Burden and clinical features of chronic obstructive pulmonary disease (COPD)

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Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality and represents a substantial economic and social burden throughout the world. It is the fifth leading cause of death worldwide and further increases in its prevalence and mortality are expected in the coming decades. The substantial morbidity associated with COPD is often underestimated by health-care providers and patients; likewise, COPD is frequently underdiagnosed and undertreated. COPD develops earlier in life than is usually believed. Tobacco smoking is by far the major risk for COPD and the prevalence of the disease in different countries is related to rates of smoking and time of introduction of cigarette smoking. Contribution of occupational risk factors is quite small, but may vary depending on a country's level of economic development. Severe deficiency for alpha-1-antitrypsin is rare and the impact of other genetic factors on the prevalence of COPD has not been established. COPD should be considered in any patient presenting with cough, sputum production, or dyspnoea, especially if an exposure to risk factors for the disease has been present. Clinical diagnosis needs to be confirmed by standardised spirometric tests in the presence of not-fully-reversible airflow limitation. COPD is generally a progressive disease. Continued exposure to noxious agents promotes a more rapid decline in lung function and increases the risk for repeated exacerbations. Smoking cessation is the only intervention shown to slow the decline. If exposure is stopped, the disease may still progress due to the decline in lung function that normally occurs with aging, and some persistence of the inflammatory response.

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide. The 2002 WHO World Health Report[1] listed COPD as the fifth leading cause of death in the world (table 1), and further increases in its prevalence and mortality are expected in the coming decades.[2] In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) issued and now updates yearly guidelines[3] that aim to improve prevention and management of COPD through a concerted worldwide effort and to encourage renewed research interest in this highly prevalent disease.

Definition

For years, clinicians, physiologists, pathologists, and epidemiologists have struggled with the definitions of disorders associated with chronic airflow limitation. The definition of COPD as given by GOLD is now rapidly gaining general acceptance: "COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases."[3]

Chronic bronchitis and emphysema are related terms but they describe different conditions. Chronic bronchitis, or the presence of cough and sputum production for at least 3 months in each of 2 consecutive years, remains a clinical and epidemiologically useful term. However, not all patients with chronic bronchitis have or will develop chronic airflow limitation.[4] The presence of chronic mucus hypersecretion in patients with COPD is, however, associated with an excess decline in lung function and an increased rate of hospitalisation and death from COPD.[5]

Emphysema—ie, destruction of the gas-exchanging surfaces of the lung (alveoli)—is a common pathological term. Although radiological techniques such as CT scanning and measurements of lung density have improved, they do not fully capture the structural abnormalities that underlie airflow limitation in COPD—ie, respiratory bronchiolitis and parenchymal destruction.

	Number of deaths
Ischaemic heart disease	7 181 000
Cerebrovascular disease	5 454 000
Lower respiratory tract infections	3 871 000
HIV/AIDS	2 866 000
COPD	2 672 000
Perinatal conditions	2 504 000
Diarrhoeal disease	2 001 000
Tuberculosis	1 644 000
Trachea/bronchus/lung cancer	1 213 000
Road traffic accidents	1 194 000

Total population 6 122 210 000.[1]

Table 1: **Ten most frequent causes of death in the world in 2001**

Search strategy

The material covered in this review is based on an extensive literature search and participation in expert meetings during the writing and updating of the GOLD guidelines, and on many years of research in the subject. We did a systematic MEDLINE search for articles in English or with English abstracts with keywords COPD, prevalence, morbidity, burden, cost, pollution, occupation, genetic, and severity, up to June, 2004.

Asthma is another major cause of chronic airflow limitation, but its pathogenesis and pathology are clearly different from those of COPD.[6] Airflow limitation in asthma is usually reversible either spontaneously or after treatment. Long-standing asthma can, however, lead to airflow limitation that is not fully reversible.[7] A history of asthma and a higher reversibility of the airflow limitation to an inhaled β_2 agonist are helpful to clinically differentiate the two diseases. A clinical overlap between asthma and COPD will obviously occur in asthmatic patients who smoke. Other pulmonary diseases such as cystic fibrosis, sarcoidosis, and interstitial lung diseases, can also cause chronic airflow limitation, but COPD can usually be differentiated from these diseases on the basis of the clinical picture and radiological findings.

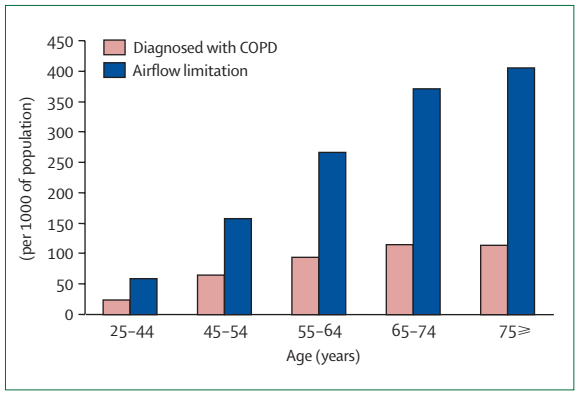

Figure 2: **Prevalence of airflow limitation and diagnosis of COPD in the USA**
Data from reference 10.

Prevalence

COPD prevalence and morbidity data probably greatly underestimate the true burden of the disease, because it is not usually recognised until it is clinically apparent and moderately advanced. Studies of COPD prevalence have used self-reported respiratory symptoms, physician diagnosis of COPD, or the presence of airflow limitation as criteria. Use of self-reported symptoms will include people with chronic bronchitis but without airflow limitation.

More recent epidemiological surveys have used spirometric tests and the presence of airflow limitation as an accurate estimate of the true burden of COPD. The use of different cutpoints to define airflow limitation makes comparison of results between studies rather difficult. Airflow limitation is usually defined as a decreased ratio of forced expiratory volume in 1 s (FEV_1) over forced vital capacity (FVC) (figure 1). Not-fully-reversible airflow limitation is characterised by an FEV_1 and an FEV_1/FVC ratio that is still decreased after administration of a bronchodilator (postbronchodilator FEV_1 is measured after the inhalation of a short-acting bronchodilator).

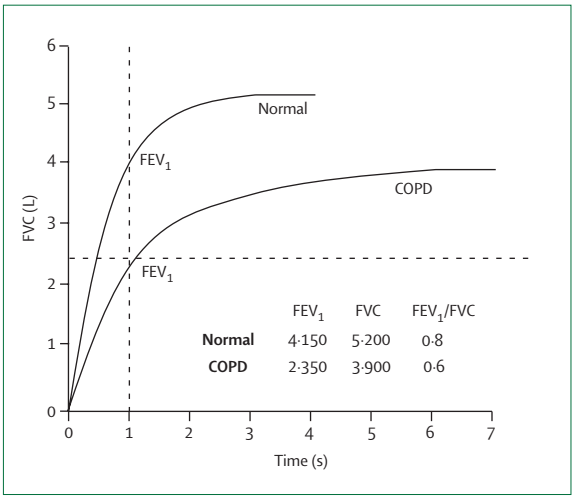

Figure 1: **Spirograms showing postbronchodilator FVC in a patient with COPD and a person without COPD**
Reproduced with permission from WHO.[1]

An important issue in defining airflow limitation spirometrically is whether to use an age-dependent FEV_1/FVC ratio, since the limits of a normal FEV_1/FVC ratio decrease with age. Some investigators use an age-dependent definition whereas others use a cutoff value of 0·7 for all age groups. There are no data on whether the decrease in FEV_1/FVC ratio with age might be the result of subclinical airflow limitation caused by the lifetime exposure to air pollution.[8]

A population survey[9] of men and women in Spain aged 40–69 years showed that, with an age-dependent and postbronchodilator definition, spirometrically confirmed COPD was present in 9·1 % of the population, 15% of smokers, 12·8% of ex-smokers and 4·1% in non-smokers. Prevalence was 14·3% in men and 3·9% in women. 78·2% of people identified with the disease had not been previously diagnosed. Only 49·3% of patients with severe COPD, 11·8 % of patients with moderate COPD, and 10% of patients with mild COPD were receiving treatment for the disease.

A large US survey on COPD[10] reported that during 2000, an estimated 10 million adults in the USA reported physician-diagnosed COPD, but that about 24 million adults had evidence of airflow limitation, again indicating that COPD is largely underdiagnosed (figure 2). The prevalence of moderate obstructive lung disease (FEV_1/FVC <0·7 and FEV_1< 80% predicted) was 7·2 % in the 45–54 years age-group, 14% between age 55 and 64 years, 20·7 % at age 65–74 years, and 22·9 % at age 75 years and older. A study in the northern part of Sweden[11] also reported a prevalence of chronic airflow limitation (FEV_1/FVC <0·7 and FEV_1 <80% predicted) of 14% above age 45 years and 50% in elderly smokers. These three studies, which use an objective measurement of airflow limitation, show the high prevalence of COPD and the frequent underdiagnosis and undertreatment.

The European Community Respiratory Health Survey[12] of more than 18 000 young adults (age 20–44 years) reported that, after exclusion of patients with asthma, 11·8% had chronic respiratory symptoms of cough, sputum, or dyspnoea, and 3·6% had airflow limitation. These data suggest that COPD develops at an earlier age than is usually believed.

COPD has a substantial morbidity that is underestimated by health-care providers and by patients. In an international survey,[13] patients with COPD seriously underestimated their morbidity, as shown by the high proportion of people whose basic daily life activities were limited by the disease, frequent absence from work (45% of COPD patients younger than 65 years reported absence from work in the past year), and frequent use of health care.

COPD also has a major effect on health status,[14] with poor status being quite strongly associated with impaired exercise performance and functional capacity. The presence of daily symptoms and a high exacerbation frequency are other important factors. Anxiety and depression are quite common in patients with COPD and contribute to their poor health status. Elderly patients with COPD show a substantial impairment in health status depending on the severity of airway obstruction; symptoms related to the disease may be exaggerated by mood deflection.[15]

COPD accounts for many visits to health-care workers. In the UK, general practice consultations for COPD in 1 year ranged from 4·17 per 1000 in people aged 45–64 years, to 8·86 per 1000 in 65–74-year-olds and to 10·32 per 1000 in 75–84-year-olds.[16] These rates are two-to-four times those for chest pain caused by ischaemic heart disease. In the USA, in 2000, COPD resulted in 8 million visits to doctors and hospital outpatient departments (45 per 1000 head of population), 1·5 million emergency department visits (8·7 per 1000), and 726 000 admissions (4·1 per 1000).[10] Young adults with an early stage of COPD visit their doctor more often, use more medications, attend the emergency department more often, and are more frequently admitted for respiratory difficulties.[12]

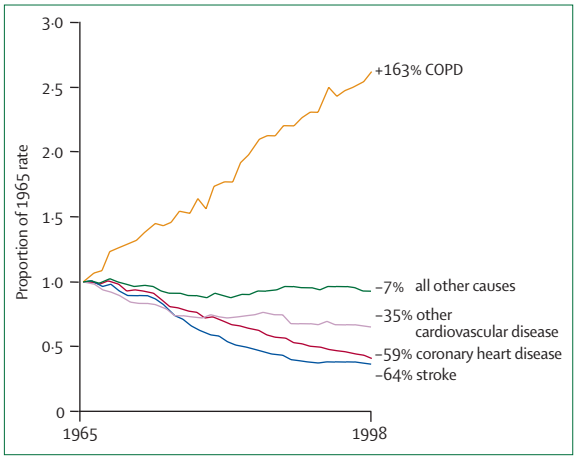

Figure 3: **Change in age-adjusted death rates for cardiovascular and pulmonary diseases in the USA 1965–98**
Adapted from reference 3.

In the USA, the death rate from COPD was 67 per 100 000 in 2000, compared with 44 per 100 000 in the rest of the world. The annual COPD death rate has been increasing in the USA in the past 20 years,[10] in contrast with a decreasing mortality for other major chronic diseases (figure 3).[17]

Economic burden

Because of the high prevalence of the disease and the potential for severe disability, COPD represents a substantial economic and social burden. It is, therefore, surprising how little information is available on the direct and indirect costs resulting from morbidity and premature death from COPD.

Some countries have attempted to assess the economic burden of COPD, separating costs directly and indirectly attributable to the disease. Data from developing countries are not yet available, but data from the USA and some European countries show the enormous economic and social burden of COPD for these societies and their respective insurance payers.

For Sweden, the direct cost of COPD-related medical care was estimated at about $US180 million in 1991.[18] The estimated indirect cost of COPD amounted to an additional $281 million. The direct cost of COPD in the Netherlands was estimated to exceed $256 million—or $813 per patient per year. Although medications contribute to 23% of these costs, admissions consume more than 50% of the total budget. Mathematical projections suggest that the direct costs of COPD in the Netherlands will rise to $410 million by 2010.

Similar data exist from NHS surveys in the UK where the direct cost of COPD was estimated to be about $1·4 billion or roughly $1900 per person per year.[19] The indirect cost of the disease including disability, work absence, and reduced productivity amounted to more than $3·0 billion,[16] representing about 24 million days of work lost.

Data from the USA have estimated the total annual economic burden of COPD at $23·9 billion in that country.[20] From these total costs, $14·7 billion were attributable to direct expenditures for medical care services, and the remaining $9·2 billion were related to indirect morbidity and premature death. The total number of COPD cases in the USA is thought to be around 15 million,[21] so that the estimated direct cost of COPD amounts to about $1500 per COPD patient per year.

Data from a US national medical expenditure survey[22] show that admission costs for COPD patients, based on 1987 estimates, are $5409 per admission—2·7 times the expenditures for patients without COPD. Data from 1992, have shown that the annual health insurance costs

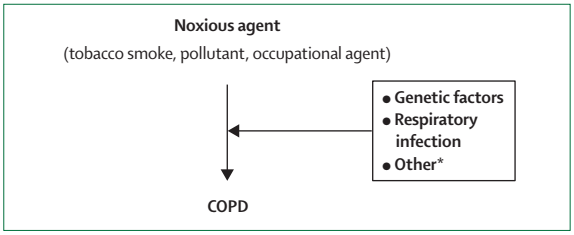

Figure 4: **Interaction between risk factors in the pathogenesis of COPD**
*Includes airway hyperresponsiveness, lung growth, and socioeconomic status. Adapted from reference 1.

WHO region	1990 prevalence (per 1000) (men/women)
Established market economies	7·0/3·8
Former socialist economies Europe	7·3/3·4
India	4·4/3·4
China	2·6/2·4
Other Asia and islands	2·9/1·8
Sub-saharan Africa	4·4/2·5
Latin America	3·4/2·7
Middle east crescent	2·7/2·8

Data from reference 30.

Table 2: **Worldwide COPD prevalence**

for patients older than 65 years with COPD were $8482—2·5 times the amount for people without the disease.[21]

Estimates of the economic burden of COPD are likely to be underestimations since society does not, for example, acknowledge the economic value of the care provided by family members. Long-term home care provided by relatives for patients with severe COPD frequently has a detrimental effect on professional careers, not only for patients, but also for other family members. Taken together, COPD represents a major global threat to economies and more studies into the true effects of this disease are needed, in both developed and less-developed countries.

Risk factors

Most evidence about exogenous risk factors for COPD comes from cross-sectional epidemiological studies that identify associations rather than links between cause and effect[3] (figure 4).

Tobacco smoke

The most convincing evidence for a direct causal relationship in COPD is for tobacco smoke. Many epidemiological studies have shown that cigarette smoking is by far the most important risk factor for COPD. Cigarette smokers have more respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV_1, and a greater death rate from COPD than do non-smokers. Age at smoking commencement, total pack-years smoked, and current smoking status are predictive of COPD mortality. Not all smokers develop clinically significant COPD, but the most recent epidemiological studies show that most smokers, if they live long enough and smoke enough, will develop airflow limitation.[9–11] Stopping smoking slows the decline in FEV_1.[23] Further evidence for the role of cigarette smoke in causing COPD comes from animal models where COPD-like pathology can be induced by exposing mice to cigarette smoke.[24] Pipe and cigar smokers have greater COPD morbidity rates and mortality than do non-smokers, although their rates are lower than those of cigarette smokers.

Passive exposure to cigarette smoke (ie, environmental tobacco smoke) increases the frequency of respiratory symptoms in adults.[25] However, the effects of environmental tobacco smoke on lung function are small and probably have limited clinical relevance for the development of COPD.

Air pollution

An important risk factor for the development of COPD worldwide is exposure to indoor air pollution caused by heating and cooking with biomass fuel in poorly ventilated dwellings, leading to high levels of particulate matter indoors.[26–29] That women are usually more exposed to this risk factor might explain why the prevalence of COPD in women is almost the same as that for men in countries such as India, China, Latin America, and the middle east, despite a clear difference between the sexes with respect to cigarette smoking (table 2).[30]

The role outdoor air pollution has in COPD is unclear, but it seems to be small when compared with that of cigarette smoking.

Occupational exposure

Sufficiently intense occupational exposure to dust, gases, or fumes is associated with an increased risk of developing COPD, independent of cigarette smoking, but the effects of occupational exposure and cigarette smoking are additive.[31] Both inorganic and organic dust exposure can accelerate the decline in FEV_1.[32]

Genetic factors

Although we know the risk of developing COPD is dependent on the amount and duration of cigarette smoking, it is clear that there is a high variation in susceptibility to the disease between individuals. The effects of exposure to other risk factors are cumulative with those from tobacco smoke, but this still does not explain the differences between smokers in the rate of FEV_1 decline. Proof that genetic factors are involved in the pathogenesis of COPD comes from the observation that individuals with severe deficiency for alpha-1-antitrypsin, a major inhibitor of serine proteases, have an increased risk of developing COPD.[33] Individuals with a severe deficiency for alpha-1-antitrypsin who smoke cigarettes tend to develop more severe COPD at an earlier age than do non-smokers with a comparable

severe deficiency.[34] Besides cigarette smoking, other environmental factors such as occupational exposure interact with severe deficiency for alpha-1-antitrypsin in the risk of developing COPD.

There are indications that genetic factors other than alpha-1-antitrypsin might contribute to the risk of developing COPD.[35] Current or ex-smoking first-degree relatives of patients with severe early onset COPD without alpha-1-antitrypsin deficiency have a higher prevalence of COPD than do controls with the same smoking habits.[36] Segregation analysis and linkage studies have not been consistent in identifying major genes for COPD other than alpha-1-antitrypsin. Associations have been described between COPD and different gene polymorphisms, including alpha-1-antichymotrypsin, microsomal epoxide hydrolase, glutathione S-transferase, haeme oxygenase-1, and TNFα.[35] However, results have been inconsistent in different populations.

Clinical features

COPD should be considered in any patient presenting with cough, sputum production, or dyspnoea, especially if the patient has been exposed to risk factors for the disease. Clinical diagnosis is confirmed by standardised spirometric tests that show the presence of airflow limitation (ie, postbronchodilator FEV_1 <80% of the predicted value in combination with an FEV_1/FVC <0·7). Clinical symptoms and signs, such as abnormal shortness of breath and increased forced expiratory time, can be used to help with the diagnosis.

Symptoms

Cough and sputum

Cough may initially occur intermittently but it is usually the first symptom of COPD to develop.[37] It may be unproductive[38] and is frequently neglected as a clinical sign by patients. Regular production of sputum for 3 months or more in 2 consecutive years has been the epidemiological definition of chronic bronchitis[39] for many years but this pattern of sputum production is not really the same as that seen in COPD patients, which is generally very variable and sometimes difficult to assess.[4]

Dyspnoea

Breathlessness in COPD is usually the first symptom that drives patients to seek a medical consultation. It is characteristically persistent and progressive. Patients may first notice impairments in daily activities[39] before their disease progresses to a more severe state and they may become confined to their homes.

Patients frequently describe their dyspnoea as a sense of increased effort to breathe, heaviness, air hunger, or gasping,[40] although a large variety in terminology exists.[41] Dyspnoea in COPD needs to be distinguished from other causes, and can be quantified by means of standard questionnaires.[42] Wheezing and chest tightness are non-specific and variable symptoms, and their absence does not exclude the diagnosis of COPD.

Severe disease

With severe disease, weight loss and anorexia are common.[43] During respiratory infections, haemoptysis can occur,[44] and requires further investigation. The development of cor pulmonale caused by secondary pulmonary hypertension is often seen in advanced COPD[45] and can present with typical signs and symptoms of depression, anxiety, or both.

Physical examination

In mild to moderate COPD, physical examination alone is not helpful for diagnosis, since physical signs are not usually present until significant impairment of lung function has occurred,[46,47] and their detection has low sensitivity and specificity. Likewise, palpation and percussion are not very helpful for diagnosis, but may sometimes serve to indicate lung hyperinflation. The frequently observed reduction in breath sounds is a clinical guide, but does not allow for diagnosis.[48]

Measurement of airflow limitation

Lung function measurements should be undertaken for any patient who may have COPD, even in patients presenting primarily with chronic cough and sputum production in the absence of dyspnoea. Although spirometric tests only measure a small aspect of the effect of COPD on a patient's health, they remain the gold standard for diagnosis because of their high reproducibility and availability. The monitoring of disease progression, the effects of drug interventions, and progress of rehabilitation might also be assessed by additional functional measurements known to be related to health status such as the measurement of hyperinflation, residual volume, and inspiratory capacity.[49,50]

Spirometric tests should measure FVC and FEV_1, and the ratio of these two measurements (FEV_1/FVC) should be calculated (figure 1). Spirometric measurements are assessed by comparison with reference values based on age, height, sex, and race.[51] Patients with COPD typically show a decrease in both FEV_1 and FVC and a decreased FEV_1/FVC ratio. Specific spirometric cutpoints (eg, FEV_1 >80% of predicted) to define different stages of COPD are used for simplicity; these cutpoints have not been clinically validated and might underestimate the prevalence of COPD in some groups, such as elderly people.

The airflow limitation in COPD patients is not fully reversible; but this does not mean that there is no reversibility. In fact, many patients with COPD will show some degree of reversibility after inhalation of a short acting bronchodilator (β_2 agonist or an anticholinergic

	Suggestive features
COPD	Onset in midlife
	Symptoms slowly progressive
	Long smoking history
	Dyspnoea during exercise
	Largely irreversible airflow limitation
Asthma	Onset early in life (often childhood)
	Symptoms vary from day to day
	Symptoms at night or early morning
	Allergy, rhinitis, or eczema also present
	Family history of asthma
	Largely reversible airflow limitation

Table 3: **COPD: differential diagnosis**

agent). A high degree of reversibility (eg, 20% or more) is usually evidence of the presence of asthma.

Measurement of peak expiratory flow cannot routinely be recommended since in COPD the relation between this variable and FEV_1 is poor and furthermore, it may underestimate the degree of airways obstruction in patients with the disease.[52] It should only be used if spirometric tests are not available.[53–55]

Other investigations

Arterial blood gases should be measured in all patients who have FEV_1 less than 40% of predicted, or clinical signs of respiratory failure or right heart failure. Additional investigations may be useful in such patients. Arterial blood-gas measurements are best for obtaining acid-base information, which will guide oxygen therapy and help to decide whether patients with exacerbations require ventilatory support.

The measurement of diffusing capacity should not routinely be done, but may be helpful in the case of diagnostic uncertainty or for preoperative assessment of patients with severe COPD who are undergoing lung resections or lung volume reduction surgery.[56]

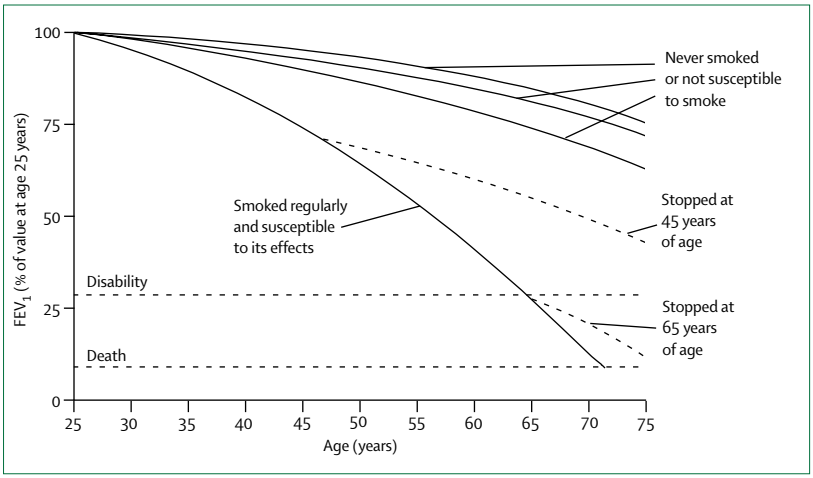

Figure 5: **Fletcher-Peto diagram showing the natural history and the change over time of the FEV_1 in non-smokers and smokers**
Adapted from reference 61 with permission.

Measurement of packed-cell volume may be useful in patients with severe COPD, since continued smoking can explain the limited effects of long-term oxygen therapy to correct increased red-cell mass.[57]

A chest radiograph is seldom diagnostic in COPD, and CT scans of the chest are not routinely recommended. Both techniques, however, might help in the differential diagnosis.

Differential diagnosis

In some patients with severe or chronic asthma, a clear clinical distinction from COPD is not possible, despite use of imaging and physiological testing techniques, and it is assumed that asthma and COPD coexist in these patients. In these patients, COPD management is similar to that for asthma. Nevertheless, physicians should aim to differentiate asthma from COPD if possible, which might include trying a course of oral steroids, since management strategies for mild to moderate disease differ (table 3).

Natural history

Studies on the natural history of COPD show that it is usually a progressive disease, although differences exist between individuals. Continued exposure to noxious agents promotes a more rapid decline in lung function and increases the risk for repeated exacerbations (figure 5). If exposure to noxious agents is stopped, the disease may still progress because of the age-related decline in lung function, and the persistence of aspects of the inflammatory response.[58] Nevertheless, efforts need to concentrate on stopping exposure to noxious agents, since some improvements in lung function and slowing—or even halting—the progression of the

***Panel:* GOLD classification of COPD by severity**

Stage 0: at risk
Normal spirometry
Chronic symptoms (cough, sputum)

Stage I: mild
$FEV_1/FVC < 0{\cdot}7$; $FEV_1 > 80\%$ predicted
With or without symptoms (cough, sputum)

Stage II: moderate
$FEV_1/FVC < 0{\cdot}7$; $50\% < FEV_1 < 80\%$ predicted
With or without chronic symptoms (cough, sputum, dyspnoea)

Stage III: severe
$FEV_1/FVC < 0{\cdot}7$; $30\% < FEV_1 < 50\%$ predicted
With or without chronic symptoms (cough, sputum, dyspnoea)

Stage IV: very severe
$FEV_1/FVC < 0{\cdot}7$; $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted
respiratory failure or clinical signs of right heart failure

disease may be expected in patients, even people with substantial airflow limitation.[23]

The degree of airflow limitation in COPD is only loosely related to symptom severity, which introduces difficulties in disease staging. The recommended management of COPD, however, is largely symptom driven, requiring a pragmatic approach to the assessment of disease severity and the prescription of drug treatment. Furthermore, for educational purposes COPD is defined on the basis of airflow limitation (panel), but in practice patients report symptoms that affect their lifestyle. Recent data also suggest that differences in health status are not evident until GOLD stages 3 and 4.[59] In principle, COPD can be diagnosed at any level of severity based on the combination of a patient's history, objective lung-function measurements, and the presence of characteristic symptoms such as cough, sputum production, and dyspnoea on exertion. Recently, a multidimensional grading system using body-mass index, airflow obstruction, dyspnoea, and exercise capacity (the BODE-score) has been shown to be a predictor for COPD mortality.[60]

Finally, the assumption that only 15–20% of smokers develop clinically significant COPD seems misleading. Patients who continue to smoke frequently develop an abnormal lung function over time and the GOLD initiative has tried to bring these patients to our attention by labelling them as at risk. Obviously, not all people at risk of COPD will follow the idealised linear course of functional deterioration shown in figure 5.[61] Such variation calls for regular follow-up of patients with COPD, regular measurement of lung function, and a continued global effort to limit exposure to noxious agents, in particular cigarette smoke. These efforts are especially important since COPD is increasingly recognised as a disease state that is, in principle, preventable and treatable.[62]

Conflict of interest statement
None declared.

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