen company had a diagnosis of COPD (Kampelmacher et al., 1998). Therefore we assumed that about 70% of the total number of patients receiving oxygen therapy at home, was COPD-patient, which resulted in a total of 7000 COPD-patients using oxygen at home in the Netherlands.
Unit costs for oxygen were 4.24 Euros per day per patient based on an agreement between the Health Insurance Companies and the oxygen supplying companies. Total costs were estimated to be almost 11 million Euros.

Surgery

Ten Vergert et al. performed an evaluation study to the effectiveness of lung transplantation (Ten Vergert, 1996). In the study period 57 lung transplantations were performed of which 40,3% were performed on patients with a diagnosis of COPD. Therefore we assumed that of all performed lung transplantations roughly 40% is due to COPD. According to Eurotransplant 17 lung transplantations took place in the Netherlands in 2000 (Eurotransplant, 2000). We estimated that 7 transplantations were performed on COPD-patients. Unit cost for lung transplantation were obtained from a study of Al et al (Al et al., 1998). Total costs of lung transplantation were 1.2 million Euros for the year 2000.

Total costs and costs by severity

Total direct medical costs for COPD (above 45 years of age) were estimated to be 280 million Euros, 915 Euros for an average COPD patient (table 3.5).

Table 3.5: Total cost in million Euros for COPD patients aged 45 years and older (n=305831) in 2000

	Total costs per patient	Total costs in million Euros
Day-care treatment in hospital	0.55	0.169
Inpatient hospital care	246	75.4
Nursing home and residential care	112	34.3
Home care	177	54.1
General practitioner	42	13.0
Medical specialist	88	26.8
Influenza vaccination	11	3.45
Medication	198	60.4
Oxygen therapy	35	10.8
Lung transplantation	4	1.25
Total	915	280

Some data on resource use, such as day-care treatment in hospital, inpatient hospital care, nursing home and residential care and medication, were age and gender specific data. If age and gender specific data on resource use were not available, total costs per age and gender class were estimated by multiplying the mean costs per patient with the number of COPD patients in that specific age and gender class. Finally for each age and gender class total costs were estimated by summing all age and gender specific costs for the different forms of health care use.

It was not possible to estimate resource use per severity stage. Therefore we have used a Swedish study to obtain ratios for the costs of a patient with moderate, severe or very severe COPD compared to the costs of a patient with mild COPD (Jansson et al., 2002). We used these ratios to assign total costs within each age- and gender class to the different severity stages (table B11). An exact description of the calculation of costs per

patient is given in appendix B11. In table 3.6 the average costs per patient for the different severity stages are shown.

Table 3.6: Costs in million Euros per severity stage

Severity stage	Ratio	Patients (n)	Costs (Euros per patient)	Total costs in million Euros
Mild	1.0	81200	277	22.5
Moderate	2.22	169000	616	104
Severe	7.51	47300	2080	98.6
Very severe	24.67	7900	6840	54.3

3.6 Sensitivity analyses

To study the robustness of the outcomes of the projections, we have done extensive one-way sensitivity analyses on the severity distribution of COPD prevalence and incidence, on lung function decline, on the one-time increase in lung function after smoking cessation, on the lung function decline among never-smokers and on the association between lung function and mortality.

Sensitivity analysis on the severity distribution of COPD prevalence

Instead of using the same base-case severity distribution for each age class, we have assigned the severity distribution as shown in figure 3.2 to a population with the age of 66, which is the mean age of the group of COPD patients on which this distribution was estimated. For each year younger than 66, the distribution shifts 0.5% predicted to the right and for each year older than 66 it shifts 0.5% to the left.

Sensitivity analyses on the severity distribution of COPD incidence

Instead of the incidence as reported in table 1, we have assumed a severity distribution that mirrors the severity distribution of the prevalence, i.e. 28% of the incidence in mild COPD, 54% in moderate COPD, 15% in severe COPD and 3% in very severe COPD. In addition we have studied the impact of assuming that 60% of the incidence occurs in mild COPD and 40% in moderate COPD. Both assumptions are extremes, the real distribution is somewhere in between and probably close to what we have estimated in section 3.2.

Sensitivity analyses on decline in lung function

We did a sensitivity analysis assuming that the decline in FEV_1% predicted was 10% lower than predicted from the LHS data and a sensitivity analysis assuming that the decline in FEV_1% predicted was 10% higher than predicted from the LHS data.

Sensitivity analysis on the one-time increase in lung function after smoking cessation

We have modelled disease progression without assigning the one-time increase in lung function to the COPD patients who stop smoking. However, those who stop smoking keep the reduction in lung function decline.

Sensitivity analysis on the lung function decline among never smokers.

Instead of assuming that the lung function decline among never smokers is equal to the decline among ex-smokers, we have assumed that the decline is equal to the decline among smokers.

Sensitivity analysis on the association between lung function and mortality

Because our meta-analysis had indicated a significant deviation from the exponential model, we have applied the log-squared model that best fitted the data we had on the association between lung function and mortality. This implies that the RR per 10-units decrease in FEV1% pred is 1.101 when the mean FEV1% pred is 100% and that this RR increases with 2.1% per 10-units decrease in mean FEV1% pred. In other words, as lung function declines the mortality risk increases more than exponentially.

4. Base-case and smoking cessation scenarios

4.1 Base-case scenario

In the base-case scenario we will project the change in COPD severity over time when the age, gender and smoking class specific lung function decline in each COPD severity class is applied to the severity distribution of COPD in 2000. In the base-case scenario the smoking cessation rates remain unchanged at the level estimated for 2000 and presented in table A4.

The results of this base-case scenario will be reported in terms of:

- Absolute numbers of COPD patients in each severity stage over time, stratified by gender, age and smoking class
- Prevalence rates by COPD severity stage over time, stratified by gender, age and smoking class
- The proportional distribution of COPD severity over time, stratified by gender, age and smoking class
- The costs of COPD by severity stage over time
- Mortality rates by COPD severity stage over time

4.2 Smoking cessation scenarios

In addition to the base-case scenario we will simulate 2 smoking cessation scenarios. In the first scenario we will assume that an additional proportion of 25% of all smoking COPD patients are offered minimal counselling by the general practitioner (H-MIS). Hence, we assume that 25% of all smoking COPD patients get the higher smoking cessation probability of the H-MIS[4], whereas 75% of all smoking COPD patients keep the current cessation probability which is on average 4.73% for both men and women. In the second scenario we will assume that an additional 25% of all smoking COPD patients are offered intensive counselling in combination with bupropion (IC+Bupr). As in the previous scenario, we assume that 25% of all smoking COPD patients get the higher

[4] The higher cessation probability was calculated by multiplying the current cessation probability in each 5-year age and gender class (Table A4) with the ratio of the cessation probability of the H-MIS and the overall current practice cessation probability of 4.73%. I.e. if the current cessation probability for 60-64 year old men is 0.049, than the probability when offered the H-MIS is 0.049 * (0.072/0.0473) = 0.082.

smoking cessation probability of IC+Bupr whereas 75% keeps the current cessation rate. Both scenarios are implemented for a period of either 1 year, 10 years or 25 years. In both scenarios we will assume that the interventions are equally effective across COPD severity categories.

A literature search learned that there are relatively few randomised clinical trials on the effects of smoking cessation interventions in patients with COPD (Pederson et al., 1991; Crowley et al., 1995; Scanlon et al., 2000; Tashkin et al., 2001). There was no study on the effects of H-MIS in COPD and only 1 study on the effects of IC+Bupr in COPD (Tashkin et al., 2001), but that study did not report 12 month continuous abstinence rates. There are 2 Dutch randomised clinical trials on smoking cessation interventions in COPD ongoing (co-ordinators: dr. Van der Palen and prof.dr. Van Schayck), but results have not yet been published. Therefore we have decided to use estimates of the effectiveness of H-MIS and IC+Bupr that were obtained among smokers in general, regardless of whether or not they had a smoking-related disease.

Table 4.1 shows the cessation rates and the intervention costs of H-MIS and IC+Bupr. Cessation rates were estimated using 12 months continuous abstinence rates as found in a Dutch randomised controlled clinical trial for the H-MIS (Pieterse et al., 2001) and reported in previous reviews (Willemsen et al., 2003) and meta-analysis for IC+Bupr (Hughes et al., 2002). Intervention costs were based on bottom up estimates of resource use and costs per unit, and refer to direct medical costs (Feenstra et al., 2003). Estimates of resource use were based on practice guidelines and the original clinical trials from which the effectiveness data were taken (Feenstra et al., 2003). Hence these costs reflect the costs of an optimal implementation of the two smoking cessation interventions, which is in line with the effectiveness figures. All costs were expressed in Euros at the price level of 2000.

Table 4.1: 12 months continuous abstinence rates (± 95% CI) and intervention costs of H-MIS and IC+Bupr.

	12-months continuous abstinence	95% IC	Source	Intervention costs in Euros
H-MIS	7.9%*	4.7-11.1	1 Dutch RCT	21
IC+Bupr	17.2%	14.0-20.4	Cochrane review: 4 RCTs	334

* *Cessation rate in trial: 8.2%. 9% used H-MIS in combination with nicotine gum. Cessation rate for minimal GP counselling: 8.2-(0.09*11.0)/0.91=7.9%*

The results of these smoking cessation scenarios will be reported in terms of:

- The additional number of COPD patients who stop smoking
- The number of life years gained
- The number of QALYs gained
- Savings in COPD related costs associated with a one-time increase in lung function and a subsequent reduced decline of lung function because of smoking cessation
- Additional costs per additional quitter
- Additional costs per life year gained
- Additional costs per QALY gained

In the latter 2 incremental cost-effectiveness ratios the costs include the intervention costs minus the above-mentioned savings.

To calculate QALYs the life-years were corrected for the quality of life during these years. However, we were not able to identify a single study that has reported QALY-weights or values by COPD severity stage for all stages simultaneously. Therefore we transformed two existing values and their confidence intervals for mild-moderate and severe COPD obtained from expert opinion to values for the four GOLD severity stages: mild (0.9), moderate (0.8), severe (0.6) and very severe (0.3) (Stouthard et al., 1997). As a consequence gain in QALYs should be interpreted with caution. It is merely reported for illustrative reasons.

5. Results: projections for the base-case scenario

5.1 Prevalence of COPD

Prevalence of COPD by gender

In figure 5.1 the development of the number of COPD patients from the years 2000 to 2025 is shown for men and women. The absolute number of COPD patients increases both in men and women, but the increase is higher for women.

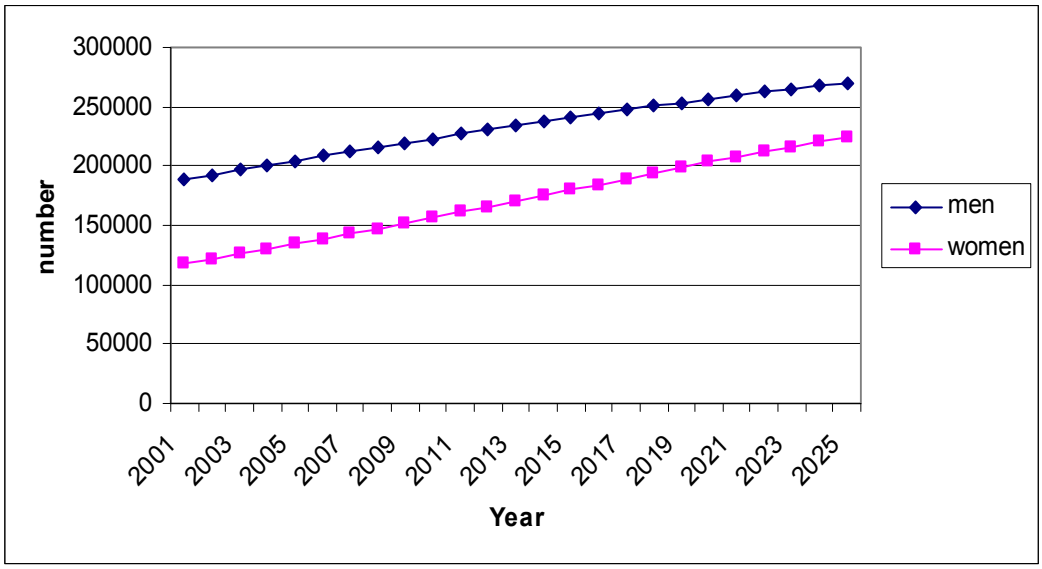

Figure 5.1: Projection of number of COPD patients over time

For men the prevalence rate for COPD increases from 24 per 1000 in 2000 to 33 per 1000 in 2025, which is an increase of 37%. For women the prevalence rate increases from 15 per 1000 in 2000 to 27 per 1000 in 2025, which is an increase of 84%. The prevalence rate of COPD for the total population increases with 55%, from 19 per 1000 to 30 per 1000. Age-specific prevalence rates for the years 2000 and 2025 are shown in appendix D, table D1. The age distribution of the COPD population in the Netherlands shifts towards older ages.

Prevalence of COPD by smoking class

In figure 5.2a and 5.2b the model projections for the proportional distribution of male COPD patients over smoking classes by age is shown for the years 2000 and 2025. In men the total proportion of smoking COPD patients decreases from 49.8 to 44.1%, while

the proportion of ex-smoking COPD patients increases from 45.8 to 50.0%. The decrease in the proportion of smokers is mostly due to a combination of aging of the COPD population and an increase in the proportion of ex-smokers in the older age classes in 2025 compared to 2000. When figure 5.2.a and 5.2.b are compared, a clear decrease in the proportion of smoking COPD patients in the last 3 age groups can be seen. Among the male COPD patients aged 75 years and older 30% is smoking in 2025 compared to 44% in 2000. Partly this reflects cohort effects, with new generations of men having lower smoking prevalence. Partly this reflects continued cessation at old ages, with restart rates in the model being zero for these ages.

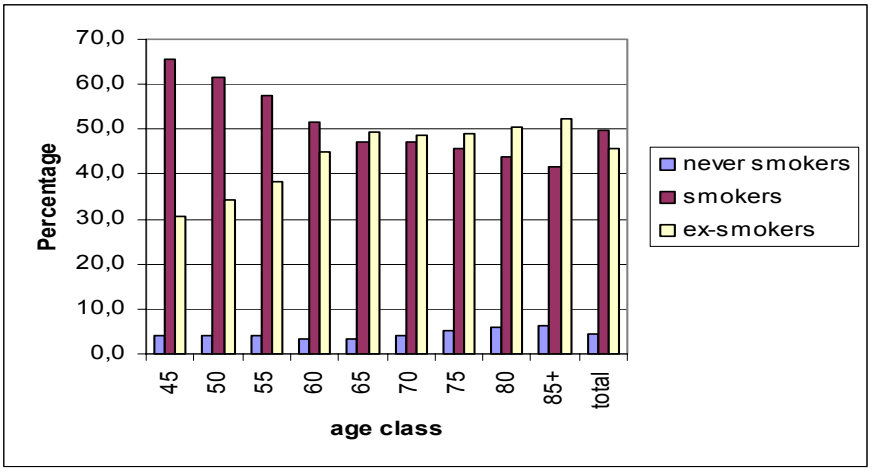

Figure 5.2a: Distribution of male COPD patients by smoking class in 2000

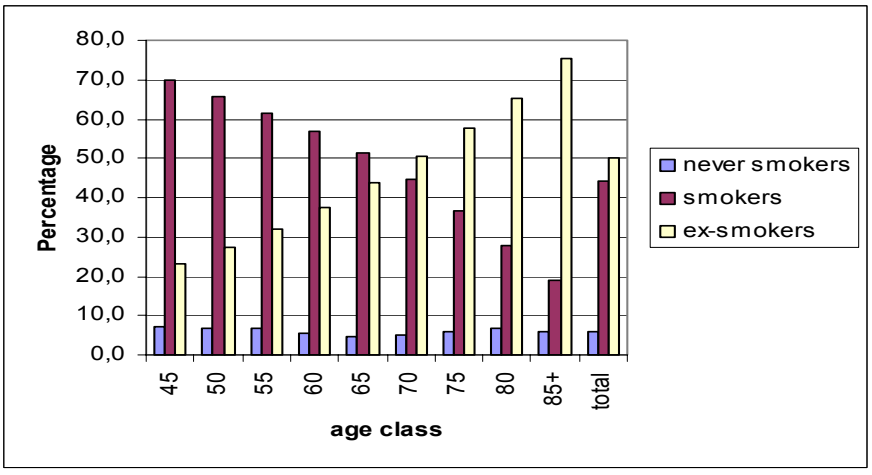

Figure 5.2b: Distribution of male COPD patients by smoking class in 2025

For female COPD patients the change in the proportional distribution of smoking by age over time is shown in the figures 5.3a and 5.3b. The proportion of ex-smokers rises from 31.6% in 2000 to 39.3% in 2025. The proportion of smokers stays constant, 49.4 to 49.9%, while the proportion of never smokers decreases from 19.0 to 10.8%. Among the female COPD patients of 75 years and over 34% is smoking in 2025 compared to 37% in 2000. The percentage of never smokers in female COPD patients aged 75 years and older falls from 31% in 2000 to 16% in 2025. Probably, this mostly reflects cohort effects.

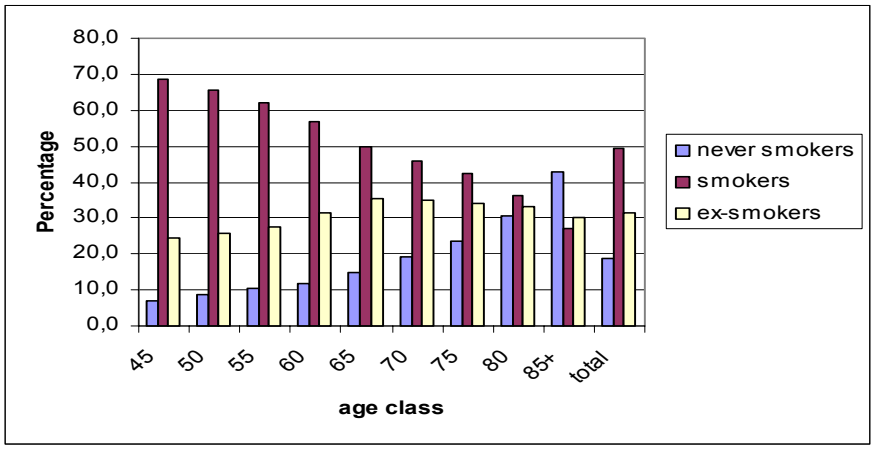

Figure 5.3a: Distribution of female COPD patients by smoking class in 2000

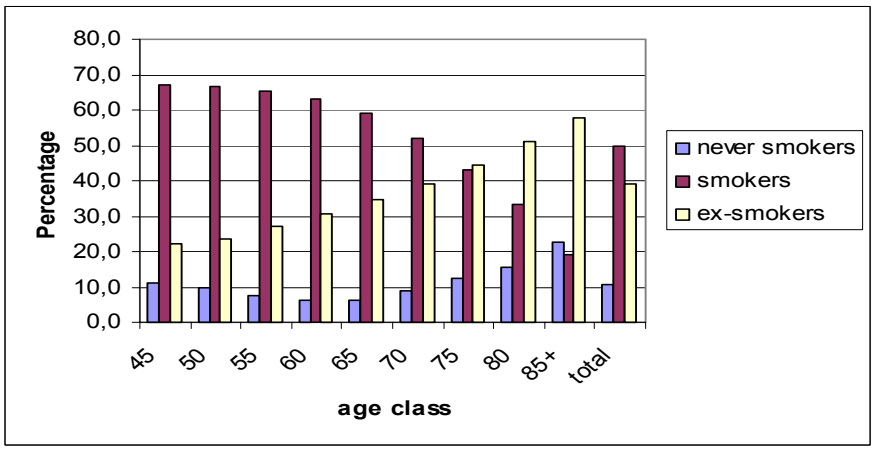

Figure 5.3b: Distribution of female COPD patients by smoking class in 2025

Prevalence of COPD by severity

The total number of patients in all the four severity stages increases between the year 2000 and the year 2025 for both men and women (Figure 5.4 and 5.5).

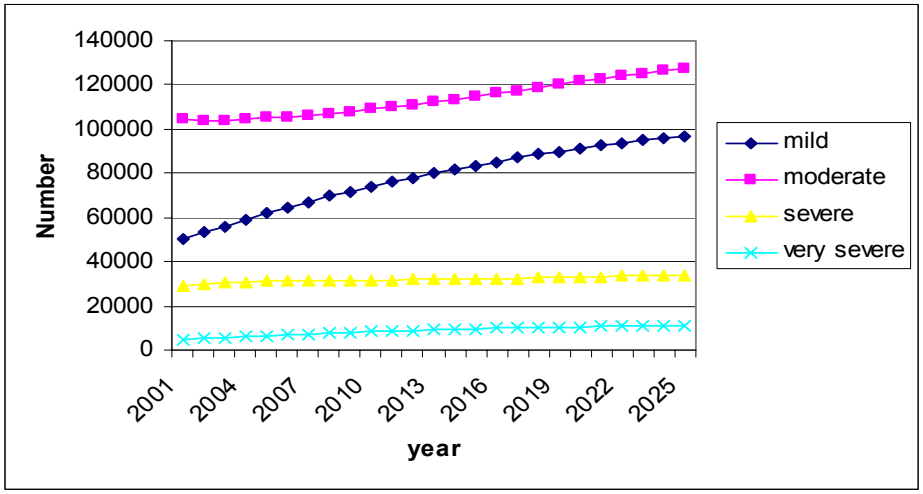

Figure 5.4: Projection of the number of patients within each severity stage among men

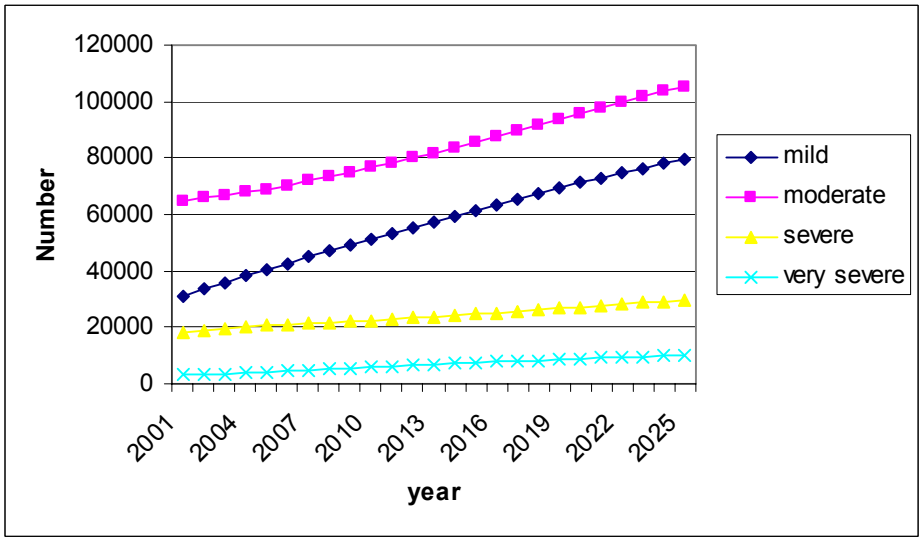

Figure 5.5: Projection of the number of patients within each severity stage among women

In table 5.1 the prevalence rates per severity stage and the proportional distribution over severity stages are shown. Age and gender specific prevalence rates are shown in table D2 of the appendix.

Table 5.1: Prevalence rates per severity stage (number per 1000 in the general population)

	Men		Women	
	2000	2025	2000	2025
Mild	6.4	11.8	3.9	9.6
Moderate	13.3	15.6	8.1	12.7
Severe	3.7	4.2	2.3	3.6
Very severe	0.6	1.4	0.4	1.2
Total	24.0	32.9	14.7	27.0

The prevalence rate of very severe COPD shows the largest relative increase between 2000 and 2025 both for men, 119%, and for women, 221%. In table 5.2 the severity distributions for the year 2000 and 2025 are given.

Table 5.2: Distribution of COPD patients over severity stages (in%) for the year 2000 and 2025

	Men		Women	
	2000	2025	2000	2025
Mild	27	36	27	35
Moderate	55	47	55	47
Severe	15	13	15	13
Very severe	3	4	3	5

Both for men and women the number of mild and very severe patients as percentage of the total number of COPD patients, increases. In appendix D, figure D1, the proportion of COPD patients in each severity stage over time is shown.

5.2 Mortality

In table 5.3 the model projections for the number of deaths from all causes among COPD patients in the year 2000 and the year 2025 are shown.

Table 5.3: Number of deaths from all causes among COPD patients

	Men		Women	
	2000	2025	2000	2025
Mild	3300	7200	1700	4700
Moderate	8200	10900	4300	7400
Severe	2800	3800	1500	2700
Very severe	600	1600	300	1200
Total	14900	23500	7900	16000

The absolute number of deaths increases with 58% among men and 104% among women. This is largely due to the increase in COPD prevalence and aging of the COPD population. The proportion of COPD patients dying per year changes little over time. In 2000 7.9% of the male COPD patients died compared to 8.7% in 2025. Among women this percentage changes from 6.7% in 2000 to 7.2% in 2025.

In figure 5.6 all-cause mortality as percentage of the total number of COPD patients per severity stage is shown for the year 2000. Mortality in the total group of COPD patients and mortality in the general population (including the COPD population) with the same age- and gender distribution as the COPD population are added for comparison.
Compared to mortality in the general population mortality in the COPD population is 2.0 times higher among men and 2.5 times higher among women.

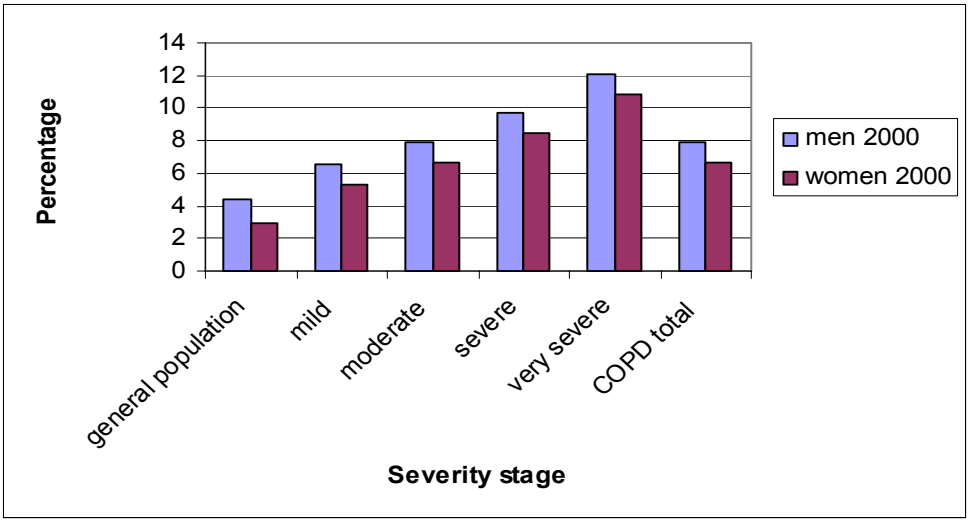

Figure 5.6: Total mortality as percentage of the total number of patients per severity stage in the year 2000

These percentages increase little over time. In 2025 the percentages for men changed to 7.4, 8.6, 11 and 14 for mild, moderate, severe and very severe COPD, respectively. For women the percentages changed to 5.9, 7.1, 9.3 and 12.
In table 5.4 mortality rates per severity stage are shown.

Table 5.4: All-cause mortality and excess mortality rates in each of the severity stages per 1000 COPD patients

	Mild	Moderate	Severe	Very severe
All-cause mortality				
Men				
2000	17.4	43.5	15.0	3.1
2025	26.6	40.4	14.1	5.9
Women				
2000	14.2	36.8	13.2	2.8
2025	20.8	33.2	12.2	5.4
Excess mortality				
Men				
2000	5.9	19.6	8.4	2.0
2025	8.4	17.2	7.2	3.4
Women				
2000	6.0	19.7	8.4	2.0
2025	8.1	16.8	7.4	3.7

The mortality rates in moderate en severe COPD decrease, while the mortality rates in mild and very severe COPD increase, largely because the percentage of mild and very severe COPD patients in the total COPD population increases.

5.3 COPD-related costs

Total costs of care for COPD in 2000 are estimated to be 280 million Euros. In 2025 costs are projected to be 495 million Euros, an increase of 77%. In figure 5.6 undiscounted total costs over time are shown for men and women separately. The increase reflects the increase in prevalence rates, combined with the change in the proportions of the different severity stages. In 2000 the mean costs for COPD per patient are 910 Euros, while the mean costs per patient are 1000 Euros in 2025.

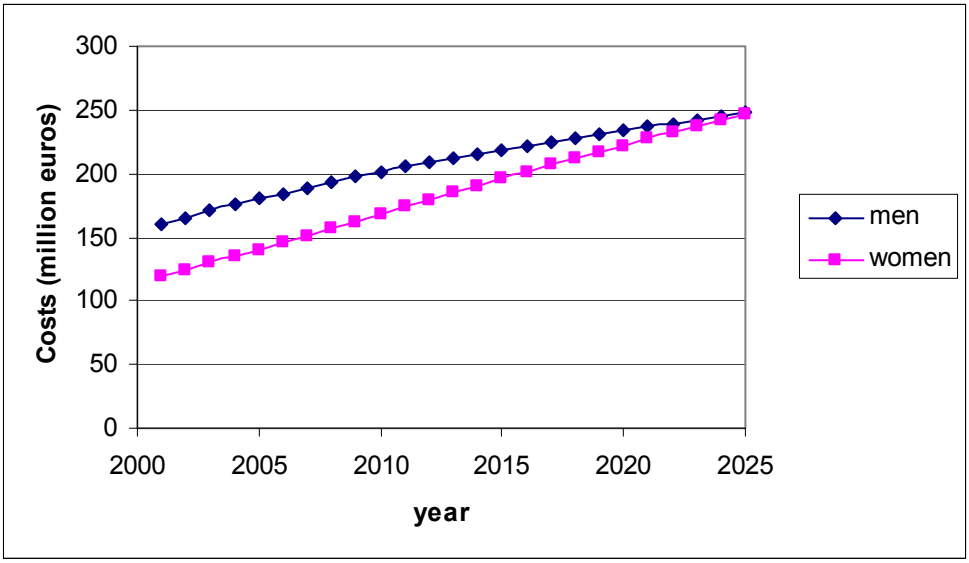

Figure 5.7: Total costs due to COPD over time

Figure 5.7 shows that the total costs for women increase more between the years 2000 and 2025 (107%) than the total costs for men (54%). Total costs by age and gender are shown in appendix D, table D3. Total costs increase in all age classes except for the lowest age classes, 45 to 49 years and 50 to 54 years in men and 45 to 49 years in women. This is due to the increase in the proportion of mild patients in these age classes.

In figure 5.8 total costs for each severity stage are shown. For men costs for mild COPD increase with 102%, for moderate COPD with 27%, for severe COPD with 23% and for very severe COPD with 145%. Compared to men, women show a higher absolute and relative increase in costs between the years 2001 and 2025 for all severity stages. Costs

for mild COPD among women increase with 160%, for moderate COPD with 64%, for severe COPD with 66% and for very severe COPD with 241%.

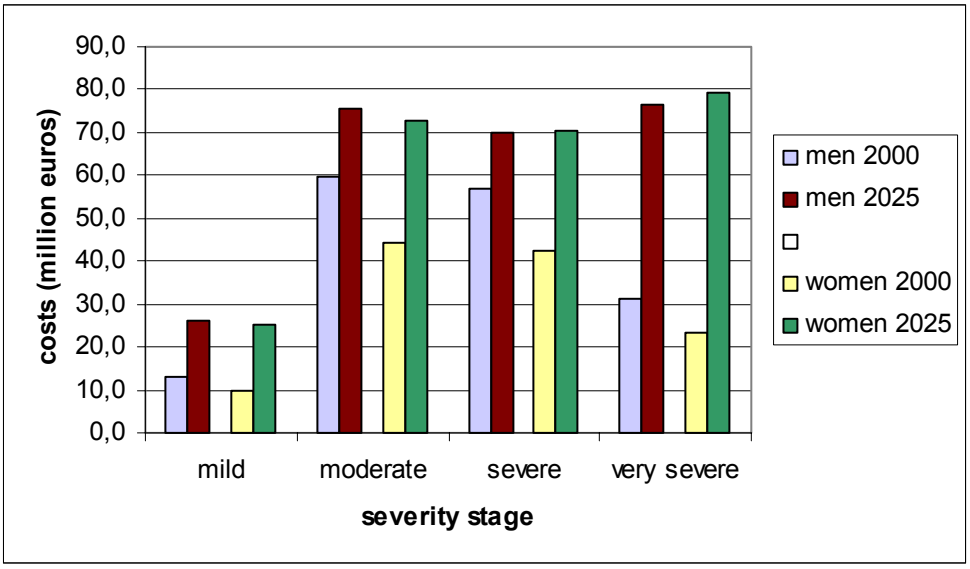

Figure 5.8: Total costs by severity stage

6. Results: sensitivity analysis for the base-case scenario

In this section we describe how sensitive the estimates of COPD prevalence, mortality and costs are to changes in the input variables and assumptions. We computed model projections for 8 different variations to the base-case. The different variables and model assumptions tested and their values were described in section 3.6.

6.1 Prevalence of COPD

Prevalence of COPD by gender

In 2000 the total number of COPD patients is 305 800, 188 400 men and 117 400 women. In table 6.1 total number of COPD patients in 2025 are shown for the different sensitivity analyses compared to the base-case scenario.

Table 6.1: Sensitivity analyses on the total number of COPD patients in 2025

	Men	Women	Total
Base-case	***269 900***	***224 400***	***494 300***
1. Distribution of prevalence over severity stages differs by age class	273 700	227 500	501 200
2. Severity distribution of incidence as prevalence	259 600	215 800	475 400
3. Severity distribution of incidence: 60% in mild, 40% in moderate	280 500	233 400	514 000
4. Decline in FEV_1% pred as base-case –10%	271 100	225 500	496 600
5. Decline in FEV_1% pred as base-case +10%	268 600	223 300	491 900
6. No increase in FEV_1% pred after smoking cessation	268 900	223 800	492 700
7. Never smoker has decline smoker	269 700	224 200	493 900
8. More than exponential association between lung function and mortality	268 900	223 500	492 400

The prevalence of COPD in 2025 is most sensitive to the assumptions that we made about the severity distribution of the **in**cidence of COPD. The two different assumptions about the distribution of incidence by severity of COPD (sensitivity analyses 2 and 3)

represent 2 extremes giving the lowest and the highest number of COPD patients. The prevalence numbers are either 4% lower or 4% higher than in the base-case. Estimates of total COPD prevalence are quite robust for the changes in the severity distribution of the COPD prevalence, the decline in lung function and the association between lung function and mortality.

Prevalence of COPD by smoking class

For all sensitivity analyses the proportional distribution of COPD patients by smoking class does not change with more than 0.3% of the base-case values (see appendix E, table E1). For base-case and all sensitivity analyses 44% of all male COPD patients is smoker at year 2025, 6% is never smoker and 50% is ex-smoker. Among female COPD patients the distribution over smoking classes also stays the same after 25 years for base-case and all sensitivity analyses; 50% is smoker, 11% is never smoker and 39% is ex-smoker.

Prevalence of COPD by severity

For the year 2000 the base-case scenario and all sensitivity analyses except one, have the same starting distribution of COPD patients over severity stages, 27% mild COPD, 55% moderate COPD, 15% severe COPD and 3% very severe COPD. Only the sensitivity analysis on the severity distribution of prevalence (sensitivity analysis 1) shows another starting distribution for the year 2000: 23% mild COPD, 54% moderate COPD, 19% severe COPD and 4% very severe COPD. However, as is shown in table 6.2 this does not very much affect the severity distribution in 2025.

In table 6.2 prevalence rates per severity stage are shown **for men** for the year 2025 for the different sensitivity analyses.

Table 6.2: Sensitivity analyses on the prevalence rates per severity stage for men in 2025

	Mild	Moderate	Severe	Very severe
Base-case	***11.8 (36%)***	***15.6 (47%)***	***4.2 (13%)***	***1.4 (4%)***
1. Distribution of prevalence over severity stages differs by age class	12.2 (37%)	15.8 (47%)	4.1 (12%)	1.3 (4%)
2. Severity distribution of incidence as prevalence	8.1 (26%)	14.3 (45%)	6.6 (21%)	2.8 (9%)
3. Severity distribution of incidence: 60% in mild, 40% in moderate	17.4 (51%)	14.7 (43%)	1.4 (4%)	0.7 (2%)
4. Decline in FEV_1% pred as base-case –10%	12.1 (37%)	15.9 (48%)	4.0 (12%)	1.1 (3%)
5. Decline in FEV_1% pred as base-case +10%	11.6 (35%)	15.2 (47%)	4.3 (13%)	1.7 (5%)
6. No increase in FEV_1% pred after smoking cessation	11.5 (35%)	15.5 (47%)	4.3 (13%)	1.5 (5%)
7. Never smoker has decline smoker	11.8 (36%)	15.5 (47%)	4.2 (13%)	1.4 (4%)
8. More than exponential association between lung function and mortality	11.7 (36%)	15.6 (47%)	4.2 (13%)	1.3 (4%)

Again, the assumptions about the severity distribution of the incidence have the highest impact on the severity distribution of COPD prevalence in 2025. If the severity distribution of incidence is assumed to be equal to the severity distribution of the COPD prevalence in 2000, the percentages of mild, moderate, severe and very severe COPD patients in 2025 are 26, 45, 21, and 9% compared to 36, 47, 13 and 4% in the base-case. If the severity distribution of incidence is assumed to be 60% in mild and 40% in moderate, the percentages of mild, moderate, severe and very severe COPD patients in 2025 are 51, 43, 4 and 2% respectively.

In table 6.3 prevalence rates per severity stage are shown **for women** for the year 2025.

Table 6.3: Sensitivity analyses on the prevalence rates per severity stage for women in 2025

	Mild	Moderate	Severe	Very severe
Base-case	***9.6 (35%)***	***12.7 (47%)***	***3.6 (13%)***	***1.2 (5%)***
1. Distribution of prevalence over severity stages differs by age class	9.9 (36%)	12.8 (47%)	3.5 (13%)	1.2 (4%)
2. Severity distribution of incidence as prevalence	6.6 (25%)	11.6 (45%)	5.5 (21%)	2.4 (9%)
3. Severity distribution of incidence: 60% in mild, 40% in moderate	14.0 (50%)	12.1 (43%)	1.2 (4%)	0.7 (2%)
4. Decline in FEV_1% pred as base-case –10%	9.8 (36%)	13.0 (48%)	3.4 (13%)	1.0 (4%)
5. Decline in FEV_1% pred as base-case +10%	9.3 (35%)	12.4 (46%)	3.7 (14%)	1.5 (5%)
6. No increase in FEV_1% pred after smoking cessation	9.3 (35%)	12.6 (47%)	3.7 (14%)	1.3 (5%)
7. Never smoker has decline smoker	9.5 (35%)	12.6 (47%)	3.6 (13%)	1.3 (5%)
8. More than exponential association between lung function and mortality	9.4 (35%)	12.7 (47%)	3.6 (13%)	1.2 (4%)

For women the sensitivity analyses on the severity distribution of the incidence also gave the highest deviation from the base-case scenario. If the severity distribution of the incidence is assumed to be equal to the severity distribution of the prevalence, the percentage of mild, moderate, severe and very severe COPD patients in 2025 is 25, 45, 21, and 9 compared to 35, 47, 13 and 5 in the base-case. If the severity distribution of incidence is assumed to be 60% in mild and 40% in moderate, the percentage of mild,

moderate, severe and very severe COPD patients in 2025 is 50, 43, 4 and 2 respectively.

As expected, sensitivity analysis 2, shows a shift towards the more severe stages. Sensitivity analysis 3 moves the severity distribution over time towards the less severe stages. The other sensitivity analyses do not have much influence on the severity distribution.

6.2 Mortality

In table 6.4 the mortality rates per 1000 COPD patients for the different severity stages are shown. For example the severe COPD mortality rate is calculated as the number of patients with severe COPD that have died per 1000 COPD patients (not per 1000 patients with severe COPD).

Table 6.4: Sensitivity analyses on the all-cause mortality rates per 1000 COPD patients for the different severity stages

		Mild	Moderate	Severe	Very severe
Base-case	Men	26.6	40.4	14.1	5.9
	Women	20.8	33.2	12.2	5.4
1. Distribution of prevalence over severity stages differs by age class	Men	27.0	40.2	13.8	5.8
	Women	21.1	32.8	11.9	5.3
2. Severity distribution of incidence as prevalence	Men	18.3	37.2	21.5	11.4
	Women	14.4	30.5	18.5	10.3
3. Severity distribution of incidence: 60% in mild, 40% in moderate	Men	39.1	38.3	4.9	3.1
	Women	30.5	31.4	4.5	3.0
4. Decline in FEV_1% pred as base-case –10%	Men	27.3	41.5	13.4	4.7
	Women	21.4	34.0	11.7	4.4
5. Decline in FEV_1% pred as base-case +10%	Men	26.0	39.5	14.6	7.1
	Women	20.4	32.3	12.7	6.5
6. No increase in FEV_1% pred after smoking cessation	Men	25.7	40.2	14.7	6.6
	Women	20.2	33.0	12.7	6.0
7. Never smoker has decline smoker	Men	26.6	40.4	14.2	6.0
	Women	20.7	33.0	12.4	5.6
8. More than exponential association between lung function and mortality	Men	26.8	40.0	14.3	6.1
	Women	21.1	32.7	12.5	5.7

Again mortality rates change the most for the sensitivity analyses where the distribution of incidence is varied. The probability of dying while being in a specific severity stage stays rather constant (see table E3), so a rise in for example the severe COPD mortality

rate, is a result of an increase of the proportion of COPD patients in that severity stage compared to the base-case scenario.

For the base-case scenario the percentage of COPD patients dying in 2025 is 8.7% for men and 7.2% for women. Outcomes of the sensitivity analyses range between 8.2 and 9.2% for men and 6.7 and 7.7% for women (see table E2).

Except for one sensitivity analysis, all analyses show that the percentage of COPD patients dying in each severity stage in 2025 (obtained by dividing number of deaths in a specific severity stage by total number of patients in that severity stage), does not differ by more than 5% from the base-case. Only the sensitivity analysis where a steeper than exponential association between lung function and mortality is assumed, gives a higher mortality percentage in the very severe stage: 15.1% compared to 14.2% among men and 12.9% compared to 12.0% among women (table E3).

6.3 COPD-related costs

Total costs for the base-case scenario rise from 280 million Euros in 2000 to 495 million Euros in 2025. In table 6.5 total costs in 2025 for the different sensitivity analyses are shown.

Table 6.5: Sensitivity analyses on the total costs due to COPD in million Euros in 2025

	Men	Women	Total
Base-case	***248***	***247***	***495***
1. Distribution of prevalence over severity stages differs by age class	249	247	496
2. Severity distribution of incidence as prevalence	348	343	691
3. Severity distribution of incidence: 60% in mild, 40% in moderate	173	175	348
4, Decline in FEV_1% pred as base-case –10%	232	231	464
5. Decline in FEV_1% pred as base-case +10%	264	263	527
6. No increase in FEV_1% pred after smoking cessation	258	256	514
7. Never smoker has decline smoker	250	251	500
8. More than exponential association between lung function and mortality	246	245	492

The sensitivity analysis where the severity distribution of the incidence is assumed to be equal to the severity distribution of the prevalence results in 40% more costs than the base-case scenario. The assumption that the incidence is 60% in mild and 40% in moderate projects 30% lower costs than the base-case. Costs per severity stage are shown in table E4. When lung function decline is either 10% lower or 10% higher than predicted from the LHS data, the costs are 6% lower or higher than the base-case.

Conclusion for the sensitivity analyses

From these sensitivity analyses it can be concluded that estimates of COPD prevalence, mortality and costs are most sensitive to the assumption we had to make on the severity distribution of COPD incidence.

If the severity distribution of COPD incidence is assumed to be the same as the severity distribution of COPD prevalence, the total number of COPD patients will be lowest. With this assumption a relative high percentage of yearly incident cases occurs in severe and very severe COPD. This results in a higher prevalence of severe and very severe COPD, which in turn results in a higher total mortality and eventually in a lower total number of COPD patients.

If 60% of the incidence is in mild COPD and 40% in moderate COPD, more patients in the mild and moderate will result in a lower total mortality and a higher total number of COPD patients.

Furthermore, the assumption on a more than exponential decline in lung function had a rather large influence on the mortality rate for very severe COPD. This did not however result in large effects on total COPD prevalence, mortality or costs.

7. Results: projections for the smoking cessation scenarios

In this chapter results are described for the two smoking cessation scenarios, H-MIS and IC+Bupr, assuming that these interventions were offered to an additional proportion of 25% of all smoking COPD patients for a period of either 1 year, 10 years or 25 years.
As a result of the two smoking cessation scenarios the proportions of smokers among the COPD population decreases, while the proportions of ex-smokers increases. Because lung function decline and mortality are lower among ex-smokers than among smokers, the course of disease improves and mortality decreases. As a result the absolute number of COPD patients increases slightly. But the severity distribution of COPD shifts toward the less severe stages. This generates a gain in life-years, quality-adjusted life-years and savings in COPD-related health care costs. Note that restart rates are larger than zero, so that in the long run, the proportions of smokers and ex-smokers return to their base-case values. The outcomes in (quality adjusted) life-years and savings will be discussed in section 7.2 after a short description of the impact of the smoking cessation scenarios on smoking status, mortality, severity distribution of COPD and the total number of COPD patients in 7.1.
Time horizons of 25 and 50 years are considered, i.e. cumulative costs and effects of the 1 year, 10 year and 25 year implementation of H-MIS and IC+Bupr are studied over a period of 25 years and 50 years.

7.1 Changes in the COPD population

Change in the proportional distribution of smoking

In 2000 4% of the male COPD patients was never smoker, 50% was smoker and 46% was ex-smoker. Among female COPD patients 19% was never smoker, 49% was smoker and 32% was ex-smoker.
In table 7.1 the distribution of COPD patients over smoking classes in 2025 is shown for the base-case and the two smoking cessation scenarios, for a 25 year implementation period.

Table 7.1: Proportion (%) of smokers and ex-smokers among COPD patients in 2025

		Never smoker	Smoker	Ex-smoker
Base-case	***Men***	***6***	***44***	***50***
	Women	***11***	***50***	***39***
25% of the COPD patients gets H-MIS	Men	6	42	52
	Women	11	48	41
25% of the COPD patients gets IC+Bupr	Men	6	37	57
	Women	11	42	47

For both scenarios the proportion of smokers decreases, while the proportion of ex-smokers increases. In the base-case scenario the total number of smoking COPD patients increases from 152000 in the year 2000 to 231000 in the year 2025. Implementation of the H-MIS scenario results in 221000 smoking COPD patients in 2025, a decrease of 10000 smoking COPD patients compared to base-case. The IC+Bupr scenario results in 195000 smoking COPD patients in 2025, which is a decrease of 35000 compared to the base-case scenario.

Change in mortality

Compared to base-case all-cause mortality decreases with 0.3% after implementation of H-MIS and 1.2% after implementation of IC+Bupr. In table 7.2 all-cause mortality rates per 1000 COPD patients are shown.

Table 7.2: All-cause mortality rates in each of the severity stages per 1000 COPD patients and mortality in absolute numbers for the year 2025

All-cause mortality rates	Mild	Moderate	Severe	Very severe
Base-case	***24.0***	***37.1***	***13.2***	***5.7***
25% of the COPD patients gets H-MIS	24.0	37.0	13.1	5.5
25% of the COPD patients gets IC+Bupr	24.1	36.8	12.8	5.2
Mortality in absolute numbers				
Base-case	***11900***	***18400***	***6500***	***2800***
25% of the COPD patients gets H-MIS	11900	18300	6500	2700
25% of the COPD patients gets IC+Bupr	11900	18200	6300	2600

For both the scenarios mortality rates in severe and very severe COPD decrease slightly. For IC+Bupr the mortality rate in mild COPD increases little, because of the increase in the total number of mild COPD patients.

Change in COPD severity distribution

After implementation of H-MIS the total number of mild and moderate COPD patients in 2025 increases with 740 and 270 patients respectively compared to the base-case scenario, while the number of patients in severe and very severe COPD decreases with 370 and 380 patients, respectively. Implementation of IC+Bupr results in an increase of mild COPD with 2800 and moderate COPD with 880 patients, while the number of patients in severe and very severe COPD decreases both with 1300 patients. In table 7.3 the proportional change of the total number of patients in each severity stage between 2000 and 2025 compared to the base-case scenario is shown for the different scenarios. For example, in the IC+Bupr scenario, the total number of female severe COPD patients is projected to be 2.0% lower in 2025 than it was in the base-case in 2025.

Table 7.3: Proportional change (%) of the total number of patients in each severity stage between 2000 and 2025 compared to base-case

		Mild	Moderate	Severe	Very severe
25% of the COPD patients	Men	+0.4	+0.1	-0.6	-1.8
gets H-MIS	Women	+0.4	+0.1	-0.5	-1.8
25% of the COPD patients	Men	+1.6	+0.3	-2.2	-6.1
gets IC+Bupr	Women	+1.5	+0.5	-2.0	-6.4

Change in total number of COPD patients

In 2000 the model projects a total number of COPD patients of 305 800, 188 400 men and 117 400 women. Total number of COPD patients in 2025 for the two smoking cessation scenarios are shown in table 7.4.

Table 7.4 Total number of COPD patients in 2025

	Men	Women	Total
Base-case	***269 900***	***224 400***	***494 300***
25% of the COPD patients gets H-MIS	270 000	224 500	494 500
25% of the COPD patients gets IC+Bupr	270 400	224 900	495 200

Because complete recovery from COPD after smoking cessation is impossible and ex-smoking is associated with a lower mortality risk, the total number of COPD patients after 25 years is slightly higher for both scenarios: about 250 more COPD patients after implementation of H-MIS and about 1000 more COPD patients after implementation of IC+Bupr.

7.2 Cost-effectiveness analyses

Table 7.5 shows the total number of additional quitters and total intervention costs in 2001, when the smoking cessation interventions are implemented for 1 year. Costs per extra quitter included only intervention costs, because savings occur later. They were 700 for H-MIS and 2700 for IC+Bupr.

Table 7.5: Number of additional quitters, total intervention costs and costs per quitter compared to the base-case scenario after a 1-year implementation of the smoking cessation interventions (Euros, year 2000 price level)

	Additional quitter	Intervention costs (*10^3)	Costs per quitter
H-MIS	1200	800	700
IC+Bupr	4700	12700	2700

Table 7.6 shows the undiscounted estimates of cumulative costs and effects over a period of 25 years and the resulting cost-effectiveness ratios in terms of life-years and QALYs gained. For both scenarios it was assumed that the smoking interventions were offered each year during a period of either 1, 10 or 25 years.

Table 7.6: Number of life-years and QALYs gained, total additional intervention costs, total savings and cost-effectiveness: costs per life-year gained and costs per QALY gained for the two scenarios, cumulative for the years 2000-2025 (Euros, year 2000 price level)

Duration of implementation	LYs gained	QALYs gained	Intervention costs (*10^6)	Savings in COPD-related costs (*10^6)	Costs per LY gained	Costs per QALY gained
1 year						
H-MIS	200	400	0.8	2.6	#	#
IC+Bupr	900	1800	13	9.9	2900	1500
10 year						
H-MIS	2000	4300	8.4	25	#	#
IC+Bupr	7300	16000	124	93	4200	2000
25 year						
H-MIS	2800	7100	24	45	#	#
IC+Bupr	10400	26000	346	160	17900	7200

H-MIS dominates the base-case, due to net cost savings and higher effects

Regardless of the duration of implementation, the H-MIS scenario saves costs. When the H-MIS is offered each year to an additional 25% of all smoking COPD patients during a period of 25 year, the cumulative net saving is 20.4 million Euros. The IC+Bupr scenario has higher costs than savings. The costs per life-year gained are estimated to be 17900 Euros and the costs per QALY gained are estimated to be 7200 Euros, when choosing a 25 year implementation period. When opting for a 1 year implementation costs per life-year gained and cost per QALY gained are 2900 Euros and 1500 Euros respectively.
Table 7.7 shows the same results as in table 7.6, but now 4% discounting is applied to both costs and effects.

Table 7.7: Number of life-years and QALYs gained, total additional intervention costs, total savings and cost-effectiveness: costs per life-year gained and costs per QALY gained for the two scenarios, cumulative for the years 2000-2025, discounted at 4% for both costs and effects (Euros, year 2000 price level)

Duration of implementation	LYs gained	QALYs gained	Intervention costs (*10^6)	Savings in COPD-related costs (*10^6)	Costs per LY gained	Costs per QALY gained
1 year						
H-MIS	100	300	0.8	1.8	#	#
IC+Bupr	500	1200	12.6	6.9	10600	4900
10 year						
H-MIS	1100	2500	7.1	15.2	#	#
IC+Bupr	4000	9400	104.6	56.6	12000	5100
25 year						
H-MIS	1400	3800	15.3	24.5	#	#
IC+Bupr	5400	14100	219.1	88.0	24500	9300

H-MIS dominates the base-case, due to net cost savings and higher effects

Regardless of the implementation period, H-MIS was still a dominant strategy compared to current practice, because effects were higher and costs savings were higher than intervention costs. When opting for a 25 year implementation period at 4% discounting,

1400 life-years are gained and 24.5 million Euros of COPD-related costs are saved. Interventions costs over the 25-year period are 15.3 million Euros, resulting in a net saving of 9.2 million Euros.

IC+Bupr is more effective. Over the 25 year period 5400 life years are saved. But the intervention costs are much higher and not fully offset by extra savings. Dividing the additional costs by the gain in health, costs per life-year gained and per QALY gained were estimated to be about 24500 Euros and 9300 Euros respectively. These ratios are considerably reduced when IC+Bupr is offered to an additional 25% of smoking COPD patients for only 1 year. Of course, total QALYs and life-years gained are also much lower.

Effects and costs over time

Figure 7.1 shows the undiscounted number of life-years gained for H-MIS and IC+Bupr with 10 years of implementation, compared to the base-case scenario, in each of the years 2000 to 2050. Gain in life-years reached a peak about 20 years after start of the implementation. The undiscounted cumulative gain in life-years was 3300 for H-MIS and 12300 for IC+Bupr.

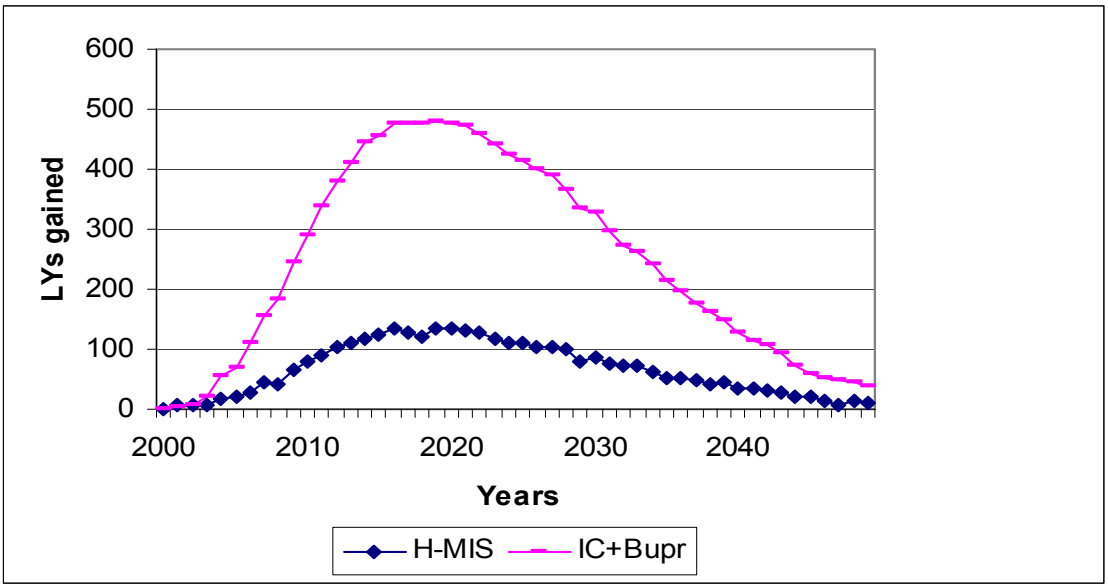

Figure 7.1: Number of QALYs gained in each individual year for the two smoking cessation scenarios, compared to base-case, over the years 2000-2050, 0% discounting, 10 year implementation period

Figure 7.2 shows the undiscounted cumulative savings in COPD-related costs of care and the additional intervention costs for the scenario in which H-MIS is offered for 1 year,

compared to base-case. The break-even point is reached after 6 years, when cumulative savings become equal to the intervention costs.

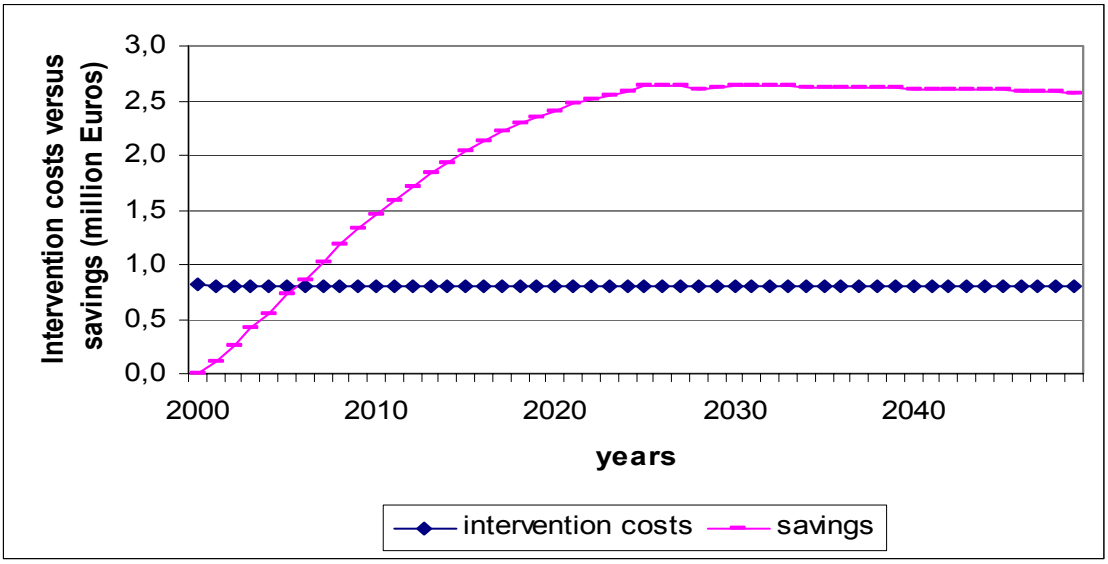

Figure 7.2: Cumulative interventions costs and savings in COPD-related costs for 1 year implementation of H-MIS, compared to base-case, over the years 2000-2050, 0% discounting.

Just like the H-MIS cumulative savings of IC+Bupr increase over time, but they never exceed the intervention costs (figure 7.3).

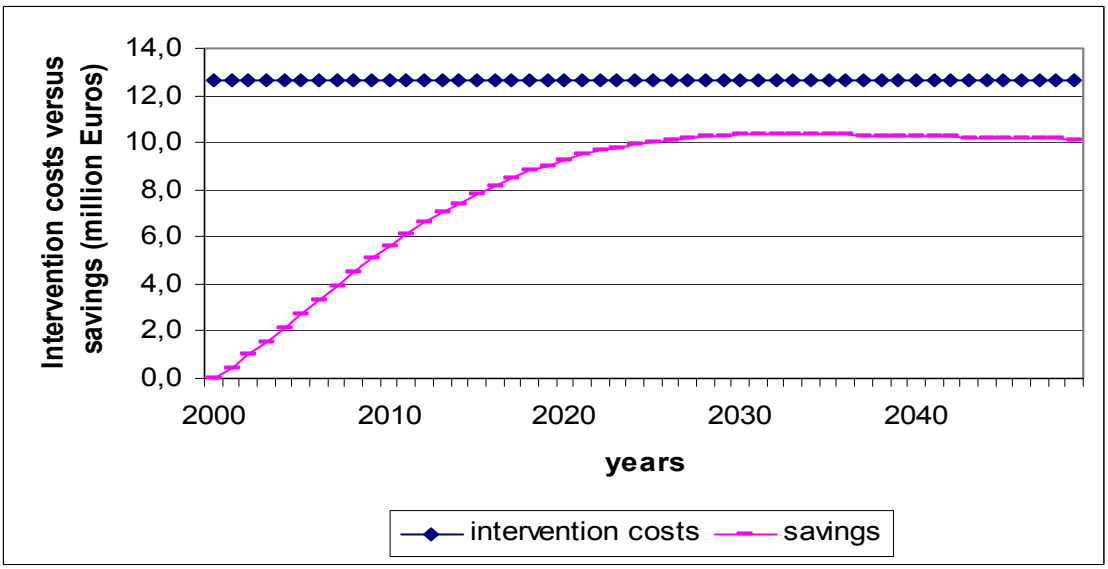

Figure 7.3: Cumulative interventions costs and savings in COPD-related costs for 1 year implementation of IC+Bupr, compared to base-case, over the years 2000-2050, 0% discounting

In figure 7.4 annual differences in total COPD-related costs per severity stage are shown for IC+Bupr compared to base case after a 25 year period of implementation.

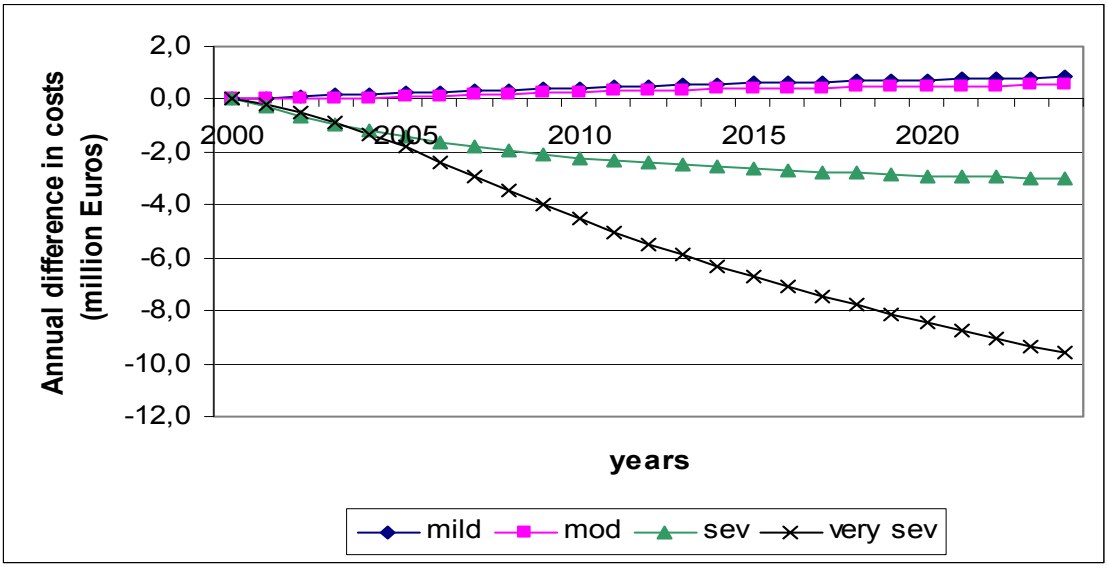

Figure 7.4: Absolute difference in total costs of care per severity class for IC+BU scenario compared to base-case, 0% discounting, 25 year implementation

Implementation of IC+Bupr results in lower total costs compared to base-case, which is mostly due to the high savings in the very severe COPD stage.

7.3 Sensitivity analyses for cost-effectiveness

From the sensitivity analyses for the base-case scenario in chapter 6 we concluded that the sensitivity analyses about the severity distribution of incidence influence the results the most. Therefore we chose these two sensitivity analyses for the sensitivity analyses of the cost-effectiveness. Table 7.8 shows results for the cost-effectiveness when the severity distribution of incidence is assumed to be equal to the distribution of the prevalence and when the severity distribution of incidence is 60% in mild and 40% in moderate. The interventions were implemented for 25 years.

Table 7.8: Number of life-years and QALYs gained, total additional intervention costs, total savings and cost-effectiveness: costs per life-year gained and costs per QALY gained for the two scenarios, for a 25 year implementation , cumulative for the years 2000-2025, with different assumptions for the severity distribution of incidence, discounted at 4% for both costs and effects (Euros, year 2000 price level)

Intervention	LYs gained	QALYs gained	Intervention costs ($*10^6$)	Savings in COPD-related costs ($*10^6$)	Costs per LY gained	Costs per QALY gained
Base-case						
H-MIS	1400	3800	15	25	#	#
IC+Bupr	5400	14100	219	88	24500	9300
Severity distribution of incidence as prevalence						
H-MIS	1600	4300	15	30	#	#
IC+Bupr	5800	15600	216	106	18900	7000
Severity distribution of incidence: 60% in mild, 40% in moderate						
H-MIS	1300	3300	16	19	#	#
IC+Bupr	4800	12000	222	68	32300	12800

A severity distribution of incidence resembling the distribution of prevalence gives a shift to the severe and very severe COPD compared to base-case. Because mortality is higher in the more severe stages, implementation of smoking cessation interventions on more severe patients will gain more life-years. Costs per life-year and costs per QALY are lower than for the base-case.

If the severity distribution of incidence is 60% in mild and 40% in moderate a shift to mild and moderate COPD occurs. Because mortality is lower in these stages, less life-years can be gained, which results in higher costs per life-year and costs per QALY than for the base-case.

Time horizon

Table 7.9 shows the impact of the time horizon on life-years, QALYS and total costs as well as the cost-effectiveness ratios. The same results as in table 7.7 are shown, but now for a time horizon of 50 years.

Table 7.9: Number of life-years and QALYs gained, total additional intervention costs, total savings and cost-effectiveness: costs per life-year gained and costs per QALY gained for the two scenarios, cumulative for the years **2000-2050**, discounted at 4% for both costs and effects (Euros, year 2000 price level)

Duration of implementa-tion	LYs gained	QALYs gained	Intervention costs ($*10^6$)	Savings in COPD-related costs ($*10^6$)	Costs per LY gained	Costs per QALY gained
1 year						
H-MIS	100	300	0.8	1.8	#	#
IC+Bupr	600	1300	13	7.0	8800	4400
10 year						
H-MIS	1400	2900	7.1	16	#	#
IC+Bupr	5400	10500	105	61	8100	4000

H-MIS dominates the base-case, due to net cost savings and higher effects

For both time horizons of 25 and 50 year H-MIS was a cost-saving intervention. For IC+Bupr cost-effectiveness ratios become more favourable for a longer time period.

8. Discussion and conclusion

In the present study we have developed a COPD model that includes the progression of COPD over time. The model can be characterised as a dynamic, population-based model, that represents the Dutch setting. It was used to simulate the incidence, prevalence, mortality and costs of COPD by severity stage over the years 2000 to 2025. It is important to stress that the current model is populated with data on physician-diagnosed COPD in the Netherlands. In contrast to population studies, these data do not cover patients with undiagnosed COPD.

In the base-case scenario, the prevalence rate of mild COPD increases from 5.1 to 10.7 per 1000 inhabitants. The prevalence rate for moderate COPD increases from 10.7 to 14.1. For severe COPD the rate increase from 3.0 to 3.9 and for very severe COPD the rates increase from 0.5 to 1.3. In absolute numbers the increase between 2000 and 2025 was highest in mild COPD, but the largest relative increase was seen in the prevalence rate of very severe COPD. As a result of the increase in COPD prevalence and aging of the COPD population, all-cause mortality rates per 1000 inhabitants increase in all severity stages. In 2000, total COPD-related costs were estimated to be 279.7 million Euros, 8% caused by care for patients with mild COPD, 37%, 35% and 19% caused by care for patients with moderate, severe and very severe COPD, respectively. Between 2000 and 2025 total projected COPD-related costs increased from 22.6 to 51.2 million Euros for mild COPD, from 104 to 148 million Euros for moderate COPD, from 99.0 to 140 million Euros for severe COPD, and from 54.5 to 156 million Euros for very severe COPD.

The reason to develop this model was to be able to evaluate the cost-effectiveness of COPD interventions in the Netherlands at a population level. To illustrate the use of this model for this purpose we have estimated the cost-effectiveness of two smoking cessation scenarios for COPD compared to current practice. In the first scenario we assume that an additional proportion of 25% of all smoking COPD patients receive the H-MIS. In the second scenario we assume that an additional proportion of 25% of all smoking COPD patients receive IC+Bupr. We reported cumulative results over the period 2000 to 2025 when implementing these smoking cessation scenarios for a period of either 1 year, 10 years or 25 years. Irrespective of the duration of implementation, the

H-MIS generates net savings, which indicates that the intervention costs of the H-MIS are offset by the savings in COPD-related health care costs. When implementing the H-MIS scenario for a period of 10 years, about 1100 life years are gained. IC+Bupr is more effective. When implementing this scenario for a period of 10 years, about 4000 life years are gained and 56.6 million of COPD-related costs are saved. However, these savings do not outweigh the interventions costs. The costs per life-year gained of implementing IC+Bupr for 10 years are estimated to be about 12000 Euros.

We have recently estimated the cost-effectiveness of smoking cessation interventions directed at the smokers among the general population in the Netherlands (Feenstra et al., 2003). These calculations included the life years gained and costs saved as a result of the primary prevention of 11 smoking related diseases. Because of the broader scope, the cost effectiveness ratio of 4700 per life year gained for 1 year implementation of IC+Bupr in that project was better than the ratio in the current project. However, for a fair comparison, that cost-effectiveness ratio should be recalculated, and only include the life years gained and savings from the primary prevention of COPD. In that case, the cost-effectiveness of primary prevention of COPD by offering IC+Bupr to 25% of all smokers in the general population is 34 000 Euros per life year gained, compared to 11 000 Euros per life year gained for offering IC+Bupr for 1 year to 25% of all existing COPD patients (costs and effects discounted at 4%). This shows that smoking cessation interventions directed at known COPD patients are cost-effective. The H-MIS generates net savings and the costs per life year gained of IC+Bupr are below the 20.000 Euros, the often cited limit for the cost-effectiveness of preventive interventions (Casparie et al., 1998).

These estimates of the cost-effectiveness of smoking cessation interventions for COPD patients are probably conservative. We only included savings that result from a slower progression through the COPD severity stages and no savings that results from a reduction in the number or severity of exacerbations or disease episodes. We also take into account that ex-smokers can restart smoking.

Obviously, dynamic disease modelling of COPD as reported here requires a fair degree of simplification. For example, we had to assume that the progression of COPD depends primarily on decline in FEV_1% predicted, which, in turn, depends on age, gender, smoking class and absolute level of FEV_1% predicted. In the real world many different

factors, such as the smoking history, the susceptibility to smoking, the number and severity of COPD exacerbations, co morbidity and nutritional status drive the progression of COPD. However, there are not enough data yet on the association between these factors and disease progression to include them into this model.

Because of the limited availability of suitable epidemiological data, making assumptions is unavoidable. For the starting year we had to assume the same distribution of COPD severity for each subgroup of COPD patients defined by age, gender and smoking status. Although the absolute number of severe and very severe COPD patients is highest among smokers and increases with age, the number of severe and very severe patients as a proportion of the total number of COPD patients is the same in each subgroup. We had to make this assumption for the severity distribution of COPD prevalence in the start year 2000 and the severity distribution of COPD incidence. This may result in underestimates for our base case projections of the difference in severity distribution between smokers and ex smokers.

There were no data from which we could estimate the severity distribution of COPD incidence. For a stable population with regard to age, gender and smoking status, and given the prevalence, decline in lung function and mortality in the year 2000, we estimated the severity distribution of the incidence in such a way that the distribution of FEV1% predicted for the entire COPD population did not change between 2000 and 2001. That same estimated severity distribution of the incidence was then applied in each of the future years. Thus the model projections reflect the effects of ageing and projected changes in the distribution of smoking status on COPD prevalence and severity. In the sensitivity analyses we have shown that our results were most sensitive to changes in the assumptions about the severity distribution of the incidence of COPD.

Estimates of the decline in FEV_1% predicted among smokers and ex-smokers were obtained from the 5-year follow-up data of the Lung Health Study. These data were also used to estimate the increase in FEV1% predicted after smoking cessation. Although the Lung Health Study is the best and largest study on the effects of smoking and smoking cessation on lung function in COPD, it has limitations for our purpose. The study primarily recruited patients with mild or moderate airflow obstruction between 35 and 60 years of age and followed them for 5 years. Decline in lung function (and increase after smoking cessation) for patients outside the observed age and lung function range had to

be based on extrapolation of the random effect model. The decline in lung function among never smokers was assumed to equal the decline among ex-smokers. We thought this would be more realistic than assuming that the decline equals the decline among never smokers in the general population, because, after all, these patients do have COPD. The alternative assumption was tested in a sensitivity analysis. Since the group of never smokers is a minority of COPD patients, changing their lung function decline did not change total results much.

We have estimated the total costs of COPD in 2000 in the Netherlands. This estimate was based on many different sources of routinely registered data and included all important cost drivers. However, there were no Dutch observational studies that reported the costs by COPD severity stage. Although we had some cost-by-severity data from Dutch randomised clinical trials we preferred to apply data from a Swedish observational study that reported costs by COPD severity to the Dutch cost estimates, because the trial data would be less representative for the total population of COPD patients.

All assumptions and choices about crucial input data were discussed with the expert panel and sensitivity analyses were performed on those assumptions and data that gave most rise to discussion by the experts. These sensitivity analyses showed that the results were quite robust to changes that we made in the severity distribution of COPD prevalence by age, the decline in FEV_1% predicted, the one-time increase in FEV_1% predicted after smoking cessation and the association between lung function and mortality.

In conclusion, dynamic disease modelling can be of great help in representing and identifying trends in the future burden and costs of COPD and in assessing the impact of smoking cessation interventions offered to patients already diagnosed with COPD. In the future the model can be used to extrapolate clinical trial results to the Dutch COPD population in a transparent and consistent way. The current model may be seen as a basis for extension, enabling new data to be included if they become available. For instance, it would be very interesting to be able to add exacerbation frequencies and costs of exacerbations to each severity stage. This would allow us to estimate the cost-effectiveness of treatments that primarily reduce the frequency and severity of exacerbations and have less impact on disease progression.

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Appendix A: Tables of chapter 2, update of the existing COPD model

Table A1: Dutch population by gender and 5-year age classes in 2000.

	Absolute numbers		Total mortality among COPD patients (/100000/year)	
	Men	Women	Men	Women
0-4	503570	479921	0	0
5-9	512470	489200	0	0
10-14	490343	470039	0	0
15-19	474911	452554	0	0.22
20-24	486242	472644	0	0.21
25-29	594775	581496	0.54	0.18
30-34	671528	642876	0.45	0.15
35-39	669674	645269	0.3	0.46
40-44	614400	599941	1.74	0.81
45-49	575390	559041	4.12	2.99
50-54	582697	562629	4.57	5.94
55-59	435692	423754	13.07	15.88
60-64	358118	365334	41.37	29.22
65-69	305154	339326	106.1	50.05
70-74	242386	307985	232.32	99.67
75-79	180613	276639	532.22	167.26
80-84	93057	181569	843.27	214.06
85+	58297	167416	1472.86	453.94

Table A2: Age- and gender-specific prevalence, incidence and mortality rates (number per 1000) for the start year 2000

	Prevalence		Incidence		COPD excess mortality per 1000 COPD patients	
	Men	Women	Men	Women	Men	Women
45-49	15.9	13.9	1.6	1.9	29.5	29.5
50-54	25.0	19.7	2.8	2.7	30.0	30.0
55-59	40.5	25.9	4.8	2.5	29.5	29.5
60-64	64.3	33.8	7.1	3.3	30.0	30.0
65-69	104.4	48.9	11.6	4.8	33.0	33.0
70-74	144.5	63.1	14.7	5.7	38.0	38.0
75-79	167.4	65.4	17.0	4.6	43.0	43.0
80-84	178.5	59.4	13.1	3.8	44.5	44.5
85+	175.7	61.6	1.9	6.0	42.5	42.5

Table A3: Proportions of non-smokers, smokers and ex-smokers

	Proportions in 1998					
	Men			Women		
	Never smoker	Smoker	Ex-smoker	Never smoker	Smoker	Ex-smoker
0-4	1	0	0	1	0	0
5-9	1	0	0	1	0	0
10-14	0.90	0.1	0	0.90	0.10	0
15-19	0.73	0.26	0.01	0.74	0.24	0.02
20-24	0.57	0.39	0.04	0.60	0.34	0.06
25-29	0.49	0.43	0.08	0.56	0.33	0.11
30-34	0.48	0.41	0.11	0.48	0.36	0.16
35-39	0.43	0.41	0.16	0.42	0.39	0.19
40-44	0.36	0.44	0.20	0.39	0.41	0.20
45-49	0.36	0.41	0.23	0.45	0.36	0.19
50-54	0.34	0.39	0.27	0.51	0.31	0.18
55-59	0.36	0.36	0.28	0.57	0.26	0.17
60-64	0.30	0.34	0.36	0.57	0.24	0.19
65-69	0.28	0.31	0.41	0.64	0.17	0.19
70-74	0.28	0.31	0.41	0.64	0.17	0.19
75-79	0.32	0.28	0.40	0.69	0.14	0.17
80-84	0.34	0.26	0.40	0.76	0.10	0.14
85+	0.36	0.24	0.40	0.84	0.06	0.10

Table A4: Age- and gender-specific start, cessation and restart probabilities for smoking

	Proportions changing smoking class					
	Men			Women		
	Start	Cessation	Restart	Start	Cessation	Restart
0-4	0	0	0	0	0	0
5-9	0	0	0	0	0	0
10-14	0.028	0.007	0	0.037	0.007	0
15-19	0.046	0.015	0	0.039	0.015	0
20-24	0.042	0.018	0.031	0.016	0.027	0.014
25-29	0.006	0.025	0.097	0	0.033	0.053
30-34	0	0.031	0.129	0	0.038	0.097
35-39	0	0.036	0.114	0	0.040	0.098
40-44	0	0.039	0.099	0	0.041	0.114
45-49	0	0.042	0.085	0	0.042	0.099
50-54	0	0.045	0.070	0	0.043	0.084
55-59	0	0.048	0.055	0	0.043	0.069
60-64	0	0.049	0.040	0	0.044	0.055
65-69	0	0.049	0.025	0	0.046	0.040
70-74	0	0.047	0.010	0	0.051	0.025
75-79	0	0.047	0	0	0.051	0.010
80-84	0	0.047	0	0	0.051	0
85+	0	0.047	0	0	0.051	0

Table A5: Relative risks of smokers and ex-smokers to get COPD

	Relative Risks for COPD incidence			
	Men		Women	
Age	Smoker	Ex-smoker	Smoker	Ex-smoker
45-49	13.6	11.2	12.3	8.3
50-54	13.6	11.2	12.3	8.3
55-59	13.6	11.2	12.3	8.3
60-64	13.6	11.2	12.3	8.3
65-69	13.6	11.2	12.3	8.3
70-74	9.8	7.4	8.9	5.9
75-79	9.8	7.4	8.9	5.9
80-84	9.8	7.4	8.9	5.9
85+	9.8	7.4	8.9	5.9

The RR for a non-smoker is 1.

Appendix B: Tables of chapter 3, description of the new COPD model

Table B1: NMP-data: General characteristics, co morbidities and medication

	With spirometry (n=307)	Without spirometry (n=223)
% Female	39.1	38.6
Age	65.6	65.9
% with angina pectoris	10.7	13.5
% with myocardial infarct	6.8	7.2
% with heart failure	7.2	9.0
% with hypertension	14.3	14.8
% with CVA	3.9	4.9
% with diabetes	7.6	9.4
“COPD-medication” in 2000 (mean prescriptions/patient):	7.2	7.7
Corticosteroids (H02)	0.4	0.6
Antibacterials (J01)	0.8	0.8
Anti-asthmatics (R03)	5.7	5.7
Cough and cold preparations (R05)	0.3	0.6

Table B2: EMGO-data: Characteristics of the study population with a physician diagnosis of COPD

Physician diagnosis:	COPD (n=138)	COPD + asthma (n=153)	Unknown whether they have asthma or COPD (n=410)	Total (n=701)
% female	44	54	54	52
	63	58	49	54
Weight (kg)	77	77	79	78
Height (m)	1.70	1.70	1.72	1.71
FEV1 (l)	2.06	2.42	2.95	2.66
FEV1% pred	72	83	92	86
Reversibility(%)	5	7	6	6
Smoking status (%)				
Never smoker	12	26	4	10
Current smoker	45	37	8	22
Ex-smoker	40	31	10	21
Missing	4	5	78	47

Table B3: Baseline characteristics of the LHS study population

N=5887	Mean
Gender (% female)	37
Age (year)	48,5
Education (years)	13,6
BMI	25,6
Smoking:	
Cigarettes/day	26,1
Age started smoking	17,5
Packyears	40,5
Lung function (post-BD):	
FEV_1 (L)	2,75
FEV_1 % pred	78,3

Table B4: Regression coefficients of the random effect model

	β-Coefficient	p-value
Intercept	-20.9546	0.26
Year	0.2394	0.33
Smoking cessation	14.3188	<0.0001
Gender	7.3174	0.10
Age	1.1132	0.13
Baseline FEV_1% predicted	1.3646	<0.0001
Year*smoking cessation	0.4556	<0.0001
Year*gender	-0.1562	<0.0001
Year*age	-0.03144	<0.0001
Year*baseline FEV_1% predicted	0.006027	<0.01
Smoking cessation*gender	1.7297	<0.0001
Smoking cessation*baseline FEV_1% predicted	-0.1242	<0.0001
Gender*age	-0.4038	<0.05
Gender*baseline FEV_1% predicted	0.02723	<0.05
Age*baseline FEV_1% predicted	-0.01818	<0.05
Age^2	-0.01213	0.10
Age^2*smoking cessation	-0.00086	<0.0001
Age^2*gender	0.004299	<0.05
Age^2*baseline FEV_1% predicted	0.000197	<0.05

Table B5a: Proportion transitioning to another severity stage associated with yearly decline in 2000

From:	Never-smokers	Smokers	Ex-smokers
Mild to moderate1	1.8%	2.5%	2.1%
Moderate1 to moderate2	7.1%	9.4%	8.2%
Moderate2 to severe	5.1%	6.4%	5.9%
Severe to very severe	2.6%	3.1%	3.0%

Table B5b: Proportion transitioning to another severity stage associated with the increase after smoking cessation:

From:	Never-smokers	Smokers	Ex-smokers
Moderate1 to mild	-	-	1.3%
Moderate2 to moderate1	-	-	1.7%
Severe to moderate2	-	-	1.7%
Very severe to severe	-	-	1.8%

Table B6: Unit costs in 2000 used to calculate total costs for COPD

Unit	Cost (Euros)
GP-visit	17
Outpatient visit	50
Home care (hour)	8.70
Daycare treatment	177
Inpatient hospital day	271
Influenza vaccination	15.
Oxygen (day)	4.20
Lung transplantation	186 000

Tabel B7: Total number of admissions for COPD in 2000 (LMR, 2000)

	Day-care treatment		Clinical admission	
	Men	Women	Men	Women
45-49 year	39	51	252	315
50-54 year	34	61	388	558
55-59 year	46	73	638	768
60-64 year	74	72	1068	862
65-69 year	122	58	1807	1347
70-74 year	130	47	2448	1410
75-79 year	78	27	2366	1238
80-84 year	12	14	1323	815
85+	7	6	606	588
Total	542	409	10896	7901

Tabel B8: Total number of inpatient days for COPD in 2000 (LMR, 2000)

	Day-care treatment		Clinical admission	
	Men	Women	Men	Women
45-49 year	39	51	3639	4412
50-54 year	34	61	4943	8450
55-59 year	46	73	8803	10658
60-64 year	74	72	15092	12069
65-69 year	124	58	26030	20112
70-74 year	134	48	35468	22753
75-79 year	78	27	36049	18428
80-84 year	12	15	19685	12537
85+	7	6	9583	8952
Total	548	411	159292	118371

Table B9: Total costs for nursing and residential care facilities in million Euros (Polder et al., 2002)

Age	Men	Women
45 - 64 year	1,1	0,9
65 - 74 year	3,4	2,4
75 - 84 year	7,4	6,0
85+	5,7	7,5
Totaal	17,6	16,8

Table B10: Total costs in million Euros for medication (SFK, 2000)

	Men	Women
45 – 54 year	4.98	6.43
55 – 64 year	6.75	6.40
65 – 69 year	4.91	3.85
70 – 74 year	5.84	4.05
75+	9.64	7.56
Total	32.1	28.3

Table B11: Costs/patient in Euros divided by age, gender and disease severity

	Mild patient	Moderate patient	Severe patient	Very severe patient
Men				
45-49 year	210	460	1600	5200
50-54 year	210	450	1500	5100
55-59 year	210	450	1500	5100
60-64 year	220	480	1600	5400
65-69 year	240	530	1800	5900
70-74 year	260	570	1900	6400
75-79 year	310	680	2300	7600
80-84 year	310	670	2300	7500
85+	410	900	3100	10000
Total	260	570	1900	6400
Women				
45-49 year	270	590	2000	6600
50-54 year	280	620	2100	7000
55-59 year	280	610	2100	6900
60-64 year	280	620	2100	6900
65-69 year	300	660	2300	7400
70-74 year	290	640	2200	7100
75-79 year	320	690	2400	7800
80-84 year	330	720	2500	8000
85+	460	1000	3500	11000
Total	310	680	2300	7600

Formula to calculate cost/patient for the different severity stages

Total costs (a, g)= costs/patient for mild COPD * number of mild patients (a,g) + 2.22 * costs/patient for mild COPD * number of moderate patients (a,g) + 7.51 * costs/patient for mild COPD * number of severe patients (a,g) + 24.67 * costs/patient for mild COPD * number of very severe patients (a,g)

a=age, g=gender

Appendix C: Mathematical description of the new COPD model

This appendix contains a formal, mathematical description of the new COPD model, in addition to the verbal description in section 3. The formulas given below summarize the Mathematica code that forms the model used in the calculations. For further details, please contact the authors.
To simplify notation, specific subscripts to specify e.g. age, time, or gender will be left out in the remainder whenever this does not cause confusion. A formal mathematical description of the original RIVM Chronic Disease Model (CDM) can be found in Hoogenveen, de Hollander and van Genugten (Hoogenveen et al., 1998). A shorter, basic description was published in Feenstra et al (Feenstra et al., 2001).

Like the CDM underlying this COPD model, the new COPD model is a dynamic population model, and implemented as a set of difference equations. These equations describe the development of the state variables over time, as a result of transitions from one state to the other. 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.
The two most important state variables in the COPD model are: 1) population numbers 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 variable has to be interpreted as the mean distribution over both genders and all ages. Basically the model describes how these variables evolve over time and how they are related.

This appendix follows the computational order in the model. First all input parameters are defined or read from data files and some help variables are computed. Then, the values of the model variables for the start year are computed or read. 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 estimated on the LHS data and the distribution of FEV1%pred in each COPD stage. The 2nd step is the calculation of new COPD and smoking prevalence numbers using these transition rates. The 3rd step is the calculation of the new FEV1% pred distributions in each COPD stage using lung function decrease and increase. Finally the prevalence rates of other smoking related diseases are computed following the general CDM disease model equations. The main COPD model equations are given below and shortly explained. Tables C1 to C3 list the symbols used.

Table C1: Definition of indexsymbols used in model formulas

Symbol	Range	Definition
ri	1,2,3	1=never smokers, 2=current smokers, 3=former smokers
j	1,2	Direction of transitions, 1=forward, 2=backward
di	1,2,3,4,5,6	COPD severity stages, 1=no COPD, 2=very severe, 3=severe, 4=moderate1, 5=moderate2, 6=mild COPD
g	1,2	Gender, 1=men, 2=women
a	1,2,…18, or 1,2,..86	Age, either in five year age classes (1=0-4, 2=5-9 etc, 18=85 and over) or in one year classes (1=0, 2=1 etc, 85=84, 86=85 and over)
n	1,2,…nstap	Time runs from t0 to nstap, the user defined value of the last year.
c	1,2	Index over severity distribution coefficients, 1= slope, 2= intercept

Table C2: Definition of input parameters used in model formulas

Symbol	Value	Definition
$RR^{smok}_{COPD}(ri,g,a)$	See table 1.5	Relative risk of smoking class for COPD incidence
$N_0(g,a)$	See table A1	Initial total population numbers
$propprev_{COPD}(di)$	See table C7	Initial distribution of COPD prevalence over severity stages.
$propinc_{COPD}(di)$	See table C7	Distribution of COPD incidence over severity stages
$distFEV_0(di,c)$	See table C4	Initial set of coefficients characterizing the distribution of FEV1%pred within each COPD severity stage.
distFEVinc(di,c)	See table C4	Initial set of coefficients characterizing the distribution of FEV1%pred within each COPD severity stage for COPD incidence.
$inc_{COPD}(g,a)$	See table A2	COPD incidence rates, as numbers per 1000 in the general population
$mort_{tot}(g,a)$	See table A1	Total mortality rates in the population in start year
$prev_{COPD0}(g,a)$	See table A2	COPD prevalence fractions, as a percentage of the total population, at baseline.
$excessmort_{COPD}(g,a)$	See table A2	Baseline COPD excess mortality rates
$trans_{smok}(j,ri,g,a)$	See table A4	Smoking class transition rates
$Prev_{smok0}(ri,g,a)$	See table A3	Smoking prevalence fractions in total population at baseline
RR^{FEV}_{tot}	1.20 (See section 3.4)	Relative risk of FEV1%pred value for excess mortality of COPD
$RM_{oth}(g,ri,a)$	See table C5	Multiplier value for non-COPD mortality, i.e. the smoking class specific risk of mortality for other causes relative to the population risk value. RM (g,2,a) divided by RM (g,1,a) is the relative risk of smokers for non-COPD mortality compared to never smokers and idem for ex smokers: RM (g,3,a) divided by RM (g,1,a)
$mFEV_0(di)$	See table C6	Values for mean FEV1%pred in each COPD severity stage in start year.
FEVlength(di),	See table C6	Length of FEV1 severity stages, computed as upper boundary of severity stage minus lower boundary, e.g. for very severe, 30-0=30.
FEVbord(di)	See table C6	Value of lower limit of FEV1 severity stages

Table C3: Definition of model variables

Symbol	Definition
$N(ri,di,g,a)_t$	Population numbers
$distFEV(ri,di,c)_t$	Coefficients of FEV1%pred distribution with each smoking and severity stage at start of year, normalized i.e. with cumulative distribution value 1
$distFEVp(ri,di,c)_t$	Idem scaled with true population numbers
$distFEVp1(ri,di,c)_{t,}$	Idem, helpvariables to denote temporary values for distFEVp
$distFEVp2(ri,di,c)_t$	
$f(j,ri,di,g,a)_t$	Change in FEV1%pred over 1 year found from estimated random effects model (j=1: decrease, j=2, increase after smoking cessation), specific for age and gender
$Mf(j,ri,di)_t$	Mean change in FEV1%pred, weighted average over age and gender
$trans_{COPD}(j,ri,di)_t$	COPD stage transition rates
$mort_{oth}(g,a)$	Mortality rate for non modelled causes
$baseinc_{COPD}(g,a)$	Incidence rate for a non smoker, (without COPD)
$prev_{smok0}(ri\|di,g,a)$	Smoking prevalence fractions in a given COPD severity stage at t=0
$embase_{COPD}(g,a)$	COPD excess mortality rate for stage mild COPD
$mFEV(ri,di)_t$	Mean FEV1%pred in each COPD severity and smoking class

Table C4: Initial set of coefficients characterizing the distribution of FEV1%pred within each COPD severity stage.

Severity stage	Intercept prevalence	Slope prevalence	Intercept incidenc	Slope Incidence
Mild	0.0166137	-0.000526855	0.0258372	-0.000847084
Moderate1	0.0211958	-0.000381843	0.0228356	0.000250135
Moderate2	0.013254	0.00044121	0.00500505	0.000990587
Severe	0.00241387	0.000542006	-0.00024786	0.000262645
Very severe	0.0000405213	0.000118668	0	0

Table C5: Values for $RR_{oth}(g,ri,a) = RM_{oth}(g,ri,a)/RM_{oth}(g,1,a)$, average over men and women.

Age class	$RM_{oth}(g,ri,a)/RM_{oth}(g,1,a)$.	
	Current smokers	Former smokers
0-29	1	1
30-49	1.9	1
50-59	1.8	1.1
60-69	2.0	1.2
70-79	1.7	1.2
80+	1.4	1.2

Table C6: Values for mFEV in start year, FEVbord, FEVlength.

Severity stage	$MFEV_0$	FEVbord	FEVlength
Mild	90	80	30
Moderate1	74	68	12
Moderate2	60	50	18
Severe	42	30	20
Very severe	23	0	20

Table C7: Initial distribution of inc and prev over each COPD severity stage.

Severity stage	prevalence	incidence
Mild	0.27	0.40
Moderate1	0.23	0.30
Moderate2	0.32	0.25
Severe	0.15	0.045
Very severe	0.026	0.0015

Initialisation

Distribute COPD prevalence over smoking and severity stages.

The baseline values for smoking and severity stage specific prevalence fractions are found as follows:

$prev_{smok0}(1|di,g,a) = RR^{smok}{}_{COPD}(1,g,a)\ prev_{smok0}(1,g,a) / (\Sigma_{ri}\ RR^{smok}{}_{COPD}(ri,g,a)\ prev_{smok0}(ri,g,a)),$
$prev_{smok0}(2|di,g,a) = RR^{smok}{}_{COPD}(2,g,a)\ prev_{smok0}(2,g,a) / (\Sigma_{ri}\ RR^{smok}{}_{COPD}(ri,g,a)\ prev_{smok0}(ri,g,a)),$
$prev_{smok0}(3|di,g,a) = RR^{smok}{}_{COPD}(3,g,a)\ prev_{smok0}(3,g,a) / (\Sigma_{ri}\ RR^{smok}{}_{COPD}(ri,g,a)\ prev_{smok0}(ri,g,a)),$
all three for di=2,..6.

And for di=1:
$prev_{smok0}(ri|1,g,a) =(prev_{smok0}(ri,g,a) - prev_{COPD0}(g,a)\ prev_{smok0}(ri|di,g,a))) /(1- prev_{COPD0}(g,a)),$
$ri=1,..3$

The relative risk values used for calculating smoking class specific COPD incidence numbers were assumed to approximate the relative risk of smoking class for COPD prevalence for the start year. Furthermore, the $prev_{smok0}$(ri|di,g,a) are assumed equal for all di>1, for the start year.

The population numbers in each severity and smoking class for the start year are then calculated as follows:

$N(ri,di,g,a)_{t=0} = N_0(g,a)\ prev_{COPD0}(g,a)\ prev_{smok0}(ri|di,g,a)\ propprev_{COPD}(di),$ di=2,..6
And for di=1:
$N(ri,1,g,a)_{\ t=0} = prev_{smok0}(ri,g,a) N_0(g,a) - \Sigma_{di>1}\ N(ri,di,g,a)_{\ t=0}$

Find initial values for distributions.

For the start year, the FEV_1%pred-distributions within each COPD and smoking class are approximated by the distribution over all smoking classes. For the latter, the distributions defined by the coefficients given in Table C4 were normalized.

$distFEV(ri,di,c)_{\ t=0} = distFEV_0(di,c)$

As a result, for the start year, the mean FEV_1%pred values within each smoking class are approximated by the mean values over all smoking classes, which are given as input variables:

$mFEV(ri,di)_{t=0} = mFEV_0(di)$

Compute baseline *incidence* and baseline mortality rates

In the model, COPD incidence and excess mortality 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 and mortality 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 disease-free population only. Incidence cannot take place from the fraction of the population with COPD. They are moreover divided by $(\Sigma_{ri}\ prev_{smok}(ri|1,g,a)\ RR^{smok}_{COPD}(ri,g,a))$ to find the incidence rate for a non smoker.

$baseinc_{COPD}(g,a) = inc_{COPD}(g,a) / (1-prev_{COPD0}(g,a)) /(\Sigma_{ri}\ prev_{smok0}(ri|1,g,a)\ RR^{smok}_{COPD}(ri,g,a))$

COPD excess mortality is divided by $(\Sigma_{di}\ RR^{FEV}_{tot}\text{^}(10-.1mFEV_0(di))\ propprev_{COPD}(di))$ to find the excess mortality rate for mild COPD.

$embase_{COPD}(g,a) = excessmort_{COPD}(g,a) /(\Sigma_{di}\ RR^{FEV}_{tot}\text{^}(10-.1mFEV_0(di))\ propprev_{COPD}(di))$

Note that for di=1 (no COPD), $mFEV_0(di)=100$, while for di=2, $mFEV_0(di)$ is very low (very severe COPD). For $mFEV_0(di)=100$ it follows that: $RR^{FEV}_{tot}\text{^}(10-.1\ mFEV_0(di))= RR^{FEV}_{tot}\text{^}0=1$.

Mortality from other causes is found as the remainder after subtraction of COPD excess mortality.

$mort_{oth}(g,a) = mort_{tot}(g,a) – excessmort_{COPD}(g,a)prev_{COPD0}(g,a)$

Simulation part 1: 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 neighbour 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 ($trans_{COPD}(j,ri,di)$).
These are calculated in the model for each year, using distribution characteristics for the distribution of FEV1%pred *within* each severity stage (see section 3.1) and lung function decrease/increase in that period, *f(j,ri,di,g,a),* that 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 (see section 3.3). From the estimated function, the *f(j,ri,di,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.

$Mf(1,ri,di) = \Sigma_{g,a} (f(1,ri,di,g,a)\ N(ri,di,g,a)) / \Sigma_{g,a}\ N(ri,di,g,a),$ di=2,..6;ri=1,..3
And
$Mf(2,3,di) = \Sigma_{g,a} (f(2,3,di,g,a)\ N(2,di,g,a)\ trans_{smok}(1,2,g,a)) / \Sigma_{g,a}\ [N(3,di,g,a) + N(2,di,g,a)\ trans_{smok}(1,2,g,a)]$
di=2,..6, with $Mf(2,ri,di)=0;$ ri=1,2

Second, new COPD stage transition fractions are calculated for each smoking and severity stage:

$$transCOPD(1,ri,di) = f1/FEVlength(di)\left[\frac{(1 + ½f1Abs[distFEV1(ri,di,1)/\ distFEV1(ri,di,2)])}{(1 + ½FEVlength(di)Abs[distFEV1(ri,di,1)/distFEV1(ri,di,2)])}\right]$$

$$transCOPD(2,ri,di) = f1/FEVlength(di)\left[\frac{(1 + ½\ (FEVlength(di) - ½f1)[distFEV1(ri,di,1)/\ distFEV1(ri,di,2)])}{(1 + ½FEVlength(di)Abs[distFEV1(ri,di,1)/distFEV1(ri,di,2)])}\right]$$

for di=2,..6, with *f1=Mf(j,ri,di)*.

The transition rates are used in part 2 of the simulation. The mean decreases are used in part 3 of the simulation.

Simulation part 2: Find new population numbers, i.e. new COPD and smoking prevalence numbers

The new smoking and COPD stage prevalence numbers are calculated. This uses the $trans_{COPD}$ values from part 1 of the simulations as well as the mFEV values.

The population numbers in each smoking and severity stage change as a result of

1. COPD related mortality
2. Mortality from other causes
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)

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

For di=1,

$N(ri,di,g,a+1)_{t+1} = N(ri,di,g,a)_t$

(2) $- RM_{oth}(g,ri,a)\ mort_{oth}(g,a)\ N(ri,di,g,a)_t$

(3) $- trans_{smok}(1,ri,g,a)\ N(ri,di,g,a)_t$

(4) $- trans_{smok}(2,ri,g,a)\ N(ri,di,g,a)_t$

(7) $- baseinc_{COPD}(g,a)\ RR^{smok}{}_{COPD}(ri,g,a)\ N(ri,di,g,a)_t$

(8) $+ trans_{smok}(1,ri-1,g,a)\ N(ri-1,di,g,a)_t$

(9) $+ trans_{smok}(2,ri+1,g,a)\ N(ri+1,di,g,a)_t$

For di>1,

$N(ri,di,g,a+1)_{t+1} = N(ri,di,g,a)_t$

(1) $- RR^{FEV}_{tot}\text{^}(10-.1mFEV(ri,di))\ embase_{COPD}(g,a)\ N(ri,di,g,a)_t$

(2) $- RM_{oth}(g,ri,a)\ mort_{oth}(g,a)\ N(ri,di,g,a)_t$

(3) $- trans_{smok}(1,ri,g,a)\ N(ri,di,g,a)_t$

(4) $- trans_{smok}(2,ri,g,a)\ N(ri,di,g,a)_t$

(5) $- trans_{COPD}(1,ri,di)\ N(ri,di,g,a)_t$

(6) $- trans_{COPD}(2,ri,di)\ N(ri,di,g,a)_t$

(7) $+ baseinc_{COPD}(g,a)\ RR^{smok}_{COPD}(ri,g,a)\ propinc_{COPD}(di)\ N(ri,1,g,a)_t$

(8) $+ trans_{smok}(1,ri-1,g,a)\ N(ri-1,di,g,a)_t$

(9) $+ trans_{smok}(2,ri+1,g,a)\ N(ri+1,di,g,a)_t$

(10) $+ trans_{COPD}(1,ri,di+1)\ N(ri,di+1,g,a)_t$

(11) $+ trans_{COPD}(2,ri,di-1)\ N(ri,di-1,g,a)_t$

These new population numbers are corrected for birth in the lowest age class to complete this part of the simulation.

Simulation part 3: Calculate new distributions of FEV1%pred and new mean FEV1% pred values specific to smoking and severity stage

The new distributions of the FEV_1%pred within each COPD stage are calculated from the existing distributions, the mean decrease and increase for each severity and smoking class (*Mf(j,ri,di)*) found in part 1, as well as the population numbers per age, gender, smoking and severity stage.

First, the normalized distributions are multiplied by the stage prevalence numbers to get absolute frequency numbers. These stage prevalence numbers are aggregations over gender and age for each smoking class and COPD stage.

$distFEVp(ri,di,c) := distFEV(ri,di,c)\ \Sigma g,a\ N(ri,di,g,a),\ for\ di=2,..6$

Second, the new frequency numbers are calculated taking into account the inflow from and outflow to neighbor COPD severity stages over 1 year (the mean decreases and increases), as well as COPD incidence and mortality. These calculations use severity and smoking class specific decreases and increases (the *Mf(j,ri,di)*) and severity and smoking class specific coefficients (the *distFEVp(ri,di,c)*) to find severity and smoking class specific new coefficients for the frequency distribution.

The frequency numbers change as a result of

1. the inflow from the previous, i.e. milder stage to decrease in lung function (based on *Mf(1,ri,di+1)*)
2. the outflow to the next, i.e. more severe stage due to decrease in lung function (based on *Mf(1,ri,di)*)
3. the inflow from the next, i.e. more severe stage due to increase in lung function for current quitters (based on *Mf(2,ri,di-1*)),
4. the outflow to the previous, i.e. milder stage due to increase in lung function for current quitters (based on *Mf(2,ri,di)*).
5. Incidence from the COPD-free population into the severity stages
6. COPD related mortality
7. Mortality from other causes

It must be remarked that the two flows 3 and 4 are in practice very small.

Changes 1 to 4 result in new frequency distributions taking into account decrease or increase, but not taking into account incidence and mortality. The specific functional form is complex and is not presented here:

$distFEVp1(ri,di,c)_{t+1} = g\ (distFEVp(ri,di,c)_t,\ di, Mf(j,ri,di), Mf(j,ri,di+1), Mf(j,ri,di-1))\ ;\ ri=1,2,3;\ di=2,..6$

By assumption, for the stage of mild COPD no outflow is allowed to the COPD-free population due to increases in lung function for current quitters. These remain in mild COPD.

Adding change 5, incidence is distributed *over* the severity stages di=2,..6, according to the input parameter $propinc_{COPD}(di)$ that gives the fractions of incidence into the severity stages. The distribution of incidence *within* each severity stage is given by *distFEVinc(di,c)*. This is also an input parameter (see table C4, the values in the table were normalized to form the *distFEVinc(di,c)*).

$$distFEVp2(ri,di)_{t+1} = distFEVp1(ri,di)_{t+1} + distFEVinc(di)_t * \Sigma_{g,a}\ [baseinc_{COPD}(g,a) * RR^{smok}_{COPD}(ri,g,a) * N(ri,1,g,a)_t * propinc_{COPD}(di)]$$

The new frequency distributions are corrected for mortality, taking into account that COPD excess mortality depends on lung function. That means, persons with lower FEV_1% values have higher COPD-related mortality risks. This differential mortality within each COPD severity stage results in a change of both intercept and slope of the linear (frequency) distribution function.

Slopes are corrected as follows:

$$distFEVp(ri,di,1)_{t+1} =$$
$$distFEVp2(ri,di,1)_{t+1} * [(1 - \{ \Sigma_{g,a} (RM_{oth}(ri,g,a)\ mort_{oth}(g,a)\ N(ri,di,g,a)) / \Sigma_{g,a}\ N(ri,di,g,a) \})$$
$$- (RR^{FEV}{}_{tot}\text{^}(10\text{-}.1mFEV(ri,di)) \{ \Sigma_{g,a} (embase_{COPD}(g,a)N(ri,di,g,a)) / \Sigma_{g,a}\ N(ri,di,g,a) \} / EFm(di))]$$
$$- distFEVp2(ri,di,2)_{t+1} * [RR^{FEV}{}_{tot}\text{^}(10\text{-}.1mFEV(ri,di)) \{ \Sigma_{g,a} (embase_{COPD}(g,a)N(ri,di,g,a))/ \Sigma_{g,a}\ N(ri,di,g,a) \} (-0.1log(RR^{FEV}{}_{tot})) / EFm(di)]$$

Intercepts are corrected as follows :

$$distFEVp(ri,di,2)_{t+1} =$$
$$distFEVp2(ri,di,2)_{t+1} * [(1 - \{ \Sigma_{g,a} (RM_{oth}(ri,g,a)\ mort_{oth}(g,a)\ N(ri,di,g,a)) / \Sigma_{g,a}\ N(ri,di,g,a) \})$$
$$- RR^{FEV}{}_{tot}\text{^}(10\text{-}.1mFEV(ri,di)) \{ \Sigma_{g,a} (embase_{COPD}(g,a)N(ri,di,g,a))/ \Sigma_{g,a}\ N(ri,di,g,a) \} / EFm(di)]$$

Here *EFm(di)* denotes an approximation of the expectation of the increased lung function dependent mortality risk over the severity stage di:

$$EFm(di) = \int_0^{FEVlength(di)} (1 - 0.10log\ (RR^{FEV}_{tot})\ y) * max\ (distFEV(ri,di,1) * y + distFEV(ri,di,2), 0)\ dy$$

for di=2,..6

The term max(.,0) is used to guarantee non-negative frequency numbers.
Finally these new frequency distributions are normalized again and new mean FEV1%pred values are calculated.

$$distFEV(ri,di) = distFEVp(ri,di) / \int_0^{FEVlength(di)} max\ (distFEVp(ri,di,1) * y + distFEVp(ri,di,2), 0)\ dy$$

$$mFEV(ri,di) = FEVbord(di) + \int_0^{FEVlength(di)} y * max\ (distFEV(ri,di,1) * y + distFEV(ri,di,2), 0)\ dy$$

for di=2,..6

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

Simulation part 4: Compute results for other smoking related diseases and save outcomes.

The remainder of the model follows the structure of the CZM and describes the incidence, prevalence and mortality from other smoking related diseases in relation to the number of never, current and ex-smokers, and to mortality and birth.

Save results

Finally the results are saved before a new simulation step is started.

Appendix D: Tables of chapter 5 results: projections for the base-case scenario

Table D1: Age-and gender specific prevalence rates for 2000 and 2025 (number per 1000)

	Men		Women	
Age class	2000	2025	2000	2025
45-49 year	15.9	12	13.9	10
50-54 year	25.0	18	19.7	20
55-59 year	40.5	31	25.9	33
60-64 year	64.3	53	33.8	48
65-69 year	104.4	85	48.8	67
70-74 year	144.5	125	63.0	85
75-79 year	167.4	164	65.4	92
80-84 year	178.5	198	59.5	92
85+	175.8	191	61.6	110
Total	24.0	33	14.7	27

Table D2: Age- and gender specific prevalence rates per severity stage in 2000 (per 1000)

	Men				Women			
	Mild	Moderate	Severe	Very severe	Mild	Moderate	Severe	Very severe
45-49 year	4.2	8.8	2.5	0.4	3.7	7.7	2.2	0.4
50-54 year	6.7	13.9	3.9	0.7	5.3	10.9	3.1	0.5
55-59 year	10.8	22.4	6.3	1.1	6.9	14.4	4.0	0.7
60-64 year	17.1	35.6	10.0	1.7	9.0	18.7	5.2	0.9
65-69 year	27.7	57.8	16.2	2.7	13.0	27.1	7.6	1.3
70-74 year	38.4	80.0	22.4	3.8	16.7	34.9	9.8	1.6
75-79 year	44.4	92.7	25.9	4.3	17.4	36.2	10.1	1.7
80-84 year	47.4	98.8	27.6	4.6	15.8	33.0	9.2	1.6
85+	46.7	97.3	27.2	4.6	16.3	34.1	9.5	1.6
Total	6.4	13.3	3.7	0.6	3.9	8.1	2.3	0.4

Figure D1a: Proportional distribution of severity stages over time for men

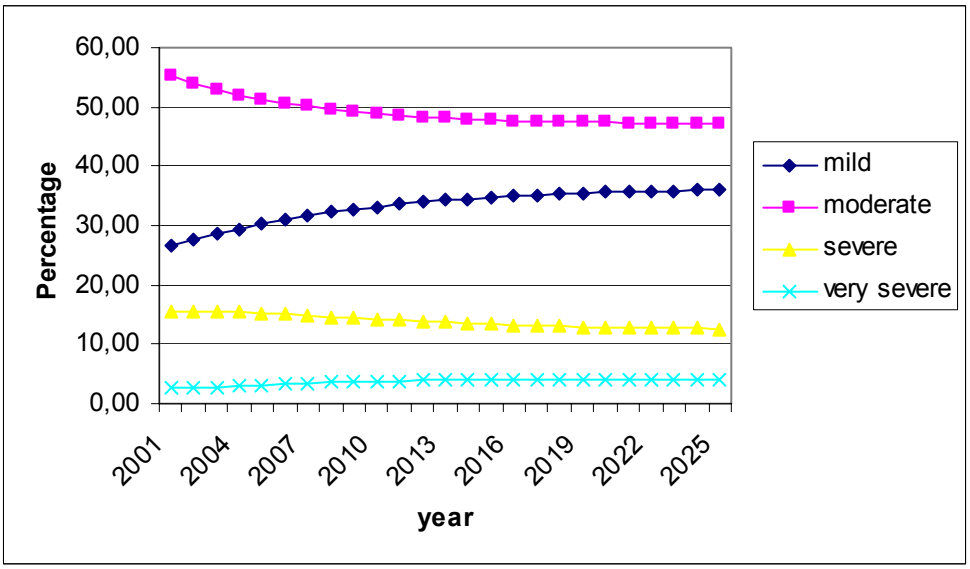

Figure D1b: Proportional distribution of severity stages over time for women

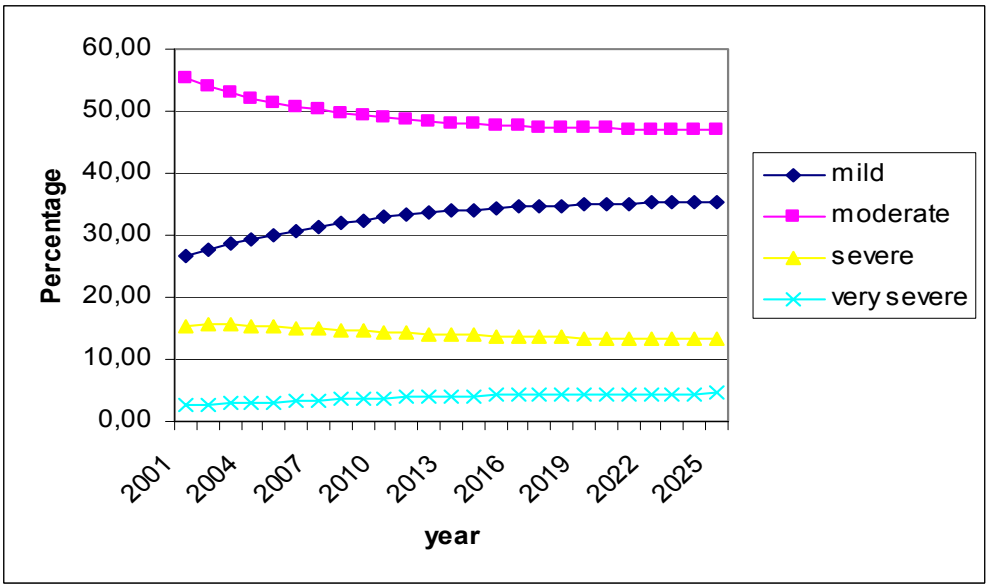

Table D3: Total costs in million Euros per age and gender class for the years 2000 and 2025

	Men		Women	
Age class	2000	2025	2000	2025
45-49 year	6.36	4.06	6.81	4.48
50-54 year	9.88	7.25	10.3	11.2
55-59 year	11.9	12.8	10.1	19.1
60-64 year	16.6	22.3	11.4	27.5
65-69 year	25.0	33.6	16.4	36.5
70-74 year	29.8	45.0	18.5	39.6
75-79 year	30.5	57.0	18.7	41.7
80-84 year	16.7	35.8	11.6	27.0
85+	13.7	30.2	15.6	40.0
Total	160	248	119	247

Appendix E: Tables of chapter 6 results: sensitivity analysis for the base-case scenario

Table E1: Sensitivity analyses on the proportional distribution over smoking classes for all sensitivity analyses for the year 2025

	Men			Women		
	Never smoker	Smoker	Ex-smoker	Never smoker	Smoker	Ex-smoker
Base-case	***5.8***	***44.2***	***50.0***	***10.8***	***49.9***	***39.2***
1. Distribution of prevalence over severity stages differs by age class	5.8	43.9	50.3	10.9	49.6	39.5
2. Severity distribution of incidence as prevalence	5.8	44.3	49.9	10.8	50.0	39.1
3. Severity distribution of incidence: 60% in mild, 40% in moderate	5.7	44.1	50.2	10.8	49.8	39.4
4, Decline in FEV_1% pred as base-case –10%	5.8	44.2	50.0	10.8	49.9	39.2
5. Decline in FEV_1% pred as base-case +10%	5.8	44.2	50.1	10.8	49.9	39.3
6. No increase in FEV_1% pred after smoking cessation	5.8	44.3	49.9	10.9	50.0	39.1
7. Never smoker has decline smoker	5.7	44.2	50.1	10.7	50.0	39.3
8. More than exponential association between lung function and mortality	5.8	44.2	50.0	10.8	49.9	39.2

Table E2: Sensitivity analyses on the percentage of COPD patients dying in 2025

	Men	Women
Base-case	***8.7***	***7.2***
1. Distribution of prevalence over severity stages differs by age class	8.6	7.0
2. Severity distribution of incidence as prevalence	9.2	7.7
3. Severity distribution of incidence: 60% in mild, 40% in moderate	8.2	6.7
4, Decline in FEV_1% pred as base-case –10%	8.7	7.1
5. Decline in FEV_1% pred as base-case +10%	8.8	7.2
6. No increase in FEV_1% pred after smoking cessation	8.7	7.2
7. Never smoker has decline smoker	8.7	7.2
8. More than exponential association between lung function and mortality	8.8	7.2

Table E3: Sensitivity analyses on the percentage of COPD patients dying per severity stage in 2025

		Mild	Moderate	Severe	Very severe
Base-case	***Men***	***7.4***	***8.6***	***11.1***	***14.2***
	Women	***5.9***	***7.1***	***9.3***	***12.0***
1. Distribution of prevalence over severity stages differs by age class	Men	7.3	8.4	11.0	14.3
	Women	5.8	6.9	9.2	12.1
2. Severity distribution of incidence as prevalence	Men	7.5	8.6	10.8	13.7
	Women	5.9	7.1	9.1	11.7
3. Severity distribution of incidence: 60% in mild, 40% in moderate	Men	7.4	8.6	11.9	14.7
	Women	5.9	7.0	9.7	12.3
4. Decline in FEV_1% pred as base-case –10%	Men	7.4	8.6	11.1	14.1
	Women	5.9	7.1	9.3	12.0
5. Decline in FEV_1% pred as base-case +10%	Men	7.4	8.5	11.1	14.2
	Women	5.9	7.1	9.3	12.0
6. No increase in FEV_1% pred after smoking cessation	Men	7.4	8.5	11.2	14.4
	Women	5.9	7.1	9.3	12.1
7. Never smoker has decline smoker	Men	7.4	8.6	11.1	14.2
	Women	5.9	7.1	9.3	12.0
8. More than exponential association between lung function and mortality	Men	7.5	8.5	11.1	15.1
	Women	6.0	7.0	9.3	12.9

Table E4: Sensitivity analyses on the total costs due to COPD per severity stage in million Euros in 2025

		Mild	Moderate	Severe	Very severe
Base-case	***Men***	***26***	***75***	***70***	***76***
	Women	***25***	***73***	***70***	***79***
1. Distribution of prevalence over severity stages differs by age class	Men	27	77	70	76
	Women	26	74	69	78
2. Severity distribution of incidence as prevalence	Men	18	69	109	152
	Women	17	66	107	152
3. Severity distribution of incidence: 60% in mild, 40% in moderate	Men	39	72	23	39
	Women	37	70	25	43
4. Decline in FEV_1% pred as base-case –10%	Men	27	77	68	62
	Women	26	74	67	64
5. Decline in FEV_1% pred as base-case +10%	Men	26	74	73	92
	Women	24	71	73	95
6. No increase in FEV_1% pred after smoking cessation	Men	25	75	73	85
	Women	24	72	72	86
7. Never smoker has decline smoker	Men	26	75	70	78
	Women	25	72	71	82
8. More than exponential association between lung function and mortality	Men	26	75	71	74
	Women	25	73	71	77