Appendix B2. COPD Model Technical Document

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases (1). It is the third leading cause of death globally, causing close to three million deaths in 2010 only (2, 3). COPD is a major cause of chronic morbidity and mortality in the world and therefore an important public health challenge. The disease is preventable and treatable and given its enormous contribution to the global burden of disease was selected to be modelled as part of the EConDA project.

Aim of the model

As part of work package 5, a multi-stage COPD disease model was developed. The aim of this model was to test the cost-effectiveness of interventions that prevent and treat COPD in selected EConDA countries.

In its most simple configuration the model considers the effect of changes in smoking prevalence over time on incidence of COPD, associated comorbidities and mortality. The multi-stage disease model further considers transitions from one COPD severity stage to the next. Prevention and treatment interventions can then be tested. For EConDA, the effect of smoking cessation services and a hypothetical treatment intervention were compared with no intervention. Outputs of the model include incidence and prevalence avoided as a result of the interventions as well as health economics indicators to assess cost effectiveness of interventions over the specified period.

Epidemiology and diagnosis of COPD

COPD prevalence, based on post-bronchodilator spirometry, among adults aged 40 years and older has been estimated to be 27.4% among smokers in Portugal (9.2% among non-smokers) (4), 22.1% in Poland (5), 24% in the Netherlands (6), 22.2% in England (7) and 7% in Finland (8). The prevalence of COPD is higher in smokers and ex-smokers than non-smokers, in those over 40 years of age than in those younger than 40 and in men than in women (1).

Death rates from COPD have been rising steadily over the past few decades (2). This has been mainly due to the epidemic of smoking and to changing demographics. People are living longer and, therefore, being at risk of COPD for longer (2).

The main risk factors for COPD are smoking, passive smoking, pollution (indoor and outdoor), exposure to certain chemicals and age. Although previously understood as a disease almost exclusively of smokers, it is now accepted that the risk of developing COPD is also determined by other genetic and environmental factors (9). COPD is non-reversible, therefore all forms of prevention are key to stop the disease from progressing.

Individuals with COPD suffer from a range of symptoms such as dyspnoea, cough, sputum production, wheezing and chest tightness which greatly affect a person's quality of life (1). Because COPD often develops in long-time smokers in middle age, patients frequently have other diseases related to smoking or ageing (1). Frequent comorbidities of COPD are CHD, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression and lung cancer. Evidence suggests that individuals with COPD have an increased risk of CHD, stroke (10-12) and lung cancer (1).

It is estimated that approximately 75% of all COPD cases remain undiagnosed and there are significant inequalities in access to early diagnosis and treatment across Europe (13). Prevalence estimates have often been based on expert opinion or self-reported doctor diagnosis, which are both an unreliable source of information for COPD (2). For example, in the USA National Health and Nutrition Examination Survey III, 70% of those with airflow obstruction had never received the diagnosis of COPD (2).

The BOLD initiative designed to provide strictly standardised, rigorous and practical methods for estimating COPD prevalence recommends high quality spirometry to diagnose COPD (14). Spirometry measures ventilation, the movement of air into and out of the lungs, the nature of any lung dysfunction and its severity. It is the most widely available and reproducible test of lung function (1). Lung function is a powerful predictor of all-cause mortality, regardless of smoking status (2).

The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms persistent airflow limitation and thus COPD. Table 1 shows the classification of airflow limitation severity in COPD proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). This classification is widely used in epidemiological research and was used in the multi-stage COPD model for EConDA. Severity classification is based on FEV_1.

Table 1 GOLD COPD staging criteria

GOLD grade	Severity	FEV1/FVC	FEV_1 % pred
1	Mild	<0.7	>80%
2	Moderate	<0.7	50-79%
3	Severe	<0.7	30-49%
4	Very severe	<0.7	<30%

Multistage model concept

The microsimulation model has been extended to include the ability to model COPD by state. The structure of the model is shown in Figure 1.

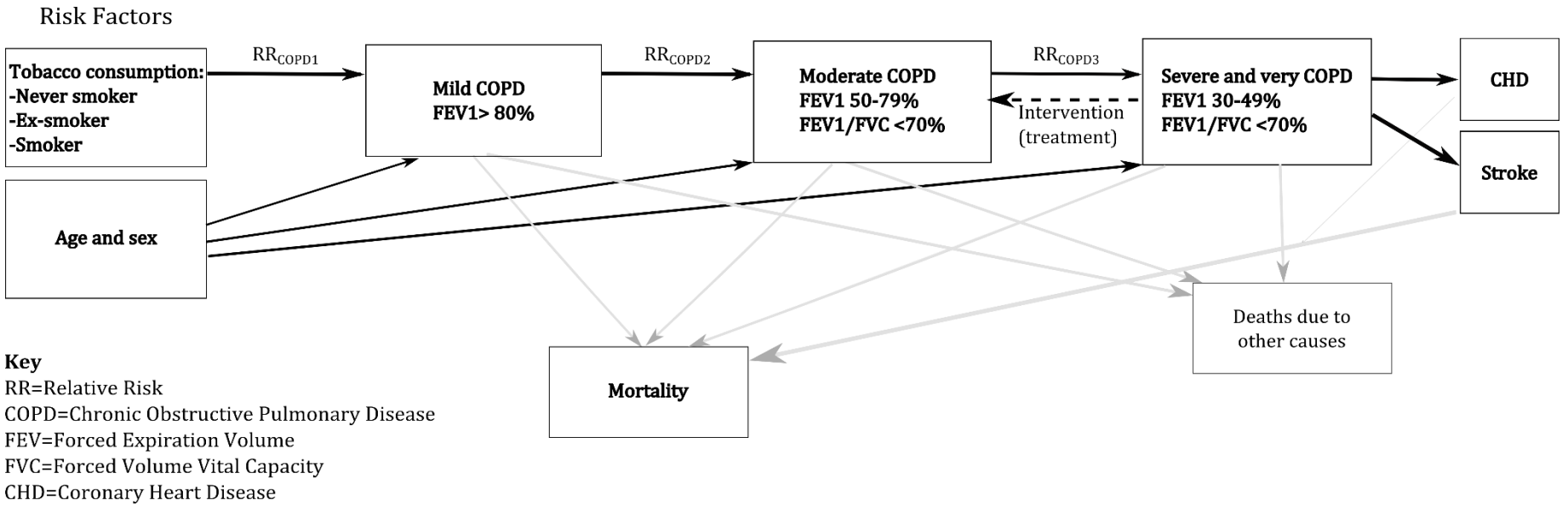

Figure 1 COPD multi-stage model concept

The modelling process used in this study is a dual modelling process. Firstly, smoking projections to 2050 have been created by fitting cross-sectional data to multivariate categorical regression models. The cross-sectional data used in this study has varied dependent on the country studied. For example in the UK, General Household Survey/General Lifestyle Survey annual datasets from 2000 until 2012 have been used. These smoking projections are used as input data for the microsimulation model. The microsimulation model originally developed for the Foresight: Tackling Obesities project (McPherson, 2007) was adapted and further developed as part of the European Commission funded project EConDA (econdaproject.eu) to model multiple stages of COPD. The smoking trends are used in the model to define an individuals' smoking status based on their age and sex and control how their smoking status will change over time as they age. An individual's smoking status, age and sex will dictate the probability of an individual contracting a disease or state of a disease such as COPD.

Model assumptions

1. COPD GOLD stages 3 and 4 have been combined. This was done in order to produce better prevalence and incidence estimates given that there are relatively few COPD stage 3 and 4 cases in the population.
2. In the baseline model, only forward transitions through COPD disease stages are possible.
3. In the intervention model a hypothetical treatment is simulated which if successful enables the remission from COPD stages 3 to 2 in the first year of treatment only
4. Incidence by stage was calculated using prevalence and mortality assuming that remission was not possible and individuals were only able to move progressively through the disease in the baseline model.
5. COPD prevalence in the UK may by slightly overestimated given that it is based on pre-bronchodilator spirometry data in the HSE. To deal with this problem as best as possible asthmatics with lung obstruction (as detected by spirometry) were assumed to be free of COPD.
6. COPD can be fatal at any COPD stage.
7. Mortality rate by stage was estimated by proportioning total COPD mortality based on respiratory deaths by COPD stage in the Finland T2000/T2011 study. It was assumed that respiratory deaths among individuals with COPD were due to COPD. It was further assumed that all COPD deaths in Finland occur after age 30 and after 35 in the UK.
8. The risk of COPD of smokers compared to non-smokers was estimated from the Finnish T2000/T2011 study because the study sample was representative of the entire population. It is assumed that these relative risks hold in the UK.

Input data and data manipulation

Table 2 describes the data inputs needed for the model. With the exception of smoking relative risks, other data inputs are country specific. For the EConDA project, a multi-stage COPD model was run for Finland and the UK only. This section details the methodology followed to analyse and collect the necessary data.

Table 2 Data inputs needed for the model (multistage)

Data	Total	by sex	by age	by stage
COPD prevalence		√	√	√
COPD incidence		√	√	√
COPD mortality rate		√	√	√
Smoking RR		√	√	√
Direct costs				√
Indirect costs	√			
Utility weights				√

Finland

The longitudinal Finland T2000/T2011 study was analysed to obtain COPD prevalence and incidence by sex, age and stage. Further, the risk of progressing from one stage to the next for smokers and ex-smokers relative to non smokers was also estimated.

Finland T2000/T2011 survey

The baseline survey used a two staged stratified random sample representative of Finnish population in the year 2000 (N=70,000 over 18 year olds). In the year 2011, people participating in the baseline survey were re-contacted and underwent both an interview and a health examination. The response rate in 2000 was 89% for the home interviews and 85% for the health examinations (15).

Spirometry was performed both at baseline and follow-up. A standard protocol was used with the aim of producing three consistent curves. From the three readings, the nurse selected the curve with the highest FEV_1 value. If obstruction was detected (<70% FEV_1), 0.1 mg of salbutamol aerosol (Ventoline Evohaler) was given to determine reversibility. The spirometry test was repeated 10 minutes later (15).

Predicted forced expiratory volume in one second (FEV1pred) was calculated using Finnish reference values for spirometry (16)(Pers Comm Kanervisto M 2015) and sex, age and height of survey participants.

Prevalence by stage

Post-bronchodilator spirometry data was used to estimate FEV1 % predicted and FEV/FVC. The highest FEV and FVC readings were used for each individual. The GOLD COPD stage definition was used to classify individuals by COPD severity stage (Table 1). Prevalence was adjusted by survey design and weighted using the survey weights provided. COPD prevalence by stage was further stratified by 20 year age groups and sex.

Prevalence of COPD in Finland in the year 2000 was 6.1% among men and 2.9% among women aged 30 or older. It was higher among older men and women and among smokers compared with non-smokers.

Incidence by stage

The incidence by stage was calculated from the data collected for prevalence and mortality by stage. The calculation assumed that remission was not possible and individuals were unable to progress across

multiple stages of COPD within a year. Further details about the methodology and algorithms developed are provided in the technical appendix [appendix B4].

Smoking relative risks

Incidence rate ratios were estimated from the Finland T2000/T2011 dataset and were used for both the UK multi-stage COPD model and the Finnish model. It was considered more appropriate to use the relative risks derived from the Finnish study since this study uses a population based sample with the whole range of age groups. The incidence rate ratio (relative risk) of smokers and ex-smokers compared with non-smokers was estimated using Poisson regression. Estimates were adjusted for age and sex. A separate Poisson regression was run for each COPD stage e.g. new COPD stage 1 cases as outcome variable.

Mortality by stage

Mortality statistics available report the total number of deaths from COPD (ICD-10 codes J40-J44) (17, 18). Total COPD deaths obtained from the WHO Global Burden of Disease study (18) for Finland were proportioned by stage based on the results of a Finnish study by Mattila et al (8). Mattila's study reported respiratory deaths by COPD stage among cohort members of the T2000/T2011 study. The main assumption made was that the cause of the respiratory death in Mattila's paper was underlying COPD. A further assumption was made that all COPD deaths occur over age 30.

UK

Prevalence by stage

COPD prevalence by stage for the UK was obtained from the Health Survey for England 2010. Spirometry data was used to classify individuals according to COPD severity. Given that a bronchodilator was not used when obstruction was detected, individuals reporting suffering from asthma who appeared to have lung obstruction were recoded as free of COPD. Estimates were adjusted for survey design and stratified by sex and age.

Prevalence of COPD in England in the year 2010 was 15.7% for men and 11.6% for women.

Incidence by stage

The incidence by stage was calculated from the data collected for prevalence and mortality by stage. The calculation assumed that remission was not possible and individuals were unable to progress across multiple stages of COPD within a year. Further details about the methodology and algorithms developed are provided in the technical appendix [appendix B4].

Mortality by stage

Total COPD deaths obtained from ONS (17) were proportioned by stage based on the results of Mattila et al (8) as for Finland (see above).

Limitations of the data

Using spirometry data on its own for the diagnosis and staging of COPD may lead to over or under estimation of prevalence. This may be due to the inclusion of false positives for example asthmatic patients and elderly patients or false negatives for example young patients with large lung compliance. In order to deal with this problem as best as possible we used post-bronchodilator spirometry data for Finland and we coded asthmatics as healthy in the Whitehall study in the absence of post-bronchodilator spirometry. This is consistent with most research studies. However, some misclassification may remain. It is important to note that the single stage disease models may rely on doctor diagnosed COPD prevalence while the multi-stage disease model for Finland and the UK is based on COPD diagnosis based on spirometry. For this reason, outputs will be considerably different and not comparable.

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