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Epidemiology of chronic obstructive pulmonary disease

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Epidemiology of chronic obstructive pulmonary disease. J.M. Antó, P. Vermeire, J. Vestbo, J. Sunyer. ©ERS Journals Ltd 2001.
ABSTRACT: Chronic obstructive pulmonary disease (COPD) is a leading cause of world-wide mortality and disability. On average ~5–15% of adults in industrialized countries have COPD defined by spirometry. In 1990, COPD was considered to be at the twelfth position world-wide as a cause of combined mortality and disability but is expected to become the fifth cause by the year 2020.

COPD has a chronic long-lasting course characterized by irreversible decline of forced expiratory volume in one second (FEV_1), increasing presence of dyspnoea and other respiratory symptoms, and progressive deterioration of health status. After diagnosis the 10-yr survival rate is ~50% with more than one-third of patients dying due to respiratory insufficiency.

Several environmental exposures such as air pollution increase the risk of death in COPD patients. The aetiology of COPD is overwhelmingly dominated by smoking although many other factors could play a role. Particular genetic variants are likely to increase the susceptibility to environmental factors although little is known about which are the relevant genes. There is clear evidence about the role of the α-1-antitrypsin but the fraction of COPD attributable to the relevant variants is only 1%. Phenotypic traits that are considered to play a role in the development of COPD include sex, with females being at a higher risk, bronchial responsiveness and atopy. There is strong causal evidence regarding the relationship between smoking and COPD with decline in FEV_1 levelling off after smoking cessation. Passive smoking has been found to be associated with a small though statistically significant decline in FEV_1. Other risk factors that are likely to be relevant in the development of COPD are occupation, low socioeconomic status, diet and possibly some environmental exposures in early life.

Although there is accumulating evidence that oxygen therapy, pharmacological treatment and rehabilitation may improve the course of chronic obstructive pulmonary disease, preventing smoking continues to be the most relevant measure, not only to prevent chronic obstructive pulmonary disease, but also to arrest its development.
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Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity both in developed and developing countries that is mainly characterized by progressive and not fully reversible airflow limitation. As an important health problem it has been the subject of many epidemiological and clinico-epidemiological investigations that have addressed a broad range of issues from aetiology to health services utilization. In the following sections a comprehensive narrative review of the epidemiological knowledge about COPD that has accumulated during the recent decades is provided.

Definition of chronic obstructive pulmonary disease

The 1995 European Respiratory Society (ERS) consensus statement [1] defined COPD as "a disorder characterized by reduced maximum expiratory flow and slow emptying of the lungs; features which do not change markedly over several months. Most of the airflow limitation is slowly progressive and irreversible. The airflow limitation is due to varying combinations of airways disease and emphysema; the relative contribution of the two processes is difficult to define *in vivo*". Unfortunately, there is no agreed labelling of the airways disease component that is mainly an inflammatory process. Labelling the airways disease component as obstructive bonchiolitis [2, 3] has some advantages but has not found general acceptance. In the 1995 American Thoracic Society (ATS) Statement COPD was defined as a "disease state characterized by presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airways hyperreactivity and may be partially reversible" [2]. However,

the use of the term chronic bronchitis in the definition of COPD may easily generate confusion since it is widely used to designate mucus hypersecretion that originates mostly from larger airways.

In order to make the definition operative the ERS consensus defined COPD as an airflow obstruction with a forced expiratory volume in one second (FEV)1/forced vital capacity (FVC)L 88% predicted in males or <89% pred in females [1]. In this definition the following entities are excluded from COPD: cystic fibrosis, bronchiectases, byssinosis and bronchiolitis obliterans. However, when both positive and negative criteria are applied to a case definition the distinction between asthma and COPD is still a major difficulty. Obviously, the adoption of different definitions or the translation of the same definition to different operational criteria may lead to different estimations of either prevalence rates or risks and consequently make more difficult the interpretation of apparently inconsistent results. A consequence of the ambiguity underlying the definition of COPD is that of smoking. Although the antecedent of smoking is not included in any of the definitions of COPD alluded to above, many clinical investigations do exclude nonsmokers.

Frequency, distribution and trends

In the USA, a history of emphysema diagnosed by a physician or a measured level of impaired lung function (usually $FEV_1 < 60$ or 65% of its predicted value) was found in 4–6% of adult White males and 1–3% of adult White females [4]. In Black populations, prevalence of COPD ($FEV_1 < 65\%$ pred) was 3.7% in males and 6.7% in females, in 1971–1975 [5]. In a review about the prevalence in the UK, STRACHAN [6] mentioned the Health and Life Style Survey as the only national study of ventilatory function among a British adult population [7]. This survey included 2,484 males and 3,063 females aged 18–65 yrs, in whom a spirometry was performed at home. Overall, 10% of males and 11% of females showed an FEV_1 of two or more standard deviations below the age and height predicted value. The prevalence of obstruction increased by age. In the IBERPOC study, carried out in a sample of the 40–69 yr old population in Spain, an FEV_1/FVC ratio <88% pred in males and <89% in females with a negative bronchodilator test was found in 15.8% of males and in 5.5% of females [8]. Prevalence rates of chronic bronchitis were similar in several European countries with rates of 3.7% in Denmark [9], 4.5% in Norway [10], 4.8% in Spain [8]. One of the major differences between epidemiology and clinical pulmonary medicine relates to mild COPD. For the clinician mild COPD is rarely seen and the term "COPD" often relates to severe disease. However, from an epidemiological perspective it is important to understand that a prevalence rate includes the entire spectrum of severity and that the majority of cases will have a mild COPD. This important distinction is well illustrated by an analysis of clinically small effects of air pollution on FVC [11]. This study shows that, in an evidence-based scenario of air pollution, a 3.14% shift in the population mean FVC may have a rather strong

impact on the prevalence of people with severely impaired FVC, although the same decrement at individual level would have no clinically relevance.

Since the duration of COPD usually involves several decades, prevalence rates poorly reflect time trends. STRACHAN [6] has reviewed data from three National Morbidity Surveys in General Practice, showing that the number of both males and females aged 65–74 yrs consulting a general practitioner for emphysema and COPD increased from 11.1% and 1.5% in 1970–1971 to 26.2% and 7.8% in 1980–1981. However, interpretation of this type of data is seriously limited, not only because of factors related to diagnostic shift and changes in services utilization but also because it is largely dependent on prevalence rather than on incidence rates.

Another source of information about time and geographical patterns is mortality. Unfortunately, in addition to the limitations in the validity of medical diagnoses in death certificates, the analysis of COPD mortality is further complicated by the lack of a well-standardized three-digit code for COPD. In a review of international patterns of respiratory mortality entities with the ICD9 490–496 codes which also include asthma (ICD9 493), the highest rates were found in UK, Eastern Europe and Australia and the lowest rates in Southern Europe, Scandinavian countries, Israel and Japan [12]. In the ERS Consensus Statement, after considering together the ICD codes 490–493, the mortality rates in males for the period 1988–1991 ranged from >30 deaths per 100,000 person-yrs in Hungary, Denmark and former East Germany to <10 in Spain, France and Greece [1]. One of the limitations of mortality studies is related to the use of the underlying cause of death as the only information to establish the cause of death. MANNINO et al. [13] used the Multiple-Cause Mortality Files compiled by the National Centre for Health Statistics in the US and found that 8.2% of all deaths had a diagnosis of obstructive lung disease (ICD-9 490–493.9, 496). COPD was recorded as the underlying cause of death in 43% of all these deaths, showing that mortality due to COPD may be severely underestimated when using only the underlying cause of death.

Studies about the trends in mortality due to COPD are useful in order to assess changing needs and to anticipate knowledge about expanding problems. This is of particular interest for COPD mortality in females. In Australia, female age-standardized mortality increased by 2.6-fold from 1964–1990 and it was predicted that female mortality by COPD may equal mortality in males by the middle of the next decade [14]. A similar pattern was shown in a study of the US national trends in mortality by obstructive lung disease from 1974–1993 with the age-adjusted rates for females increasing by 126% [13]. World-wide distribution of disability-adjusted life's year (DALYS) due to COPD has been assessed within the frame of the Global Burden Disease Study [15]. The DALYS result from the sum of life's years lost due to premature death and the years lived with disability. COPD was responsible for 2.1% of DALYS and, among the most common causes, ranked twelfth in 1990. When current trends were projected according to several scenarios, COPD

was estimated to be the fifth cause of DALYS in the year 2020 accounting for 4.1% of DALYS appearing as one of the most important increasing public health problems world-wide

Course and progression of chronic obstructive pulmonary disease

In general, a first diagnosis of COPD is established in subjects >40–50 yrs who have been smokers for several decades. However, before reaching this clinical stage a long course of structural and functional changes in the lungs has occurred. This course includes relevant changes and events involving deterioration of lung function, appearance of symptoms, worsening of health-related quality of life, active use of health services and frequently, death due to COPD.

Decline in forced expiratory volume in one second

The natural history of COPD is mainly characterized by a progressive, irreversible, decline in lung function. In healthy subjects lung function achieves its maximum value at the age of 20–25, followed by a slow progressive decline with age. In a study of 792 healthy males, 30–59-yr-olds followed for up to 8 yrs [16], the decline of $FEV1$ in nonsmokers was ~ 25 mL·yr^{-1} in contrast to 50 mL·yr^{-1} in smokers. Those with the sharpest decline had a slope of $FEV1$ decline about 100 mL·yr^{-1} and then developed respiratory symptoms and severe obstruction. A later study by BURROWS et al. [17] did show that the decline in $FEV1$ was independent of its basal value. The decline of the $FEV1$ has been the subject of several reviews [18, 19]. The results of the longitudinal studies have been summarized by RIJCKEN and BRITTON [19] showing $FEV1$ declines ranging from 7 mL·yr^{-1} in the six-city study to 33-mL·yr^{-1} in the University of California Los Angeles (UCLA) population study. An important issue is that the earliest step of COPD may involve a suboptimal development of lung function during childhood and adolescence which in combination with a slightly accelerated decline at a later age may lead to significant airflow limitation [20].

Symptoms and quality of life

When and how symptoms appear during the silent evolution of $FEV1$ decline has been a contentious issue. Although most smokers do experience chronic cough and expectoration at an early age, its relationship with COPD is far from clear. FLETCHER et al. [16] observed that about one-quarter of smokers with a low $FEV1$ did not present chronic cough and expectoration whereas 20% of smokers with chronic productive cough showed a normal $FEV1$, and concluded that mucus hypersecretion and decreased $FEV1$ were different entities. This conclusion was supported by several subsequent studies that have shown either no, or small, association of mucus hypersecretion and the decline of $FEV1$ [21, 22]. These findings are consistent with the notion that the decline in $FEV1$ in COPD is due mainly to smoking with, at most, only a weak relationship with chronic

bronchitis or mucus hypersecretion. Since mucus hypersecretion is frequently associated with lower respiratory tract infections, additional support to this notion was provided by trials of preventive antibiotic therapy in subjects with chronic bronchitis showing no influence on the rate of $FEV1$ decline [23]. As a consequence there is the extended belief that chronic cough and expectoration in absence of COPD is a minor disorder without a relevant impact in the health status. By contrast, ANNESI and KAUFFMAN [24] found in a longitudinal study that after adjustment for relevant covariates, working people with chronic mucus hypersecretion had an increase of 35% of the all-cause mortality. More recently, VESTBO et al. [25] have found an association between mucus hypersecretion and a decline in both $FEV1$ and hospital admissions because of COPD. These studies do clearly question the idea that chronic cough and expectoration is a minor disorder although the reasons for this discrepancy have not yet been clarified.

Breathlessness is another important symptom in COPD. FLETCHER and PETO [26] found that breathlessness was the symptom associated with the largest loss of lung function over time as well as to a worse prognosis. When breathlessness appears, as a consequence of loss of lung function, is not known with precision. In addition, the coexistence of decreased $FEV1$ and dyspnoea do show a wide interindividual variability [27].

Another relevant aspect in the course of COPD is health-related quality of life (HRQL). There are several cross-sectional studies showing that there is a relevant deterioration of quality of life in COPD [28]. Although it has been considered that a relevant impairment of quality of life only occurs in advanced COPD there are few studies conducted in milder stages. FERRER et al. [29] in a cross-sectional study of 321 COPD patients, showed that those with an $FEV1 > 49\%$ pred had a substantial impairment of their quality of life (34 points in the Saint George Respiratory Questionnaire (SGRQ) total score as compared to 6 in the reference value). Also a substantial impairment was found for those who were not troubled with shortness of breath except with strenuous exercise [29]. Knowledge about the longitudinal decline in health status in patients with COPD has been gained in the inhaled steroids in obstructive lung disease (ISOLDE) study, a randomized placebo-controlled trial of inhaled corticosteroids, assessing the placebo group [30, 31]. OSMAN et al. [32] have shown that HRQL scores can predict re-admission for COPD. In a study of 266 patients admitted with an exacerbation of COPD, these authors showed that those with a worse score on the SGRQ had a higher rate of re-admission for COPD independently of $FEV1$. This type of longitudinal evidence reinforces the current understanding that quality of life is among the most important dimensions in the evolution of COPD.

Acute exacerbations

The exacerbation of COPD is considered the most common cause for hospital admission in COPD patients. Despite the fact that COPD patients may

experience several exacerbations per year [33] the influence of acute exacerbations on the progression of COPD has not been established. SEEMUNGAL et al. [34] have recently reported a longitudinal study of 70 COPD patients showing that those with more frequent exacerbation (3–8 during follow-up) had SGRQ scores significantly worse than those with less frequent exacerbation. Acute exacerbations, at least the most severe ones that require hospital admission, are associated with high risk of death with ~10–30% of subjects dying during the admission and about 40–60% during the year following the admission [35, 36]. It is of interest here that in the Copenhagen City Heart Study [25], as mentioned earlier, chronic mucus hypersecretion was also associated with an increased risk of hospital admissions because of COPD. Because the limited lung function in the advanced COPD is likely to be a risk factor for an acute exacerbation the causal path between infection induced exacerbations and progression of COPD may involve complex interactions between acute events across short time periods. This type of inter-relationship is further strengthened by another analyses from the Danish group showing that the relationship between chronic mucus hypersecretion and COPD mortality was entirely due to death from COPD when a terminal infection was present [37].

Mortality

After years of suffering dyspnoea and disability many patients with COPD die as a consequence of the disease. Mortality from COPD, however, is often underestimated due to misclassification and frequent comorbidity. In the study of FLETCHER et al. [16] the 10-yr survival after a clinical diagnosis, in those who persisted in smoking, was ~50% whereas in exsmokers it was ~80%, a pattern that correlates with decline in FEV1 according to smoking. Among cohorts in the Seven Countries Study, the relative risk of death from any cause in 15 yrs of follow-up, adjusted for several risk factors including age and smoking, was 1.67 (95% confidence interval (CI):1.48–1.88) for those with COPD and it showed large variability between countries [38]. Other functional traits like bronchial responsiveness and reversibility have also been investigated in its relationship with prognosis of COPD. ANTHONISEN et al. [39] did follow-up a population of 985 patients with COPD for 3 yrs in Canada. As expected age and FEV1 were the strongest predictors of death. The same was found in a population study where COPD was not subject to any referral bias [40]. In the Canadian study, the response to the bronchodilator test was significantly related to death when the pre-bronchodilator FEV1 was included but the association became nonsignificant when post-bronchodilator FEV1 was used as primary predictor [39]. Another study found an opposite effect of bronchodilator response on survival [41]. The main understanding today seems to be that as prebronchodilator FEV1 is subject to large variability and postbronchodilator FEV1 is an excellent predictor of vital status, reversibility may falsely be interpreted as a marker of good prognosis [42].

In addition to FEV1 other lung and heart function parameters have been found associated to survival in COPD. Follow-up of a series of cases with well advanced COPD have shown that in addition to respiratory parameters like oxygen tension in arterial blood (Pa,O_2), carbon dioxide tension in arterial blood (Pa,CO_2), FEV1, FVC and cor pulmonale, other markers of the cardiovascular function like ventricular ejection fraction and ECG abnormalities are also associated to increased mortality [43–45]. Little is known about the specific causes of death in subjects with COPD. In a study of ~200 COPD patients, the most common causes of death were respiratory failure (38%), cor pulmonale with oedema (13%), pulmonary infections (11%), and pulmonary embolism (10%) [44] suggesting that progressive respiratory failure is only responsible for a proportion of deaths in COPD patients, and that other conditions also play a role. To which extent the previously described factors may be clinically useful to predict death after an admission for COPD is difficult to answer. In a prospective cohort of 1,016 adult patients admitted with an exacerbation of COPD and a Pa,CO_2 of ⩾50 mmHg, the survival time was independently related to severity of illness, body mass index, age, prior functional status, Pa,O_2/inspiratory oxygen fraction(FI,O_2),congestive heart failure, serum albumin, and the presence of cor pulmonale [36]. A multivariate model based on these variables was used to predict the probability of death at 6 months, but the accuracy of the model was similar to the prognoses predicted by the responsible physicians [36]. A number of studies have considered whether mucus hypersecretion, that in severe COPD may promote infection, is associated with an increased risk of death. The results of several studies have been inconsistent with ones showing no or small association [46, 47] and others showing a moderate to strong association [48, 49]. The possibility that clinical heterogeneity in COPD could be associated to mortality had been suggested by BURROWS et al. [3] who found that in a sample of general population with chronic airflow obstruction at recruitment those with asthmatic characteristics had a lower mortality than those with an emphysematous form of COPD.

Few studies have considered the existence of sex-related survival differences in COPD and have shown that survival rates were lower in males compared to females. One of these studies included 2,237 patients aged 65–69 yrs with a first hospital admission due to COPD during the period 1986–1990 with mortality assessed until 1993 [50]. Overall mortality in this group at the end of the study period was ~48% with a median survival time of 5.7 yrs with female COPD patients having a more favourable prognosis than males. In a study of 15,517 subjects visiting an emergency room service in Barcelona, Spain, with either asthma or COPD, fatality rates after a diagnosis of COPD were higher in males than in females. The higher fatality rates in males were seen for all-cause mortality, for all respiratory deaths, and for mortality due to COPD [51]. Whether the higher lethality in males as reported in these studies was due to differences in management or in severity requires further investigation.

Environmental influences in the course of chronic destructive pulmonary disease

Modern evidence about the effects of air pollution on lung health started in the early fifties with thousands of deaths occurring during the fog episode in London 1952, the majority of whom involved subjects diagnosed of bronchitis [52]. Further studies conducted in panels of patients suffering from chronic bronchitis in UK [53] and USA [54] confirmed an association between air pollution and exacerbation of chronic bronchitis. These studies were very influential and clean air policies were developed in many industrialized countries and air pollution levels did show a generalized decrease. Subsequent studies conducted in areas with lower levels of air pollution did not observe an increase of respiratory symptoms or respiratory diseases associated with air pollution [55, 56]. Although disputed there was a widespread belief that air pollution levels achieved through the establishment of environmental standards did protect health with a margin of safety. However, a new generation of time series studies was reported in the 1990s showing an increase in all-cause mortality and mortality from COPD in days with higher levels of particulate pollution [57, 58]. Studies conducted in very different environments have consistently observed that admissions due to COPD increased on days with high pollution levels [59–65]. That these results were not due to site selection bias has been strongly supported by a recent study in the USA [66]. To which extent the increase in hospital admissions and mortality from COPD is due to a small anticipation of events, that nevertheless would have occurred some days later, has been a matter of debate. However, several recent studies have shown only a small if any impact of anticipation of effects [67].

Aetiology

Genetic determinants

Since only 10–20% of smokers develop COPD a strong role of genetic susceptibility seems reasonable. However, it is increasingly recognized that the genetic determinants of COPD are likely to be complex and have only recently started to receive attention. In a comprehensive recent review [68], the following candidate genes were seen as potentially responsible for COPD: α-1-antitrypsine gene, α-1-quimitrypsine genes, α-2-macroglobuline genes, the vitamin D coupling protein and the blood-serotype group genes. However, there was only definite evidence for α-1-antitrypsine (AAT). The AAT gene is highly polymorphic with >75 different alleles described some of them expressing low serum levels of AAT. The more common variants were the alleles M, S and Z with population frequencies of about 0.93, 0.05 and 0.02 respectively. Almost all persons affected by a severe AAT deficiency are homozygous for the Z allele. However, because the low prevalence of the relevant AAT variants, the proportion of COPD attributable to this gene was only ~1%. A few studies assessing the association between different genotypes and the development of COPD suggested that those with an MZ genotype could be at higher risk of COPD than those with an MM genotype [69, 70]. Other recent findings include studies showing an association between the presence of deoxyribonucleic acid (DNA) instability and COPD in smokers [71] and a higher frequency of the glutathione S-transferase (GSTP1) polymorphism in patients with COPD [72]. As with many other chronic diseases the hope is that after identification of the relevant genetic determinants of COPD the analysis of gene-environment interactions may allow for a more complete identification of environmental risk factors.

Phenotypic susceptibility: sex, bronchial hyperresponsiveness and atopy

Several studies have suggested that females may be at higher risk of developing COPD, although none of these studies have totally controlled for circumstances of exposure. The underlying physiological mechanisms for the females to be at an increased risk have been considered to involve either hormonal homeostasis or structural development of lungs. Recent evidence that adolescent females exposed to smoking may have a higher risk of reaching a lower maximally attained lung function than nonsmokers compared to males has been provided by GOLD *et al.* [73]. However, the interpretation of the studies in this age group is limited by the different age-pattern of lung function development in both sexes [74]. In addition, most biases in this field will tend to underestimate the effects of smoking in females, as males not only smoke more than females, they often have started earlier and have a higher rate of inhalation than females [75]. Further evidence in support that females are at a higher risk of COPD due to smoking has been recently provided by the analysis of two population-based cohorts in Denmark. Overall, 13,897 subjects born after 1920 were followed up for 7–16 yrs. In both cohorts, risk of hospital admission due to COPD associated with pack-years was higher in females than in males [76]. Similar results have been reported by SILVERMAN *et al.* [77] in a study on first-degree relatives of patients with severe, early onset COPD showing that both current and exsmoking females had a significantly greater decrease of $FEV1$ than males. The finding reported by PAOLETTI *et al.* [78] that females have a higher rate of bronchial hyperresponsiveness after adjusting for baseline lung function, may provide a mechanism to explain the higher risk of females' $FEV1$ decline.

The role of bronchial responsiveness and atopy as possible effect modifiers of COPD risk has been reviewed in close detail in two reviews [19, 79] showing that subjects who are hyperresponsive have lower lung function either at a given time or over a period of time with a difference between both groups that in some studies was large. Whereas some authors have considered that bronchial hyperresponsiveness does predispose to loss of lung function, others have considered that bronchial responsiveness may be a result of smoking induced airways inflammation instead of a direct cause of lung damage. In a 24-yr follow-up of

2,684 people from Vlagtwedde and Vlaardingen in Netherlands [80], it was shown that the odds for bronchial responsiveness among incident cases of chronic cough and chronic phlegm, after adjusting for age, sex, area, and smoking, were about two-fold the corresponding odds in those who persisted without these symptoms until the end of the follow-up. Similarly, those with bronchial responsiveness were at a lower risk of remission of these symptoms, after excluding subjects with asthma from the analysis. That these findings are relevant for COPD is supported by a further analysis in the same study showing that mortality from COPD increased with increasing bronchial hyperresponsiveness [81].

Asthma in itself should in general be regarded as a disease entity separate from COPD. It may thus seem confusing to add asthma to the risk factors for COPD. There is, however, increasing evidence from well-conducted population surveys that asthmatics have a more rapid decline in FEV1 than nonasthmatics [82, 83] and the excess decline is not trivial. In the Southern California cohort study a history of asthma was associated with a deficit in the maximum mid expiratory flow that was larger in male children than in female, although the influence of duration of asthma could not be excluded [84]. In addition, asthma in The Copenhagen Heart Study was associated with an increased mortality, primarily due to an increased COPD mortality [85]. The mechanism behind these observations are likely to be airways remodelling and a fixed airflow obstruction fulfilling all the definitions of COPD secondary to asthma not properly controlled for.

Active and passive smoking

Beyond any reasonable doubt the most important causal factor of COPD is active smoking even though only a proportion of the heavy smokers will develop the disease. Following the natural history of COPD, the first question is to what extent smoking is a cause of fixed airways obstruction and loss of function. The available evidence consistently shows that smokers are at a higher risk of decreased FEV1 both in cross-sectional and longitudinal studies with an FEV1 decline ranging from 7 mL·yr^{-1} [86] to 33 mL·yr [87]. There is also consistent evidence about a dose-response relationship between the amount of smoking and the decline in FEV1. Regarding the reversion of COPD after smoking cessation, the available evidence [88] is consistent with the results of the seminal study by Fletcher *et al.* [16] who showed that after smoking cessation the FEV1 decline levels off without returning to the basal level.

A more contentious issue has been the assessment of the relationship between passive exposure to smoking and risk for COPD, although its understanding has been facilitated by a recent systematic review on this topic [89]. In this review it was concluded that maternal smoking is associated with small but statistically significant deficits in FEV1 and other spirometric indices in school-aged children and that this association was almost certainly causal [89]. One of the largest studies included in this review was the Six Cities Study

[73] which showed that the association between exposure to environmental tobacco smoke and FEV1 although significant, was of a small magnitude (-3.8 mL·yr^{-1}).

Air pollution

The evidence about a relationship between outdoor air pollution and the development of COPD is still incomplete since most of the studies have focused on lung function, chronic bronchitis and mortality rather than on clinical definitions of COPD. Regarding lung function, there is abundant data from both studies in adults and in children. Evidence that adults living in areas with higher levels of air pollution have lower levels of lung function has been obtained in studies on British postmen during the 1960s [90], general population in Holland [91] and young adults in Southern California (The UCLA-Chronic Obstructive Respiratory Disease (CORD) study) [92, 87]. In the UCLA-CORD study no differences in FEV1 by area were observed in females who smoked. More recently the SAPALDIA study in Switzerland also found that levels of particulate matter <10 μm (PM10) and home outdoor measurements of NO$_2$ [93] as well as personal measurements of NO$_2$ [94] were related with a lower FVC. In the ASHMOG cohort of nonsmoking subjects in California, the assigned personal air pollution to PM10, based on distance of the residence from 348 monitoring stations, was associated with lower levels of FEV1 [95]. Similar findings have been obtained for children although in this case the process of growth complicates the analysis of changes in lung function. An association between increased levels of particulate air pollution and a decreased lung function growth has been reported in cross-sectional studies in the USA and Canada [96–98]. On the other hand, cohort studies in Poland [99] and Southern California [100] have shown that both particles and NO$_2$ were related to lower levels of lung function. In addition, in a further cohort study in children from Austria and Germany ozone levels were associated with decreased lung function growth [101].

The assessment of the association between air pollution and clinical phenotypes related to COPD has included chronic bronchitis and mortality. During the 1950s, researchers in the UK had shown that prevalence of chronic bronchitis and cor pulmonale appeared to be greater in postmen from areas with higher pollution than in postmen from other areas [102], which was confirmed in a later study on the general population [103]. A higher prevalence of respiratory diseases compatible with COPD in areas with higher air pollution was also observed in the USA [104–106] and Poland [107]. The AHSMOG study [108] and SAPALDIA study [109] consistently found a higher prevalence of symptoms of hypersecretion, breathlessness, or diagnoses of chronic bronchitis, emphysema or COPD in areas with higher particulate air pollution. There have been three prospective cohort studies in the USA [110–113] on the relationship between residential exposure to air pollution and mortality in the general population. Two of the studies reported an increase in mortality for cardiopulmonary

conditions [110, 111] and a third for nonmalignant respiratory diseases in areas with higher levels of air pollution [112, 113].

It is difficult to conclude from these studies that a certain pollutant is related with the slowing of the lung function development, due to the poor characterization of the atmosphere components and the problem of comparing between few levels of exposure (*i.e.* high and low exposures). However, the prospective nature of some studies, and the inclusion of the main covariates, suggests that urban air pollution may be involved in lung function development and consequently be a risk factor of COPD.

Occupation

In a recent review, HENDRICK [114] concluded that some occupational environments are likely to involve a risk of COPD, that this effect, although variable, is likely to be less potent than the smoking effect and that interactions between smoking and occupations are probably relevant. In industry-based studies, several exposures in particular occupations have been considered a risk for COPD including: grain, isocyanates, cadmium, coal and other mineral dust and welding fumes. Population-based studies have the advantage of providing a comprehensive view of the relationship between occupation and COPD. In the frame of the European Community Respiratory Health Society (ECRHS) study in young general population, exposure to high levels of biological dust, measured with a job exposure matrix, was associated with lower levels of $FEV1$ in Spain [51]. However, this association was only of a significant magnitude in some of the participating countries in the ECRHS, but not in the overall population. In a longitudinal population-based study in Zutphen, Holland, the occupations that were found to be at higher risk of nonspecific chronic lung disease were: wood and paper workers, tailors, construction and transport workers; among the exposures the ones with an increased risk included heavy metals, mineral dust and adhesives [115]. In this study almost 40% of males were occupationally exposed and had a risk ratio of 1.46 [116], suggesting that although the occupational risk is small it affects a large proportion of the population and their contribution to the ultimate incidence of COPD may not be negligible. By contrast, in population-based studies it may be difficult to assess a complete life-exposure. The Zutphen study showed that the use of a complete occupational history leads to a stronger association between occupation and chronic obstructive lung disease as compared to analysis considering occupation since the start of the follow-up [116]. The important different types of bias in the occupational studies on COPD were illustrated in a review of studies in gold and coal miners performed by OXMAN et al. [117]. Following a well-defined methodology for systematic reviews, encompassing more than 2,500 citations, 74 articles met the initial criteria and only 13 used quantitative measurement of dust exposure and controlled for both smoking and age. The authors concluded that biases were likely to result in a substantial underestimation of ~50% of the true effects [118].

Nutrition

In the last years the potential protective role of some nutrients in the development of COPD has received increasing attention. Because of the wide availability of some of these dietary components, their potential role in the prevention of COPD is a relevant issue. Most of the evidence refers to vitamins C and E, which have an antioxidant action which may supposedly counteract the oxidative damage produced by exposures like smoking and air pollution. Subjects with a low intake of fresh fruits had an $FEV1$ on average 80 mL lower than expected in a study conducted in the UK [119], with a similar finding being reported in the NHANES I population in the USA [120]. Regarding other nutrients, BRITTON et al. [121] have reported an association between $FEV1$ and magnesium intake independent of the association with vitamin C. It has also been reported that a relatively high intake of ω-3 fatty acids, which are inhibitors of the arachidonic acid metabolism, may protect against the development of COPD [122] in smokers. This latter type of protective effect is consistent with the Zutphen Study [123]. In a recent analysis of the smokers in the NHANES I population adults reporting a high fish consumption had a higher $FEV1$ than those with low fish consumption [124]. Several human intervention studies have been conducted showing inconsistent associations between supplements of eicosapentaenois acid and respiratory outcomes suggesting a possible difference between long-term and short-term effects [124].

Socioeconomic status

In a recent review, a consistent association between socioeconomic status and COPD was reported [125]. These studies included a variety of COPD related entities. Some of the studies have focused on respiratory symptoms and lung function. Regarding lung function, these studies have reported significant adjusted associations between low socioeconomic status and lower $FEV1$ and or FVC, with a difference in $FEV1$ between the extreme groups of socioeconomic status of 200–400 mL [126, 127]. Similar results have been obtained in studies of children [128]. BAKKE et al. [129] found that subjects with a primary and secondary education had a higher prevalence of spirometric airflow limitation than subjects with a university education with statistically significant age, sex, smoking, and occupation adjusted odds ratios of 5.2 and 1.8 respectively.

The types of symptoms included in many studies do not refer directly to COPD but rather to chronic bronchitis. In general, most of the studies on symptoms have reported results that are consistent with those previously described for lung function [130, 131]. Although the reported studies have used different indices of socioeconomic status including family income, education, residence or occupation, the specific contribution of each of these components is difficult to assess. In a cross-sectional study carried out in Brazil, MENEZES et al. [132] found that poor schooling, poor

housing and family income were independently associated to chronic bronchitis.

The possibility that the socioeconomic status in early life could be a relevant risk factor of obstructive lung disease was suggested by the results of a longitudinal analysis of the Medical Research Council's national survey of health and development of the 1946 birth cohort [133]. BRITTEN *et al.* [121] assessed the presence of respiratory symptoms and peak expiratory flow when the subjects included in the study were 36 yrs old and found that in both males and females these respiratory events were independently associated, not only with current indices of poor social circumstances but also with poor home environment at age 2 yrs. In a Danish study the effect of education and income on adult lung function seemed independent of age which could also indicate that the mechanism is related to events taking place before reaching maximally attained lung function in early adulthood [126]. There are many mechanisms that have been considered to be involved in the relationship between socioeconomic status and COPD including intrauterine lung growth, early life exposures, childhood respiratory infections, smoking through childhood to adulthood, occupation, housing and nutrition [125].

The fact that the association between socioeconomic status and COPD is consistent across different types of studies in different populations, has a relevant magnitude and refers to a sizeable segment of the overall population, confers to this relationship a public health relevance that deserves further consideration.

Environmental risk factors in infancy

One factor that has received close attention is the presence of lower respiratory infection during childhood which has been found to increase the risk of respiratory symptoms [134] and of functional impairment [135]. MANN *et al.* [136] examining a national birth cohort, found that although bronchitis, bronchiolitis, and pneumonia before the age of 2 yrs were associated with lower peak expiratory flow at the age 36 yrs such association disappeared after adjustment by socioeconomic status and smoking. It is unclear whether constitutional undergrowth of lung function may be a common antecedent for both lower respiratory infections in early life and later development of COPD.

Prenatal smoke exposure has been previously mentioned as a potential risk factor for COPD. The rationale for this hypothesis is based on animal studies showing that foetal lung development is adversely influenced by maternal smoking [137] although it is very difficult to separate the *in utero* effects from the effects in the postnatal period. Postnatal exposure to smoking has been related to a higher risk of lower respiratory infections and to a decreased FEV1, although the evidence is based on cross-sectional studies or studies including only young people who can not properly inform about the risk of COPD. It has been suggested that passive exposure to smoking may account for a 5% reduction in the maximal attainable level of FEV1 [138, 139].

Interventions

The ultimate aim of epidemiology is to identify modifiable determinants of disease occurrence and progression and to contribute in testing the efficacy and effectiveness of interventions on these determinants including the health services. Reducing smoking is, so far, the only well established way for primary prevention of COPD. Although secondary prevention is progressively reaching a major development, in the control of some types of cancer its role in COPD has, so far, received little attention. The use of oxygen therapy and pulmonary rehabilitation do illustrate the role of tertiary prevention in COPD.

The importance of preventing smoking is beyond any doubt one of the most relevant and complex issues in public health and its detailed consideration is beyond the scope of this chapter. However, the prediction of future trends on COPD due to the failure of large-scale prevention of smoking do deserve some attention here. In the frame of the Global Burden of Disease Study MURRAY and LOPEZ [140] have provided mortality projections for the leading causes of death including COPD and shown that, assuming the current trends in smoking the mortality by COPD will see a sharp increase to became the third cause of death in the world by the year 2020. This alarming prediction will be the result of the spread of smoking consumption which has occurred among females in the industrialized countries and that is occurring in the developing world [141, 142]. An example of a recent response to the magnitude of the smoking problem are the guidelines for smoking cessation commissioned by the Health Education Authority in England strongly arguing for a multilevel approach within the National Health Service [132].

The rationale for secondary prevention of COPD is based on the evidence that after smoking cessation the rate of decline of FEV1 becomes slower [16] and parallels the one of nonsmokers, thus reducing the risk of developing COPD. The fact that COPD can be diagnosed at an early stage and that those with diminished lung function may have an important stimuli to either quit smoking or to participate in smoking cessation programmes are arguments in favour of early detection. A prominent study in this field was the Lung Health Study which assessed whether an intervention including smoking cessation and use of inhaled bronchodilator in smokers 35–60 yrs with mild COPD could slow the rate of decline of FEV1 [143]. The smoking intervention consisted in a 12-session smoking cessation programme combining behaviour modification and nicotine gum, followed by a 5-yr maintenance programme to minimize relapse. The results did show that the smoking cessation intervention resulted in a relevant reduction of the decline in FEV1 whereas the impact of the bronchodilator was smaller and reversed after the drug was discontinued [143]. The existence of an effective early treatment may also be a justification for secondary prevention. Several randomized-controlled trials of inhaled steroids therapy in the early stage of COPD have been recently conducted. Although no effect of inhaled corticosteroids on FEV1 decline has been documented this class of drugs may have a role in

reducing exacerbations in moderate-to-severe COPD [144].

When COPD is already established, medical diagnosis and appropriate treatment are the only alternatives to slow progression, reduce disability and increase life-expectancy. However, the assessment of the final benefit of medical interventions is a complex issue that involves intricate assessments of efficacy, effectiveness and efficiency. Randomized-controlled trials are the gold standard for this type of assessments and the importance of its use in clinical research can not be overemphasized. The only randomized-control trial in support of the influenza vaccination in COPD was provided by a study of general older population with no particular selection of COPD subjects [145]. Although the study did show a statistically significant reduction in the rate of hospital admission for all chronic respiratory causes, it was not possible to estimate the specific effectiveness for COPD patients. In order to assess the influence of influenza vaccination in the course of COPD several observational studies have been reported. HAK et al. [146] carried out a prospective cohort study of 1,696 patients with chronic lung disease including both asthma and COPD and found that in vaccinated $\geqslant 65$ yr olds the occurrence of any complication was reduced by 50% (95% CI: 17–70%). NICHOL et al. [147] performed a retrospective seasonal cohort study of 1,898 persons $\geqslant 65$ yrs with a diagnosis of COPD and found that influenza vaccination was associated with a lower risk of both hospital admission for pneumonia and influenza (adjusted risk ratio, 0.48 (95% CI, 0.20–0.82) and death (adjusted risk ratio 0.30 (95% CI, 0.21–0.43)). These studies, although based on uncontrolled interventions, do offer useful information that supports the effectiveness of influenza vaccination in COPD and its recommendation in the current guidelines.

Systematic reviews and meta-analysis have recently emerged as an appropriate approach for summarizing the results of a series of observational or experimental studies on the same topic. The application of meta-analysis to the assessment of an intervention in chronic obstructive pulmonary disease is well illustrated by two studies conducted in chronic obstructive pulmonary disease patients to evaluate pulmonary rehabilitation [148] and respiratory muscle training [149]. Whereas the former did show that participation in general rehabilitation programmes was effective for improving quality of life in chronic obstructive pulmonary disease patients [148] and extended the evidence provided by smaller trials, the latter did not show any relevant benefit for people with chronic obstructive pulmonary disease who followed respiratory muscle training alone [149].

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