

Global burden of COPD: risk factors, prevalence, and future trends

David M Mannino, A Sonia Buist

Chronic obstructive pulmonary disease (COPD) continues to be an important cause of morbidity, mortality, and health-care costs worldwide. It is a global health issue, with cigarette smoking being an important risk factor universally; other factors, such as exposure to indoor and outdoor air pollution, occupational hazards, and infections, are also important. As the global population ages, the burden of COPD will increase in years to come. Prevalence estimates of the disorder show considerable variability across populations, suggesting that risk factors can affect populations differently. Other advances in our understanding of COPD are increased recognition of the importance of comorbid disease, identification of different COPD phenotypes, and understanding how factors other than lung function affect outcome in our patients. The challenge we will all face in the next few years will be implementation of cost-effective prevention and management strategies to stem the tide of this disease and its cost.

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in countries of high, middle, and low income. Estimates from WHO's Global Burden of Disease and Risk Factors project¹ show that in 2001, COPD was the fifth leading cause of death in high-income countries, accounting for 3·8% of total deaths, and it was the sixth leading cause of death in nations of low and middle income, accounting for 4·9% of total deaths. In this same report, COPD was also estimated to be the seventh and tenth leading cause of disability-adjusted life years in countries of high income and in those of low or middle income, respectively.¹ COPD has been the focus of recent Reviews in *The Lancet*, including one from 2003 by Calverley and Walker² and another published in 2004 by Pauwels and Rabe.³ Our Review will focus on advances in understanding of COPD and its risk factors, prevalence, and natural history since these Reviews were published, address some of the questions that still persist, and raise some of the issues that health-care planners will have to consider as the burden of COPD increases as the world's population ages.

Definition

The working definition of COPD, as noted in the 2006 update of the Global Initiative for Obstructive Lung

Disease (GOLD) guidelines, is that COPD is “a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.”⁴ Some of the key components of this definition, which are similar to those in the definition adopted by the American Thoracic Society and European Respiratory Society,⁵ are described below.

First, COPD is a preventable disease. Primary, secondary, and tertiary prevention strategies exist for COPD. These

Lancet 2007; 370: 765–73

See *Perspectives* page 733

Department of Preventive Medicine and Environmental Health, University of Kentucky College of Public Health, Lexington, KY, USA (D M Mannino MD); and Department of Medicine, Pulmonary and Critical Care Medicine, Oregon Health and Science University, Portland, OR, USA (A S Buist MD)

Correspondence to: Dr David M Mannino, Department of Preventive Medicine and Environmental Health, University of Kentucky College of Public Health, 121 Washington Avenue, Suite 220, Lexington, KY 40536, USA

dmannino@uky.edu

Search strategy and selection criteria

The material covered in this Review is based on an extensive literature search and participation in expert meetings during the writing and updating of guidelines for the treatment of chronic obstructive pulmonary disease, along with many years of research in the area. We did a systematic Medline search for articles in English or with English abstracts with the keywords: “COPD” or “emphysema” or “chronic bronchitis” AND “prevalence” or “burden” or “risk factors” or “cost” or “morbidity” or “mortality”; up to April, 2007. We were especially interested in reports published within the past 6 years.

	Suggestive features
COPD	Onset in midlife Slowly progressive symptoms Tobacco smoking history
Asthma	Onset early in childhood Variable symptoms History of allergy
Congestive heart failure	Basilar crackles on auscultation Dilated heart on chest radiograph Restriction on spirometry
Bronchiectasis	Large volumes of purulent sputum Radiograph shows bronchial dilatation or wall thickening
Tuberculosis	Classic radiographic findings High local prevalence Microbiological confirmation
Obliterative bronchiolitis	Onset in young age and non-smokers History of fume exposure or rheumatoid arthritis CT scan shows hypodense areas on expiration
Diffuse panbronchiolitis	Patients typically male non-smokers History of chronic sinusitis CT scan shows diffuse centrilobular nodular opacities and hyperinflation

The features noted here tend to be characteristic of the respective diseases but do not occur in every case. Furthermore, there could be overlap between two or more categories, and diseases might coexist. Table modified from the GOLD guidelines,⁴ with permission.

Table 1: Differential diagnosis of COPD

range from increasing smoking cessation and adequate treatment of asthma (primary)^{6,7} to early detection of disease and subsequent modification of risk factor exposure (secondary)⁸ to prevention of complications in patients with established disease (tertiary).^{9,10}

Second, COPD is a treatable disorder. Treatment of stable COPD and exacerbations are the subject of other Reviews to be published in *The Lancet*.^{11,12}

Classification based on post bronchodilator lung function	
GOLD 1 (mild)	FEV ₁ /FVC <0.70 and FEV ₁ ≥80% predicted
GOLD 2 (moderate)	FEV ₁ /FVC <0.70 and 80% >FEV ₁ ≥50% predicted
GOLD 3 (severe)	FEV ₁ /FVC <0.70 and 50% >FEV ₁ ≥30% predicted
GOLD 4 (very severe)	FEV ₁ /FVC <0.70 and FEV ₁ <30% predicted or FEV ₁ <50% predicted plus chronic respiratory failure

People with an FEV₁/FVC ≥0.70 and respiratory symptoms of chronic cough and sputum production are no longer included as a COPD stage (formerly GOLD stage 0). Patients with an FEV₁/FVC ≥0.70 but an FVC <80% predicted meet spirometric criteria for a restrictive process. Although this is not regarded as COPD, patients might present with several symptoms similar to those seen in COPD, and these patients have an increased risk of death.

Table 2: Classification of COPD severity according to the 2006 revision of the GOLD criteria⁴

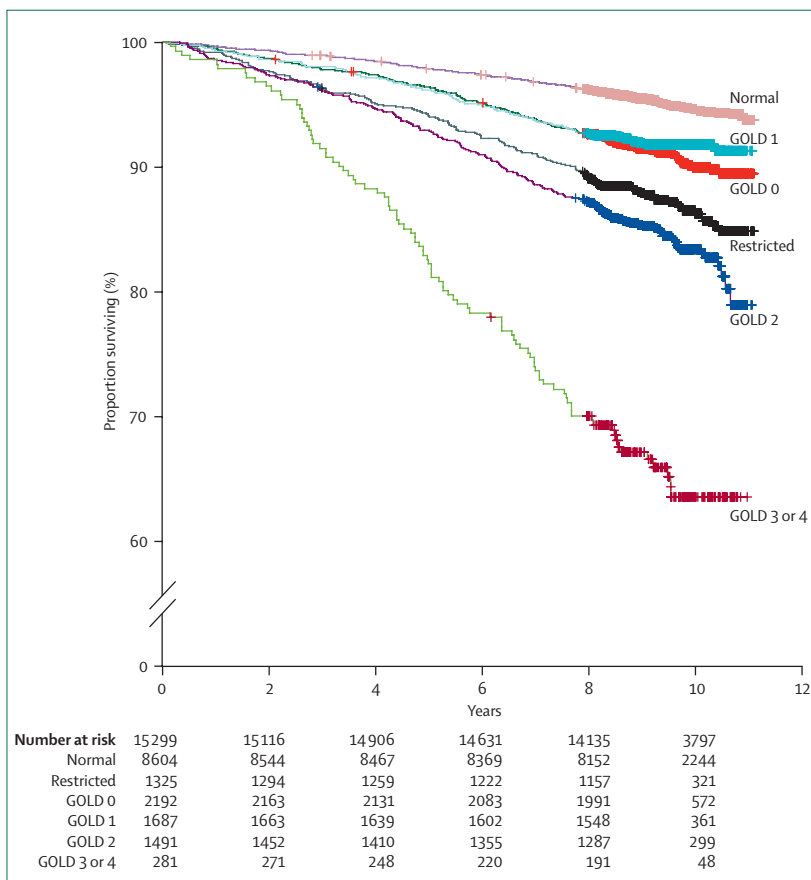


Figure 1: Kaplan-Meier survival curves for patients in the Atherosclerosis Risk in Communities Study, stratified by level of lung function impairment
Reprinted from reference 33, with permission of Elsevier. Lung function strata are defined in table 2.

Third, extrapulmonary effects are seen frequently in patients with COPD and some of these other diseases are probably related to the respiratory disorder. These include muscle wasting,¹³ cardiovascular disease,¹⁴ depression,¹⁵ reduced fat free mass, osteopenia, and chronic infections.^{4,16}

Fourth, individuals with similar smoking and exposure histories can vary a great deal in the severity of their disease and response to intervention.^{17,18} Interventions should be tailored to the individual, with recognition that the disease process we call COPD has many different phenotypes (see Disease classification section). Use of lung function to characterise severity is, currently, the best system available to clinicians, but it clearly falls well short of being ideal.

Fifth, the airflow limitation or obstruction that happens in COPD is caused by a mixture of small airway disease, parenchymal destruction (emphysema), and, in many cases, increased airways responsiveness (asthma).^{4,6} These findings tend to worsen with age but are also affected by exacerbations or other events marked by an acute worsening.¹⁹

Sixth, COPD is not fully reversible: the obstruction noted does not revert either in response to bronchodilators, anti-inflammatory treatment, or spontaneously.⁴ This lack of full reversibility is a means of trying to distinguish COPD and asthma, although many patients have features of both.²⁰

The final key component of this COPD definition relates to the inflammation present in the lung. Although the definition states that this effect is in response to noxious particles or gases, such as those in tobacco smoke, there is also some evidence that infections can have an important role in the presence of chronic inflammation in the lung.²¹

Disease classification

COPD can be classified with respect to both phenotype and disease severity. It is a heterogeneous disease process that varies greatly from person to person with respect to lung pathology, natural history of disease, and comorbidity. A result of this heterogeneity is that different researchers have championed alternative hypotheses about COPD development over the past four decades: the British hypothesis stated that the presence of cough and sputum was the key factor in COPD,²² and the Dutch hypothesis pointed to the presence of increased airways responsiveness.²³ Less widely known hypotheses stressed the part of genetic factors (the Swedish hypothesis)²⁴ and the role of impaired repair processes in the development of emphysema (the American hypothesis).²⁵ All these hypotheses probably have elements of truth since COPD is a classic gene-by-environment disease with various manifestations that include increased airways reactivity, a characteristic response to infections, abnormal cellular repair, and development of complications or comorbid disorders.

Table 1 lists the key diseases to be considered in the differential diagnosis of COPD. However, these diseases can coexist with COPD and contribute to disease prevalence or severity. For example, results of the Burden of Lung Disease (BOLD) study—a multinational investigation of the prevalence of COPD using a standard methodology and reported in this issue of *The Lancet*, show that one of the highest prevalences of COPD was recorded in South Africa, a country that also has a high prevalence of tuberculosis.²⁶ Asthma can coexist with COPD in clinical settings and is a risk factor for development of COPD.²⁷ Another example of disease overlap can be noted in the cluster of cases of so-called popcorn workers' lung, which is related to diacetyl exposure, in which affected individuals were diagnosed with COPD and, in fact, would meet criteria for COPD diagnosis.²⁸

Table 2 shows classification of disease severity, according to the current GOLD criteria.⁴ Classification should be done on post-bronchodilator lung function, although in many epidemiological studies, prebronchodilator lung function has been used, which can overestimate the presence of airflow obstruction by up to 50%.^{29,30} Missing from the 2006 GOLD guidelines is what was previously called GOLD stage 0, consisting of patients with normal lung function but presence of chronic respiratory symptoms. Also omitted from the GOLD classification are individuals with so-called restrictive spirometry—ie, an FEV₁/FVC ratio (forced expiratory volume in 1 s/forced vital capacity) of at least 0.70 but an FVC of less than 80% of the predicted value. Some would argue that this group of individuals have airflow limitation in the absence of airways obstruction³¹ and that this pattern can be seen in many patients who have a clinical COPD diagnosis.³² Lung function impairment is a strong predictor of mortality (figure 1). Although simple, use of lung function alone to classify disease severity does not capture the multi-dimensional component of COPD. Celli and colleagues showed that by incorporating the measures of body-mass index, lung function, dyspnoea score, and exercise level (as measured with a 6-min walk test) into a common index (BODE index) the ability to predict mortality was enhanced (figure 2).¹⁷

Risk factors

Risk for COPD is related to an interaction between genetic factors and many different environmental exposures, which could also be affected by comorbid disease. Risk factors for the disease are described below.

Genetic factors

The best known genetic factor linked to COPD is a deficiency of the serine protease $\alpha 1$ antitrypsin, which arises in 1–3% of patients with COPD.²⁴ Having low concentrations of this enzyme, particularly in combination with smoking or other exposures, increases the risk of panlobular emphysema.²⁴

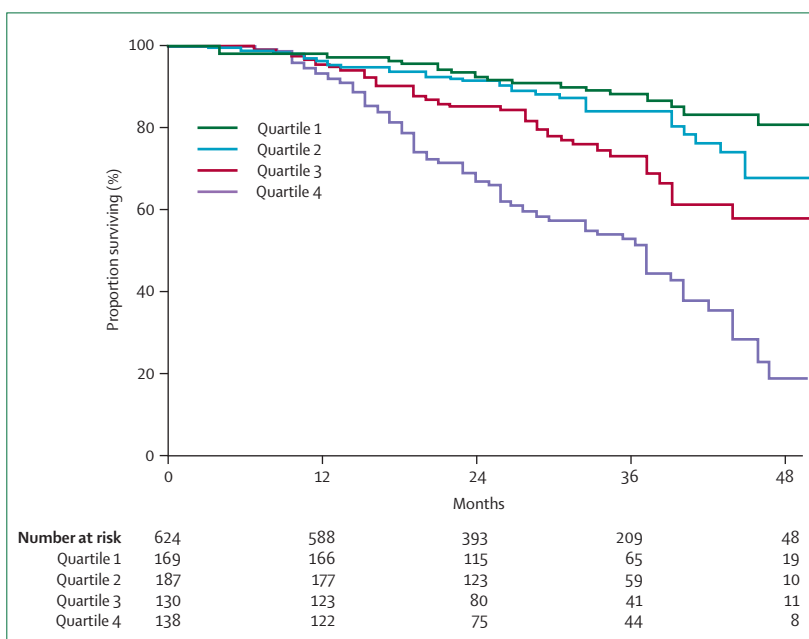


Figure 2: Kaplan-Meier survival curves for four quartiles of the body-mass index, degree of airflow obstruction and dyspnoea, and exercise capacity (BODE) index

Quartile 1 is a score of 0–2, quartile 2 is a score of 3–4, quartile 3 is a score of 5–6, and quartile 4 is a score of 7–10. Reprinted from reference 17, with permission of the Massachusetts Medical Society.

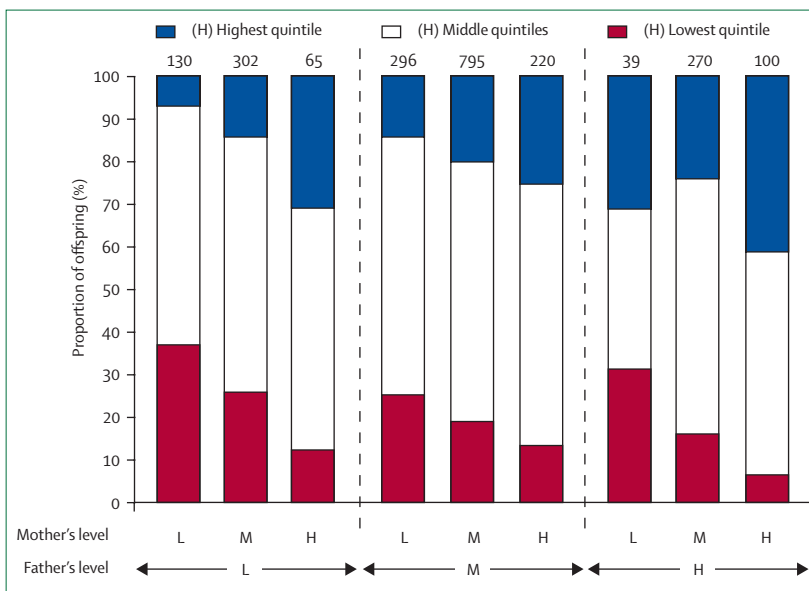


Figure 3: Familial aggregation of FEV₁

Family descriptions are based on combinations of maternal and paternal FEV₁ values in the highest (H=blue), middle three (M=white), and lowest (L=red) quintiles of the distributions of age-specific and sex-specific z-scores. Numbers above every column are people in every group. Data taken from the Renfrew and Paisley (MIDSPAN) study and reprinted from reference 34, with permission of European Respiratory Society Journals.

As noted in figure 3, parental lung function is related to lung function in offspring but in a very complex way. Of children whose parents were both in the lowest quintile of lung function, 37% were in the lowest quintile of function when compared with their peers (red part of

lower left corner of graph). Conversely, of children with both parents in the highest quintile of lung function, 41% were in the highest quintile of function when compared with their peers (blue part of upper right corner of graph).

Several genes have been implicated in COPD, including those coding transforming growth factor β 1,³⁵ tumour necrosis factor α ,³⁶ and microsomal epoxide hydrolase 1.³⁷ To date, however, work done to examine specific polymorphisms in these genes for the development of disease has been, at best, inconsistent.

Tobacco smoke

Worldwide, tobacco smoke remains the most important cause of COPD. WHO estimates that in high-income countries, 73% of COPD mortality is related to smoking, with 40% related to smoking in nations of low and middle income.¹ This relation is affected highly by genes, because not all smokers go on to develop COPD. Lately, however, a much higher proportion of smokers—perhaps as much as 50%—have been noted to develop COPD.^{34,38,39} Furthermore, smoking during pregnancy can negatively affect fetal lung growth and result in development of lung disease.⁴⁰ Smoking of marijuana has been linked to respiratory symptoms but not conclusively to development of COPD.^{41,42}

Occupational dust, vapours, and fumes

Exposure to various dusts, chemicals, vapours, and fumes in the workplace is a factor for many people with COPD. In one report, estimates showed that 19.2% of COPD cases in the USA were attributable to work exposures, with this proportion being 31.1% in never-smokers.⁴³ In countries of low and middle income, where occupational exposures to dust and fumes could be greater than in high-income nations because of less stringent laws, work exposures can assume high importance as a risk factor. Data of another study showed that people who reported a diagnosis of COPD or chronic bronchitis were twice as likely to recall previous worksite exposures to gases, dusts, vapours, or fumes.⁴⁴

Indoor air pollutants

Globally, the most important risk factor for development of COPD might be exposure to biomass fuels such as coal, straw, animal dung, crop residues, and wood, which are used to heat and cook in poorly ventilated homes. WHO estimates that, in countries of low and middle income, 35% of people with COPD developed the disorder after exposure to indoor smoke from biomass fuels.¹ Furthermore, WHO suggests that 36% of mortality from lower respiratory disease is also related to indoor smoke exposure.¹ Findings of a report from China showed that COPD prevalence in never-smoking women is two to three times higher in a rural area where women are exposed to biomass smoke compared with urban women without this exposure.⁴⁵ Second-hand smoke,

which is another form of biomass smoke, has been linked to respiratory symptoms but not to development of COPD.⁴⁶

Outdoor air pollutants

The risk attributable to outdoor pollutants in development of COPD is much smaller than that for indoor air pollutants. WHO estimates that urban air pollution causes 1% of COPD cases in high-income countries and 2% in nations of low and middle income.¹ Air pollution is also linked to lower respiratory infections and acute cardiopulmonary events, which are also important in both the development and progression of COPD.

Ageing

COPD prevalence, morbidity, and mortality increase with age. Lung function, which reaches its peak level in young adults, starts to decline in the third and fourth decades of life.⁴⁷ Although this diminished function is judged normal, some researchers have reported that elderly people with high levels of lung function live longer than do those with low levels of lung function.⁴⁸ One reason for the increasing prevalence of COPD in recent years is the changing demographic of the world's population, attributable to good nutrition and elimination or reduction of some childhood infectious diseases and falling mortality rates from diseases that kill young people, such as cardiac disease and acute infections. The result is that a larger proportion of the world's population is living longer and is at risk for chronic medical disorders, such as COPD.⁴⁹

Infections

Infections have an important role in both development and progression of COPD. Exposure to infection in early life could predispose an individual to bronchiectasis or changes in airway responsiveness. Most COPD exacerbations are related to bacterial or viral infections and are the subject of a separate Review in this issue of *The Lancet*.¹²

Asthma

According to the Dutch hypothesis, increased bronchial responsiveness, a hallmark of asthma, leads to development of COPD, although this topic remains controversial. Findings of cross-sectional studies have shown a large overlap of up to 30% between people who have a clinical diagnosis of COPD and asthma.⁵⁰ Other work has shown that people with asthma, especially if they are smokers, can lose lung function more rapidly than individuals without asthma.²⁷

Gender

The role of gender in development and progression of COPD is controversial and has been the topic of a great deal of research.⁵¹ Historically, COPD has been far more frequent in men than in women, related to patterns of

smoking and occupational exposures.^{52,53} Lately, however, COPD prevalence seems to be becoming equal in men and women from high-income countries in which smoking habits are similar between the sexes. Whether women are more susceptible to development of COPD than men, given equal exposures, continues to be a topic of investigation, but some evidence lends support to this hypothesis.^{26,54} This question is important since women in countries of low and middle income have, historically, had a low prevalence of smoking but are increasingly targeted by advertising to increase their use of cigarettes.

Socioeconomic and related factors

Poor populations tend to have a higher risk of developing COPD and its complications than their wealthier counterparts.^{55–57} However, poverty is regarded as a surrogate measure for many factors that subsequently increase the risk of COPD, such as poor nutritional status, crowding, exposure to pollutants including high work exposures and high smoking rates (in countries of low and middle income), poor access to health care, and early respiratory infections.^{55–57}

Prevalence estimates

Two reviews have been published^{58,59} in which the prevalence of COPD was noted to be highly variable, probably because of differences in methods for establishment of disease prevalence. Figure 4 shows the findings from the 12 sites of the BOLD study²⁶ and the five sites in the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study.⁶⁰ These estimates, even with identical methodologies, show a large amount of variability. For example, in the BOLD study,²⁶ GOLD stage II COPD in women ranged from 5.1% in Guangzhou, China, to 16.7% in Cape Town, South Africa, and in men it ranged from 8.5% in Reykjavik, Iceland, to 22.2% in Cape Town, South Africa (figure 4). In both the BOLD and PLATINO studies, post-bronchodilator lung function was used to obtain estimates of disease burden. Other researchers, as noted above, have shown that disease prevalence after use of a bronchodilator could be 5–50% lower than the prebronchodilator prevalence.^{29,30} Whereas post-bronchodilator lung function is the standard according to current GOLD guidelines, most studies in which health effects and outcomes related to lung function impairment are examined have used prebronchodilator measurements.^{48,61} Moreover, we do not know whether post-bronchodilator lung function is better or worse at predicting mortality and other adverse outcomes. Finally, in studies that look at prebronchodilator and post-bronchodilator lung function, the process by which individuals actually increase their FEV₁/FVC is not well-defined—ie, small increases in FEV₁ versus small decreases in FVC, or both. Additional understanding of how the FEV₁/FVC increases in response to a bronchodilator is needed to accurately classify patients.

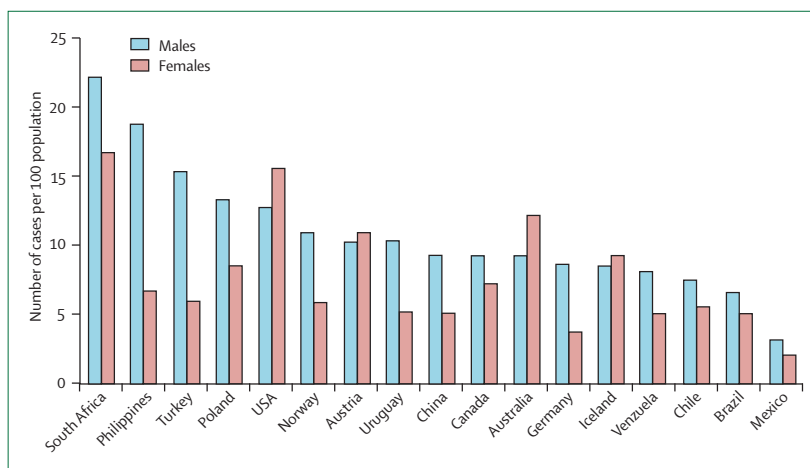


Figure 4: Estimated prevalence of GOLD stage 2 or higher COPD

Data taken from the PLATINO study⁶⁰ and the BOLD project.²⁶ Estimates are for small regions of the listed countries and do not necessarily represent national prevalence estimates.

Morbidity and mortality

Additional measures of the burden of COPD, such as morbidity, mortality, and costs, present challenges similar to those seen in attempting to measure disease prevalence. Table 3 shows WHO estimates of deaths and disability-adjusted life years attributable to COPD for the world's 25 most populous nations.¹ This table highlights some of the difficulties with these other measures of COPD. For example, the estimated COPD death rate in Japan of 4.4/100 000 is nearly 30 times lower than that in China (130.5/100 000). Findings of an epidemiological study of COPD in Japan, however, showed that 16.4% of men and 5.0% of women aged 40 years and older had disease of GOLD stage I or higher,⁶² which is similar to the 15.3% of men and 7.6% of women with a similar COPD stage in the Guangzhou study reported in the BOLD study.²⁶ The difference between Japan and China in mortality rates versus the similarity in prevalence suggests that other factors might affect how disease is diagnosed and cause of death is attributed between countries.

We also know that patients with COPD typically have comorbid diseases, such as muscle wasting, cardiovascular disease, depression, reduced fat-free mass, osteopenia, and chronic infections.⁶³ These disorders contribute to a high disease burden and early mortality in patients with COPD. As figure 1 shows, people with moderate and severe COPD die more quickly than do those with normal lung function.³³ Deaths in individuals with COPD, however, are frequently attributed to a cause other than COPD. For example, in a large prospective cohort from the USA of deaths in people with GOLD stage III or IV disease, 31.5% were recorded as a respiratory cause, 23.9% were due to lung cancer, 13.0% were due to cardiovascular disease, and 31.5% were from other causes.³³ Of those with GOLD stage II disease at baseline, only 3.5% of deaths were attributed to respiratory causes.

	Age-adjusted deaths/100 000	Age-adjusted DALYs/100 000
Japan	4.4	120
France	12.0	270
Germany	12.5	291
Italy	13.7	191
Russian Federation	16.2	242
UK	23.1	442
Iran (Islamic Republic of)	26.3	395
Philippines	26.7	282
Mexico	26.8	247
USA	27.2	426
Ukraine	31.6	477
Egypt	35.9	302
Turkey	40.3	521
Brazil	42.2	504
Thailand	48.0	245
Congo	49.4	297
Nigeria	49.4	296
Ethiopia	55.4	330
Myanmar	56.4	570
Indonesia	58.4	613
Bangladesh	66.4	559
Pakistan	71.1	584
India	73.2	667
Vietnam	86.4	488
China	130.5	622

Table 3: Estimates of deaths and disability-adjusted life years (DALYs) due to COPD for the 25 most populous nations in the world¹

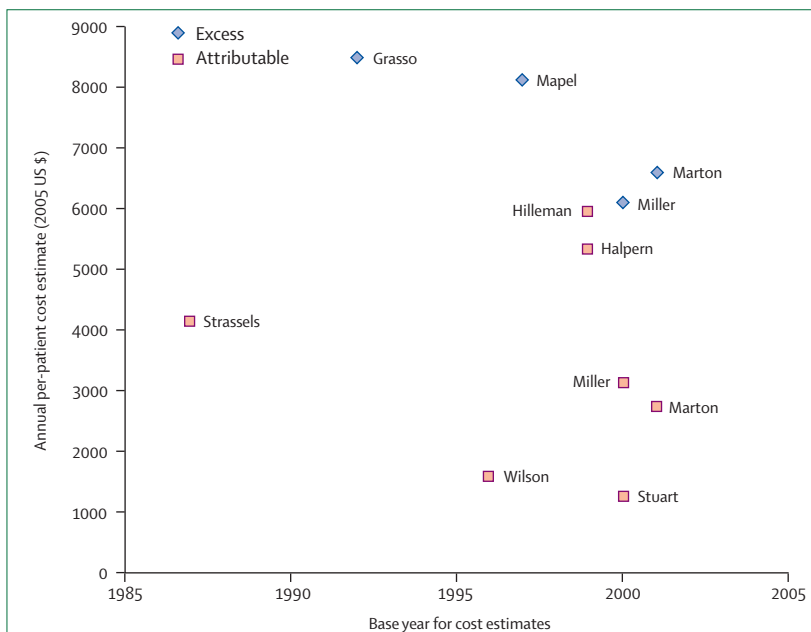


Figure 5: Estimates of costs of COPD in patients in the USA
 Reprinted from reference 64, with permission of *COPD: Journal of Chronic Obstructive Pulmonary Disease*. Estimates are in 2005 US\$. The base year is the year the study data are from (but cost has been adjusted for inflation to 2005 \$). Thus, every point is the estimate of COPD medical costs (either excess or attributable) from nine different studies (two studies did both excess and attributable costs).

These data suggest that COPD might be underappreciated as a contributor to mortality, particularly when it could be an important comorbid disorder that leads to development of a lethal disease, such as lung cancer or stroke.

A similar difficulty in underestimating the negative effects of disease is seen when looking at admissions for COPD, which are the largest contributor to the direct medical costs of the disease in the USA and many high-income countries.⁶⁴ From 1979 to 2001, in the USA, COPD was the primary reason for hospital discharge 9.8 million times and a secondary reason for discharge an additional 37.5 million times.⁶⁵ In this study, COPD as a primary or secondary cause of admission was associated with a higher mortality and more comorbid disease when compared with admission without COPD mentioned.⁶⁵ These data also suggest that the role of COPD as a contributor to admissions and their high costs might also be underappreciated.

Estimating the costs of COPD is similarly challenging, related to some of the difficulties noted above, such as under-diagnosis and presence of comorbid disease. Many different methodologies are used to estimate costs of chronic diseases such as COPD. There are direct costs of health-care services (ie, admissions, medications, durable medical equipment) and indirect costs (ie, lost work and productivity, premature death) that can be included in total costs. Furthermore, one can look at either attributable costs (ie, costs related specifically to COPD) or excess costs (additional costs of treatment in COPD vs non-COPD patients for both COPD and non-COPD illnesses).

In a review of annual direct medical costs of COPD in the USA, in 2005, the cost per patient was estimated at US\$2700–5900 for attributable costs to US\$6100–6600 for excess costs (figure 5).⁶⁴ In 2003, the US National Heart, Lung, and Blood Institute estimated that total costs (direct and indirect) of COPD were US\$32.1 billion, with direct costs of US\$18.0 billion.⁶⁶ Globally, costs vary between countries that have reported them (table 4), although more severe disease consistently incurs more costs than less severe disease.^{67–69,72}

Another means of measuring costs is to ascertain how expensive a specific intervention would be per quality-adjusted life year of improvement. Using this approach, WHO estimates that costs per quality-adjusted life year for COPD range from US\$6700–8900 for inhaled ipratropium to US\$13 400 for inhaled corticosteroids to US\$238 200 for lung transplantation.¹ Although one would expect smoking cessation to also be very cost effective, this invention has not been assessed with respect to quality-adjusted life years for COPD.

Future trends

When Calverley and Walker reviewed COPD in 2003 they made some predictions about progress in disease.² With respect to pathogenesis, they forecast that there would be greater phenotypic characterisation of COPD,

	Country	Cost (per patient per year)
Hilleman ⁶⁷	USA	Stage I \$1681 Stage II \$5037 Stage III \$10812
Dal Negro ⁶⁸	Italy	Stage I €151 Stage II €3001 Stage III €3912
Miravittles ⁷¹	Spain	Stage I €1185 Stage II €1640 Stage III €2333
Masa ⁶⁹	Spain	Stages I-III €909

Table 4: Estimates of direct costs of COPD in different countries⁷⁰

identification of candidate susceptibility genes, clarification of the basis of steroid resistance, and enhanced animal models of the disease. With respect to clinical characteristics, they predicted that there would be better methods of detecting flow limitation and staging systems that go beyond lung function measurement. For treatment, which is the focus of another Review in this issue of *The Lancet*,¹¹ they suggested several potential advances, such as enhanced smoking cessation treatments, better antioxidant treatments, biological agents targeting specific cytokines, and development of interventions to mechanically decrease lung hyperinflation. Some of their predictions have been partly realised, such as the development of the BODE index to predict COPD mortality,¹⁷ greater understanding of the role of inflammation in disease,²¹ and enhanced understanding of mechanisms of steroid resistance.⁷³ We still, however, have many important questions, which will provide the basis for future research in COPD.

Projections for COPD prove challenging and can differ between high-income countries and those of low or medium income. In general, the disease is associated strongly with ageing and factors that allow people to survive into old age, such as enhanced interventions for acute cardiovascular disease, and acute infections, will result in higher COPD prevalence, morbidity, and mortality. Although smoking is a strong risk factor for COPD, the relation between changing smoking prevalence in a population and disease outcomes is complex. For example, in the USA, smoking prevalence in men has been falling since the mid 1960s whereas COPD mortality has been increasing.⁵² This occurrence is probably related to several factors, such as acute mortality from cardiac events being much higher in current smokers with a rapid decrease in risk after smoking cessation. Conversely, in populations in which smoking is increasing, there could be a time lag of many years before smoking-related COPD becomes apparent.

Occupational and environmental exposures are, in general, more frequent in countries of low and middle income than in those with high income. With the development and dissemination of better stoves and

heating devices, these exposures should diminish with time. Similarly, prevalence of early respiratory infections and tuberculosis and malnutrition, which are all more typical in nations of low and middle income, hopefully will also decrease over time.

With the ageing of the global population, COPD is one of several chronic diseases that will continue to become more frequent. Such disorders will be best managed in an integrated and comprehensive way, with careful attention to prevention and cost-effectiveness of interventions.^{17,75}

Conclusion

Our knowledge of COPD has grown over the past few years. Additional questions are raised by this new knowledge, which are discussed here. One of the biggest advances in COPD is greater understanding of disease burden in different countries and cultures. Publication of data from the PLATINO⁶⁰ and BOLD²⁶ studies is vital to establish how important COPD is, particularly in view of the disease's consistent underdiagnosis at sites where it has been investigated.⁷⁶⁻⁷⁸ Other relevant components of disease burden relate to costs of treatment and disability associated with COPD. Why are there such striking differences between COPD prevalence in various countries even when using identical detection methods? Should we be talking about COPD phenotypes when we describe the prevalence of disease? Is so-called undiagnosed COPD clinically important and a predictor of bad outcomes? Does our current methodology fully capture the costs associated with COPD?

A second major advance in COPD over the past few years relates to the systemic nature of the disease process, with some of the most important effects arising in organs outside the respiratory system.^{79,80} What is a comorbid disease and what is a complication of COPD? Should comorbidity be part of the disease severity classification scheme? Should early treatment of COPD focus on prevention of comorbid disease? Should we be using the term polymorbid to indicate that many disease processes happen simultaneously?

In looking to the future, one cannot ignore the changing demographics of the world's population and the reality that COPD is a disease of ageing. Furthermore, if every smoker in the world were to stop smoking today, the rates of COPD would probably continue to increase for the next 20 years.^{81,82} Are primary, secondary, and tertiary intervention strategies available that are low-cost, effective, and amenable to implementation in all parts of the world? After people have stopped smoking, are there additional means of preventing disease progression? Does early detection of disease with spirometry result in enhanced outcomes? Is the loss of lung function with ageing truly inevitable?

COPD remains an important disease globally. Our greater understanding of disease pathogenesis, prognosis, and treatment should result in better outcomes for many of our patients.

Conflict of interest statement

DMM has received research grants or served on advisory boards or speakers bureaus for GlaxoSmithKline, Pfizer, Ortho Biotech, Novartis, AstraZeneca, Dey, and Boehringer-Ingelheim. ASB has served on advisory boards for Altana, GlaxoSmithKline, Merck, Novartis, Pfizer, and Sepracor.

References

- Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global burden of disease and risk factors. Washington: The World Bank, 2006.
- Calverley PM, Walker P. Chronic obstructive pulmonary disease. *Lancet* 2003; **362**: 1053–61.
- Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). *Lancet* 2004; **364**: 613–20.
- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for diagnosis, management, and prevention of COPD. <http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=989> (accessed April 16, 2007).
- Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; **23**: 932–46.
- Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. *JAMA* 1994; **272**: 1497–505.
- National Heart, Lung, and Blood Institute. Expert panel report: guidelines for the diagnosis and management of asthma—update on selected topics 2002. <http://www.nhlbi.nih.gov/guidelines/asthma/asthmafullrpt.pdf> (accessed April 12, 2007).
- Bednarek M, Gorecka D, Wielgomas J, et al. Smokers with airway obstruction are more likely to quit smoking. *Thorax* 2006; **61**: 869–73.
- Croton TL, Bailey WC. Long-term oxygen treatment in chronic obstructive pulmonary disease: recommendations for future research—an NHLBI workshop report. *Am J Respir Crit Care Med* 2006; **174**: 373–78.
- Celli B, Cross S, Grossman R, et al. Improving the care of COPD patients: suggested action points by the COPD exacerbations taskforce for reducing the burden of exacerbations of COPD. *Prim Care Respir J* 2006; **15**: 139–42.
- Calverley P, Rennard SL. What have we learnt from large drug treatment trials in COPD? *Lancet* 2007; **370**: 774–85.
- Wedzicha JA. COPD exacerbations: defining their cause and preventions. *Lancet* 2007; **370**: 786–96.
- Agusti AG. Systemic effects of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; **2**: 367–70.
- Curkendall SM, Lanes S, de Luise C, et al. Chronic obstructive pulmonary disease severity and cardiovascular outcomes. *Eur J Epidemiol* 2006; **21**: 803–13.
- Di Marco F, Verga M, Reggente M, et al. Anxiety and depression in COPD patients: the roles of gender and disease severity. *Respir Med* 2006; **100**: 1767–74.
- Mallia P, Johnston SL. Mechanisms and experimental models of chronic obstructive pulmonary disease exacerbations. *Proc Am Thorac Soc* 2005; **2**: 361–66.
- Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; **350**: 1005–12.
- Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; **348**: 2059–73.
- Wilkinson TM, Donaldson GC, Hurst JR, et al. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **169**: 1298–303.
- Anthonisen NR, Woodruffe K, Manfreda J. Use of spirometry and respiratory drugs in Manitobans over 35 years of age with obstructive lung diseases. *Can Respir J* 2005; **12**: 69–74.
- Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* 2004; **364**: 709–21.
- Anthonisen NR. The British hypothesis revisited. *Eur Respir J* 2004; **23**: 657–58.
- Vestbo J, Prescott E. Update on the “Dutch hypothesis” for chronic respiratory disease. *Thorax* 1998; **53** (suppl 2): S15–19.
- Stoller JK, Aboussouan LS. α 1-antitrypsin deficiency. *Lancet* 2005; **365**: 2225–36.
- Rennard SI. COPD: overview of definitions, epidemiology, and factors influencing its development. *Chest* 1998; **113**: 235S–41S.
- Buist AS, McBurnie MA, Vollmer WM, et al, on behalf of the BOLD Collaborative Research Group. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. *Lancet* 2007; **370**: 741–49.
- Lange P, Parner J, Vestbo J, et al. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; **339**: 1194–200.
- Kreiss K, Gomaa A, Kullman G, et al. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N Engl J Med* 2002; **347**: 330–38.
- Johannessen A, Omenaas ER, Bakke PS, et al. Implications of reversibility testing on prevalence and risk factors for chronic obstructive pulmonary disease: a community study. *Thorax* 2005; **60**: 842–47.
- Kim SJ, Suk MH, Choi HM, et al. The local prevalence of COPD by post-bronchodilator GOLD criteria in Korea. *Int J Tuberc Lung Dis* 2006; **10**: 1393–98.
- Snider GL. Nosology for our day: its application to chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; **167**: 678–83.
- Kohler D, Fischer J, Raschke F, et al. Usefulness of GOLD classification of COPD severity. *Thorax* 2003; **58**: 825.
- Mannino DM, Doherty DE, Buist AS. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. *Respir Med* 2006; **100**: 115–22.
- Mannino DM, Watt G, Hole D, et al. The natural history of chronic obstructive pulmonary disease. *Eur Respir J* 2006; **27**: 627–43.
- Celedon JC, Lange C, Raby BA, et al. The transforming growth factor-beta1 (TGFB1) gene is associated with chronic obstructive pulmonary disease (COPD). *Hum Mol Genet* 2004; **13**: 1649–56.
- Keatings VM, Cave SJ, Henry MJ, et al. A polymorphism in the tumor necrosis factor-alpha gene promoter region may predispose to a poor prognosis in COPD. *Chest* 2000; **118**: 971–75.
- Cheng SL, Yu CJ, Chen CJ, Yang PC. Genetic polymorphism of epoxide hydrolase and glutathione S-transferase in COPD. *Eur Respir J* 2004; **23**: 818–24.
- Rennard SI, Vestbo J. COPD: the dangerous underestimate of 15%. *Lancet* 2006; **367**: 1216–19.
- Lundback B, Lindberg A, Lindstrom M, et al. Not 15 but 50% of smokers develop COPD? Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respir Med* 2003; **97**: 115–22.
- Gilliland FD, Li YF, Dubeau L, et al. Effects of glutathione S-transferase M1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2002; **166**: 457–63.
- Tashkin DP. Smoked marijuana as a cause of lung injury. *Monaldi Arch Chest Dis* 2005; **63**: 93–100.
- Tashkin DP, Simmons MS, Sherrill DL, Coulson AH. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age. *Am J Respir Crit Care Med* 1997; **155**: 141–48.
- Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2002; **156**: 738–46.
- Trupin L, Earnest G, San Pedro M, et al. The occupational burden of chronic obstructive pulmonary disease. *Eur Respir J* 2003; **22**: 462–69.
- Ran PX, Wang C, Yao WZ, et al. [The risk factors for chronic obstructive pulmonary disease in females in Chinese rural areas]. *Zhonghua Nei Ke Za Zhi* 2006; **45**: 974–79.
- US Department of Health and Human Services. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Atlanta: Department of Health and Human Services, 2006.
- Fletcher C, Peto R, Tinker CM, Speizer FE. The natural history of chronic bronchitis and emphysema. Oxford: Oxford University Press, 1976.
- Mannino DM, Davis KJ. Lung function decline and outcomes in an elderly population. *Thorax* 2006; **61**: 472–77.

- 49 Jemal A, Ward E, Hao Y, et al. Trends in the leading causes of death in the United States, 1970–2002. *JAMA* 2005; **294**: 1255–59.
- 50 Soriano JB, Davis KJ, Coleman B, et al. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest* 2003; **124**: 474–81.
- 51 de Torres JP, Casanova C, Hernandez C, Abreu J, Aguirre-Jaime A, Celli BR. Gender and COPD in patients attending a pulmonary clinic. *Chest* 2005; **128**: 2012–16.
- 52 Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance: United States, 1971–2000. *Respir Care* 2002; **47**: 1184–99.
- 53 Silverman EK, Weiss ST, Drazen JM, et al. Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; **162**: 2152–58.
- 54 Watson L, Vonk JM, Lofdahl CG, et al. Predictors of lung function and its decline in mild to moderate COPD in association with gender: results from the Euroscop study. *Respir Med* 2006; **100**: 746–53.
- 55 Anto JM, Vermeire P, Vestbo J, et al. Epidemiology of chronic obstructive pulmonary disease. *Eur Respir J* 2001; **17**: 982–94.
- 56 Shohaimi S, Welch A, Bingham S, et al. Area deprivation predicts lung function independently of education and social class. *Eur Respir J* 2004; **24**: 157–61.
- 57 Lawlor DA, Ebrahim S, Davey SG. Association between self-reported childhood socioeconomic position and adult lung function: findings from the British Women's Heart and Health Study. *Thorax* 2004; **59**: 199–203.
- 58 Halbert RJ, Isonaka S, George D, et al. Interpreting COPD prevalence estimates: what is the true burden of disease? *Chest* 2003; **123**: 1684–92.
- 59 Halbert RJ, Natoli JL, Gano A, et al. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006; **528**: 523–32.
- 60 Menezes AM, Perez-Padilla R, Jardim JR, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005; **366**: 1875–81.
- 61 Purdue MP, Gold L, Jarvholm B, et al. Impaired lung function and lung cancer incidence in a cohort of Swedish construction workers. *Thorax* 2007; **62**: 51–56.
- 62 Fukuchi Y, Nishimura M, Ichinose M, et al. COPD in Japan: the Nippon COPD Epidemiology study. *Respirology* 2004; **9**: 458–65.
- 63 Sin DD, Anthonisen NR, Soriano JB, et al. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006; **28**: 1245–57.
- 64 Foster TS, Miller JD, Marton JP, et al. Assessment of the economic burden of COPD in the US: a review and synthesis of the literature. *COPD* 2006; **3**: 211–18.
- 65 Holguin F, Folch E, Redd SC, et al. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest* 2005; **128**: 2005–11.
- 66 National Heart, Lung, and Blood Institute. Chronic obstructive pulmonary disease. http://www.nhlbi.nih.gov/health/public/lung/other/copd_fact.pdf (accessed April 12, 2007).
- 67 Hilleman DE, Dewan N, Malesker M, et al. Pharmacoeconomic evaluation of COPD. *Chest* 2000; **118**: 1278–85.
- 68 Dal Negro R, Rossi A, Cerveri I. The burden of COPD in Italy: results from the Confronting COPD survey. *Respir Med* 2003; **97** (suppl C): S43–50.
- 69 Masa JF, Sobradillo V, Villasante C, et al. Costs of chronic obstructive pulmonary disease in Spain: estimation from a population-based study. *Arch Bronconeumol* 2004; **40**: 72–79.
- 70 Chapman KR, Mannino DM, Soriano JB, et al. Epidemiology and costs of chronic obstructive pulmonary disease. *Eur Respir J* 2006; **27**: 188–207.
- 71 Miravittles M, Murio C, Guerrero T, Gisbert R. Costs of chronic bronchitis and COPD: a 1-year follow-up study. *Chest* 2003; **123**: 784–91.
- 72 Miravittles M, Murio C, Guerrero T, et al. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. *Chest* 2002; **121**: 1449–55.
- 73 Barnes PJ, Ito K, Adcock IM. Corticosteroid resistance in chronic obstructive pulmonary disease: inactivation of histone deacetylase. *Lancet* 2004; **363**: 731–33.
- 74 Wagner EH. Chronic disease care. *BMJ* 2004; **328**: 177–78.
- 75 Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? *Eff Clin Pract* 1998; **1**: 2–4.
- 76 Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med* 2000; **160**: 1683–89.
- 77 Kim DS, Kim YS, Jung KS, et al. Prevalence of chronic obstructive pulmonary disease in Korea: a population-based spirometry survey. *Am J Respir Crit Care Med* 2005; **172**: 842–47.
- 78 Shahab L, Jarvis MJ, Britton J, West R. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. *Thorax* 2006; **61**: 1043–47.
- 79 Decramer M, De Benedetto F, Del Ponte A, et al. Systemic effects of COPD. *Respir Med* 2005; **99** (suppl B): S3–10.
- 80 MacNee W. Pulmonary and systemic oxidant/antioxidant imbalance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; **2**: 50–60.
- 81 Kojima S, Sakakibara H, Motani S, et al. Incidence of chronic obstructive pulmonary disease, and the relationship between age and smoking in a Japanese population. *J Epidemiol* 2007; **17**: 54–60.
- 82 Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J* 2006; **27**: 397–412.