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A microsimulation model for the development and progression of chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease that is thought to affect over one million people in Great Britain. The main factor contributing to the development of COPD is tobacco smoke. This paper presents a microsimulation model for the development of COPD, incorporating population dynamics and trends in smoking. The model simulates a population longitudinally throughout their lifetimes, providing projections of future COPD prevalence and evaluation of the effects of changes in risk factor prevalence such as smoking. Sensitivity analysis provides information on the most influential model parameters.

The model-predicted prevalence of COPD in 2040 was 17% in males over the age of 35 years (13% amongst non-smokers and 22% amongst smokers), and a modest decline over the next 25 years due to recent trends in smoking rates.

The simulation model provides us with valuable information on current and future trends in COPD in Great Britain. It was developed primarily to enable easy extension to evaluate the effects of occupational and environmental exposures on lung function and the prevalence of COPD and to allow evaluation of interventions, such as introducing health surveillance or policy changes. As longitudinal studies for investigating COPD are difficult due to the lengthy follow-up time required and the potentially large number of drop-outs, we anticipate that the model will provide a valuable tool for health impact assessment. An extended model for occupational exposures is under development and will be presented in a subsequent paper.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterised by airflow obstruction that is thought to affect over a million people in Great Britain [1], costing the National Health Service an estimated £800 million in direct healthcare costs [2]. The clinical diagnosis is made using a combination of symptoms and lung function as measured by spirometry. However, for the majority of cases, COPD remains clinically undiagnosed [2,3].

The main factor contributing to the development of COPD is tobacco smoke, with smokers having greater declines in forced expiratory volume in one second (FEV_1) than non-smokers [4–8]. Certain types of environmental and occupational exposures have also been found to contribute to excess decline in lung function and COPD; exposure to coal mine dust and respirable crystalline silica have been associated with excess lung function decline [9–12] and increased risk of mortality from COPD [13].

Disease simulation models have been developed for COPD in recent years for a variety of applications, several of which have been Markov-type models, using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages [14] as the discrete states being simulated. Some of these models have evaluated the cost-effectiveness of treatment interventions [15–20] and some studied the impact of smoking interventions [21,22]. In particular, one such model is a dynamic population model of disease progression

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in Dutch patients with diagnosed COPD, allowing projections to be made of the future burden, as well as the evaluation of the impact on future prevalence of different smoking cessation interventions on the illness [19,22]. None of these models, however, consider the impact of occupational or environmental exposures.

This paper presents a stochastic microsimulation model for the development and progression of COPD, in discrete time steps of one year, via continuous changes in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). It enables the projection of the future burden of COPD, evaluation of the impact of future changes in smoking trends, and the impact of interventions that aim to reduce smoking.

2. Methods

2.1. Model structure

A microsimulation model was developed to simulate certain attributes (e.g. gender, height) of each individual in the population, updating their lung function in discrete time steps of one year. The model comprises:

- A **population** model, describing the attributes and dynamics of the population;
- A **smoking** model, representing demographic and individual trends in smoking; and
- A **disease** model, characterising FEV_1 and FVC and thus COPD stage.

In the first simulation year, an initial population of 20 year olds was generated, based on input data that described the attributes of the initial cohort. Appropriate spirometric reference equations were then utilised to simulate FEV_1 and FVC, incorporating between-person variability in lung function. In every subsequent simulation year, the existing cohort aged by one year, and each individual's FEV_1 and FVC was updated by applying annual declines in FEV_1 and FVC based on the individual's attributes in that year. In each year, an individual's COPD severity status was determined using the GOLD criteria ($FEV_1/FVC < 0.7$, and GOLD stage determined by FEV1% predicted). New cohorts enter the population in every year and their attributes are simulated. In addition, mortality rates were applied to remove certain individuals from the population, based upon age, birth year, gender, smoking status and COPD severity, although their sets of attributes remained stored to enable extraction at the end of the simulation.

2.2. Initial lung function and subsequent decline

The model was developed so that the user could select from a choice of spirometric reference equations for simulating FEV_1 and FVC, including the European Coal And Steel Community (ECSC) [23] and those based on the Health Survey for England 1995/1996 [24]. Initial FEV_1 at entry into the simulation was assumed to be highly correlated with FVC, as studies have shown [25]. As several of the reference equations were based on data from "healthy" individuals and excluded those with reported diagnosis of asthma and respiratory symptoms [24] who generally have lower lung function than the "healthy" population [26], adjustments to FEV_1 and FVC had to be made. In terms of initial FEV_1 and FVC, no difference between asthmatics and non-asthmatics was assumed (informed by analysis of data from the Health Survey for England 2001 [27]).

Lung function was assumed to decline over time, with the total decline comprising components due to ageing (which is dependent on the age, height and gender of the individual), smoking and asthma status. Each component was assumed to vary between individuals according to a lognormal distribution. The variation in initial lung function and subsequent declines was implemented by assigning all individuals four standardised random effects associated with initial FEV_1, initial FVC, FEV_1 decline and FVC decline. The first two random effects were assumed to be highly correlated with each other, as were the last two. That is, individuals with large initial FEV_1 were assumed to have large initial FVC, and those who were susceptible to large FEV_1 declines were assumed to be susceptible to large FVC declines.

The random effects were assigned at entry into the simulation and remained with them throughout the simulation period. That is, once a susceptible individual entered the population, that individual remained susceptible throughout their lifetime within the simulation timeframe. The random effects were then scaled according to the variance components for annual FEV_1 and FVC declines associated with age, smoking and asthma. Thus smokers with relatively large age-related declines (after adjusting for height) would also have had relatively large smoking-related declines. Further details on the random effects and characterisation of variability can be found in the Appendix.

The model inputs associated with FEV_1 and FVC declines were the mean annual FEV_1 and FVC declines due to smoking status, asthma, and their associated coefficients of variation that characterised the between-person variability in these declines. The mean age-related declines were derived at the start of the simulation and were based on the set of reference equations selected by the user. The mean excess FEV_1 declines in light and heavy smokers (defined as those consuming fewer than 24 cigarettes and 25+ cigarettes a day respectively) were set to the declines found in moderate and heavy smokers in a Dutch study with a 24 year follow-up [6] of 9.5 ml/year and 13.5 ml/year respectively. These figures were comparable to the excess declines of 8 ml/year and 12 ml/year found in those who smoked <20 and 20+ cigarettes a day in the Honolulu Heart Program [28], 11 ml/year seen in a longitudinal study in Busselton, Western Australia [5] and 12.2 ml/year from a longitudinal analysis of ventilator capacity in The Copenhagen City Heart Study [26].

The Dutch study [6] did not present FVC declines that were required for the model. However [26] did present both FEV1 and FVC declines but did not stratify by cigarette consumption; they found the excess decline in FVC to be about 90% of the decline in FEV1 (11 ml vs 12.2 ml). We applied this ratio to the estimates from the Dutch study, in order to derive FVC declines of 8.6 ml/year and 12.2 ml/year as inputs to the model.

In the Dutch study [6], no significant difference was found between lifetime male non-smokers (mean age 32 years) and former male smokers (mean age 45 years) in terms of FEV_1 decline, therefore no excess declines were assumed for male ex-smokers in the simulation model. The same study found an excess decline of −4.4 ml/year in former female smokers, which is the value used by the model for females. The mean annual excess declines for FEV_1 and FVC in asthmatics were set to 11.6 and 7.7 ml/year respectively [26].

2.3. Demographics

The attributes that were simulated within the population component were those on which absolute values of FEV_1, FVC and their declines have been found to be dependent (besides age), namely gender [24], height [24] and whether the individual was asthmatic [26]. Smoking status, another risk factor for excess lung function declines, is simulated within the smoking model and is described under the 'Smoking model' section.

For application of the model to Great Britain (GB), historical

national population estimates and national population projections were obtained from the Office for National Statistics [29]. Based upon the proportion of males in the Health Survey for England 2001 reporting ever being told by a doctor that they had asthma (The Health and Social Care Information Centre), it was assumed that 15% of the GB population were asthmatic. Once individuals entered the model as asthmatics, they remained asthmatic throughout the simulation.

The model was set up such that the individuals in each new cohort entered the simulation at age 20 and the attributes (gender, height, asthma status and smoking status) of each individual were randomly generated, based on the GB population.

In the first year, and in each subsequent year, of the simulation, the size of the added cohort of 20-year olds was proportional to the actual number of 20-year olds in GB in that year. As the simulation moved forward in time, the simulated population began to resemble the true male adult population of GB. However the simulation has to run for at least 60 years before the population comprises individuals aged 80 years and over. Historical and future mortality rates by gender, age and birth year were obtained from the Office for National Statistics [29]. For smokers, and those with COPD, their mortality rate in a particular year was multiplied by the appropriate risk ratios associated with smoking [31] and COPD [32] respectively. Migration, both inbound and outbound, was not included in the model.

2.4. Smoking model

A Markov model was used to describe smoking cessation and relapse in each individual (Fig. 1). It was assumed that non-smokers entering the simulation remain non-smokers for the remainder of their lives. Current smokers (categorised into light and heavy smoking categories) were permitted to stop smoking to become ex-smokers; ex-smokers were subsequently allowed to restart smoking. Data on historical GB smoking prevalence were obtained from The Office for National Statistics [30]. The cessation rate, assumed to be the same across all age groups and for the years 2007 onwards (after the smoking ban in England came into force), was set to 4.8%, which is the percentage of smokers in the Smoking Toolkit Study who smoked in the past 12 months prior to 2010 but reported not smoking in 2010 [33]. The cessation rate prior to 2007 was set to half of the 2007 rate, as research [34] suggested a cessation rate in 2004 of between 2 and 3%.

The restart rate during the first year of abstinence (15%) was sourced from a recent study on long-term smoking relapse in the British Household Panel Survey [35]. For model simplicity, it was assumed that once a smoker had quit for two or more years, they remained ex-smoker for the remainder of their lifetime; based on the same study [35], the restart rate during the second year of abstinence within the model was also set to 15% to account for this assumption.

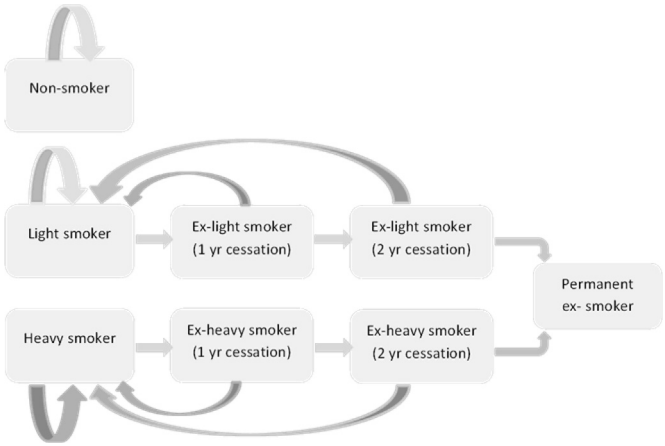

Fig. 1. Schematic of smoking model.

2.5. Variance-based sensitivity analysis

The simulation model contained a large number of input parameters and the influence of some of these parameters on the model outputs was not transparent. A sensitivity analysis can help identify the parameters that are most influential for specific model outputs and assess the robustness of the model-predicted prevalence of COPD to changes in parameter values. In this paper, a variance-based sensitivity analysis is carried out, whereby the total variance in the output is apportioned to the sources of variation in the model inputs, thus enabling identification of the most influential model parameters. Although there were several different outputs that may be evaluated following running of the simulation, the focus of the sensitivity analysis was on the prevalence of COPD (GOLD I to IV) in non-smokers and smokers at age 35, 45, 55 and 65 years. More details on the sensitivity analysis can be found in the Appendix.

2.6. Implementation

The model was implemented in MATLAB [36] and run from 1961 to 2040 for a GB scenario with a total population size of 1.5 million males (large enough that there was minimal variation due to population stochasticity between model runs). For simplicity and ease of demonstrating the model, females have not been simulated in this paper. However females can be included in the model with relative ease as the model incorporates female-specific reference equations, smoking rates and mortality rates.

The spirometric reference equations selected for use in the simulation were those based on the Health Survey for England 1995/1996 [24], which are appropriate for simulating a GB population. Table 1 presents a list of the parameter inputs used in the model and the associated data sources. The model provides data on all simulated individuals such as their smoking history and COPD severity stage in each year, allowing the population prevalence of smoking and COPD to be calculated. In addition, a variety of other individual-level outputs such as absolute FEV_1 and FVC, annual declines in FEV_1 and FVC (stratified by risk factor group) and population-level outputs such as annual incidence of COPD may be determined.

Data presented in this paper reflect a first application of the model, to predict the current and future smoking prevalence in the GB population by age group under the 'baseline scenario'. It was assumed that current trends in smoking prevalence amongst 20 year olds was maintained, i.e. a reduction of 0.5% per year as derived from national prevalence data [30], whilst ignoring migration and temporal trends in environmental and occupational exposures that may also influence national prevalence of COPD. Although the model uses smoking prevalence data in the 20–24 age group as inputs, it did not use data for the older age groups, instead relying on the smoking cessation and relapse rates to mimic smoking trends in GB across all ages. A second application of the model was to predict the likely future prevalence of COPD in males in GB under the 'alternative scenario', where the future cessation rate was assumed to double.

The sensitivity analysis was then carried out in two stages, the first focusing on the influence of the input parameters on COPD prevalence in non-smokers, and the second focusing on the

Table 1
List of model parameters, their input values and data source.

Parameter	Value	Data source
Proportion asthmatic	0.15	[27]
Asthma adjustment to baseline FEV_1 (ml)	0	[27]
Asthma adjustment to baseline FVC (ml)	0	[27]
Asthma adjustment to FEV_1 decline (ml)	11.6	[26]
Asthma adjustment to FVC decline (ml)	7.7	[26]
Excess FEV_1 decline, light smoker (ml)	9.5	[6]
Excess FEV_1 decline, heavy smoker (ml)	13.5	[6]
Excess FVC decline, light smoker (ml)	8.6	Informed by Refs. [6,26]
Excess FVC decline, heavy smoker (ml)	12.2	Informed by Refs. [6,26]
Coefficient of variation for baseline FEV_1	0.13	[27]
Coefficient of variation for baseline FVC	0.13	[27]
Coefficient of variation for age-related FEV_1 decline	0.4	Expert judgement
Coefficient of variation for smoking-related FEV_1 decline	0.2	Expert judgement
Coefficient of variation for asthma-related FEV_1 decline	1	Expert judgement
Coefficient of variation for age-related FVC decline	0.2	Expert judgement
Coefficient of variation for smoking-related FVC decline	0.5	Expert judgement
Coefficient of variation for asthma-related FVC decline	1	Expert judgement
Random effects correlation coefficients:		
Baseline FEV_1, FEV_1 decline	0.4	Expert judgement
Baseline FEV_1, baseline FVC	0.88	Expert judgement
Baseline FEV_1, FVC decline	0.4	Expert judgement
FEV_1 decline, FVC decline	0.4	Expert judgement
FEV_1 decline, FVC decline	0.9	Expert judgement
Baseline FVC, FVC decline	0.4	Expert judgement
Mortality risk ratio, light smoker	1.31	[31]
Mortality risk ratio, heavy smoker	1.79	[31]
Mortality risk ratio, ex-smoker	2.61	[31]
Risk ratio, GOLD II	1.41	[32]
Risk ratio, GOLD III	2.42	[32]
Risk ratio, GOLD IV	3.57	[32]

influence in smokers. For the former, 16 parameters were varied within a 400-point Latin hypercube design matrix, maximising the minimum distance between points. These 16 parameters and their ranges used in the design matrix are presented in Table A1 in the Appendix.

The simulation model was run at each of these design points starting in 1961 for a single cohort of 500,000 males. For the latter stage, an additional seven parameters associated with smoking were considered (Table A2 in the Appendix). The influence of the parameters on COPD prevalence in non-smokers and smokers at ages 35, 45, 55 and 65 (i.e. in years 1976, 1986, 1996 and 2006) were investigated. For each parameter, the main effect variance (the percentage of the total variance due to just the individual parameter) and the total effect variance (the percentage of the total variance due to the main effect of the parameter and its interaction with other parameters) were calculated.

3. Results

Fig. 2 shows the historical and future smoking prevalence in males in Britain as simulated by the model, for the age groups for which national smoking prevalence data were available (ONS). As the earliest year from which simulation could start is 1961 due to availability of population data, the simulated population did not include 25 year olds until at least 1966 and 50 year olds until 1991. The model provided adequate predictions of smoking prevalence in the general population over the simulation timeframe, mimicking general trends. A local peak was seen in the 25–34 age group around the year 2000, which may be explained in part by the establishment of the NSH Stop Smoking Services in England and Wales in 2000. This peak could not be reproduced by the model in its current form; nevertheless the rates observed within the last few years closely match the projected rates of this model. Under the alternative smoking scenario, the impact of doubling smoking cessation was, as expected, to decrease smoking prevalence. The difference was more noticeable in the older age groups, where the prevalence under the two scenarios diverged due to the proportion of smokers having quit increasing with increasing age. The alternative smoking scenario led to a halving of smoking rates within the 50–59 year age group by the year 2040. Although this alternative smoking scenario may not necessarily represent a realistic future trend in national smoking cessation rates, its intention was to represent a hypothetical example of application of the model to future interventions aimed at reducing smoking.

The model-predicted prevalence of COPD in 2014 (by smoking status) was 9%, 18% and 15% in never smokers, smokers (light and heavy) and ex-smokers between the ages of 35 and 73 years of age respectively. These prevalence figures are comparable to those based on a study of COPD in adults over 35 years of age in the Health Survey for England 2001 [37], where the prevalence of COPD (across both genders) was found to be 8.7%, 19.3% and 15.2% amongst never smokers, smokers and ex-smokers respectively, and in the Health Survey for England 2010 [38] with prevalence in males over 35 years of 6%, 21% and 15% respectively.

The model-predicted prevalence of COPD in 2040 was 17% over the age of 35 years (13% amongst non-smokers and 22% amongst smokers); a modest decline was predicted over the next 25 years prior to 2040 due to recent trends in smoking participation rates. Fig. 3 shows the projected prevalence of COPD in males aged between 20 and 80 years in the year 2040. The overall COPD prevalence was predicted to be greater in current smokers (light and heavy smokers combined) than never smokers. Across all ages, the majority of COPD cases were GOLD I and II. However, a greater proportion progressed to GOLD III/IV with increasing age especially amongst smokers. By age 70 years, over a third of smokers were predicted to develop COPD, with approximately a third of these in the highest severity categories (GOLD III or IV).

Fig. 4 presents the distributions of FEV_1 decline in male heavy smokers and non-smokers at age 40, as simulated by the model. The variation in declines amongst smokers was greater, due to

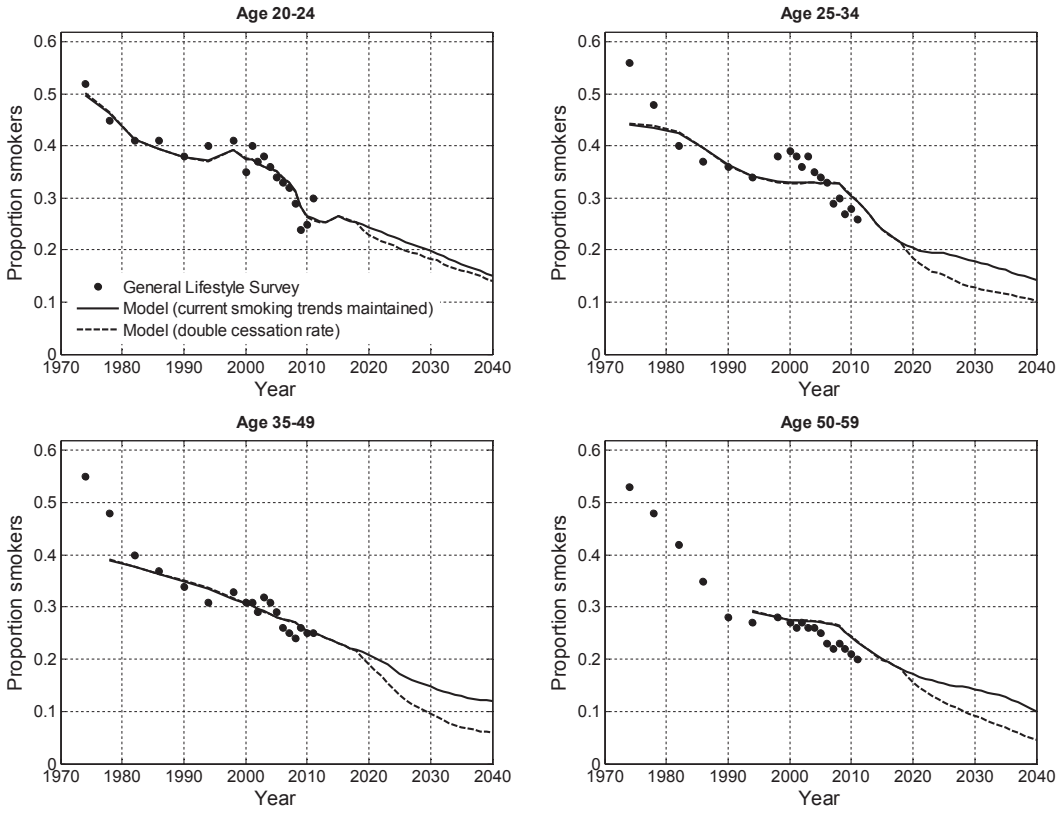

Fig. 2. Model-predicted smoking prevalence in males by age group under the baseline (current smoking trends maintained) and alternative smoking scenario (doubling of cessation rate after 2017).

variation induced by smoking as well as variation from ageing. Very few experienced declines of less than 10 ml/year. At the upper end of the distributions, few non-smokers and smokers had decline greater than 60 and 100 ml/year respectively.

The results of the sensitivity analysis can be found in Tables A1 and A2 in the Appendix. The greater the variance contribution of a parameter, the more influential that parameter and its interactions were on COPD prevalence. The results indicate that amongst non-smokers, the correlation between the random effects for baseline FEV_1 and baseline FVC was the most influential parameter for the COPD prevalence in younger adults. This parameter and its interactions explained 41% and 29% of the total variation at ages 35 and 45 respectively. The coefficient of variation of baseline FEV_1 was also influential at these ages, explaining 31% and 29% of the total variation respectively; this input and associated uncertainty range were obtained from analysis of spirometric measurements from the Health Survey for England, 2001 [27]. Amongst 55 and 65 year olds, the coefficient of variation of the age-related FEV_1 and

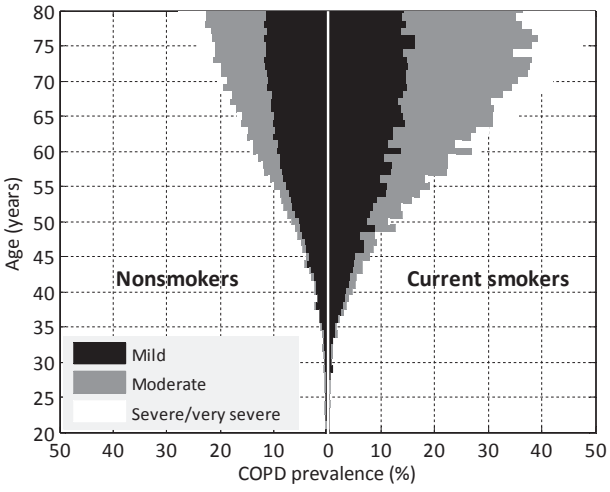

Fig. 3. Model-predicted COPD prevalence for male non-smokers and current smokers (light and heavy smokers combined) in GB in 2040 by severity stage, assuming that current smoking trends are maintained.

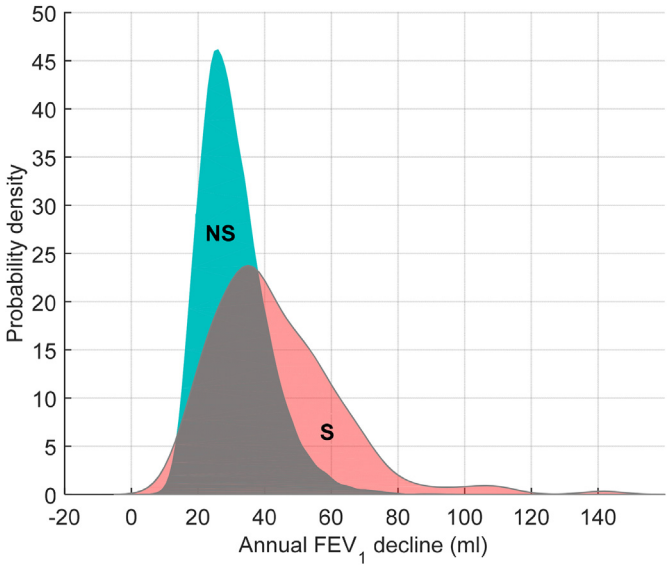

Fig. 4. Probability distribution of annual FEV_1 decline in 40 year old males by smoking status (NS = non-smoker, S = heavy smoker).

FVC declines were the most influential parameters and explained between 18% and 47% of the total variation respectively.

Amongst younger adult smokers, the correlation between the random effects for baseline FEV_1 and baseline FVC was most influential, explaining 28% of the total variation in COPD prevalence at age 35. The mean smoking-related FEV_1 decline was also highly influential, explaining between 24% and 51% of the total variation amongst all age groups. The model inputs and associated uncertainty ranges for the declines were sourced from international literature [6]; hence there is relatively high confidence in the model inputs and associated uncertainty. The results of the sensitivity analysis are presented in Table A1 and A2 in the Appendix, for non-smokers and smokers respectively.

3.1. Validation

Validation is an important aspect of model development, ensuring that the model provides robust forecasts of health outcomes under various scenarios. Obstructive lung disease models and their validity have been reviewed [39]; four types of model validation were defined for the purpose of the review. The aim within the current model development was to achieve at least third-order validation. First-order validation, defined as the process by which the model structure is examined for coding errors, logical inconsistency, and accuracy of mathematical calculations, has been carried out by having a second modeller examine the code for coding errors, both modellers examining the outputs of the model and verifying their plausibility (such as FEV_1 and FVC lying within plausible ranges and declining over time). Second order validation, defined as comparison of model predictions with existing data from studies that were used to parameterize, construct, or develop the model, was carried out by comparing the mean of the model-predicted FEV_1 and FVC for non-smokers at various ages with those predicted by the FEV_1 and FVC reference equations used in the model. These values were found to be very similar. A comparison for smokers was not attempted as the reference equations were based on spirometric measurements of a population that excluded smokers and ex-smokers. In addition, it was shown there was good agreement between the predicted prevalence of smoking in 25+ year olds and the ONS smoking data [30].

Third order validation, defined as comparison of model estimates with published data from studies that were not used to parameterize, construct or develop the model, was then carried out by comparing the model-simulated FEV_1/FVC ratios with those from the Health Survey for England, 2010 (HSE 2010) [38]. The median values of FEV_1/FVC for white males aged 35–45, 45–55 and 55–65 years from the HSE 2010 were 0.79 (5th and 95th percentiles 0.68–0.87), 0.78 (0.66–0.85) and 0.76 (0.62–0.84), comparable to the model-simulated values for white males of 0.80 (0.69–0.91), 0.78 (0.66–0.90) and 0.77 (0.64–0.91). In addition, the coefficient of variation of FEV_1 and FVC produced by the model at various age groups were comparable to those from the HSE 2010 (the coefficient of variation increasing with age), providing additional reassurance of the validity of these model components.

4. Discussion

The model presented in this paper has been applied to the general male population of GB to provide projections of future smoking prevalence as well as the future burden of COPD, providing adequate predictions of smoking prevalence in the general population over the simulation timeframe and mimicking general trends. Application of the model to alternative populations, including females, may be carried out with relative ease by substituting the GB-specific demographic data and smoking prevalence rates with those for the specific population of interest. It should be noted, however, that the spirometric reference equations used in this study to simulate FEV_1 and FVC, and that are currently incorporated in the simulation model were based on white Caucasian adults. Thus their use may not be appropriate for populations with mixed ethnicity. Alternative reference equations such as those based on the third National Health and Nutrition Examination Survey (NHANES III) [40] for African-American and Mexican-American populations, and the GLI-2012 set of equations [41] for North East Asian and South East Asian populations may easily be accommodated. Currently the model includes four choices of spirometric reference equations (for males and females) for use in simulating lung function; the ECSC, GLI-2012, NHANES III and those based on the HSE [24], with the choice being given to the user.

The development and progression of COPD was modelled via changes in FEV_1 and FVC on the continuous scale, allowing for continuous distinctions in lung function between risk factor groups. The model was set up such that every individual enters the simulated population aged 20 years. The reason for this is that lung function increases during childhood and is thought to peak or reach a plateau during early adulthood [42]. Rather than attempt to model the potentially complex pattern of lung function in those aged below 20 years, where there are very few cases of COPD, the simulation included only those aged 20 years and above. The effects of teenage smoking prior to age 20 have been ignored due to the difficulty in simulating smoking habits in young adults and the lack of relevant data for this age group.

The model assumes that the excess decline in lung function in an individual is independent of the presence of COPD. However, as a greater proportion of the 'susceptible' individuals (i.e. those with greater than average annual declines) are likely to develop COPD than the rest of the population, and as these individuals will remain susceptible throughout their lifetimes, greater excess declines in the presence of COPD is implicit.

Under the alternative smoking scenario where smoking cessation doubled, lower subsequent smoking rates were seen in comparison to the baseline scenario with the differences being more apparent in the older age groups. The model provided data on the simulated annual declines which could be beneficial for comparing the variation in annual declines by risk factor groups.

The model-predicted COPD prevalence rates, by smoking status and age group, have been compared with those based on the Health Survey for England 2001 (HSE 2001) [27] and 2010 (HSE 2010) [38] and found to be comparable. As additional validation steps, the model-predicted coefficient of variation of FEV_1 and FVC within various age groups were also found to be comparable to those from the HSE surveys. As data from the HSE 2010 survey was not used to develop the model, the comparison provides verification that the simulation model results are plausible and consistent with actual data that did not contribute to model development.

The model inputs and uncertainty distributions for the most influential parameters in young adults were obtained from analysis of the Health Survey for England 2001 [27], which provided lung function data for almost 20,000 individuals in England; the inputs are therefore considered to be obtained from a reliable source. Although the COPD model aims to simulate lung function, the model is, to a certain extent, a simplification of reality. It is unfeasible to incorporate every relevant parameter and assumptions are therefore unavoidable. Information on all elements of inter-individual variation in lung function was not available and some expert judgements were necessary to provide the necessary inputs into the simulation model. However, the sensitivity analysis suggests that those elements of variation were generally not influential for the COPD prevalence outputs.

An advantage of the disease modelling approach presented in

this paper is that it does not rely on estimates of the incidence of COPD and extrapolation of historical trends in COPD incidence or prevalence in order to predict future disease burden. This allows application of the model to other countries where population-level information on COPD is unavailable or less reliable. It is worth noting that although the model can follow a cohort over time, it is not limited to modelling a cohort and an advantage is that it can follow individuals entering the model at various time points, within the simulation timespan.

Computer simulation models for long-latency diseases have been popular in recent years due to their wide range of potential applications. For COPD, simulation models allow the evaluation of the impact of changing smoking habits within a population, or the comparison of different treatments for COPD. One such model is a dynamic population model of disease progression in Dutch patients with diagnosed COPD, allowing projections to be made of the future burden of COPD in The Netherlands, as well as the evaluation of the long-term impact of different smoking cessation interventions on national COPD prevalence [19,22]. A recent study [43] compared different COPD cost-effectiveness models with respect to structure and input parameters. Like those models, our COPD simulation model uses the GOLD classification, however at a conceptual level, there are several differences. For example, our model is a micro-simulation model that simulates both FEV_1 and FVC annually, which both then determine whether the individual develops COPD or progresses to the next GOLD stage. In addition, our model is able to capture heterogeneity of lung function between individuals via the random effects. In comparison, most other COPD models do not simulate absolute values of lung function, instead using transition probabilities (some of which are specified by age, smoking status and disease severity) to simulate movement of individuals between COPD states [15,44]. Unlike most other models, we have not modelled the frequency of exacerbations, however the intention is to eventually incorporate this aspect.

The simulation model presented in this paper allows an assessment of the impact of smoking cessation interventions, changing trends in smoking, or changing demographics. However, the primary aim of the work was to develop a model for COPD that can subsequently be adapted to take into account other influences on long function decline, including occupational and environmental exposures, and genetic effects, in order to inform policy-makers and healthcare providers. Such extensions should be relatively straightforward as long as the required dose responses (e.g. declines in FEV_1 and FVC per unit of exposure) are available. For this reason, a more comprehensive evaluation of the impact of smoking interventions has not been presented in this paper. As longitudinal studies for investigating occupationally-related COPD are difficult due to the lengthy follow-up time required and the potentially large number of drop-outs, the extended model for occupational exposures will provide a valuable tool for health impact assessment. The extension and application of the model to occupational exposures are currently under development will be presented in a subsequent paper.

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The Health Survey for England is a series of annual surveys that were designed to measure health and health related behaviours. The 2001 survey focused on respiratory health and atopic conditions, disability and non-fatal accidents. Data from the Health Survey for England are available through the UK Data Service.

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Appendix

Characterising lung function variability.

The COPD disease model simulates every individual's lung function from the age of 20 years. For this step, the mean FEV_1 and FVC at age 20 are determined using a user-specified spirometric reference equation. As most reference equations include height as a covariate, the mean FEV_1 and FVC are likely to vary with height of the individual. Then, for each individual, the means are scaled by a lognormally distributed random effect. For individual i, this corresponds to FEV_1 and FVC at age 20 of:

$$FEV_i = e^{\mu_{FEV} a_{i11} \upsilon_1}$$

$$FVC_i = e^{\mu_{FVC} a_{i12} \upsilon_2}$$

where μ_{FEV} and μ_{FVC} are the means of the underlying normal distribution of initial FEV_1 and FVC respectively, a_{i11} and a_{i12} are normally distributed random effects with mean 0 and variance 1 and ν_1 and ν_2 are the standard deviations of the underlying normal distribution for FEV_1 and FVC at age 20 respectively. In each year of the simulation, lognormally distributed annual declines related to age, smoking and asthma are applied to the previous year's lung function, i.e. lung function in year t is calculated by subtracting each of the decline components from lung function at $t-1$. Each individual is assigned a standardised random effect at entry into the population, which is then scaled according to the variance components for each of the age, smoking and asthma-related declines. Let $a_{i,21}$ and $a_{i,22}$ represent random effects from a standard normal distribution for worker i, for FEV_1 and FVC respectively, and let the subscripts *age*, *sm* and *asthma* refer to age, smoking and asthma. The annual FEV_1 and FVC declines are denoted by ΔFEV_i and ΔFVC_i respectively and can be expressed as the sum of three components:

$$\Delta FEV_i = \Delta FEV_{i,age} + \Delta FEV_{i,sm} + \Delta FEV_{i,asthma}$$

$$\Delta FEV_{i,age} = e^{\mu_{age,1} + a_{i,21}\sigma_{age,1}}$$

$$\Delta FEV_{i,sm} = e^{\mu_{sm,1} + a_{i,21}\sigma_{sm,1}}$$

$$\Delta FEV_{i,asthma} = e^{\mu_{asthma,1} + a_{i,21}\sigma_{asthma,1}}$$

$$\Delta FVC_i = \Delta FCV_{i,age} + \Delta FVC_{i,sm} + \Delta FVC_{i,asthma}$$

$$\Delta FVC_{i,age} = e^{\mu_{age,2} + a_{i,22}\sigma_{age,2}}$$

$$\Delta FVC_{i,sm} = e^{\mu_{sm,2} + a_{i,22}\sigma_{sm,2}}$$

$$\Delta FVC_{i,asthma} = e^{\mu_{asthma,2} + a_{i,22}\sigma_{asthma,2}}$$

where $\mu_{age,1}$ and $\sigma_{age,1}$ are the mean and standard deviation of the underlying normal distribution for the age-related FEV_1 decline respectively, $\mu_{sm,2}$ and $\sigma_{sm,2}$ are the mean and standard deviation of the underlying normal distribution for the smoking-related FVC decline etc.

It is more convenient to specify the variability in lung function in terms of mean and coefficient of variation (CV) for initial lung function and for the subsequent annual decline (rather than the mean and standard deviation of the underlying normal distribution), which is why the model has been developed to accept a user-specified mean and CV of the lognormal distribution, which we represent by *mean*

and *CV* respectively. The mean μ and standard deviation σ of the underlying normal distribution can easily be derived as follows:

$$CV = \sqrt{e^{\sigma^2} - 1}$$

$$CV^2 + 1 = e^{\sigma^2}$$

Therefore

$$\sigma = \sqrt{\log(CV^2 + 1)},$$

and

$$mean = e^{\mu + \frac{1}{2}\sigma^2}$$

therefore

$$\mu = \log(mean) - \frac{1}{2}\sigma^2.$$

After simulation year t, the updated FEV_1 for the ith individual is:

$$FEV_{i,t} = FEV_{i,t-1} + \Delta FEV_{i,t}$$

The assumption is made that the random effects for initial FEV_1, initial FVC, FEV_1 decline and FVC decline are correlated, and follow a multivariate normal distribution as follows:

$$a_i = \begin{pmatrix} a_{i1} \\ a_{i2} \\ a_{i1} \\ a_{i2} \end{pmatrix} \sim N(\mu, \Sigma)$$

$$\mu = \begin{pmatrix} \mu_{i1} \\ \mu_{i2} \\ \mu_{i1} \\ \mu_{i2} \end{pmatrix}$$

$$\Sigma = \begin{pmatrix} \sigma_{11}^2 & \rho_{12}\sigma_{11}\sigma_{21} & \rho_{13}\sigma_{11}\sigma_{12} & \rho_{14}\sigma_{11}\sigma_{22} \\ \rho_{12}\sigma_{11}\sigma_{21} & \sigma_{21}^2 & \rho_{23}\sigma_{21}\sigma_{12} & \rho_{24}\sigma_{21}\sigma_{22} \\ \rho_{13}\sigma_{11}\sigma_{12} & \rho_{23}\sigma_{21}\sigma_{12} & \sigma_{12}^2 & \rho_{34}\sigma_{12}\sigma_{22} \\ \rho_{14}\sigma_{11}\sigma_{22} & \rho_{24}\sigma_{21}\sigma_{22} & \rho_{34}\sigma_{12}\sigma_{22} & \sigma_{22}^2 \end{pmatrix}$$

This representation allows for correlation in the random effects through the parameters ρ_{12}, ρ_{13}… The correlation coefficients are model inputs, taking baseline values of $\rho_{12} = 0.88$, $\rho_{34} = 0.9$, $\rho_{13} = \rho_{14} = \rho_{24} = 0.4$ (see Table 1).

The change in lung function with age, the variability between individuals and between smokers and non-smokers can be seen in Video 1 (in the online supplementary material). The animation begins in year 1961 with an initial cohort of 20 year olds, and ends in year 2020 with the same individuals, who by that time are 79 years of age. The blue dots indicate permanent non-smokers (i.e. those who remain non-smokers between 1961 and 2020); the red dots indicate smokers. The model attempts to simulate variability between individuals thus some individuals do not develop COPD within the simulation timeframe, and the most susceptible individuals progress quickly to GOLD IV.

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.rmed.2015.09.011.

Sensitivity analysis

Sensitivity analyses can be carried out using a variety of different approaches. In recent years, the use of Gaussian process emulators [45] has gained popularity; an emulator is a statistical representation of a more complex model and can be used as a surrogate, in situations where running many instances of the model would be computationally expensive. In the case of the COPD simulation model, replacing the computationally expensive simulator with the more efficient Gaussian process emulator enables a global sensitivity analysis to be carried out at significantly less computational expense. In this paper, a variance-based sensitivity analysis is carried out, whereby the total variance in the output is apportioned to the sources of variation in the model inputs, thus enabling identification of the most influential model parameters.

Tables A1 and A2 present the parameter inputs that were considered in the first and second stages of the sensitivity analysis, along with their limits, and the total effect variance contribution associated with each parameter. Figures A1 and A2 show the expected value of COPD prevalence in non-smokers and smokers respectively at ages 35, 45, 55 and 65, when each input parameter was varied between its limits and averaged over all the other input parameters.

Table A1
Model parameters and their contribution to the variance of COPD prevalence in male non-smokers at ages 35, 45 55 and 65.

Parameter	Range		Total effect variance contribution to COPD prevalence at age … (%)			
	Min	Max	35	45	55	65
Proportion asthmatic	0.119	0.179	0.49	1.24	1.24	1.16
Additive asthma adjustment to baseline FEV_1	−0.486	0	7.43	6.64	4.32	1.64
Addition asthma adjustment to baseline FVC	−0.405	0	3.87	2.90	2.08	1.16
Additive asthma adjustment to FEV_1 decline	0.00078	0.0224	3.44	5.69	8.16	3.70
Additive asthma adjustment to FVC decline	0	0.0204	8.26	19.21	24.44	17.35
Coefficient of variation for baseline FEV_1	0.08	0.18	31.25	29.44	13.87	2.98
Coefficient of variation for baseline FVC	0.08	0.18	22.85	18.50	8.72	2.45
Coefficient of variation for age-related FEV_1 decline	0.01	0.8	1.08	2.54	17.90	47.46
Coefficient of variation for age-related FVC decline	0.01	0.8	0.21	5.28	19.06	26.30
Correlation coefficient: baseline FEV_1, FEV_1 decline	0	0.4	0.35	0.00	0.29	0.24
Correlation coefficient: baseline FEV_1, baseline FVC	0.7	0.95	40.70	29.14	12.30	2.78
Correlation coefficient: FEV_1 decline, FVC decline	0.4	1	0.26	1.17	1.95	3.29
GOLD II risk ratio, GOLD I	1.26	1.77	0.16	0.10	0.00	1.28
GOLD III risk ratio, GOLD II	1.69	3.46	0.09	0.14	1.04	0.00
GOLD IV risk ratio, GOLD III	1.93	6.61	2.97	0.49	0.08	0.88
FEV_1 decline (expressed as proportion of baseline)	0.90	1.10	4.63	6.98	8.97	5.91

Table A2
Model parameters and their contribution to the variance of COPD prevalence in male smokers at ages 35, 45, 55, 65 and 75.

Parameter	Range		Total effect variance contribution to COPD prevalence at age … years (%)			
	Min	Max	35	45	55	65
Proportion asthmatic	0.119	0.179	1.05	0.02	0.17	0.35
Additive asthma adjustment to baseline FEV_1 (litre)	−0.486	0	5.08	3.34	1.62	1.29
Addition asthma adjustment to baseline FVC (litre)	−0.405	0	3.19	1.54	1.89	0.56
Additive asthma adjustment to FEV_1 decline (litre)	0.00078	0.0224	1.55	2.01	2.89	1.08
Additive asthma adjustment to FVC decline (litre)	0	0.0204	4.17	5.50	5.57	6.20
Coefficient of variation for baseline FEV_1	0.08	0.18	22.19	11.09	4.55	1.94
Coefficient of variation for baseline FVC	0.08	0.18	18.01	8.83	3.90	1.46
Coefficient of variation for age-related FEV_1 decline	0.01	0.8	0.87	0.44	5.60	16.64
Coefficient of variation for age-related FVC decline	0.01	0.8	0.62	1.36	4.62	7.63
Coefficient of variation for smoking-related FEV_1 decline	0.5	1.5	1.15	0.91	3.00	5.42
Coefficient of variation for smoking-related FVC decline	0.5	1.5	0.12	0.44	0.85	1.24
Correlation coefficient: baseline FEV_1, FEV_1 decline	0	0.7	0.59	0.09	0.00	0.00
Correlation coefficient: baseline FEV_1, baseline FVC	0.832	0.935	28.10	10.82	3.97	1.68
Correlation coefficient: FEV_1 decline, FVC decline	0.7	1	1.02	0.95	0.48	0.56
GOLD II risk ratio	1.26	1.77	0.07	0.41	0.39	0.16
GOLD III risk ratio	1.69	3.46	0.00	0.00	0.00	0.13
GOLD IV risk ratio	1.93	6.61	0.09	0.28	0.45	0.41
FEV_1 decline (expressed as proportion of baseline)	0.90	1.10	0.51	1.33	2.06	1.90
FEV decline in heavy smoker (litre)	0.007	0.018	23.87	46.85	50.65	40.65
FVC decline in heavy smoker (litre)	0.004	0.015	8.44	17.77	21.47	22.53
Risk ratio, ex-smoker	1.15	1.50	0.02	0.34	0.00	0.00
Risk ratio, light smoker	1.57	2.04	0.64	0.70	0.15	0.23
Risk ratio, heavy smoker	2.29	2.97	0.91	0.50	0.03	0.52

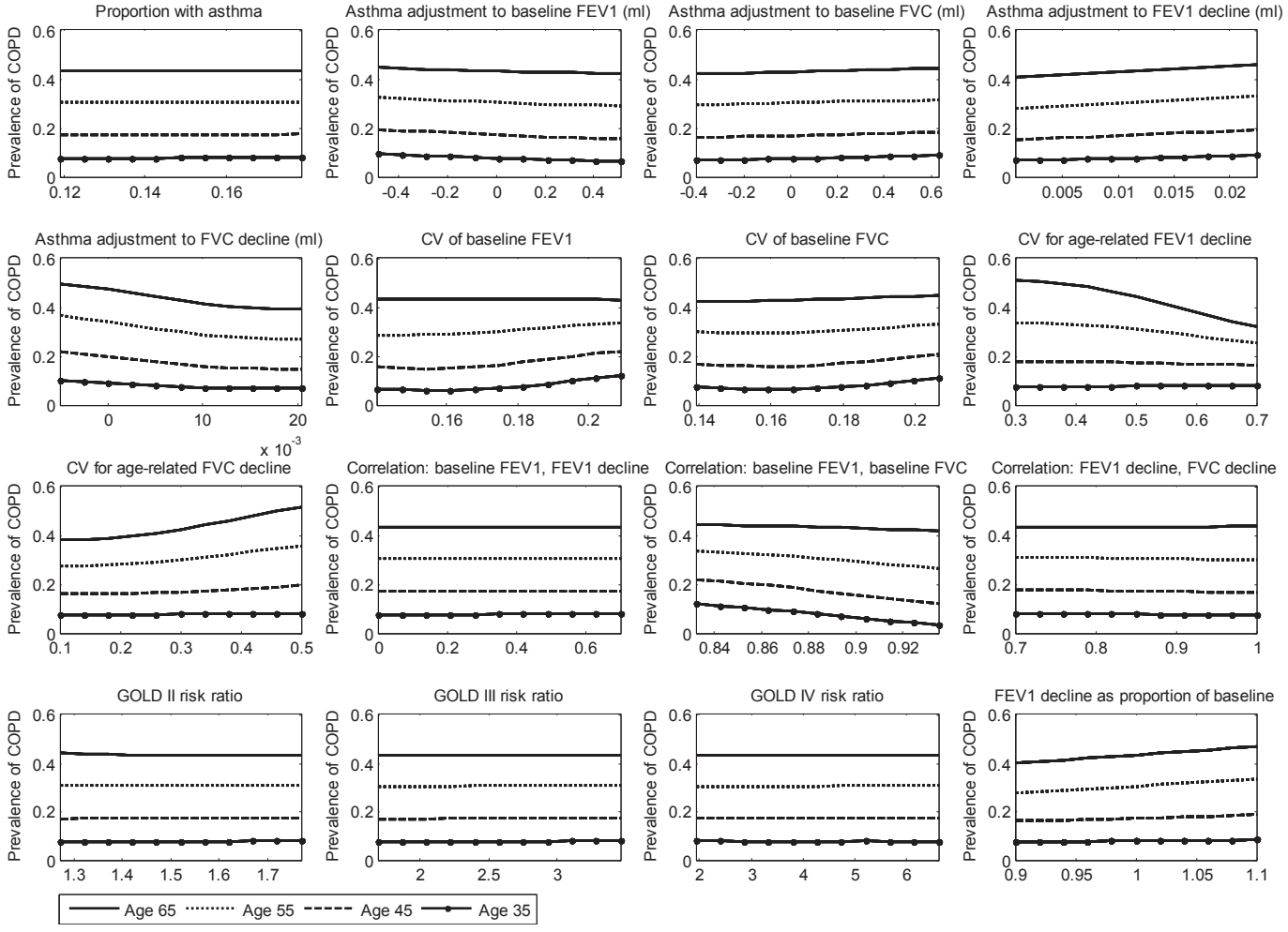

Fig. A1. Sensitivity of the prevalence of COPD in non-smokers aged 35, 45, 55 and 65 years to model parameters.

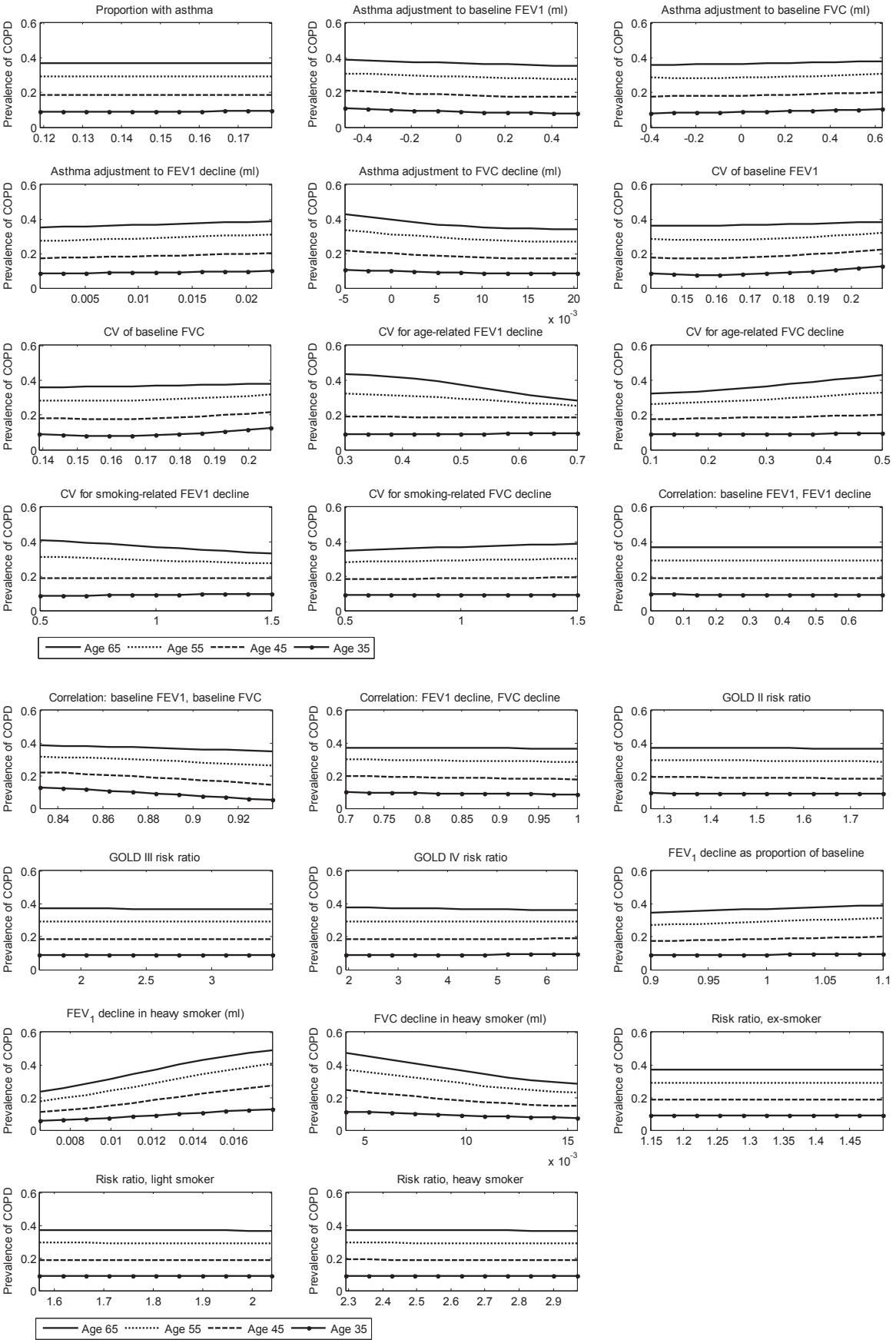

Fig. A2. Sensitivity of the prevalence of COPD in smokers aged 35, 45, 55 and 65 years to model parameters.

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