Models for estimating projections for the prevalence and disease burden of chronic obstructive pulmonary disease (COPD): systematic review protocol

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Introduction

Policymakers and governments must decide their healthcare priorities on the basis of the best healthcare intelligence available to them. Recent interest has increasingly focused on the global implications of an increasing and elderly population with long-term conditions.¹ The most recent figures from the Global Burden of Disease Study 2010 show that the third top global cause of death was chronic obstructive pulmonary disease (COPD),⁴ rising from fourth place in 1990.⁵ It is predominantly caused by cigarette smoking and leads to lung airflow limitation, cough, excessive sputum production, and breathlessness. People with COPD can suffer from substantial disability as the condition progresses.⁶ A pressing challenge for governments is how best to project the future trend in the prevalence and burden of COPD in order to plan adequate health and social care for those affected by this condition within the scope of limited resources. Governments should ideally be planning for COPD on two levels: (1) they should consider how to manage resources to care and treat people who are already affected by COPD; and (2) how to prevent a greater increase in the burden from COPD by minimising the continuing smoking epidemic.

In order to make such calculations, governments and other healthcare providers need to draw on epidemiological models. Merriam-Webster’s dictionary defines a ‘model’ as ‘a system of postulates, data, and inferences presented as a mathematical description of an entity or state of affairs’. This is a useful starting point when considering the role of models in epidemiology. Most models are explanatory in nature and describe the relationships between different parameters. The focus of this study is on models which help to project future epidemiological trends and patterns in populations with COPD. Governments and policymakers have access to many models, but a review is required to appraise the published COPD models to aid selection between them.

Various features of COPD present a particular challenge to mathematical and epidemiological modelling, including the many different definitions of a COPD diagnosis and its overlap with a diagnosis of asthma. Although COPD is most clearly attributable to cigarette smoking, there is debate over how best to classify non-smokers who develop COPD with the immunological and pathological features of COPD as a result of exposure to occupational dusts and gases or recurrent chest infections. In addition, there is uncertainty as to the correct classification of older non-smoking adults who have evidence of lung cell remodelling including squamous metaplasia following chronic inflammation due to long-term asthma. Such older adults have often lost the reversibility in their airways obstruction and demonstrate spirometry which is consistent with the thresholds for COPD.⁷,⁸

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the diagnosis of COPD is characterised by an obstructive lung defect with forced expiratory volume in one second to forced vital capacity (FEV1/FVC) ratio <0.7.¹⁰ Controversy regarding this threshold also complicates decisions of precisely which population to include in modelling. Lung function decreases with age, so a proportion of elderly people (age 75+) who have never smoked still fit these criteria for COPD. Some doctors reasonably argue that such elderly people really have normal lung function for their age and that medicalisation of the elderly should be avoided.¹¹ An alternative threshold of the lower limit of normal for FEV1/FVC has been proposed with a decreasing threshold according...
to age by percentile. The bottom 5% of FEV1/FVC measurements for whichever total population being measured would be considered abnormal in the older age group. However, no up-to-date large standardised population database currently exists to validate such a measure. The nearest is the use of the European Coal and Steel Workers Population to provide percent predicted FEV1 values; however, this population was standardised over 20 years ago and is based on a working white European population without ethnic minorities. Similarly, younger people (age 30–40 years) with larger FVC values and greater respiratory reserve may already have sustained COPD-type damage to their lungs before they reach the <0.7 ratio threshold, so at this end of the age range there is a risk of under-diagnosis of COPD.

The debate regarding the diagnosis of COPD is more than just a debate over spirometry thresholds. As many developing countries do not have access to spirometry or even to a reliable power supply, the usefulness of such diagnostic thresholds is limited. It has been proposed that COPD may also be diagnosed on history and clinical features. However, studies have shown that using clinical indicators of pulmonary function to diagnose COPD missed many participants who had low lung function and airways obstruction, especially in current smokers. Therefore, in many countries the current situation has evolved where COPD is diagnosed from physician opinion without corroborating evidence from spirometry, resulting in a significant overlap between a diagnosis of COPD and a diagnosis of asthma.

It seems likely that classifications in the future will evolve as the role of host susceptibility is increasingly understood in terms of genetic and epigenetic features. Several candidate genes related to COPD have been identified. In addition, the science of epigenetics helps to explain how DNA transcription has been activated or suppressed by DNA methylation, acetylation, or other mechanisms in response to predominantly prenatal and early life environmental influences. The result of such switching on or off of DNA transcription is to determine the host’s response to noxious stimuli including cigarette smoke. Increased understanding of these factors is helping to unravel the mysteries of why some life-long smokers are virtually unaffected by their habit while others have severe COPD. Estimates as to the prevalence of COPD among smokers aged >45 years vary from 15% to 50% according to the criteria used for diagnosis.

Modelling COPD is also challenged by the key feature of exacerbations. An exacerbation may be triggered by increased bacterial or viral load in the lungs which induce an aggressive immune response and associated clinical features. Associated with a greater frequency of exacerbations is higher morbidity, due to faster disease progression in terms of loss of lung function, and also mortality.

An additional challenge is the level of mathematical sophistication within each model. Ideally, a researcher with considerable statistical skill would be available to check the algorithms that drive each model and so provide a full appraisal of the quality of each model. In the absence of this ideal, it was decided to appraise the quality of reporting of each model as a proxy for the model’s mathematical quality. Taking these challenges into account, it will be necessary to describe a degree of context with each model in order that it can be applied in an appropriate setting. This will help subsequent researchers to understand the necessary caveats to include when describing the results from each model.

**Objectives**

To identify all available models for estimating projections of COPD prevalence and burden, and to assess the quality of reporting of each model in its key publication.

**Methods**

A search strategy has been developed using search terms to cover the three concepts of ‘modelling’, ‘disease burden’, and ‘chronic obstructive pulmonary disease’ (see Appendix 1 for full details). Searches will be conducted in the following electronic databases: MEDLINE, EMBASE, CAB Abstracts, World Health Organization (WHO) Library and Information Services (WHOILS – library catalogue of books and reports), WHO Regional Indexes (AIM (AFRO), LILACS (AMRO/Paho), IMEMR (EMRO), IMSEAR (SEARO), WPRIM (WPRO)), and a modified search strategy will be used to identify reports from the WHO home website and Google. Searches will be for both published and unpublished modelling studies from 1980 (when modelling methods first began to be widely used) to 2013. Two authors will independently review the studies against the inclusion criteria and make a decision as to whether the study is suitable. Disagreements will be resolved by discussion and, if this is not possible, a third reviewer will arbitrate.

**Inclusion criteria**

Any modelling study which uses demographic and epidemiological data to project the prevalence and disease burden will be included. The included projected outcomes which are of interest are one or more of: incidence, prevalence and mortality, and disease burden. With regard to ‘disease burden’, the outcomes of interest can be considered from the individual’s point of view, from the point of view of the healthcare system, and from the point of view of broader society. For the purposes of this review, the focus is on the perspective of the healthcare system. Other perspectives are valid; however, different instruments are used to measure them and the purpose of this study is to guide policymakers who will focus on the healthcare system perspective. Quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs) are often used to measure and quantify the burden to the individual of the morbidity they are suffering. Treatments are assigned a cost per restored QALY, and this is an important measure used in cost-effectiveness studies. However, the scope of this study is more limited in order to avoid confusion of perspectives. Some of the studies included may discuss QALYs and DALYs, but they have not been chosen as primary disease burden outcomes for this review. Instead, we will concentrate on primary care visits, emergency department visits, hospital admissions, and COPD treatment costs.

**Exclusion criteria**

There will be no exclusions on the basis of language of the report. Studies which are population-based surveys of prevalence without...
modelling will be excluded as there has recently been a systematic review of such studies. 

'Models' will be excluded if they describe animals, cell lines, clinical series, or estimates of individual risk (such as individual prognostic models). Decision analytical models or decision support models will be excluded where they refer to clinical decision-making for individuals rather than populations. Models that compare one intervention with another intervention will also be excluded, as the aim is accurately to project the baseline outcomes so it is premature to take into account the effect of interventions. Also excluded will be regression models which start with a COPD population and 'back-calculate' the prevalence or burden using regression to quantify risk factors, as this follows a different logic from that of projection modelling.

Participants

The source population for the model may be from anywhere in the world. The model will pertain to adult populations aged >40 years as it is usually not appropriate to diagnose COPD in younger people. COPD may be diagnosed by physician, spirometry, or by questionnaire. Other assumptions regarding the diagnosis of COPD will be evaluated in the context of the model.

Data extraction

The data will be extracted by one author and checked by a second. Data will be extracted using a pre-piloted data extraction form. The following identification details will be extracted for each model: author and email address, year, institution, and funding source. These data will be followed by: the purpose of the model, model title, model type, model setting, time period, and population (age, sex and country). Also extracted will be: inputs to the model, source of input data, details of processing of the model, outcomes for COPD (incidence, prevalence, mortality, GP visits, emergency department visits, hospitalisations, treatment costs), model output/results, details of the model's availability, any comparisons with other studies, social and economic policy implications of model outcomes, and future research recommendations. In this way, the data extraction form aims to encompass a comprehensive picture of the model.

Quality appraisal framework

Ideally, a quality appraisal of the actual modelling process would be undertaken. However, this requires significant statistical technical expertise. A pragmatic decision has therefore been made to quality appraise the reporting of the models rather than the actual modelling process for those that have full published reports. In order to do this, a quality of reporting framework has been designed following review of key guidelines as to good practice in modelling. 

A scoring mechanism was devised in collaboration with Simon Capewell of Liverpool University to weight the importance of the different elements required to produce a relevant high-quality model (see Appendix 2).

Strategy for data synthesis

The study will be the unit of analysis. Models will be described and classified. A detailed critical narrative synthesis of the highest scoring models will be undertaken. Where the models are not available, we will write to the model authors for further clarification. No subgroup analysis is planned.

Handling editor David Bellamy

Conflicts of interest The authors declare that they have no conflicts of interest in relation to this protocol. AS is Joint Editor-in-Chief of the PCRJ, but was not involved in the editorial review of, nor the decision to publish, this protocol.

Contributorship SM drafted the article with oversight from CS SW and AS. AS and SM conceived the project as part of SM's PhD.

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Protocol registration A shortened version of this protocol has been registered online in the PROSPERO University of York database: Systematic review of models for estimation and future projection of the prevalence and the disease burden of chronic obstructive pulmonary disease (COPD), PROSPERO 2012:CRD42012002623, available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002623

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Appendix 1: Search Strategy

**Medline copd and burden model** - 1946 to week 4 March 2012

animals/
2 humans/
3 1 not (1 and 2)
4 2 not 3
5 lung diseases, obstructive/
6 exp pulmonary disease, chronic obstructive/
7 emphysem*.mp.
8 (chronic* adj3 bronchiti*).mp.
9 (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).mp.
10 COPD.mp.
11 COAD.mp.
12 COBD.mp.
13 AECB.mp.
( exacerbation* adj3 bronchiti*).mp. [mp=title, abstract, original title, name of substance
14 word, subject heading word, protocol supplementary concept, rare disease supplementary
concept, unique identifier]
15 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 4 and 15
17 prevalence/
18 Incidence/
19 "cost of illness"/ or forecasting/ or "quality of life"/
20 "burden of illness".mp.
21 quality-adjusted life years/ or models, statistical/ or monte carlo method/
22 Health Care Rationing/ or "disability adjusted life years".mp.
23 "Cause of Death"/
24 Hospitalization/
25 house calls/ or office visits/ or "referral and consultation"/
Appendix 1: Search Strategy

26 16 and (17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25)

27 (model.mp. or modelling.mp.)

28 26 and 27

**Embase copd and burden model**

1. exp ANIMAL/
2. Nonhuman/
3. Human/
4. 1 or 2
5. 3 not 4
6. Chronic obstructive lung disease/
7. Obstructive airway disease/
8. chronic bronchitis/
9. lung emphysema/
10. (Chronic$ adj3 bronchiti$).mp.
11. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
12. COPD.mp.
13. COAD.mp.
14. COBD.mp.
15. AECB.mp.
16. (Acute exacerbation adj3 chronic bronchitis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
17. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 5 and 17
19. prevalence/
20. incidence/
21. "cost of illness"/ or "health care cost"/
22. mortality/
23. "burden of disease".mp.
24. quality adjusted life year/ or "quality of life"/
25. "disability adjusted life year".mp.
26. morbidity/
27. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 18 and 27
29 (model.mp. or modelling.mp.)
30 28 and 29

**CAB abstracts**

**COPD and burden model**
Models for estimating projections for the prevalence and disease burden of COPD

Appendix 1: Search Strategy

1. Animal.mp. [mp=abstract, title, original title, broad terms, heading words]
2. animal.mp.
3. human diseases.sh.
4. 3 not 2
5. chronic obstructive pulmonary disease.sh.
6. (chronic adj3 bronchit$).mp. [mp=abstract, title, original title, broad terms, heading words]
7. pulmonary emphysema/
8. chronic obstructive lung disease.mp.
9. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
10. COPD.mp.
11. COAD.mp.
12. COBD.mp.
13. AECD.mp.
14. (exacerbat$ adj3 bronchi$).mp. [mp=abstract, title, original title, broad terms, heading words]
15. bronchitis.sh.
16. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 3 and 16
18. prevalent.mp. or disease prevalence.sh.
19. incidence.sh.
20. "burden of disease".mp.
21. economic impact.sh.
22. "causes of death"/
23. morbidity/
24. health services/
25. "house call".mp.
26. health care costs/
27. "cost benefit analysis"/
28. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 17 and 28
30. (model.mp. or modelling.mp.)
31. 29 and 30
Appendix 1: Search Strategy

WHOLIS (World Health Organization Library Information Services)

"chronic obstructive pulmonary disease" and prevalence - 0 results

("chronic obstructive pulmonary disease" or bronchitis or emphysema) and prevalence – 0

("chronic obstructive pulmonary disease" or bronchitis or emphysema) and (prevalence or incidence or mortality or morbidity)

Global Health Library Regional Indexes

("chronic obstructive pulmonary disease" or bronchitis or emphysema) and (prevalence or incidence or mortality or morbidity)

AIM (AFRO),

LILACS (AMRO/PAHO),

IMEMR (EMRO),

IMSEAR (SEARO),

WPRIM (WPRO)
### Appendix 2: Data extraction and quality of reporting

| Reference | |
|-----------|---|
| Author and email address | |
| Year | |
| Institution | |
| Funding source | |
| Purpose of model | |
| Model Title | |
| Model Type | |
| Model setting, time period and population (age, sex and country) | |
| Inputs to model | |
| Details of model’s processing (including algorithm) | |
| Model output/results | |
| Model availability | |
| Comparisons with other studies | |
| Social and economic policy implications of model outcomes | |
| Future research recommendations | |
| Any other comments | |

### Risk Factors Included - not a risk factor study

| Risk Factor | Tick if included | Form (Con/Cat) | Describe intervention |
|-------------|------------------|----------------|-----------------------|
| Smoking     |                  |                |                       |
| Indoor air pollution |                |                |                       |
| Outdoor air pollution |              |                |                       |
| Socioeconomic deprivation |           |                |                       |
| Nutrition   |                  |                |                       |
| Other       |                  |                |                       |
| Pulmonary rehabilitation |            |                |                       |
| Smoking cessation |                |                |                       |
| Bronchodilator |                  |                |                       |
| Corticosteroid  |                 |                |                       |
| Other treatment |                 |                |                       |
Appendix 2: Data extraction and quality of reporting

| Disease categories included – please tick | NICE 2004 | ATS/ERS 2004 | GOLD 2010* | NICE update 201110 | Please Tick Category |
|------------------------------------------|----------|--------------|------------|-------------------|---------------------|
| Post-bronchodilator FEV1/FVC             | FEV1 % predicted | Severity of airflow obstruction |            |                   |                     |
| < 0.7                                    | ≥ 80%    | Mild         | Stage 1 – Mild | Stage 1 – Mild*  |                     |
|                                          | 50-79%   | Mild         | Moderate     | Stage 2 – Moderate |                     |
|                                          | 30-49%   | Moderate     | Severe       | Stage 3 – Severe  |                     |
|                                          | < 30%    | Severe       | Very Severe  | Stage 4 – Very Severe** |                     |

* symptoms should be present to diagnose COPD in people with NICE 2011 mild airflow obstruction.

** or FEV1<50% with respiratory failure
## Appendix 2: Data extraction and quality of reporting

### Outcomes studied

| What is the prevalence of COPD per region? | Prevalence rate |
|------------------------------------------|-----------------|
| What is the incidence of COPD per region? | New cases per thousand person years |
| What is the COPD disease-specific mortality? | COPD-related mortality |
| What is the COPD disease-specific burden to the individual? | Disability/quality adjusted life years lived with mild/moderate/severe COPD, Monetary cost of COPD healthcare to the individual |
| What is the COPD disease-specific burden to the healthcare system? | Average annual GP visits, Average annual emergency dept visits, Average annual hospital admissions per patient for COPD exacerbations, Average annual readmissions per patient (measure of effectiveness of treatment) |
| What is the COPD-specific burden to society | Cost of healthcare, cumulative loss of earnings by patients, cumulative loss of time at work/study, carers burden |

**Other**

| What is the “main outcome” of the study in the author’s words | |
|---------------------------------------------------------------|---|
## Appendix 2: Data extraction and quality of reporting

### QUALITY OF REPORTING ASSESSMENT

**Model purpose and aim**

| Statement of the question which the model is trying to answer |
|---------------------------------------------------------------|
| Perspective of model                                          |
| Time horizon of model                                         |
| Model type                                                    |

**Transparency**

| Transparency             | Not available | Available |
|--------------------------|---------------|-----------|
| Illustrations/examples   |               |           |
| Assumptions              |               |           |
| Model availability for reader |         |           |

**Data input: - not much detail given**

| Type of data        | Source  | Comment on quality (sample size and response rate for surveys etc.) | Limitations |
|---------------------|---------|---------------------------------------------------------------------|-------------|
| Population data     |         |                                                                    |             |
| Mortality data/rate |         |                                                                    |             |
| Morbidity data/rate |         |                                                                    |             |
| Treatment uptake    |         |                                                                    |             |
| Risk factor prevalence/trends | |                                                                    |             |
| Treatment effectiveness | |                                                                  |             |
| Risk factor change effectiveness/Betas | |                                                                  |             |
| Costs               |         |                                                                    |             |
| Health utilities    |         |                                                                    |             |

**Data modelling**

| Discussion of model’s derivation |       |
|----------------------------------|-------|
| Assumptions documented and justified |     |
| Model consistent with accepted techniques of statistics and epidemiology |   |
Appendix 2: Data extraction and quality of reporting

Data Incorporation:

| Methodology | Deterministic methodology | Probabilistic methodology |
|-------------|----------------------------|---------------------------|

Sensitivity analysis:

| Analysis | Were sensitivity analysis carried out (Y/N) | Were 95% CI for RRS used for sensitivity analyses | Which analyses | Was the discussion of sensitivity analyses |
|----------|---------------------------------------------|------------------------------------------------|-----------------|------------------------------------------|
|          |                                              |                                                |                 | Poor | Reasonable | Good |
|          |                                              |                                                |                 | Please tick |                          |      |

Internal validation:

| Validation | Was there evidence that the model had undergone debugging | Was there evidence that the model had been calibrated | How was the model calibrated? (describe) |
|------------|-----------------------------------------------------------|--------------------------------------------------------|----------------------------------------|

Was the predictive validity of the model tested? (Y/N)....

| Validation | How was the predictive validity of the model checked? (Describe) |
|------------|------------------------------------------------------------------|
|            |                                                                 |
|            | How was the validity quantified? e.g. % explained                |
|            |                                                                 |

Potential Limitations:

| Limitations         | Not Reported | Reported | Discussed | Method refined |
|---------------------|--------------|----------|-----------|----------------|
| Assumptions         |              |          |           |                |
| Confounding         |              |          |           |                |
| Lag times           |              |          |           |                |
| Competing causes    |              |          |           |                |

Involvement of policy makers, planners and decision makers in model:

| Involvement | Who was involved? | How and at what stage were they involved? | Will policy makers, planners and decision makers have an opportunity to respond to the results of the study? |
|------------|--------------------|------------------------------------------|------------------------------------------------------------------------------------------------|

Other comments on the study:

| Comments |
|----------|
Appendix 2: Data extraction and quality of reporting

**Overall summary**

| Category                              | Score |
|---------------------------------------|-------|
| Purpose and aim                       | 4     |
| Transparency                          | 3     |
| Data                                  | 1     |
| Data modelling                        | 3     |
| Sensitivity analysis                  | 2     |
| Internal validity                     | 1     |
| Calibration                           | 1     |
| Involvement of policymakers           | 1     |
| Predictive validity                   | 3     |
| Discussion of limitations             | 1     |
| Overall mark                          | 20    |