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SERIES "COMPREHENSIVE MANAGEMENT OF END-STAGE COPD"
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Definition, epidemiology and natural history of COPD

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) is the fifth cause of morbidity and mortality in the developed world and represents a substantial economic and social burden. Patients experience a progressive deterioration up to end-stage COPD, characterised by very severe airflow limitation, severely limited and declining performance status with chronic respiratory failure, advanced age, multiple comorbidities and severe systemic manifestations/complications.

COPD is frequently underdiagnosed and under-treated. Today, COPD develops earlier in life and is less gender specific. Tobacco smoking is the major risk factor for COPD, followed by occupation and air pollution. Severe deficiency for α_1-antitrypsin is rare; several phenotypes are being associated with elevated risk for COPD in the presence of risk factor exposure. Any patient presenting with cough, sputum production or dyspnoea should be assessed by standardised spirometry. Continued exposure to noxious agents promotes a more rapid decline in lung function and increases the risk for repeated exacerbations, eventually leading to end-stage disease.

Without major efforts in prevention, there will be an increasing proportion of end-stage patients who can live longer through long-term oxygen therapy and assisted ventilation, but with elevated suffering and huge costs. Smoking prevention and smoking cessation are the most important epidemiological measurements to counteract chronic obstructive pulmonary disease epidemics.

KEYWORDS: Air pollution, chronic obstructive pulmonary disease clinical/basic investigations, cor pulmonale, epidemiology of asthma/chronic obstructive pulmonary disease, smoking, spirometry

Chronic obstructive pulmonary disease (COPD) is one of the most important causes of morbidity and mortality worldwide [1], representing the largest fraction of mortality for respiratory diseases, which are the third most common cause of death (8%) in the 25 member states of the European Union (EU) [2]. However, these figures are likely to be underestimated [3, 4]; for instance, in only 21.7% and 45.5% of Danish COPD patients (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV) was COPD reported as the cause of death or mentioned in the death certificate, respectively [3].

Continuing increases in COPD prevalence and mortality are anticipated in the coming decades [5]. In 2004, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) issued COPD guidelines [6]. Another international guideline is issued and updated yearly by GOLD [7]. A concerted worldwide effort for increasing awareness on COPD has been called for by the World Health Organization (WHO) and the partners (respiratory, allergological and general practitioner societies, patients and governmental organisations) within the Global Alliance against chronic Respiratory Diseases (GARD) [8].

With the attempt to increase the awareness of the huge burden of respiratory diseases among public opinion and the policy makers, the ERS and the European Lung Foundation (ELF) published the *European Lung White Book* in 2003 [9]. The book contains comprehensive figures on the mortality, morbidity and costs of COPD. The ERS is now preparing the second edition, in line with the new opportunities offered by the EU for research on chronic respiratory diseases [10], which should help to alleviate the suffering of millions of citizens of Europe or from across the world.

For editorial comments see page 828.

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DEFINITION

Definitions of COPD by the ATS/ERS and GOLD are reported in table 1. Both point to the preventability and treatability of this inflammatory disease, in which airflow limitation (AL) is usually progressive and not fully reversible, and mention systemic or extrapulmonary elements, along with the role of exposure to noxious particles or gases.

The main components of COPD are chronic bronchitis and emphysema [11]. The former is ''defined by the presence of chronic or recurrent increase in bronchial secretions sufficient to cause expectoration. The secretions are present on most days for a minimum of 3 months per year for at least two successive years and cannot be attributed to other pulmonary or cardiac causes. Hyper-secretion can occur in the absence of airflow limitation.'' The latter is ''defined anatomically by permanent, destructive enlargement of airspaces distal to the terminal bronchioles without obvious fibrosis.''

Asthma, due to its pathogenesis and pathology, is generally excluded from the definition of COPD [7]; yet, the 1995 version of the ATS COPD guidelines [12] depicted a Venn diagram describing the overlaps among the three diagnostic labels in the general population.

Differential diagnosis of COPD comprises asthma, congestive heart failure (CHF), bronchiectasis, tuberculosis, operative bronchiolitis and diffuse panbronchiolitis [11]. Clinical history, chest examination, lung function tests and imaging techniques may help in the decision process. 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 1996, a very specific definition of end-stage pulmonary disease was pursued by the US National Hospice Organization (NHO) through a set of empirical criteria, with the aim of identifying patients eligible for hospice care, *i.e.* with expected survival of <6 months (table 2) [13]. Apart from being inaccurate, the aims are not COPD specific and arbitrarily define the last 6 months of life as end-stage disease, a rather short period.

A definition of end-stage COPD is based on very severe AL, severely limited and declining performance status, advanced age, multiple comorbidities, and severe systemic manifestations/complications of COPD with common underlying pathophysiological mechanisms (*e.g.* systemic inflammation and endocrine disturbances) (table 3) [14].

The use of an ''operational'' definition allows physicians to identify a substantial fraction of patients with chronic respiratory failure (CRF) in the general population, namely those with fairly advanced hypoxaemia or gas exchange impairment.

PREVALENCE AND INCIDENCE

Since 2000, an increasing number of epidemiological studies on COPD prevalence have been published (fig. 1) [22].

Dependence of estimates upon diagnostic criteria

Estimates ranging from 0.2% in Africa to 1.7% in the Western Pacific (including China) were elaborated from WHO data [15].

VIEGI *et al.* [23] indicated the large variability in prevalence estimates depending on definition of airways obstruction (AO). In adults aged 25–73 yrs from a general population sample of North Italy, AO prevalence rates ranged from 11% with the ERS criterion (forced expiratory volume in one second (FEV_1)/vital capacity (VC) % <88th percentile in males and <89th percentile in females) to 18.3% with the ''clinical'' criterion (which later became GOLD stage I+). Subsequently, CELLI *et al.* [16], in the US national adult representative sample of the National Health And Nutrition Examination Survey (NHANES) III, showed values ranging from 7.7% for self-reported diagnosis of chronic bronchitis or emphysema to 16.8% with GOLD stage I+. Furthermore, the extensive review of HALBERT *et al.* [24] reported prevalence rates ranging 0.23–18.3%, with the lowest rates (0.2–2.5%) based on WHO expert opinions. Recently, HALBERT *et al.* [17], through a meta-analysis, estimated a prevalence of 9.2% using a spirometric definition in adults aged >40 yrs, *i.e.* almost 10 times higher than the WHO estimate [5].

In the WHO Large Analysis and Review of Housing and Health Status Study (LARES) [18], prevalence of reported

TABLE 1 Chronic obstructive pulmonary disease (COPD) definitions

Source	Definition
ATS and ERS[#]	''A preventable and treatable disease state 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, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.''
GOLD[¶]	''A preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.''

ATS: American Thoracic Society; ERS: European Respiratory Society; GOLD: Global Initiative for Chronic Obstructive Lung Disease. [#]: taken from [6]; [¶]: taken from [7].

TABLE 2 Definition of end-stage pulmonary disease to identify patients eligible for hospice care

Severe chronic lung disease

1) Disabling dyspnoea at rest, poor or no response to bronchodilators, resulting in decreased functional capacity, *e.g.* bed-to-chair existence, fatigue and cough (documentation of FEV_1 <30% pred after bronchodilator is objective evidence for disabling dyspnoea, but is not necessary to obtain)
2) Progression of end-stage pulmonary disease, as evidenced by increasing visits to the emergency dept or hospitalisations for pulmonary infections and/or respiratory failure or increasing physician home visits prior to initial certification (documentation of serial decrease of FEV_1 >40 $mL \cdot yr^{-1}$ is objective evidence for disease progression, but is not necessary to obtain)

Either hypoxaemia at rest on room air, as evidenced by P_{O_2} ⩽55 mmHg

Or oxygen saturation ⩽88% on supplemental oxygen determined either by arterial blood gases or oxygen saturation monitors

Or hypercapnia, as evidenced by P_{CO_2} ⩾50 mmHg

Right heart failure secondary to pulmonary disease (cor pulmonale), *e.g.* not secondary to left heart disease or valvulopathy

Unintentional progressive weight loss >10% of body weight over the preceding 6 months

Resting tachycardia >100 $beats \cdot min^{-1}$

FEV_1: forced expiratory volume in one second; % pred: % predicted; P_{O_2}: partial pressure of oxygen; P_{CO_2}: carbon dioxide tension. 1 mmHg=0.133 kPa. Data from [13].

chronic bronchitis and emphysema in the past year was 6.2% among adults in eight European cities.

In the Northern Ireland Cost and Epidemiology of Chronic Obstructive Pulmonary Disease (NICECOPD) study [19], the estimated prevalence of obstructive lung disease in those aged 40–69 yrs was 14.4% (6.3% COPD).

When considering mature adults and the elderly, the project PLATINO (Proyecto Latinoamericano de Investigación Obstrucción Pulmonar) showed prevalence estimates ranging from 11.9% in Mexico City (Mexico) to 19.4% in Montevideo (Uruguay) [20]. Such elevated figures were confirmed in Salzburg (Austria), within the Burden of Obstructive Lung Disease (BOLD) initiative. The overall prevalence of COPD at stage I or higher was 26.1%, regardless of sex, while at stage II or higher the prevalence was 10.7%. A doctor diagnosis of COPD was reported by only 5.6% of participants [21].

Recent studies from Scandinavia provided incidence rates, *i.e.* estimates of newly occurring cases in follow-up surveys of population samples (fig. 2) [25–29].

In a symptomatic cohort in Northern Sweden, LINDBERG *et al.* [25] reported a 10-yr cumulative incidence rate of 15.3 and 11.8% in males and females, respectively (range: 9.4% in persistent never-smokers to 24.5% in persistent smokers). LINDBERG *et al.* [26] recently reported on an age-stratified general population sample of middle-aged and elderly individuals. The 7-yr cumulative incidence of COPD was 11.0 and 4.9%, respectively, according to GOLD and GOLD II. It was significantly higher in smokers (18.8 and 10.6%, respectively). Most respiratory symptoms at study entry were markers of increased risk for incident COPD, indicating the importance of GOLD stage 0.

JOHANNESSEN *et al.* [27], in a 9-yr follow-up of a general population sample in Bergen (Norway), found cumulative incidence rates of GOLD-defined COPD of 8.6% in males and 3.6% in females, and of 1.8% in never-smokers and 22.7% in current smokers with a lifetime cigarette consumption of >20 pack-yrs.

In total, 8,045 males and females aged 30–60 yrs with normal lung function at baseline were followed for 25 yrs in Copenhagen, Denmark [29]. Abnormal lung function ranged from 4% of male never-smokers (9% in females) to 41% of male continuous smokers (31% in females). The 25-yr cumulative incidences of moderate and severe COPD were 20.7 and 3.6%, respectively.

Among 1,711 middle-aged males from two rural Finnish cohorts within the Seven Countries Study [28], the 30-yr cumulative incidences of chronic bronchitis and COPD were 42 and 32%, respectively, in continuous smokers, compared with 22 and 12% in never-smokers, respectively. During the follow-up, subjects with chronic bronchitis had a 252 mL lower forced expiratory volume.

Measurement of disease severity

In the Obstructive Lung Disease in Northern Sweden (OLIN) study [30], the prevalence of mild, moderate and severe British Thoracic Society (BTS)-defined COPD was 5.3, 2.2 and 0.6%, respectively (GOLD-COPD: mild 8.2%, moderate 5.3%, severe 0.7% and very severe 0.1%). All subjects with severe COPD were symptomatic.

In the Po Delta survey, Italy, the prevalence of GOLD-COPD, in males and females, respectively, was as follows. Mild: 12.3 and 7.3%; moderate: 4.5 and 2.2%; and severe–very severe: 0.4 and 0.3% [31]. People with chronic cough or phlegm ranged from 20–30% in the mild category to ~80% in the severe–very severe category.

Lung function impairment represents the severity of AL, but the end-stage of COPD is accompanied by other clinical features, which are not easily measurable in epidemiological settings [14]. Pathophysiological mechanisms involved in the advanced stages of the disease lead to CRF. Long-term oxygen therapy and noninvasive mechanical ventilation are the two major treatments for respiratory failure (RF), according to standardised criteria. The use of these data, as indicated below, may help identify the fraction of COPD patients with fairly advanced hypoxaemia or gas exchange impairment.

Overcoming old myths

For many years it has been considered that only ~15% of smokers would develop COPD [32], *i.e.* those particularly susceptible to the effect of smoking, as indicated in the figure of FLETCHER and PETO [33], which represents the natural history

TABLE 3 Definition of end-stage chronic obstructive pulmonary disease (COPD) based on clinical features

Domain	Qualification
Airflow limitation	Very severe (FEV_1 <30% pred) COPD
Performance status	Severely limited and declining
Other criteria[#]	Advanced age
	Presence of multiple comorbidities
	Severe systemic manifestations/complications of COPD (*e.g.* body composition alterations, peripheral muscle dysfunction, respiratory muscle dysfunction, osteoporosis, pulmonary hypertension, cardiac impairment, fluid retention/oedema)

FEV_1: forced expiratory volume in one second; % pred: % predicted. [#]: at least one. Reproduced and modified from [14].

of FEV_1 with ageing. Indeed, according to LUNDBÄCK *et al.* [34], if people continue to smoke, the AO prevalence rate could be as high as ~50% in those aged >70 yrs. Likewise, MANNINO *et al.* [35], in the elderly (75–84 yrs) of the US NHANES III general population sample, reported values as high as 60% in smokers, 50% in ex-smokers and 30% in nonsmokers.

Moreover, COPD has always been considered a disease of those aged >50 yrs. However, according to DE MARCO *et al.* [36], the disease is already present at the age of 20–45 yrs, as reported in the European Community Respiratory Health Survey (ECRHS) study. Indeed, the prevalence rates were: 11.8% in the pre-clinical stage when AO is not yet developed (GOLD stage 0), and 2.5 and 1.1% in GOLD stages I and II+, respectively.

COPD has also been traditionally regarded as a disease of males [37]. However, in 2000 the absolute number of USA COPD deaths in females overtook that of males [38]. Furthermore, using a large database of medical practitioner records in the UK, SORIANO *et al.* [39] demonstrated that between 1990 and 1996, COPD became more frequent in 20–44-yr-old females. COPD was more frequent in 45–65- and >65-yr-old males, but gender-related differences decreased. In the ECRHS study, CERVERI *et al.* [40] found that female gender was significantly associated with chronic cough and phlegm (adjusted odds ratio (OR) 1.22).

In the Tucson Epidemiological Study of Airways Obstructive Disease, SHERRILL *et al.* [41] observed that physician-confirmed COPD was reported more frequently among males (13.6%) than females (9.1%), although there were no significant differences in concomitant diseases (4.7 and 3.9% in males and females, respectively). However, females reported significantly more concomitant asthma and chronic bronchitis (45.3%) than males (19.7%).

COPD and asthma are regarded as two different entities, mainly for different cellular components [42]. However, similarities in risk factors and in inflammatory and hyperreactive disease mechanisms recently revitalised the Dutch hypothesis [43]. Epidemiologically, the two diseases partly coexist in the general population. In fact, SORIANO *et al.* [44] first described the nonproportional Venn diagram of obstructive lung diseases in USA and UK data. In Italy, VIEGI *et al.* [45] found that, among those with a medical diagnosis of asthma,

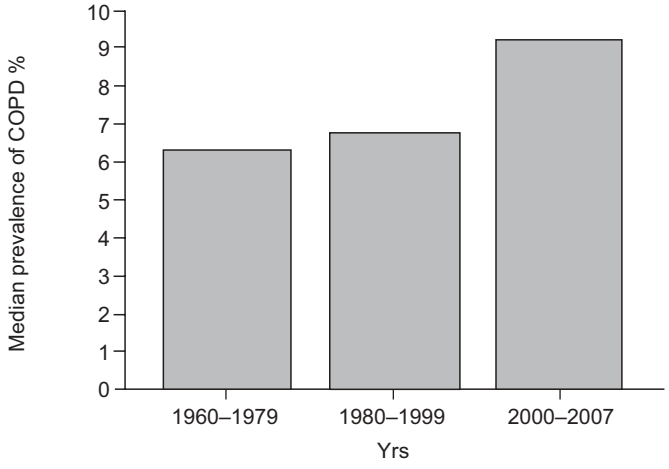

FIGURE 1. Chronic obstructive pulmonary disease (COPD) prevalence by period of survey publication. The period 2000–2007 includes data from references [15–21]. Reproduced and modified from [22].

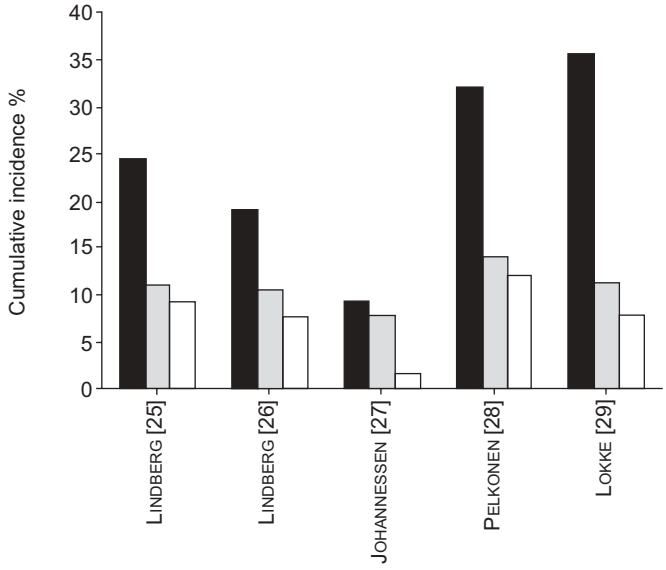

FIGURE 2. Incidence rates of chronic obstructive pulmonary disease-related conditions in Nordic European Countries. ■: current smokers; ■: former smokers; □: never-smokers. Studies are indicated as first author [ref.].

14% in Po Delta and 11% in Pisa (Italy) also reported chronic bronchitis or emphysema, whereas, among those with chronic bronchitis or emphysema, 31% in Po Delta and 14% in Pisa also reported a medical diagnosis of asthma. There were similar patterns after stratifying the populations by sex [31]. In the Tucson (USA) longitudinal study, active asthma at baseline was associated with a significantly increased risk of developing incident chronic bronchitis (OR 10.0), emphysema (OR 17.0) or COPD (OR 12.5) at follow-up [46].

Screening

In order to overcome COPD underdiagnosis, some screening programmes were performed in the population at risk. In a primary care setting in Sweden, 27% of the 512 invited smokers (aged 40–55 yrs) showed AO (85% mild, 13% moderate and 2% severe, according to ERS classification) [47]. Similar findings were found in Spain (AO: 22% of 164 high-risk smokers aged 40–76 yrs [48]) and in the Netherlands (FEV_1 <80% predicted: 18% in 169 smokers aged 35–70 yrs [49]). A more recent Dutch study, in 702 male smokers aged 40–65 yrs, reported figures of GOLD stage I ranging from 19% in individuals aged 40–44 yrs to 38% in individuals aged >55 yrs [50].

A promising approach in the early detection of COPD in high-risk populations using spirometric screening comes from Poland. AO spirometric signs were found in 24.3% of smokers aged >40 yrs with a smoking history of >10 pack-yrs (n=11,027) [51]. After a minimal anti-smoking intervention, the validated smoking cessation rate in those with AO was 16.3%, compared with 12.0% in those with normal spirometric parameters ($p<0.001$) [52]. The study then continued with a total of 110,355 subjects (aged 53.5 ± 11.5 yrs; 58.2% males), of which 64% were current smokers, 25.1% former smokers and 10.9% lifelong nonsmokers. In total, 20.3% showed signs of AL (mild in 7.6%, moderate in 6.7% and severe in 5.9%) [31]. AL was found in 23% of smokers aged $\geqslant$40 yrs with a history of $\geqslant$10 pack-yrs. Therefore, a large-scale voluntary spirometry screening of the population with high risk for COPD detects a large number of subjects with AL at a reasonable cost.

Lack of disease awareness

COPD is underestimated not only by healthcare providers but also by patients. In an international survey, 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 aged <65 yrs in the previous year) and frequent healthcare use [53].

In a Spanish telephone survey among 6,758 subjects aged >40 yrs, up to 24% reported at least one chronic respiratory symptom and 20.9% had a self-reported respiratory diagnosis [54]. Only 60% of those with chronic symptoms had consulted a physician. Of them, only 45% had undergone spirometry, which was requested more frequently by pulmonologists than by general practitioners (GPs; 67.6 *versus* 28.6%; $p<0.001$). The term COPD was identified by only 8.6% of the participants.

A study comparing prevalence estimates of asthma or COPD derived from self-reports in a health interview survey (n=19,685) and from 104 GPs' medical records was carried out in the Netherlands [55]. The prevalence of self-reported asthma or COPD (9.7%) was almost twice as high as the prevalence based on GPs' information (5.2%).

In Italy, a comparison of the prevalence of four chronic conditions for 432,747 patients from GPs, records (Health Search Database; HSD) and 119,799 individuals from a Health Interview Survey was carried out [56]. Similar prevalence for diabetes and hypertension but lower HSD prevalence for COPD and gastroduodenal ulcer was reported.

Comorbidity

In recent years an increasing interest has been devoted to comorbidity (table 4).

In 2006, the Presidents of the international respiratory societies [57] criticised the approach used in a report on mortality in China [58], in which respiratory diseases were not among the most important causes of death. Cardiopulmonary illnesses had been included among the cardiovascular diseases (CVD). The re-analysis showed that, if cardiopulmonary diseases are included among the respiratory diseases, the latter are a frequent cause of death in China [59].

Indeed, in Canada, CVD morbidity and mortality rates were higher in a large cohort of COPD patients aged $\geqslant$55 yrs than in the general population (standardised rate ratios of 1.9 and 2.0, respectively) [60]. More hospitalisations for CVD than for COPD itself were reported. Among CVD, heart failure represented the most frequent cause of hospitalisation (58.8 per 1,000 person-yrs (PY)). CVD and, more specifically, ischaemic heart disease (19.6 per 1,000 PY) were reported as a more frequent cause of death than COPD itself (15.5 per 1,000 PY).

When COPD as an associated cause of death was analysed together with the underlying causes in France, a significant association was found for CVD, ischaemic heart disease, lung cancer and asthma [61]. GUDMUNDSSON *et al.* [62] analysed mortality in COPD patients discharged from hospital in Scandinavia, and pointed out the negative effect on survival by lower health status (total St George's Respiratory Questionnaire score >60) and diabetes.

In the USA, COPD increased both frequency and mortality of hospitalisations associated with several comorbidities, such as hypertension, ischaemic heart disease, diabetes, pneumonia, CHF, RF, pulmonary vascular disease and thoracic malignancy [63]. Indeed, from 1979 to 2001 the percentages of hospital discharges with COPD increased from <5% to ~12%, mostly due to the increased proportion of those with COPD as secondary diagnosis.

In addition, a negative COPD effect on the survival of patients with coronary heart disease having percutaneous coronary intervention was reported [64, 65], as well as on prognosis of patients with acute myocardial infarction (MI), especially when associated with CHF [66].

In the Kaiser Permanente Medical Care Program, a large series of comorbidities were found to be significantly associated with COPD: obesity, diabetes, hypertension, hyperlipidaemia, ventricular tachycardia/ventricular fibrillation/cardiac arrest, atrial fibrillation, other arrhythmias, angina, MI, stroke, pulmonary embolism, CHF and renal disease [67]. An excess

TABLE 4 Main chronic obstructive pulmonary disease comorbidities recently reported

Respiratory	
	Respiratory failure, asthma, allergy, pneumonia, pulmonary embolism, pulmonary vascular disease, respiratory infections, rhinitis
Cardiovascular	
	Ischaemic heart diseases, hypertension, congestive heart failure, VT/VF/cardiac arrest, atrial fibrillation, other arrhythmias, angina, myocardial infarction, stroke, peripheral atherosclerosis
Malignant	
	Lung cancer, thoracic malignancy, malignancies
Endocrin	
	Obesity, diabetes, hyperlipidaemia, nutritional depletion
Gastrointestinal	
	Digestive ulcer, gastro-oesophageal reflux symptoms, faecal incontinence (females >40 yrs of age), *Candida esophagitis* in elderly patients
Renal disease	
Osteo-articular	
	Bone fractures, fractures, articular disorders, arthritis, osteoporosis or osteopaenia
Ocular	
	Cataracts, glaucoma
Psychiatric	
	Depression/anxiety
Others	
	Skin diseases, migraine, poor health-related quality of life

VT: ventricular tachycardia; VF: ventricular fibrillation.

of CVD comorbidities in COPD patients in the Veterans Administration Medical System hospitals was also reported, with special remark for CHF (prevalence of 24.4% in cases *versus* 13.5% in controls) [68]. Indeed, according to the Atherosclerosis Risk in Communities (ARIC) study, in white Americans the level of FEV_1 is negatively related to the incidence of stroke [69]. With respect to those with FEV_1 >105% pred, relative hazard risks were 1.26 for those with 105–96% pred, 1.52 for those with 95–85% pred, and 1.59 for those with <85% pred.

In 1998, SORIANO *et al.* [70], using the UK General Practice Research Database, compared incident COPD patients (physician diagnosed, n=2,699) with age, sex, time and practice-matched cohorts. Among incident COPD patients, the total sum of diagnoses related to major organ systems was higher and a frequency of >1% within the first year after diagnosis was observed for angina, cataracts, bone fractures, osteoporosis, pneumonia and respiratory infections (RI), with the highest being angina with 4.0%. COPD patients were at increased risk for pneumonia (relative risk (RR) 16.0), osteoporosis (RR 3.1), RI (RR 2.2), MI (RR 1.7), angina (RR 1.7), fractures (RR 1.6) and glaucoma (RR 1.3; all $p<0.05$).

In the WHO LARES study [18], the following comorbidities were significantly associated with reported chronic bronchitis and emphysema in the previous year: asthma, allergy, hypertension, osteoporosis, articular disorders, digestive ulcer, cataract, skin diseases, migraine, depression, and, at borderline level, cerebral stroke, diabetes and malignant tumour.

Over two-thirds of COPD patients report one or more comorbidity. In the Longitudinal Aging Study Amsterdam, COPD was present in 10.4% of the 2,497 subjects with different index diseases at baseline [71]. Of them, 69.4% reported at least one comorbidity (cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, arthritis, malignancies, other).

Even the prevalence of gastro-oesophageal reflux symptoms, a well-known comorbidity with asthma, was shown to be significantly higher in patients with COPD [72], as well as prevalence of faecal incontinence in females aged >40 yrs (OR 1.9) [73] and *Candida esophagitis* in elderly patients [74].

In a small Danish population of patients with severe COPD [75], 68% of the participants had osteoporosis or osteopaenia, but glucocorticoid use alone could not explain the increased prevalence of osteoporosis. Thus, it was stated that there is a significant need to screen patients with COPD to select the individuals at risk of fracture and to initiate prophylaxis or treatment for the disease.

In the Netherlands, the prevalence of nutritional depletion (defined as body mass index (BMI) $\leqslant 21$ $kg \cdot m^{-2}$ and/or fat-free mass index (FFMI) $\leqslant 15$ or $\leqslant 16$ $kg \cdot m^{-2}$ in females and males, respectively) was high (27%) in a multicentre outpatient COPD population (389 patients with moderate-to-severe COPD) [76]. Prevalence of normal BMI and low FFMI was 15%, and of low BMI and low FFMI was 11%. Low BMI and low FFMI were significantly more frequent in female than in male COPD patients, 18 and 40% *versus* 10 and 20%, respectively (both $p<0.01$). In addition, depletion of fat-free mass was associated with impaired peripheral muscle strength, independent of disease severity.

In the Pisa Prospective Study, information on cough, rhinitis and other risk factors was collected by a standardised questionnaire from 1,670 subjects (aged $\geqslant 15$ yrs, without history of cough apart from colds at the baseline survey) [77]. After adjustment for age, sex, asthma status, smoking and

occupational exposure, rhinitis remained significantly associated with an increased risk for both any cough (OR 1.8, 95% confidence interval (CI) 1.2–2.6) and for occasional and chronic cough separately (OR 2.2, 95% CI 1.1–4.5 and OR 1.7, 95% CI 1.1–2.6, respectively).

Another important domain is the psychiatric comorbidity. Prevalence rates up to 47% of clinically important symptoms of depression/anxiety have been reported [78]. Furthermore, smoking patients with asthma or COPD were shown to be at an increased risk of becoming depressed (OR 3.52, 95% CI 2.04–6.07) with respect to nonsmokers [79].

Indeed, COPD has a negative impact on health-related quality of life (HRQoL) [80]. In a large multicentre observational study, using a generic quality-of-life questionnaire, the SF-12 (with the physical (PCS-12) and the mental (MCS-12) component summary scores), compared with the reference population, patients with COPD aged >40 yrs had a reduction of PCS-12, even in mild stages of the disease. The correlation with FEV_1 was higher for PCS-12 ($r=0.38$) than for MCS-12 ($r=0.12$). Predictors for both HRQoL components were sex, FEV_1, use of oxygen therapy and number of visits to emergency rooms and hospital admissions. Moreover, HRQoL, as assessed by the SF-36V, was demonstrated as an independent predictor of mortality, hospitalisation and outpatient utilisation in persons with self-reported obstructive lung disease in a large cohort of veterans with reported asthma or COPD [81].

ECONOMIC BURDEN

In 2001, according to the ERS *European Lung White Book* [9], the overall annual cost (excluding mortality and rehabilitation) for COPD in Europe was €38.7 billion (€4.7 billion for ambulatory care, €2.7 billion for drugs, €2.9 billion for inpatient care and €28.4 billion for lost work days).

After the international study mentioned previously [53], a series of national cost estimates were published in 2003. For example, in Italy, DAL NEGRO *et al.* [82] estimated the mean social cost per patient as €6,365 for severe condition (Medical Research Council dyspnoea scale). According to MASA *et al.* [83], in Spain the cost per person of severe COPD was more than three and more than seven times that of moderate and mild COPD, respectively. In Sweden, the costs for hospitalisations represented the largest expenditure in those with FEV_1 <40% pred, accounting for ~60% of direct costs [84].

A comparison of the costs of COPD in different countries (Spain, USA, Sweden, the Netherlands and Italy) was published by CHAPMAN *et al.* [22]. Global annual costs for individual European countries ranged €109–541 million, whilst annual costs per patient were €151–€3,912.

Average total medical resource consumption of a COPD patient per year was estimated at €4,366 by the French SCOPE (SoCiO-Pharmaco-Economique de la BPCO en France) study [85]. Of this cost, 41% was directly related to COPD follow-up, 25% to COPD-related complications (mainly exacerbations) and 34% to other diseases. Over one-third of the total direct COPD cost was related to hospitalisations and 31% to drug consumption. COPD-related costs increased markedly with severity based on FEV_1. The total medical consumption of COPD patients in France was €3.5 billion and accounted for 3.5% of the total medical expenditures.

Through a screening of the Danish Patient Registry for patients admitted with COPD diagnoses in 1998–2002, the gross cost of treating COPD patients corresponded to 10% of the total cost of treating patients aged >40 yrs [86]. The net cost for COPD patients was €256 million (6% of the total). The incidence of inpatient hospital admissions was almost four-times higher in the COPD population, who also contacted the GP 12 times more per year, but there was no significant difference for specialist and paramedic treatment in the primary care sector. Only one-third of the COPD costs were due to treatment of COPD as the primary diagnosis, whilst the remaining two-thirds were mainly due to admissions for other diseases such as CVD, other respiratory diseases and cancer.

Even the economic burden of COPD is likely to be underestimated since, for example, the economic value of the care provided by family members is not generally acknowledged. Long-term home care provided by relatives for patients with severe COPD often has a negative impact on professional careers, not only for patients but also for other family members. Thus, COPD represents a very important threat to global economies.

RISK FACTORS

Conventionally, risk factors are subdivided into endogenous or host risk factors and exogenous or environmental risk factors [37]. Risk factors were shown to be differently associated with AO definitions in the current authors' general population study (table 5) [23].

Tobacco smoke

According to the 2004 US Surgeon General Report on ''The Health Consequences of Smoking'' [87], the available epidemiological evidence is sufficient to infer a causal relationship between active smoking and COPD morbidity and mortality; thus, the elimination of smoking could largely prevent COPD.

Age of starting smoking, total pack-yrs smoked and current smoking status are all predictive of COPD mortality. Age-standardised mortality rate per 1,000 males·yr^{-1} calculated by DOLL *et al.* [88] in a 50-yr observation of male British doctors were as follows: 0.64 in former cigarette smokers and 1.56 in current cigarette smokers (stratifying by consumption: 1.04, 1.41 and 2.61 in 1–14, 15–24 and ⩾25 cigarette·day^{-1}, respectively).

Active cigarette smoking is consistently associated with an increased risk for cough, phlegm, wheezing and dyspnoea. The occurrence of respiratory symptoms increases with the number of cigarettes smoked and decreases with smoking cessation. In the 11-yr community cohort Hordaland County Study in Norway, ex-smokers had higher cumulative remissions for several respiratory symptoms (morning cough, chronic cough, phlegm cough, attacks of dyspnoea, wheezing) than persistent smokers, while the remission of symptoms decreased with pack-yrs (statistically significant for phlegm cough, chronic cough and dyspnoea grade 2) [89].

Active smoking in adulthood causes a premature onset of an accelerated age-related decline in lung function. As the amount of cigarette smoking increases, the rate of decline increases. For

TABLE 5 Increased risks (%) of getting a chronic obstructive pulmonary disease (COPD) definition[#] by sex associated with some risk factors

Variables	ERS %		Clinical %		ATS %	
	Males	Females	Males	Females	Males	Female
Age[¶]	NS	NS	71***	85***	63***	89***
Height[+]	NS	NS	34*	46*	49***	28§
Pack-yrs[¶]	22***	36*	30***	45**	32***	34*
Familial history for COPD	NS	NA*	90**	NS	53*	NS
Childhood respiratory infections	63*	81**	39§	71*	55*	NS
Work exposure to dusts/chemicals	NS	NS	NS	NA§	53**	NS
Low socioeconomic condition	NS	NS	NS	NS	41§	NS

ERS: European Respiratory Society; ATS: American Thoracic Society; NS: nonsignificant; NA: not applicable, protective result in the multiple logistic regression analysis. [#]: derived by multiple regression models; [¶]: expressed in decades; [+]: expressed in dm; [§]: borderline significance (0.1>p>0.05). *: p<0.05; **: p<0.01; ***: p<0.001. Data from [23].

some smokers, the increased rate of decline eventually results in an FEV1 level associated with dyspnoea and a limitation of activities; at this level the clinical diagnosis of COPD is usually made [87]. Rates of FEV1 decline associated with tobacco smoke in some relevant longitudinal studies [90–93] are shown in figure 3.

Sustained cessation from smoking is associated with a return of the rate of decline in pulmonary function to that of never-smokers. The highest benefits are seen in quitters at younger ages. In the Lung Health Study (LHS), sustained quitters lose lung function at a considerably slower rate than continuing smokers (27 mL·yr^{-1} *versus* 60 mL·yr^{-1}), with intermittent quitters' data lying in between (48 mL·yr^{-1}) [94]. COPD patients who stopped smoking during the first year of the trial had a 47 mL FEV1 increase compared with a 49 mL FEV1 decrease among continuing smokers; those with the highest cigarette consumption before quitting had the largest improvements in FEV1 levels [95].

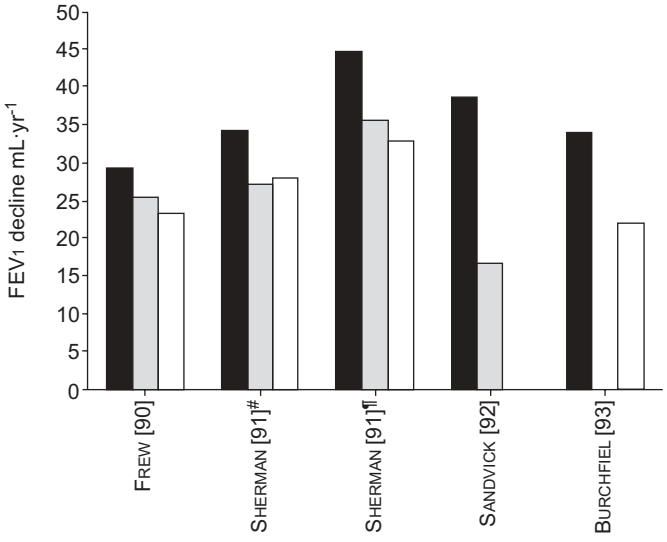

FIGURE 3. Rates of forced expiratory volume in one second (FEV1) decline associated with tobacco smoke in longitudinal studies. ■: current smokers; ■: former smokers; □: never-smokers. [#]: males; [¶]: females. Studies are indicated as first author [ref.].

In large cohort studies, exclusive pipe smoking was found to be associated with higher mortality rates from COPD (RR 2.98) [96], while exclusive cigar smoking was associated with higher risk for COPD (RR 1.45) [97].

According to the 2006 Surgeon General Report on The Health Consequences of Involuntary Exposure to Tobacco Smoke, the available evidence is suggestive, but not sufficient, to infer a causal relationship between environmental tobacco smoke (ETS) exposure and risk for COPD [98].

However, in US adults aged 55–75 yrs, an increased risk of COPD was observed with elevated home (OR 1.55) and work ETS exposure (OR 1.36). The population attributable fraction was 11 and 7% for home and work ETS exposure, respectively [99]. In a longitudinal analysis of the same study, the highest level of baseline cotinine was associated with worse COPD severity (4.7 points) [100].

ETS exposure was also related to an increased risk of hospital readmission for COPD (hazard ratio 1.63) [101]. In Italian general population samples, ETS exposure both to husbands' smoking and smoking in workplaces was a significant risk factor in females for respiratory symptoms/diagnosis, including diagnosis of asthma or chronic bronchitis/emphysema (OR 2.24) [102]. Moreover, analyses in the elderly showed a trend of higher occurrence of acute respiratory symptoms in relation to ETS exposure both in the winter (31% in ETS exposed *versus* 29% in unexposed) and in the summer (33 *versus* 16%; p<0.001), while the presence of ETS at home was associated with a decrease in the mean daily peak expiratory flow (effect estimate -19.2 L·min^{-1}; p<0.01) [103].

Other studies on the association between ETS and COPD were recently reviewed [104]. Smokers with COPD have higher tobacco consumption, higher dependence on nicotine and higher concentrations of carbon monoxide in exhaled air [105]. Furthermore, the level of nicotine dependence is associated with a higher risk for COPD [106].

Although smokers with respiratory complaints seem more motivated to stop smoking, COPD patients are a difficult target for smoking cessation. An ERS Task Force issued guidelines for smoking cessation in patients with respiratory diseases to ensure that pulmonary physicians act to help COPD patients in quitting smoking [107].

Air pollution

The association of COPD and outdoor air pollution is clear (table 6) [108] and biologically plausible [109]. Many studies confirmed an excess of cardiopulmonary deaths with increased objective measures of air pollution [110, 111] or with a proxy of exposure as home residence near busy roads [112].

Also reported were increased prevalence rates of COPD diagnosis or symptoms in urban and more polluted areas [113–116], and elevated risk due to pollutants for COPD or respiratory hospitalisation [117–119] and for disease parameters in advanced COPD panels [120].

The ''urban factor'' is still important for chronic bronchitis, as recently demonstrated by SUNYER *et al.* [121]. The prevalence and new onset of chronic phlegm during follow-up were associated with traffic intensity (adjusted OR for constant traffic 1.86), as well as home outdoor NO_2 (OR >50 $\mu g \cdot m^{-3}$ *versus* <20 $\mu g \cdot m^{-3}$ of 2.71) among females. Similar results were obtained with chronic productive cough.

Recently, in a follow-up from 10–18 yrs of age, particle and gaseous pollutants were found by GAUDERMAN *et al.* [122] to be associated with reduced maximal attainment in lung function and with increased proportion of abnormal FEV_1, *i.e.* with risk factors for developing COPD later in life. The same authors subsequently reported that children who lived within 500 m of a motorway had deficits in 8-yr growth of FEV_1 (-81 mL), compared with children who lived $\geqslant$1,500 m from a motorway [123]. These at-risk children showed pronounced deficits in attained lung function at 18 yrs of age.

The beneficial effect of reducing air pollution on COPD patients was demonstrated by the decrease of respiratory death rates in Dublin (Ireland) after the introduction of a ban for marketing, sale and distribution of bituminous coals [124], as well as by the reduced proportional hazard mortality rate ratios for total, cardiovascular and respiratory mortality with decreasing particulate matter (PM) with a 50% cut-off aerodynamic diameter of 2.5 μm in the US six city study [125].

TABLE 6 Adverse health effects of air pollution linked to chronic obstructive pulmonary disease

Mortality
Increased incidence of lower respiratory tract infections
Increased exacerbations
Less ability to cope with daily activities
Increased frequency and duration of hospitalisations
Increased emergency ward or physician visits
Increased pulmonary medication
Decreased pulmonary function
Reduction in FEV_1 or FVC associated with clinical symptoms
Increased prevalence of wheezing in the chest apart from colds
Increased prevalence or incidence of chest tightness
Increased prevalence or incidence of cough/phlegm requiring medical attention

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity. Data from [108].

Common indoor pollutants are ETS, PM, NO_2, CO, volatile organic compounds and biological allergens. In developing countries, relevant sources of indoor pollution include biomass and coal burning for cooking and heating. Concentrations of these pollutants can be several times higher indoors than outdoors. Indoor air pollution may increase the risk of irritation phenomena, allergic sensitisation, acute and chronic respiratory disorders and lung function impairment. According to recent conservative estimates, 1.5–2 million deaths per year worldwide could be attributed to indoor air pollution; ~1 million of these deaths occur in children aged <5 yrs due to acute RI, and significant proportions of deaths occur in females due to COPD and lung cancer. Today, indoor air pollution ranks 10th amongst preventable risk factors contributing to the global burden of disease [126].

Obstructive airway disease is common in females exposed to biomass smoke [127], who develop COPD with clinical characteristics, quality of life and increased mortality similar in degree to that of tobacco smokers [128].

Also in the case of indoor pollution, there is evidence that prevention works; for example, through instalment of a chimney for a stove in China the risk of developing COPD was decreased [129].

Occupational exposure

According to an estimate through workforce data and the Carcinogen Exposure (CAREX) database [130], worldwide in 2000 there were 318,000 deaths from COPD and nearly 3,733 million disability-adjusted life-yrs (DALYs) for COPD due to exposure to occupational airborne particulates. The figures for Europe were 39,300 deaths and 468,000 DALYs.

The population attributable risk from occupational exposure is estimated at ~15% by the ATS (fig. 4a and b) [131]. This is far more than anticipated from earlier studies, when smoking was thought to account for all or most of the disease. In Swedish construction workers the attributable fraction of dusty environments was even higher (10% in smokers and 50% in never-smokers) [132].

In the ECRHS survey, high exposure to dust and fumes increased the risks from smoking by 160% for chronic bronchitis [133]. During the follow-up, individuals exposed to dusts, gases and fumes did not have a steeper decline of FEV_1, nor an increase of AO prevalence or incidence [134]. However, the incidence of chronic phlegm increased in males exposed to mineral dust (RR 1.94) and gases and fumes (RR 1.53).

In Australia [135], exposure to biological dusts was associated with an increased risk of chronic obstructive bronchitis (OR 3.19), emphysema (OR 3.18) and COPD (OR 2.70). The risks were higher in females.

Furthermore, in a large cohort of male Swedish construction workers [136], increased rates of lung cancer were observed for COPD patients (mild: RR 1.5; moderate/severe: RR 2.2)

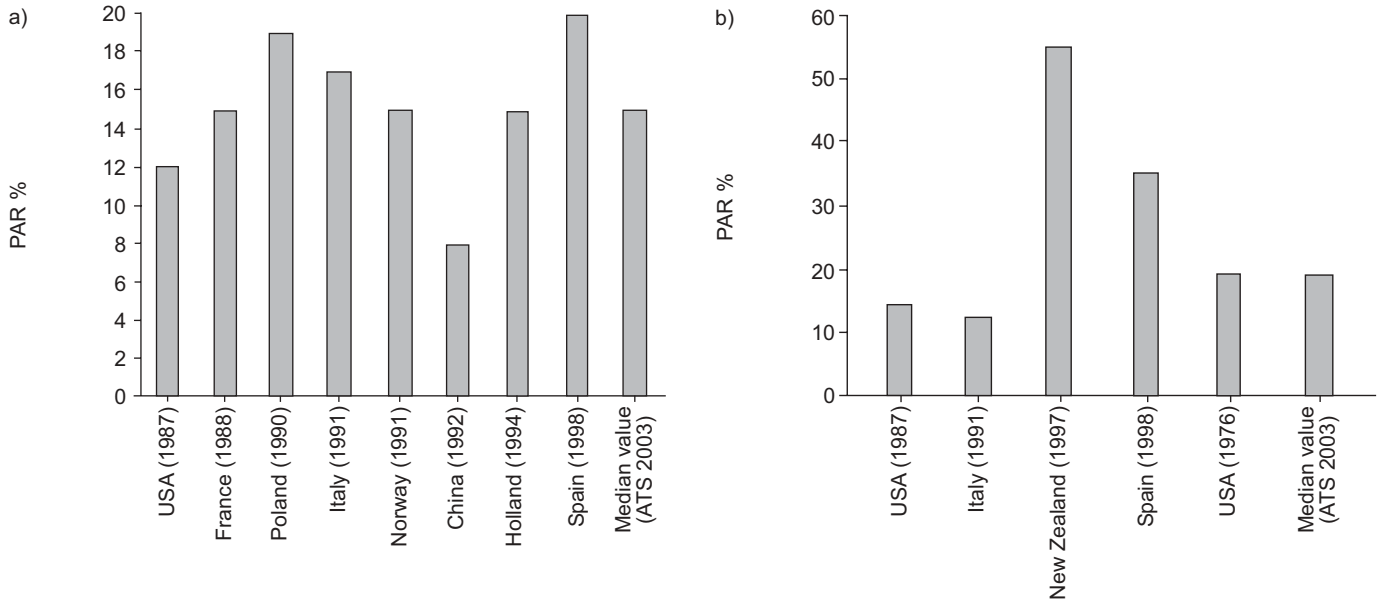

FIGURE 4. Population attributable risk (PAR) due to occupational exposure in a) chronic bronchitis (PAR median (range) 15 (4–29)%) and b) lung function impairment (PAR median (range) 19 (9–56)%). ATS: American Thoracic Society. Data from [131].

relative to normal lung function. COPD was also associated with increased rates of total mortality.

GENETIC FACTORS OF COPD

The results from studies assessing the genetic components of COPD are not always consistent, probably reflecting differences in disease diagnosis criteria, different phenotypes and difficulty in assessing gene by environment interactions [137, 138]. Research in this area started with basic demonstrations of familial correlations of markers of COPD, followed by searches for patterns of inheritance consistent with genetic transmission, and later linkage and association analyses in an effort to identify likely candidate genes.

Early familial correlation studies

BURROWS *et al.* [139], using data from the Tucson Epidemiological Study, demonstrated a statistically significant dose–response association between the number of pack-yrs smoked and the reduction of FEV1 % pred. However, only around 15% of the inherent variability in the measure was explained, suggesting that genetic factors were likely to influence the variable susceptibility to develop COPD. Several studies subsequently reported significant familial correlation of FEV1 in different populations (range 0.11–0.66) in nuclear families [140–144]. These cross-sectional findings were further supported by KURZIUS-SPENCER *et al.* [145], who reported a significant correlation between FEV1 slopes among all sibling pairs ($r=0.256$, $p<0.001$) that was stronger among ever-smoking concordant pairs ($r=0.483$, $p<0.01$), suggesting a strong genetic component relating susceptibility to smoking and rate of decline in FEV1.

Segregation models

Segregation analyses, used to detect distributional patterns consistent with genetic inheritance, were fitted to data from both random population samples and clinical populations. Reports of segregation modelling on randomly selected families in population studies generally found significant familial aggregation of lung function and no evidence of major gene effects on FEV1 [146–148]. In contrast, studies involving families with members with symptomatic disease reported evidence of genetic influence on FEV1 [148, 149]. For example, RYBICKI *et al.* [149] found a major gene effect in the families of COPD patients but found no evidence of even residual familiar effects in non-COPD families. Although population segregation studies were not able to establish a major gene effect, they suggested the presence of polygenes and/or effects due to a shared environment, *i.e.* multifactorial effects, which in part may explain the inconsistencies observed in many association studies.

Role of α_1-antitrypsin

The discovery of the link between α_1-antitrypsin (AAT) deficiency and COPD raised hopes that these genotypes would explain the increased susceptibility between smoking and COPD [150, 151]. The detected alleles and their frequencies are: M (population frequency 95%), associated with normal AAT levels; S (2–3%), associated with mild reductions in AAT; and Z (around 1%), associated with more severe disease. However, only a small proportion of COPD patients (1%) inherit the severe PI Z form of the AAT deficiency [152] and not all PI Z smokers develop COPD [137].

Genetic association and linkage studies

Association studies were conducted in order to identify candidate genes involved in COPD development [153]. Using different study designs and phenotypes, several potential candidate genes were identified. A partial list of loci [132] includes: AAT 3′ flanking region [154], vitamin D binding protein [155], cystic fibrosis transmembrane regulator gene [156], ABO blood group [138], AAT [157], microsomal epoxide hydrolase [158] and tumour necrosis factor-α or tumour

necrosis factor [159]. A more complete list of potential candidate genes is reported by MOLFINO [153].

Some results were replicated in other populations, but there were also conflicting reports [137]. The difficulty in using association studies to identify genes was recently highlighted in a unique study reported by HERSH *et al.* [160], in which 12 candidate genes and 29 polymorphisms were examined in both a family based study and a case–control study. Out of the other previously reported COPD gene associations, only the surfactor protein B (SFTPB Thr131Ile polymorphism) and haemoxygenase (HMOX1) were replicated in both studies. The authors thus suggest that ''the regulation of genes in response to environment (*i.e.* smoking) may be at least as important as deciphering the DNA sequence'' [161, 162].

CLINICAL FEATURES

The symptoms characterising the natural history of COPD are cough, phlegm and effort dyspnoea. They vary over time in each individual patient and are often underreported. Even in advanced disease not all patients complain of all symptoms. There is a poor relationship between symptoms and the underlying level of lung function, and often a significant amount of ventilatory capacity has been lost before the COPD diagnosis.

SYMPTOMS

Cough and sputum

Since the Ciba Foundation Guest Symposium, the presence of cough and sputum (on most days for $\geqslant$3 months in 2 consecutive yrs) is the condition characterising chronic bronchitis [11]. In the adult general population, prevalence rates of chronic cough or phlegm may range 15–44% in males and 6–17% in females [113]. They increase with ageing and are strongly related to the presence of smoking habit (~60% of smokers aged >60 yrs reported these symptoms), as well as other respiratory risk factors (occupational exposure, childhood RI, air pollution) [163–165]. Over time, changes of these symptoms (incidence, remission) are associated with variations of smoking status over time [25, 27].

According to the COPD GOLD staging, the presence of cough and/or phlegm represents the stage 0, at risk, of disease classification. However, some longitudinal studies do not confirm that the presence of these symptoms (in AO absence) is in fact associated with the development of the obstruction [166]. Conversely, there is an increasing trend to have a larger proportion of patients with AO and simultaneous presence of symptoms in mild-to-severe COPD both in males and females. In the severe category, ~80% of subjects are symptomatic [31].

Dyspnoea

Breathlessness is the most significant symptom in COPD patients and is the usual reason for seeking medical help. It is characteristically persistent and progressive. In early COPD, behaviour can be modified to limit breathlessness, but when the FEV_1 value is <30% pred, the patient is usually breathless on minimal exertion [167]. The Medical Research Council dyspnoea scale is a validated epidemiological tool that relates well to other measures of health status and may help to predict resource utilisation and mortality more accurately than FEV_1 alone [168].

Severe disease

From an epidemiological point of view, severe COPD can be identified by the presence of moderate/severe AO (assessed by lung function test) and by the occurrence of CRF (measured by the use of long-term oxygen therapy (LTOT)).

As mentioned before, in an Italian general population sample [31], the proportions of patients with moderate or severe COPD (defined by the presence of AO according to the GOLD criteria) were 5.5 and 0.4% in males, and 2.2% and 0.3% in females, respectively. They were 26% (moderate) and 3% (severe) of all COPD patients [45]. These results are consistent with other European epidemiological studies, in which different AO criteria have been used [30]. In fact, in both Sweden and in Norway the proportion of severe COPD patients was <1%, whilst in the USA NHANES percentages around 1.7% were recorded in the 1970s and the 1990s [30]. Distribution by severity of incident data over 15 yrs in a Copenhagen study confirms this burden: 5.2% for moderate and 0.2% for severe COPD [166].

LTOT is a major therapeutic tool for CRF that can be used as an epidemiological proxy of this condition. Progressive RF accounts for approximately one-third of the COPD-related mortality. Conversely, COPD is the condition leading or contributing to CRF which accounts for most patients in LTOT (table 7) [169–172]. Of the possible interventions applied in the end-stage of stable diseases, LTOT has the largest proven impact on public health. LTOT is indicated for many patients with severe diseases, yields robust effects on survival, is widely available in many countries, significantly reduces mortality in patients with COPD and severe resting arterial hypoxaemia, and it improves exercise, sleep and cognitive performance in hypoxaemic patients [6].

Oxygen treatment is assigned following some established criteria, mainly defining a fixed threshold value of arterial oxygen tension and/or the evidence of specific cardiopulmonary abnormalities. There are national or regional networks of LTOT suppliers in many countries. However, in order to use these kinds of data either for epidemiological or public health settings, some problems and possible sources of bias have to be noted. Criteria used to assign the treatments vary according to the different regional and national health systems [173, 174]; data may derive from different collections' modalities (national or regional population registries, prescription files, *ad hoc* associations, oxygen supply firms). In addition, treatment may be prescribed out of the recommended selection criteria and the aptitude of physicians towards prescription could influence the prevalence estimate.

The comparison of COPD mortality and LTOT data collected in the same populations allows interesting considerations. In Sweden, the prevalence of patients on LTOT in the general population was compared with the mean annual crude death rate per million inhabitants from bronchitis, emphysema and asthma [175]. No correlation was seen between the level of domiciliary oxygen usage per unit of the population and the mean annual crude death rates in different regions. The same kind of analyses was conducted with more recent data in Tuscany (Italy) [176]. There were some trends for correlation between LTOT prevalence and COPD mortality, but the data variability was large (fig. 5). Thus, other factors, rather than the

TABLE 7 Distribution of diagnoses among patients receiving long-term oxygen therapy in different studies

	Miyamoto [169]	Waterhouse [170]#,¶	Chailleux [171]	Neri [172]#
Diagnosis				
COPD	13380 (41.0)	285 (60.0)	14349 (54.8)	1041 (69.2)
Interstitial lung disease	5272 (16.2)	55 (11.5)	3417 (13.1)	169 (11.2)
Fibrosis post-TB	8095 (24.8)	10 (2.1)	4147 (15.9)	142 (9.4)
Bronchiectasis	1217 (3.7)	13 (3.5)	1556 (5.9)	89 (5.9)
Others (cancer, neuromuscolar, PH, not classified)	4657 (14.3)	150 (31.5)	2671 (10.2)	207 (13.8)
Total patients	32621	477	26140	1504

Data are presented as n (%) or n. COPD: chronic obstructive pulmonary disease; TB: tuberculosis; PH: pulmonary hypertension. #: total number of diagnoses is greater than the total number of patients because it was possible to fill in more than one category (*e.g.* COPD and bronchiectasis); ¶: self reported. Studies are indicated as first author [Ref.].

epidemiological distribution of the diseases, are related to the use of LTOT.

Indeed, the different LTOT use and, probably, some increments with time can reflect not only the increasing burden of the underlying diseases and changes in their natural history, but also different aptitudes of prescription. There are discrepancies between scientific evidence, physicians' practices and insurance reimbursement policies with regard to indications for LTOT. A strong evidentiary basis is needed for guidelines for oxygen prescription [177]. Recently, a report from a National Heart, Lung, and Blood Institute (NHLBI) workshop was published [178]. Those attending the workshop were charged with the tasks of evaluating the current state of knowledge regarding LTOT, identifying research questions of clinical importance, and discussing technical issues that might influence the feasibility and design of LTOT trial. They examined the current reasons for patients with COPD to receive or not receive LTOT, and the reasons for uncertainty regarding prescription to particular patients. Some important issues for future research were identified, including: efficacy of LTOT in patients with moderate resting hypoxaemia; efficacy in patients' normoxaemic at rest but who desaturate during physical activity or sleep; optimal timing and dosage; mechanisms of action; clinical and biochemical predictors of responsiveness; and methods for enhancing compliance with the treatment.

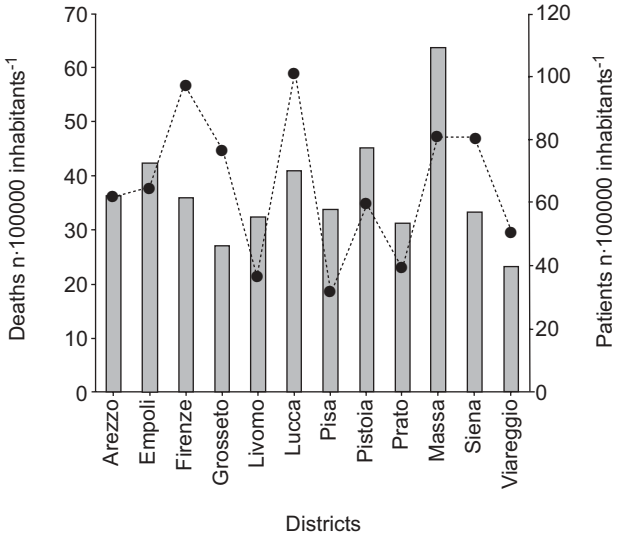

FIGURE 5. Patients administered long-term oxygen therapy (●; ·····) *versus* mean annual crude mortality rates (■) of the population living in Tuscany (Italy) in 2002, in 12 local health districts. Data taken from oxygen supply firms [176].

The European figures on home mechanical ventilation (HMV) use were recently updated by the Eurovent study, which was conducted in 16 countries [179]. The overall estimated prevalence of HMV is 6.6 per 100,000 people. A large variation among the countries is still present, with a close relationship between the median year each country started HMV services and their prevalence. Different patterns of HMV use are also present, either in the proportion of the specific conditions or in its application (namely in older patients with COPD or in the use of tracheostomies in neuromuscular users) [179]. The COPD users in the latter survey were more likely to be male and aged >65 yrs. The survey showed that 34% of HMV users (7,000 people) had parenchymal lung diseases including COPD. Therefore, despite conflicting evidence of a long-term benefit for ventilation in COPD patients [180], this survey found that HMV was used on a wide scale in COPD patients. Previous reports indicated an increasing rate of ventilation for COPD patients in France [181] and Switzerland [182]. However, high levels of variation in the relative percentage of lung users demonstrate that this is not true for all countries.

Notwithstanding its relevant clinical impact, COPD is also underestimated and unrecognised in its advanced stages. According to an analysis of hospital discharges conducted in Italy, only the most severe cases of COPD are recognised during hospitalisation and, even in those with severe COPD, a large proportion of patients are admitted to the hospital for other comorbidities [183]. In a group of consecutive patients attending the emergency dept because of COPD exacerbations, 28% had never been diagnosed prior to the exacerbation, although 30% of them showed severe AO and 12% already had

RF [183]. Thus, the proactive management of patients presenting at the emergency dept with an exacerbation may allow identification of COPD and help minimise the underdiagnosis and under-treatment within the healthcare system.

Indeed, exacerbation of COPD is the fourth leading cause of death in the USA [184], with 500,000 hospitalisations annually, which are often precipitated by RI, CHF and arrhythmias. Estimates of in-hospital mortality ranged 4–30%. In an analysis on a 20% sample of nonfederal US hospitals concerning >70,000 patients with an acute exacerbation of COPD at hospital discharge, in-hospital mortality for COPD exacerbation was 2.5%, *i.e.* lower than in previous studies of selected patients. Age, sex, income, comordity and source of hospitalisation were potential predictors of mortality. Further studies, from routinely collected administrative data, can be useful for the assessment of risk prediction models for in-hospital mortality of COPD and can help manage the endstages of the disease.

A promising approach to the management of COPD exacerbations was recently developed by CONFALONIERI *et al.* [185], who developed a chart of failure risk for noninvasive ventilation.

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. In severe COPD, physical signs are quite specific and sensitive [186]. Moreover, they may be particularly helpful in the early diagnosis of acute COPD exacerbations.

In severe COPD, inspection reveals tachypnoea and speaking in an interrupted fashion. Patients may sit leaning forward with their arms resting on a stationary object. Some patients purse the lips during expiration with exertion. The tympanic percussion note is neither sensitive nor specific for pulmonary hyperinflation. The decrease in intensity of normal breath sounds is generally related to the AL degree, yet there is a considerable inter-individual variability. While wheezing heard during unforced tidal breathing is specific for AL, obstruction can be present in COPD patients in the absence of wheeze. Discontinuous adventitious sounds (crackles) are heard as a series of few explosive sounds that begin with the onset of inspiration, and are due to the sudden opening of small airways with rapid equilibration of pressures.

In severe COPD, signs of pulmonary hypertension and right ventricular failure (cor pulmonale), including peripheral oedema, raised jugular venous pressure and hepatomegaly, may be detected.

MEASUREMENT OF AIRFLOW LIMITATION

Lung function measurements are essential for diagnosing and grading COPD. Although the updated GOLD guidelines [7] disregarded the stage 0 ''at risk'' (reporting chronic cough or phlegm) and based the grading only on FEV_1 % pred level, people seek medical assistance when they perceive symptoms. Indeed, 8–13% of people in general population surveys have AO without having a diagnosis of obstructive lung disease [31] and the proportion of symptomatics increases with worsening COPD [187]. Furthermore, in a series of incident COPD cases [188], symptoms leading patients to seek medical advice were not only cough (84%) and sputum (45%), but also exertional dyspnoea (75%). In total, 37% had stage 0, 5% stage I, 46% stage II and 12% stage III COPD. GOLD grade 0 patients had significantly reduced FEV_1 % pred with respect to age-matched nonsmoking controls. Thus, although most COPD patients seek medical advice at advanced disease stages, the fact that ~40% present at stages 0–I suggests that early detection and possible prevention of COPD progression might be achieved through an extended use of spirometry.

The ATS/ERS Task Force on standardisation of pulmonary function tests recently published a series of documents [189–194], which contribute to yield high precision and repeatability of the tests. The recommendation for the diagnosis of AL is to use FEV_1/VC % pred instead of the fixed ratio FEV_1/forced vital capacity (FVC) since the latter underestimates the AO rate in youth and overestimates it at >50 yrs of age, especially in the elderly [16, 195, 196]. Thus, AO is now defined as FEV_1/VC <5th percentile of predicted, *i.e.* values below the 5th percentile of the frequency distribution of values measured in the reference population are below the expected ''normal range'' [194]. A concomitant decrease in FEV_1 and VC (most commonly caused by poor effort) may rarely reflect AO and its confirmation requires measurement of lung volumes. The latter may be useful in assessing lung hyperinflation and, together with the diffusing capacity for carbon monoxide ($D_{L,CO}$), may assist in the diagnosis of emphysema, bronchial asthma and chronic bronchitis.

No single set of reference values can be recommended in Europe and more work is necessary in this area [189, 197]. Predicted values should be obtained from normal or healthy subjects with the same anthropometric and ethnic characteristics of the patients being tested [194]. When comparing selected reference equations with measurements performed on a sample of healthy subjects in a laboratory, the reference equations that provide the sum of residuals (observed-predicted computed for each subject) closest to zero should be chosen. The severity of pulmonary function abnormalities is based on FEV_1 % pred, knowing that FEV_1 may sometimes fail to properly identify the severity of a defect, especially at the very severe stages of the disease. In such conditions, one can usefully categorise the severity of lung function impairment through lung hyperinflation and presence of expiratory flow limitation during tidal breathing.

AL in COPD patients is not fully reversible. Indeed, many patients with COPD will show some degree of reversibility after inhalation of a short-acting bronchodilator. In addition, a number of COPD patients are more likely to respond with improvements of lung volumes than FEV_1 [189]. An increase in FEV_1 and/or FVC $\geqslant$12% of control and $\geqslant$200 mL constitutes a positive bronchodilator response [194]. However, the lack of a bronchodilator response in the laboratory does not preclude a clinical response to bronchodilator therapy. Furthermore, a Norwegian group [198], using a bronchodilator test, estimated AL prevalence (FEV_1/FVC <0.7) 27% lower than the pre-bronchodilator values. Also in the PLATINO study [199], approximately one-third of those with pre-bronchodilator AO did not have AO post-bronchodilator. However, the necessity of using a therapeutic agent in general population studies is

questionable, in view of the widespread lack of awareness of the disease in the general public who, in real life, are unlikely to seek medical advice at the early stage of the disease. In addition, the same group subsequently published a paper [200] to describe reference values for post-bronchodilator FEV_1, FVC and FEV_1/FVC. These equations gave higher predicted FEV_1 and FEV_1/FVC than pre-bronchodilator equations. The authors concluded that post-bronchodilator prediction equations can facilitate better management of patients with COPD by avoiding falsely high FEV_1 % pred with a subsequent underestimation of disease severity. Conversely, it could be argued that post-bronchodilator reference values, by increasing the denominator of the ratio observed/predicted, would facilitate exceeding the threshold of abnormality for FEV_1 % and FEV_1/VC % pred and overestimating disease severity.

OTHER INVESTIGATIONS

$D_{L,CO}$ is reduced in virtually all COPD patients in the presence of severe emphysema. The reduction of the $D_{L,CO}$/alveolar volume ratio (K_{CO}) is related to the extent of emphysema, and in AO patients it helps to distinguish emphysema from asthma, in which K_{CO} is usually not reduced. In severe COPD, information from arterial blood-gas measurements will guide oxygen therapy and help decide whether patients with exacerbations require ventilatory support. Blood tests are important to identify patients with severe COPD who develop polycythaemia, since it predisposes to vascular events [201]. The accuracy of diagnosing emphysema by plain chest radiography increases with the severity of the disease up to 50–80% in moderate-to-severe patients [201]. On computed tomography, low attenuation areas correlate with macroscopic emphysema, whereas recognition of microscopic emphysema is more difficult [201]. However, both techniques may help in the differential diagnosis.

NATURAL HISTORY

COPD is generally a progressive disease but it has variable natural history and not all individuals follow the same clinical course over time. Chronic cough and phlegm may predominate in some COPD patients, while others may report only effort dyspnoea. Some individuals show a rapidly accelerated lung function decline, while in others a slowly progressive, roughly ''stable'' decline is observed. While an almost irreversible AO is usually observed, a partially reversible AL may be observed in some COPD patients.

Importantly, stopping exposure to noxious agents related to COPD may slow the disease progression, and a regular treatment may control symptoms and improve quality of life. However, once developed, COPD cannot be cured.

A study in outpatients with stable COPD [202] showed that, besides a decreased FEV_1, chronic mucus hypersecretion (OR 1.54) and older age (OR 1.21 for every 10 yrs of increasing age) were predictors for two or more exacerbations per year, while comorbidities, including cardiac insufficiency, ischaemic heart disease and diabetes, were more likely to be associated with hospital admissions (OR 1.97). The role of chronic mucus hypersecretion in the natural history of COPD and its progression towards the end stages is consistent with other studies [203]. In a study based on prospectively collected data from 22,044 individuals participating in the Malmö Preventive Program, symptoms fulfilling the definition of chronic bronchitis were associated with an increased mortality risk, even among male smokers with normal pulmonary function (GOLD stage 0) and smoking individuals with mild-to-moderate COPD (GOLD stages 1 and 2) [204].

More recently, attention has been focused on measuring serum C-reactive protein (CRP) in so far as patients with COPD have an ongoing systemic inflammation. According to DAHL *et al.* [205], in the longitudinal Copenhagen City Heart Study, the hazard ratios for hospitalisation and death due to COPD were increased at 1.4 and 2.2 in individuals with baseline CRP >3 mg·L^{-1} *versus* <3 mg·L^{-1}. The absolute 10-yr risks for COPD hospitalisation and death in individuals with CRP >3 mg·L^{-1} were 54 among those aged >70 yrs with a tobacco consumption >15 g·day^{-1} and 57% among those with an FEV_1 <50% pred. In addition, plasma CRP concentration, in the presence of a major exacerbation symptom, is useful in the confirmation of COPD exacerbation [206].

End-stage COPD patients do not exclusively suffer from severe COPD-related complications [207]. They often present with multiple comorbidities, in line with their advanced age and the common underlying risk factor of smoking [208]. The characterising symptom of end-stage COPD is progressively worsening dyspnoea, initially during exercise, eventually during activities of daily living, and ultimately even at rest, being the main cause of their limited performance status [209, 210]. Other physical (cough, retained secretions, pain, fatigue, weakness, weight loss, delirium, poor sleep quality) and emotional (anxiety, panic, depression) symptoms are common in these patients [209–213], resulting in poor quality of life [209, 214, 215]. Frequently, patients are readmitted to hospital [215–217], where they spend a considerable amount of their remaining life [209]. Out of hospital, patients spend the last months of their lives limited at home, or under hospice care, gradually losing their autonomy and becoming more and more dependent on caregivers for their daily living activities [214]. Nonetheless, end-stage COPD patients receiving adequate supportive care can survive in this poor functional status for a prolonged period [209, 218], and die of an event such as an acute exacerbation of COPD or an acute intercurrent illness [4].

Predictors of survival in end-stage COPD patients have been explored. Current smoking, presence of comorbidity and the level of hypoxaemia predicted survival in a cohort of 47 clinically stable hypercapnic COPD patients followed up for an average of 3.8 yrs [219]. In a cohort of 139 subjects with severe COPD (FEV_1 <40% pred) in the Boston Early-Onset COPD Study, the number of pack-yrs smoked prior to study enrolment as well as smoking during the follow-up period were both independent predictors of mortality [220]. BMI <25 kg·m^{-2} and comorbidity were predictors of all-cause and respiratory mortality in a cohort of COPD patients treated with LTOT [221].

CONCLUSION

Chronic obstructive pulmonary disease is one of the main chronic diseases contributing to a huge burden for the population worldwide. It could be easily and early diagnosed if spirometry were frequently performed, which, unfortunately, is not the case. Most relevant risk factors have been

identified; their removal could substantially reduce the prevalence. If there is no major effort in prevention, the natural history of the disease will lead to augment the proportion of patients at end stage, who can live longer today due to long-term oxygen therapy and assisted ventilation, but with elevated suffering for them and their families and huge costs for society.

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