

# 13

## Chronic obstructive pulmonary disease

### Introduction



#### Key points

- 5–10% of adults aged over 40 years have COPD, with a higher prevalence in men than women.
- The key risk factor for chronic obstructive pulmonary disease is tobacco smoke, but occupational exposures, pollution and genetic factors play a role.
- The most important symptoms of chronic obstructive pulmonary disease are breathlessness on exertion and chronic cough with or without phlegm, but fatigue, anorexia and weight loss can arise as the disease progresses.
- Treatment is multimodal, including smoking cessation, medical treatment with bronchodilators as well as inhibitors of inflammation, physical exercise and oxygen therapy.

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation that is usually progressive and associated with a chronic inflammatory response in the airways and lungs to noxious particles or gases. The persistent airflow limitation results from a combination of diffuse small airway disease and destruction of the lung parenchyma (emphysema).

COPD is a syndrome with many phenotypes. They have been poorly defined and knowledge of their specific aetiology, pathogenesis, management and meaningful outcomes is limited. Chronic bronchitis (defined as cough and phlegm for at least 3 months per year in 2 consecutive years) may precede or coincide with airway narrowing but may also be seen in patients without COPD.

The diagnostic criterion for COPD is based on spirometry confirming a reduction in the ratio of forced expiratory volume in 1 second (FEV<sub>1</sub>) to forced vital capacity (FVC). Severity is graded as shown in table 1. There is, however, ongoing discussion about the most appropriate spirometric criterion to use, either reduction of the ratio of FEV<sub>1</sub>/FVC below a fixed value (usually 70%) or below the lower limit of normal FEV<sub>1</sub>/FVC for the age and sex of the subject. Since even in healthy individuals the FEV<sub>1</sub>/FVC ratio declines with age, use of the former criterion rather than the latter can result in overdiagnosis of COPD in the elderly and underdiagnosis in younger subjects.

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*The risk of developing COPD is inversely related to socioeconomic status based on education or income*

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### ATS/ERS criteria

Mild	FEV <sub>1</sub> /VC <5th percentile of predicted and FEV <sub>1</sub> ≥70% pred
Moderate	FEV <sub>1</sub> /VC <5th percentile of predicted and FEV <sub>1</sub> 60–69% pred
Moderately severe	FEV <sub>1</sub> /VC <5th percentile of predicted and FEV <sub>1</sub> 50–59% pred
Severe	FEV <sub>1</sub> /VC <5th percentile of predicted and FEV <sub>1</sub> 35–49% pred
Very severe	FEV <sub>1</sub> /VC <5th percentile of predicted and FEV <sub>1</sub> <35% pred

### GOLD criteria

Mild (stage I)	FEV <sub>1</sub> /FVC <0.70 and FEV <sub>1</sub> >80% pred
Moderate (stage II)	FEV <sub>1</sub> /FVC <0.70 and 50% ≤ FEV <sub>1</sub> <80% pred
Severe (stage III)	FEV <sub>1</sub> /FVC <0.70 and 30% ≤ FEV <sub>1</sub> <50% pred
Very severe (stage IV)	FEV <sub>1</sub> /FVC <0.70 and FEV <sub>1</sub> <30% pred or FEV <sub>1</sub> /FVC <0.70 and FEV <sub>1</sub> <50% pred and chronic respiratory failure

**Table 1** – Classification and severity staging of airflow obstruction according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. FEV<sub>1</sub>: forced expiratory volume in 1 second; VC: vital capacity; % pred: % of predicted value; FVC: forced vital capacity. Reproduced from Бакке *et al.*, 2011.

COPD is a major burden to many individuals, societies and healthcare budgets throughout the world. Its impact is expected to rise both in industrialised and developing countries in the decades to come, partly due to continued exposure to risk factors for COPD and partly due to an ageing world population. People who live longer are more likely to experience the consequences of long-term exposure to COPD risk factors.

The aim of this chapter is to describe the epidemiology, risk factors, clinical picture, management, and future trends of COPD in Europe.

## Epidemiology



Europe, as defined by the World Health Organization (WHO), has a population of approximately 750 million in 54 countries, among which there are large differences in population structure and health services and great environmental heterogeneity. Europe should therefore be an ideal region in which to explore environmental as well as

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genetic influences on the mortality, prevalence, incidence and hospital admission rate of COPD. Several large single-centre population studies of COPD in Europe have been in progress for some time: since 1972 in Oslo, Norway; since 1976 in Copenhagen, Denmark; since 1980–1982 in the Po river delta, Italy; and since 1985 in northern Sweden and in Bergen, Norway. In addition, multicentre surveys of COPD in single countries have been conducted in Switzerland and Spain, and studies have been coordinated across many European countries simultaneously in the European Community Respiratory Health Survey (ECRHS) and the Burden of Obstructive Lung Disease (BOLD) study. However, estimates of mortality, hospital admissions, prevalence and incidence are still lacking from many European countries in 2012.

The data in this chapter are based on the International Classification of Disease, 10th revision (ICD-10) codes J40–J44 and J47, chronic obstructive pulmonary diseases and bronchiectasis (which have much in common). The diagnostic codes J45 and J46 (asthma and status asthmaticus) have generally not been included. Differences in coding may be a cause of variations both within regions of a country and between countries, as combinations of these diseases are not uncommon. Some physicians responsible for recording cause of death still use the diagnosis of asthma/status asthmaticus instead of COPD and both under- and overdiagnosis of COPD are frequent on death certificates as well as in clinical practice.

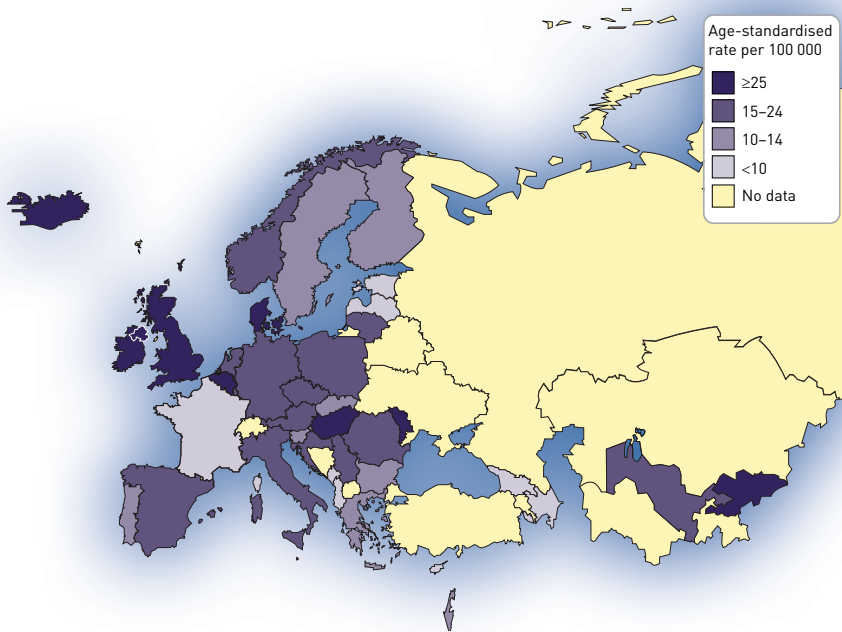
### ***Mortality***

Overall, the COPD mortality rate for men and women in Europe, age-standardised to the European Standard Population, is about 18 per 100 000 inhabitants per year. The variation of age-standardised mortality rates is, however, more than 10-fold among the 39 countries that provided data on mortality to the WHO (figure 1). Data are scarce from countries in eastern Europe. There is a general trend for countries with higher prevalence of cigarette smoking to have higher mortality from COPD. According to the WHO, in 1997, COPD was the cause of death in 4.1% of men and 2.4% of women in Europe. However, in Denmark, deaths due to COPD are more frequent in women than in men.

It is noticeable that over a short period of time there has been a substantial decline in death rates from many causes, including cardiovascular disease, but for COPD mortality, this tendency to decline started much later in some countries.

### ***Hospital admission***

Hospital admission rates for COPD are available for 31 European countries, with the majority of data coming from

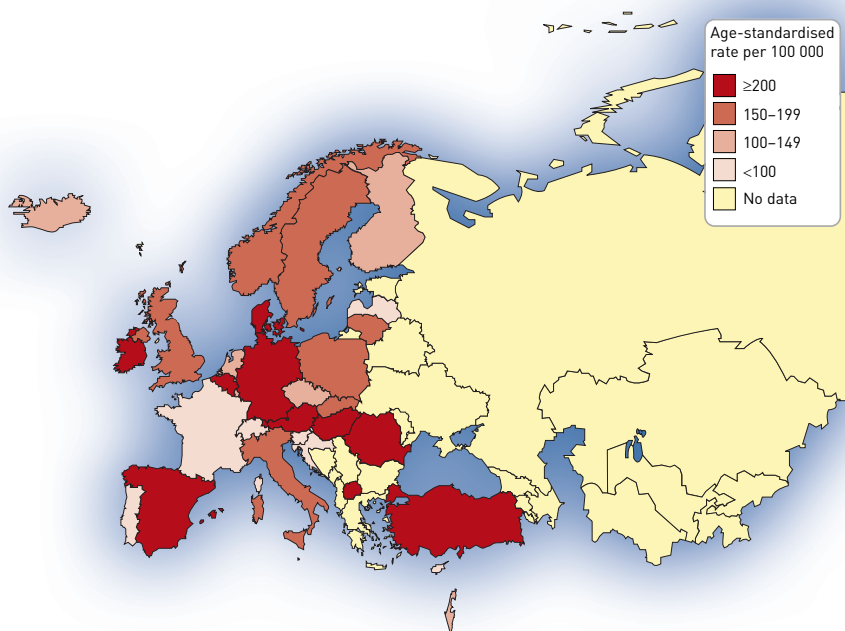


**Figure 1** – Mortality rate for chronic obstructive pulmonary disease (COPD). Data from World Health Organization World and Europe Mortality Databases, November 2011 update. Data for some countries are missing because mortality data for asthma and COPD are not reported separately.

western Europe. The average age-standardised admission rate for COPD is about 200 per 100 000 people per year, being highest in Denmark, Hungary, Romania, Turkey, Macedonia, Austria, Germany, Belgium, Spain and Ireland, and lowest in Switzerland, France, Portugal, Slovenia, Croatia and Latvia. The variation in admission rates is as high as 10-fold between European countries (figure 2). Hospitalisation rates for COPD are heavily dependent on the average age of the population in the community and the organisation of emergency units, as well as the availability of hospital beds. In western and central Europe there has been a steady decrease in the overall number of hospital beds as a result of changes in the structure of healthcare. Predictors of exacerbations and hospital admissions for COPD include a previous history of exacerbations, more severe disease, impaired quality of life and the presence of comorbidities. In several countries in northern Europe, the admission rates are higher in women than men. A study including 234 hospitals in the UK showed an in-hospital mortality of 7% and a 90-day mortality of 15% following admission for COPD exacerbations. More than 50% of COPD patients discharged from hospital after an exacerbation are readmitted within a year.

### *Incidence and prevalence*

Precise estimates of incidence of spirometry-defined COPD are lacking for most countries in Europe. A population-based study in Norway showed an overall incidence of 1% per year in 18–74 year olds during 9 years of follow-up. The incidence did not vary according to sex; it increased with increasing age; and it was 10 times higher in smokers than in never-smokers. More than 100 studies of COPD prevalence have been published since the 1970s and most estimates from large-scale studies are between 5% and 10%. These studies vary in survey methods, diagnostic criteria, analytical approaches and age distribution of the populations examined, making comparison between study results difficult.



**Figure 2** – Hospital admission rate for chronic obstructive pulmonary disease (COPD). Data from World Health Organization Hospital Morbidity Database, October 2011 update, and Eurostat, March 2012 update. The following countries supplied data to Eurostat that cover both COPD and bronchiectasis: Germany, France, Hungary, Ireland, Macedonia, the Netherlands, Romania, Sweden and Turkey.

The international, population-based BOLD study aims to use standardised survey methods and a spirometric criterion for COPD, enabling direct comparison between study populations. The prevalence of spirometry-defined COPD (FEV<sub>1</sub>/FVC < 0.7, FEV<sub>1</sub> < 80% of predicted value) is about 10%. It varies considerably between European countries (figure 3). This may partly be due to small sample sizes in the studies and partly due to age distribution and different environmental exposures. The prevalence of COPD is higher in men than in women (figure 3). All studies show a clear increase of prevalence with age. In people aged > 70 years, the prevalence of COPD is about 20% in men and 15% in women.

## *Causes/pathogenesis*

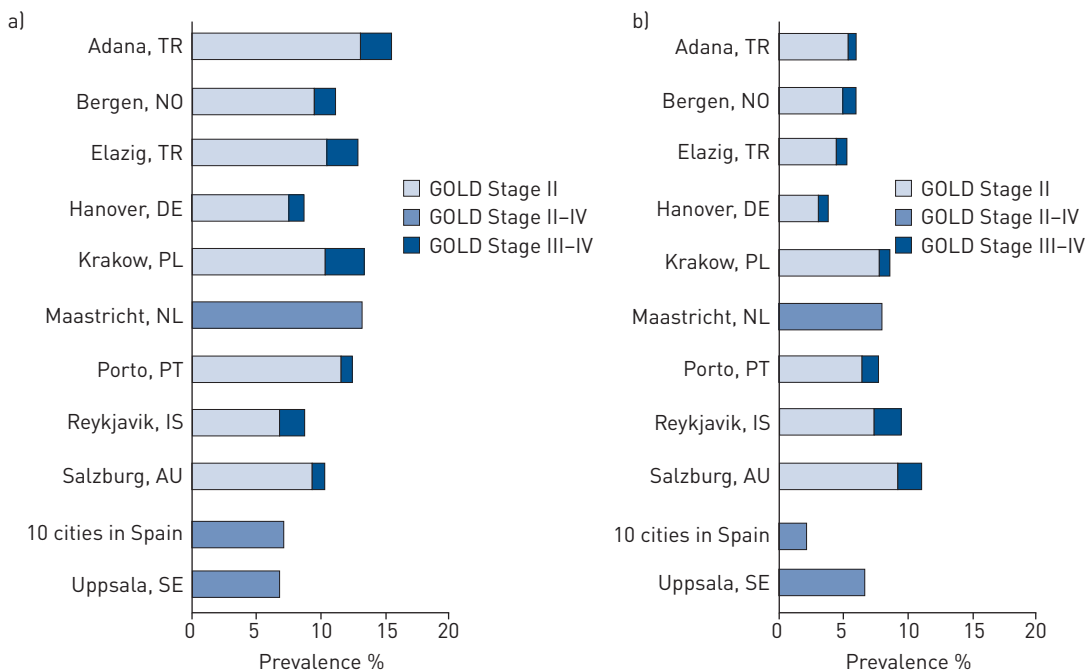


COPD is a chronic inflammatory process in the lower airways and the lung parenchyma caused by many factors that trigger and maintain inflammation. An imbalance between proteases and anti-proteases may be a contributory factor.

### *Tobacco smoke*

The most important and modifiable aetiological factor for COPD is smoking.

Smokers have a higher prevalence of respiratory symptoms and lung function abnormality, a greater annual rate of



**Figure 3** – Prevalence of chronic obstructive pulmonary disease (COPD) in a) men and b) women aged  $\geq 40$  years in European cities, by Global Initiative for Obstructive Lung Disease stage, ranked by national prevalence of current smoking. Data from multiple publications resulting from the Burden of Obstructive Lung Disease (BOLD) study.

decline in FEV<sub>1</sub>, and higher death rates from COPD than nonsmokers. Women may have more symptoms than men for the same number of pack-years smoked. About 40–50% of lifelong smokers will develop COPD, compared with only 10% of never-smokers. Passive exposure to cigarette smoke may also contribute to respiratory symptoms and impaired lung function in schoolchildren. However, not all smokers develop clinically significant COPD, which suggests that genetic factors may modify individual risk. The proportion of the risk of COPD attributable to smoking has been estimated as 40–60%, depending on how many risk factors have been taken into account.

Although never-smokers are less likely to have COPD and have less severe COPD than ever-smokers, never-smokers nonetheless comprise about one-quarter of those classified with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II+ COPD.

### *Occupational airborne exposure*

Several studies show that 30–40% of the general population report having been exposed to airborne pollutants at work (for further information, see chapters 7 and 24). When the exposure is sufficiently intense or prolonged, occupational dust, chemicals and vapours can cause COPD independently of cigarette smoking. Studies of general populations and working groups show that about 15–20% of COPD cases are due to occupational exposure. In never-smokers, the fraction of COPD attributable to occupational exposure is estimated to be 30%. A variety of occupations may represent an increased risk of COPD, such as mining, agriculture, and textile, paper, wood, chemical, and food processing.

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*Smoking  
cessation is the  
most important  
intervention  
that affects the  
prognosis of  
the disease*  
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## ***Outdoor and indoor pollution***

A high level of urban air pollution is harmful to individuals with COPD, as it can result in exacerbations and a poorer quality of life (for further information on air pollution, see chapter 6). The role of outdoor air pollution in Europe in causing COPD is unclear. The relative importance of short-term, high peak exposures compared with long-term, low-level exposures is not known. Heavy indoor air pollution caused by the use of biomass fuel is a risk factor for the development of COPD.

## ***Socioeconomic status***

The risk of developing COPD is inversely related to socioeconomic status based on education or income. The effects of various indicators of socioeconomic status may differ between men and women, and socioeconomic status may also reflect factors such as nutrition, overcrowding and air pollution, as well as genetic determinants.

## ***Early life environmental factors***

Smoking mothers, frequent respiratory infections and asthma in childhood, and bronchial hyperreactivity are important risk factors for COPD. The proportion of the risk of COPD attributable to these early childhood events may be as great as that attributable to smoking (see also chapter 4).

## ***Genetic factors***

The best documented genetic risk factor for COPD is hereditary  $\alpha_1$ -antitrypsin deficiency (see also chapter 3). However, in most populations, homozygous  $\alpha_1$ -antitrypsin deficiency is found in fewer than five people per 10 000. Polymorphisms of many genes or combinations of genes may increase (or decrease) the risk of an individual developing COPD. Individual genes may be related to specific phenotypes of COPD. Single genes, such as the gene encoding matrix metalloproteinase (MMP)-12, may be related to decline in lung function. Genome-wide studies of gene expression and genetic variation have provided exciting new avenues for future investigation and potentially new approaches to risk prediction and therapy.

## ***Clinical manifestations***



The most important symptoms of COPD are breathlessness on exertion and chronic cough with or without phlegm. The dyspnoea usually worsens over time but is often not present in mild or moderate COPD. The cough may be dry or productive. Cough and phlegm often precede dyspnoea on exertion by

many years. Other symptoms include wheezing and chest tightness. As the disease progresses and reaches the severe stages, fatigue, weight loss and anorexia may increase. To establish the diagnosis of COPD, lung function measurement by spirometry is necessary.

A characteristic of COPD is exacerbations or episodes of acute worsening of the respiratory symptoms. The most common causes of exacerbations are viral or bacterial infections. Increased air pollution also appears to precipitate exacerbations of COPD. Some patients are particularly prone to exacerbations while others are not. Two or more exacerbations during the previous year is the most important indicator of a future exacerbation.

Exacerbations accelerate the decline in lung function that characterises COPD, resulting in reduced physical activity, poorer quality of life, and an increased risk of death; they are also responsible for a large proportion of the healthcare costs attributable to COPD.

Patients with COPD often suffer from other diseases (comorbidities). The comorbidities may share common risk factors with COPD, in particular cigarette smoking. They may also represent extrapulmonary manifestations or complications of COPD, such as muscle dysfunction due to inactivity. Comorbidities may be secondary to treatment of COPD; for example, osteoporosis due to oral corticosteroid treatment. The most common comorbidities in COPD are ischaemic heart disease, anxiety and depression, osteoporosis, skeletal muscle dysfunction, gastro-oesophageal reflux, anaemia, lung cancer, diabetes and metabolic syndrome. Comorbidities contribute to the overall severity and manifestations of the disease. They can occur in mild, moderate or severe COPD and they increase the risks of hospitalisation and mortality of COPD independently.

The clinical effects of COPD show considerable inter-individual variation, depending on which respiratory symptoms predominate, the frequency of exacerbations, the level and rate of lung function decline and the amount of emphysema, as well as comorbidities. Various subtypes of the disease are often termed phenotypes of COPD.

## Prevention



Identification and reduction of exposure to risk factors are important steps in the prevention and treatment of COPD. All individuals who smoke should be encouraged to quit regardless of their disease status. In addition, smokers without COPD should be offered smoking-cessation advice.

Preventing passive smoking in fetal and early life is important to reduce the risk of COPD in adult life. Smoking cessation is the most cost-effective form of both primary and secondary intervention in COPD. On a global scale, reduction of exposure to smoke from indoor biomass combustion, particularly among women and children, is important to reduce the prevalence of COPD.

Prevention of COPD exacerbations is important: influenza and pneumococcal vaccination as well as treatment with inhaled long-acting bronchodilators and inhaled corticosteroids all work to reduce exacerbations and hospitalisations for COPD.





## Management



A COPD management programme includes the following four components: assessment and monitoring of disease; reduction of risk factors; management of stable COPD; and management of exacerbations. The goals of COPD management are to relieve symptoms, prevent disease progression, improve exercise tolerance, improve health status, prevent and treat complications and exacerbations, reduce mortality and prevent or minimise side-effects from treatment.

Important components of management are smoking cessation, medical treatment with bronchodilators as well as inhibitors of inflammation, physical exercise and, in advanced disease, oxygen therapy (see chapter 28).

Early rehabilitation after exacerbations is important (see chapter 29). The most effective component of pulmonary rehabilitation is physical exercise.

In the future, better classification of the different phenotypes of COPD is likely to enable implementation of personalised treatment, in which the characteristics of the patient together with the severity of the disease are the keys to choosing the best treatment option.

Comorbidities should be assessed at all stages of COPD. Differential diagnosis can often be difficult, as comorbidities with symptoms commonly seen in COPD may be overlooked, for instance heart failure or lung cancer causing breathlessness or depression presenting with fatigue. In general, any comorbidity should be treated as in patients who do not have COPD.

## Prognosis



COPD is a chronic, progressive disease showing great variation in its natural history. Spirometry providing data on FEV<sub>1</sub> and FVC is the most common measure of disease progression. A large cohort of patients with COPD of GOLD stage II+ followed up every 6 months for 3 years showed a mean annual decline in FEV<sub>1</sub> of 33 mL. An annual decline in FEV<sub>1</sub> >40 mL was seen in 38% of the patients, while 8% showed an average annual increase of 20 mL. Current smoking and emphysema are related to more rapid decline in FEV<sub>1</sub>.

In addition to rapid decline in FEV<sub>1</sub>, factors that indicate a poor prognosis in established COPD are frequent exacerbations, respiratory insufficiency, nutritional status and comorbidities.

Smoking cessation is the most important intervention that affects the prognosis of the disease.

## Future developments



There is a great deal of room for improvement in COPD care in Europe, and current trends suggest the following developments are possible and desirable.

- More accurate data on illness, exacerbations, natural history, cost and deaths, particularly in eastern Europe, will provide a stronger foundation for fighting COPD.
- Studies of the effectiveness of current prevention, education, medication, rehabilitation and terminal care will help to spread best practice and drive higher standards of COPD care.
- New therapeutic modalities will inhibit the decline in lung function.
- As smoking remains the key risk factor for COPD, several measures will reduce the burden of disease: more effective smoking cessation interventions and techniques to prevent people from starting to smoke; better surveillance of harmful occupational exposures; and protection in early childhood against harmful exposure and events that affect the lung.
- Governments, industry and the general public need to be made aware of the high burden of COPD in Europe. European countries should implement common strategies for effective prevention, diagnosis and treatment of this disabling and life-threatening disease.

## Research needs



Research is needed in six key areas related to COPD.

- As smoking rates in Europe are declining, the relative importance of other risk factors to COPD will increase. There is a need to know how this will affect the clinical manifestations and prognosis of the disease.
- Although spirometry is a prerequisite in COPD studies, more extensive characterisation of disease than that offered by spirometry is required. Novel imaging techniques and biomarkers offer the potential to characterise subgroups, or phenotypes, of COPD.
- Limited data are available about the prevalence, incidence and natural history of various phenotypes of COPD, and their economic burden on European societies.
- Our knowledge of the pathogenesis of COPD and how this can be modified is still limited. Novel molecular and genetic techniques offer promising possibilities for gaining important knowledge on disease mechanisms, which opens up possibilities for development of new drugs.
- Cohort studies should be conducted to assess the long-term natural history of COPD and its phenotypes.
- The lungs are extremely exposed to the environment. There are few data on how global warming will affect the risk factors for, and eventually the incidence of, COPD.



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