Eur Respir J 2003; 21: Suppl. 41, 4s–12s
DOI: 10.1183/09031936.03.00077702



European Respiratory Journal
ISSN 0904-1850

# COPD: problems in diagnosis and measurement

S.T. Weiss*, D.L. DeMeo*, D.S. Postma#

*COPD: problems in diagnosis and measurement. S.T. Weiss, D.L. DeMeo, D.S. Postma. ©ERS Journals Ltd 2003.*
**ABSTRACT: Chronic obstructive pulmonary disease (COPD) is the most rapidly rising cause of death in individuals >65 yrs of age, the most rapidly growing segment of the USA population.**

**Advancing the clinical research agenda for COPD entails careful consideration of several issues and problems: defining COPD, reliance on physiological testing, outcome measurements and comorbidities.**

**In addition, issues pertaining to the recent dramatic increase in chronic obstructive pulmonary disease mortality in females, smoking susceptibility and the relationship of respiratory symptoms with hyperresponsiveness, as well as chronic obstructive pulmonary disease heterogeneity, are discussed.**
*Eur Respir J 2003; 21: Suppl. 41, 4s–12s.*

*Channing Laboratory, Brigham & Women's Hospital, Boston, MA, USA. #University Hospital, Groningen, The Netherlands.

Correspondence: S.T. Weiss, 181 Longwood Avenue, Channing Laboratory, Boston, MA 02115, USA.
Fax: 1 6175252745
E-mail: Scott.weiss@channing.harvard.edu

Keywords: Airway hyperresponsiveness, comorbidities, exacerbation, pulmonary function testing, outcome measurement

Received: August 21 2002
Accepted after revision: February 20 2003

Chronic obstructive pulmonary disease (COPD) is a major public health problem. Recent prevalence estimates suggest that ~15 million people have COPD; in 1996, 14.1 million people had chronic bronchitis and 1.8 million had emphysema [1]. This disease is the most steeply rising cause of death in individuals >65 yrs of age, which represents the most rapidly growing segment of the USA population. Disability from COPD is expected to rise by 2020 with ageing of the population and the increase in disease prevalence. It will be the fifth-leading cause of disability-adjusted life years lost [2], and it will rise worldwide from being the sixth to the third most common cause of death [1]. Excessive focus on the single environmental factor of cigarette smoking has been to the detriment of COPD research, as it has tended to minimise an understanding of genetic, developmental and other environmental risk factors that may be important in disease susceptibility and disease progression. Although cigarette smoking is most certainly the major risk factor for the development of COPD [3], only a small percentage of cigarette smokers develop the disease [4]. In addition, a variable response to cigarette smoking clearly suggests genetic susceptibility.

This article briefly considers a series of important issues that need attention in COPD research. These issues include defining and diagnosing the disease, understanding the problems inherent in relying on physiological testing alone to make a diagnosis, the importance of not discounting childhood episodes as irrelevant to adult pathology, the lack of well-defined phenotypes for tracking the disease, risk factors (related to sex, hyperresponsiveness, respiratory symptoms), genetics and the important issue of comorbidities. Only careful consideration of these problems and an attempt at mitigating their ramifications will allow the advancement of the clinical research agenda for COPD and improve treatment for what is a serious, life-threatening disease.

## Defining chronic obstructive pulmonary disease

One of the critical issues in COPD research has been the lack of a cohesive definition for the disease. The lack of an international standard has confounded the comparability of COPD studies. True incidence and prevalence trends may be obscured by this definitional variability, illustrated in a study by VIEGI *et al.* [5] that compared prevalence rates of COPD in the Po Delta Valley, Italy, using European Respiratory Society (ERS) and American Thoracic Society (ATS) criteria. In subjects ⩾46 yrs of age, ERS criteria suggested a 12.2% prevalence of COPD compared with a 57% prevalence by ATS criteria. Of note, clinical criteria suggested a prevalence of 28.8% [5]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) represents a viable international effort to codify the definitions and criteria for diagnosis and management of COPD [6].

According to the GOLD criteria, "COPD is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases" [7]. Spirometric evaluation should be used to confirm the diagnosis when suggestive symptomatology is present. Chronic cough and sputum production have a variable relationship to airflow limitation, which is the *sine qua non* of COPD [8]. The epidemiological manifestations of the disease (chronic cough, phlegm and dyspnoea on exertion) and the pathological manifestations (enlarged and increased numbers of mucus-secreting glands, destruction of the lung parenchyma and the development of emphysema) have a statistically significant, but not a high degree of, correlation with COPD confirmed by physiological testing. Some individuals with airflow obstruction do not have severe emphysema and some individuals with emphysema do not have airflow limitations [9, 10]. Epidemiological studies demonstrate that respiratory symptoms may precede or follow the development of airflow limitation by many

Table 1. – Risk factors for the development of chronic obstructive pulmonary disease

| Host susceptibility factors | Environmental risk factors |
|---|---|
| Age | Smoking |
| Airway responsiveness | Occupational exposures |
| Allergy | (Indoor) Air pollution |
| Sex | Diet |
| Genetics | Environmental allergens |

Table 2. – Classification of chronic obstructive pulmonary disease (COPD) by severity

| Stage | Classification | Characteristics |
|---|---|---|
| 0 | At risk | Chronic respiratory symptoms, smoking and normal spirometry |
| 1 | Mild COPD | FEV1 ⩾80% pred<br>FEV1/FVC <70% |
| 2 | Moderate COPD | FEV1 30–80% pred<br>FEV1/FVC <70% |
| 3 | Severe COPD | FEV1 <30% pred<br>FEV1/FVC <70% |

All spirometry is postbronchodilator. FEV1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity. Adapted from [7] with permission.

years. The presence or absence of symptoms also depends largely on the constellation of risk factors to which an individual is exposed (table 1).

Importantly, peak flow alone has a low specificity for the diagnosis of COPD, as decrements in peak flow can be present in other pulmonary diseases. When spirometry is performed, a diagnosis of COPD is considered to be present if the postbronchodilator forced expiratory volume in one second (FEV1) is <80% of the predicted value in combination with an FEV1/forced vital capacity (FVC) ratio of <70% [11]. Recently, standards of severity have also been defined with a goal toward global uniformity in the diagnosis of COPD [11] (table 2). It should be noted that the role of classifying individuals into GOLD stage 0 (with absence of airflow limitation but presence of cough and sputum) may not actually be useful for identifying the individuals "at risk" for future development of obstructive pulmonary disease. VESTBO and LANGE [12] analysed 5- and 15-yr data from The Copenhagen City Heart Study using multivariate regression techniques; this analysis suggested that GOLD stage 0 did not effectively identify the future development of airways obstruction at these time points [12].

## Physiological testing

Pulmonary function testing is reproducible and FEV1 tracks consistently during growth from an early age, which can be used to track individuals over time [13] (fig. 1). Pulmonary function testing is generally not administered to patients during routine outpatient visits. This greatly hinders the potential for COPD diagnosis at early stages of the disease and has direct relevance to prevalence estimates and the clinical practices of COPD [14]. Spirometry has been demonstrated to be an efficient method for detection of airway obstruction in outpatient clinics in specifically targeted higher-risk groups. In a large-scale effort to demonstrate the efficacy of spirometry for screening, ZIELINSKI and BEDNAREK [15] offered spirometry to 11,027 individuals >39 yrs of age with at least 11 pack-yrs of smoking. Spirometric criteria for obstructive lung disease were observed in

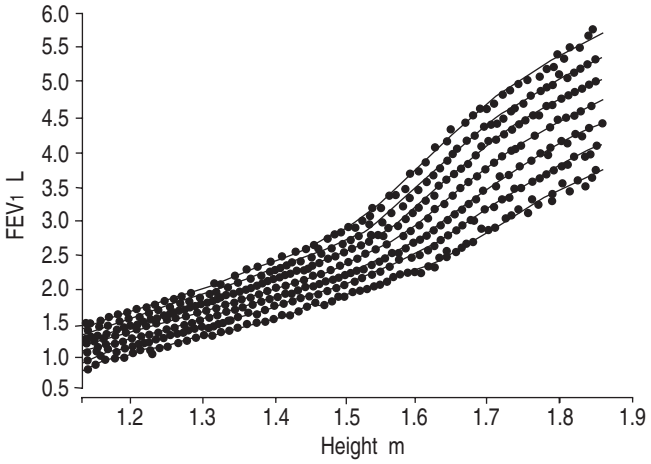


Fig. 1. – Growth of forced expiratory volume in one second (FEV1) for seven selected male children followed for repeatability over an 11-yr interval. Individuals track along their growth curves. From the lower to the upper line, the percentage smoothed percentiles of FEV1 by height are 3, 10, 25, 50, 75, 90 and 97%, respectively. Reproduced from [13] with permission.

24.3% of the cohort. Of 2,200 participants who were lifetime never-smokers, 14.4% had demonstrable airway obstruction [15]. Recent trends in the prevalence of COPD are suggested in the third National Health and Nutrition Examination Survey (NHANES III) [14]. Outcome measures included a physician diagnosis of asthma, chronic bronchitis, emphysema, respiratory symptoms and low lung function. Low lung function was defined as both an FEV1/FVC ratio of <0.70 and an FEV1 <80% pred. Of the cohort of 20,050 individuals, 6.8% had low lung function as defined and 8.5% reported a diagnosis of COPD. The majority (63.3%) of those individuals with documented low lung function had no prior physician diagnosis of COPD. Data from this NHANES study also suggested that a significant amount of disease remains undiagnosed when in the mild stage, thus underestimating the actual prevalence and burden of disease [14]. The classic estimates are that 10–15% of all adults >55 yrs of age have undiagnosed airflow limitation. This increases with advancing age and may reach as high as 30–40% in individuals >70 yrs of age [16, 17]. In Spain, a similar observation was made regarding underdiagnosis of COPD. In a large population study of 4,045 males and females (aged 40–69 yrs), the prevalence of COPD was 9.1%; although the majority of this disease was observed in current and former smokers, there was a component of disease that was observed among nonsmokers. In 78.2% of cases there was no prior physician diagnosis of COPD. Individuals who were male, >60 yrs, more educated and had >15 pack-yrs of smoking were more likely to have received a prior diagnosis of COPD [18]. In a sample of 353 individuals in a British general practice, 58 patients had obstructive lung disease noted with screening spirometry; 52% had no prior diagnosis of lung disease [19]. The use of spirometry in health clinics is important to be able to estimate the true burden of COPD and its impact on health as the population ages.

Variability in patterns of clinical presentation is common in COPD, which also makes diagnosis difficult. Patients may not focus on respiratory complaints when they visit a physician. Decline of pulmonary function is present in all individuals with ageing, thus, most older persons will accommodate their physical activity to encompass their respiratory reserve. Consequently, they will not consult a physician for respiratory complaints alone or mention them to the physician during a visit. This is particularly true in Western industrialised

society, in which people do not have to engage in strenuous physical activity and can thus modify their personal and occupational activities to be energy and breath conserving. It is not unusual for some intervening event such as a respiratory illness to cause a patient to visit a physician. Yet, most likely, and erroneously, the patient will attribute shortness of breath to that specific episode rather than accept the event as part of a gradual underlying, unremitting decline in pulmonary function. The net result of these patterns is that physicians are not predisposed to perform pulmonary function testing. Consequently, a substantial portion of COPD remains undiagnosed [14].

## Risk factors and diagnostic obstacles

Risk considerations in COPD should be divided into risk for disease development and risk for disease progression. Intrinsic to the consideration of risk for the development of COPD are both host susceptibility and environmental factors, as enumerated in table 1 and discussed below.

Childhood asthma and increased airways responsiveness may also represent the most important events that mark susceptibility for lung function decline and subsequent development of COPD [20]. During childhood, pulmonary function increases and given that symptoms are loosely correlated with pulmonary function, asthma-type symptoms tend to decline with lung growth. Childhood events are important in that they reduce maximal lung growth and may precipitate early decline [21] (fig. 2). A retrospective study of asthma incidence rates in Rochester, MN, USA, showed that 40% of children who wheezed during their first year of life went on to develop asthma and that 90% of all asthma was diagnosed by age 6 yrs [22].

Most adults who are susceptible to lung damage from smoking have also had some childhood episode or illness that marked them as susceptible for developing COPD [23], which is of concern with regard to trends in COPD. Data from the National Health Interview Survey revealed that self-reported asthma rates have increased by 75% during the years 1980–1994. The most significant increase was in children from birth to 4 yrs of age, whose rates were noted to increase by 106% [24]. These trends may influence the future burden of disease secondary to COPD. Unfortunately, adult patients with respiratory problems are often unable to recall those episodes from the distant past. Consequently, both patients and physicians regard current symptoms to be new-onset adult disease, when, in fact, the symptoms may represent a recrudescence of disease that began early in life.

Although different aspects of indoor air pollution such as chronic biomass or wood smoke may be relevant to the development of obstructive lung disease [25–28], globally, cigarette smoking is the most important environmental risk that contributes to COPD [3]. Factors that appear to be important host characteristics with regard to susceptibility to smoking-related COPD include genetic predisposition, female sex, the presence of underlying asthma or airways responsiveness and, possibly, the presence of underlying allergy

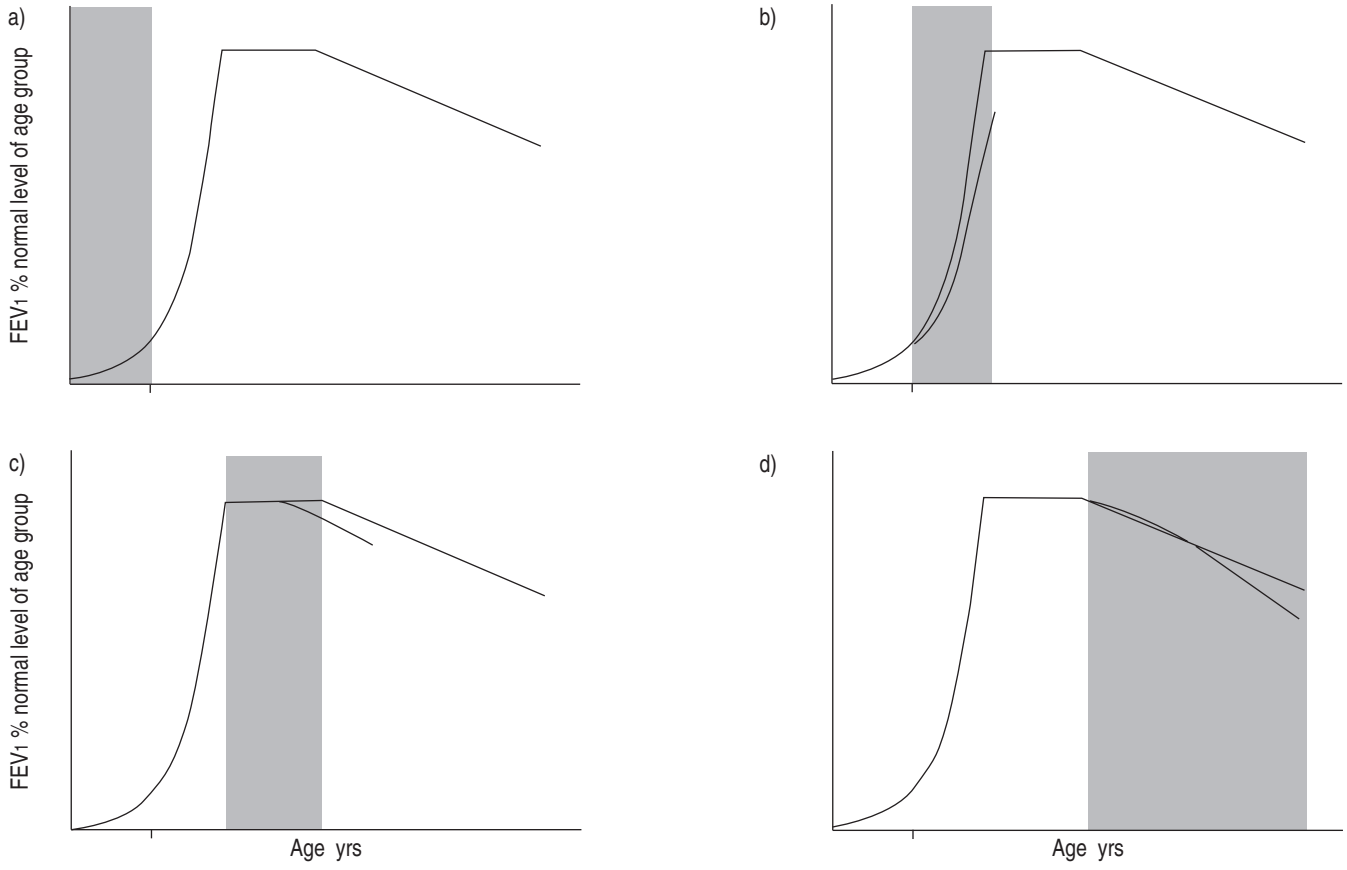


Fig. 2. – The four phases of growth and decline in lung function through the life cycle; curves begin at birth and proceed through the life course. a) Decreased intra-uterine growth, b) decreased growth, c) shortened plateau and d) increased rate of decline. Childhood events may reduce maximal lung growth and may precipitate early decline. The shaded areas indicate periods of time during different ages in which different mechanisms contribute to processes that may result in low forced expiratory volume in one second and, potentially, chronic obstructive pulmonary disease later in life. Reproduced from [21] with permission.

[29, 30]. When a patient with such host susceptibilities begins to smoke cigarettes, disease is produced at a much lower dose (as measured by pack-yrs of cigarette smoking) [4]. Since individuals vary in their genetic susceptibility to cigarette smoking, there is substantial variation in the pulmonary function for any given dose of cigarette smoking [4] (fig. 3). Regardless of smoking status, however, clinicians are much more likely to diagnose males with COPD and females with asthma or asthmatic bronchitis. In a longitudinal study, females >40 yrs of age are often deemed "asthmatic" when compared with males of the same age and with similar symptoms [31]. The combination of recall bias on the part of the patient and diagnostic bias on the part of the physician consequently creates diagnostic uncertainty and potential misdiagnosis of COPD [32]. FEENSTRA *et al.* [33] recently showed that there will be an increase in the burden of COPD between 1994–2015. This will result in a 43% increase in prevalence of COPD for males and a 142% increase for females.

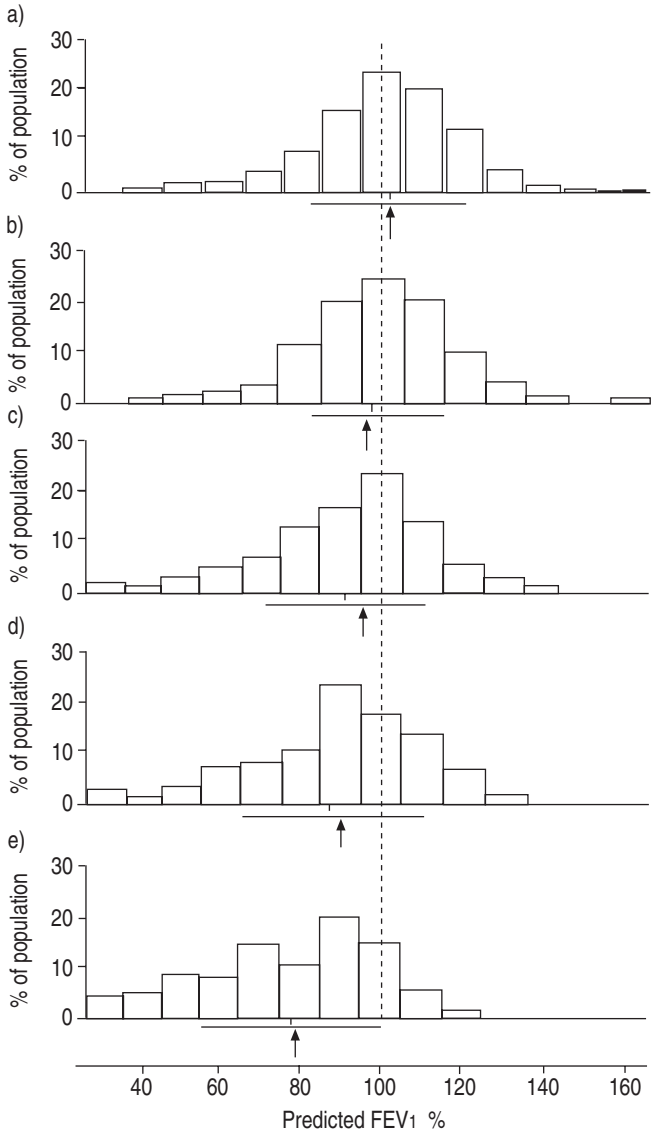


Fig. 3. – Percentage distribution of predicted forced expiratory volume in one second ($FEV_1$) values in subjects with varying pack-yrs of smoking: a) 0, b) 0–20, c) 21–40, d) 41–60 and e) >60 pack-yrs. Subjects with respiratory symptoms before age 16 yrs were excluded. The dashed vertical line indicates the 100% predicted point for $FEV_1$. The arrows indicate median $FEV_1$ and the short vertical lines indicate the mean. The horizontal lines represent ±1 SD. Reproduced from [4] with permission.

## Allergy

Allergic phenotypes represent immediate hypersensitivity to antigen and may manifest as an elevation in total or specific immunoglobulin E, elevated total eosinophil counts and positive skin-test reactions to specific allergens. Skin-test reactivity increases until age 15 yrs [34] and the decline in reactivity after age 35 yrs confounds the measurement of this intermediate phenotype in individuals suspected to have COPD. Although the findings of association between skin-test reactivity and $FEV_1$ have not been consistent [35–37], GOTTLIEB *et al.* [37] investigated this prospectively and found that positive skin-test reactivity predicted increased rates of decline in $FEV_1$ and $FEV_1$/FVC ratio. It has also been suggested that immediate type-I hypersensitivity is a risk factor for the development and progression of COPD [30]. In this model, atopy may influence childhood asthma and thus limit maximally attained lung growth, accelerate $FEV_1$ decline and enhance interaction with cigarette smoke, thus promoting lung function decline and the development of COPD [30].

## Airway hyperresponsiveness

Airway hyperresponsiveness to methacholine may help identify individuals susceptible to the development of COPD and those susceptible to progressive lung function decline [38]. This intermediate phenotype is not only a cardinal feature in asthma, but also an important finding in a subset of individuals with COPD [30, 37, 38]. Baseline levels of lung function, age and smoking history all play a role in this phenotype. In some individuals, airway hyperresponsiveness predicts an acceleration in lung function decline and the development of COPD [38]; in others, this phenotype may predict COPD-related mortality [39]. In at-risk individuals, airway responsiveness may be demonstrated in the majority of instances when it is actually measured [40]. However, methacholine challenge is often avoided in individuals already suspected of having low lung function.

An important consideration is that airway hyperresponsiveness may be a cause and not a result of COPD. A 25-yr study in the Netherlands demonstrated that increased airway hyperresponsiveness is an independent risk factor for decline in $FEV_1$ [41]. In a study of individuals with early-onset COPD, those with increased airway hyperresponsiveness had an accelerated decline in $FEV_1$ [42]. It is still debatable whether hyperresponsiveness improved by anti-inflammatory therapy may improve the course of the disease. One study has shown that inhaled corticosteroids improved hyperresponsiveness after 4 yrs of treatment. Despite this improvement, pulmonary function decline did not cease [43].

## Respiratory symptoms

Respiratory symptoms have been associated with lower levels of pulmonary function [44–47], although patients may underestimate the morbidity associated with their disease. In a large international telephone screening of 201,921 households (in the USA, Canada, France, Italy, Germany, the Netherlands, Spain and the UK), 3,265 individuals with probable obstructive lung disease were identified. For example, among individuals with the most severe breathlessness and limitation (unable to leave home secondary to dyspnoea), 35.8% described their

disease as mild; of those unable to ambulate for a few minutes on level ground, 60.3% described their disease as mild [48]. Although the impairment associated with chronic cough was observed predominantly in males [44], it has been reported that females and males with chronic cough and chronic mucus hypersecretion have an accelerated decline in FEV1 [45, 46] and greater mortality from COPD [47]. Whether these symptoms are markers of pathological alteration of the airways is not known.

The relationship between symptoms and hyperresponsiveness has been studied in Vlagtwedde/Vlaardingen in the Netherlands. The more severe hyperresponsiveness a subject had without respiratory symptoms, the more likely they were to develop respiratory symptoms in later life [49]. Furthermore, in a subsequent analysis, it has been shown that individuals with hyperresponsiveness and eosinophilia are more prone to develop respiratory symptoms [50]. Thus, both hyperresponsiveness and eosinophilia may constitute risk factors for the development of symptoms and are worthwhile measuring in studies assessing COPD risk. These parameters may also be useful for assessing the impact of prevention and intervention strategies.

## Sex and sex differences

A difference has always existed in the prevalence of COPD in males and females, with males having higher rates. The gap between males and females has been narrowing, however, and the increased rates of females smoking cigarettes in the last 20–30 yrs have been associated with steadily increasing rates of COPD in females. Figure 4 illustrates that females have been catching up with males rapidly in COPD mortality, particularly during the last decade [51]. MANNINO *et al.* [52] analysed data concerning death from 1979–1993 and found that although mortality rates for males with COPD have started to stabilise, these rates were continuing to increase among females.

There are alternative explanations for increasing COPD mortality among females. One proposal is that females are more susceptible than males to the effects of cigarette smoke. For any given level of smoking, females have a lower FEV1 [53]. Furthermore, there have been significantly greater rates of FEV1 decline among female smokers compared with male smokers, as shown in an epidemiological setting in the Netherlands [54]. Finally, a sex difference in severe, early-onset COPD has been demonstrated [55]. In the offspring of 84 individuals with severe, early-onset COPD, there was a markedly elevated prevalence (71.4%) in females. Current or exsmoking female first-degree relatives appeared to have a significantly greater risk of a low FEV1, with odds ratios of 1.91 for FEV1 <80% pred and 3.65 for FEV1 <30% pred. These data suggest that females may be more susceptible to the development of COPD. Interestingly, there was no significant risk for chronic bronchitis in females, although there was a risk in males. CHEN *et al.* [56] showed that females have more severe small airway disease for a similar level of smoking (fig. 5). Emphysema occurs predominantly in the small airways and this finding may suggest a greater likelihood for females to develop emphysema when smoking. LEYNAERT *et al.* [57] demonstrated that females were more likely to have airway hyperresponsiveness than males; this could not be explained by sex differences in the presence of asthma, respiratory symptoms, atopy or lung function. A bronchoconstrictive response to methacholine was associated with heavy tobacco consumption only in females. They concluded that the excess of airway hyperresponsiveness in females is not due to their having a smaller lung function size or airway calibre than males, but to a greater susceptibility to the effects of cigarette smoking [57].

Airway hyperresponsiveness is a risk factor for both the development and progression of COPD. The more severe the hyperresponsiveness, the more rapid the decline in pulmonary function [35, 42, 58, 59]. Thus, the higher prevalence of airways hyperresponsiveness in females may indeed explain the difference between males and females with respect to smoking-induced COPD. Females in the Lung Health Study had greater airway hyperresponsiveness to methacholine than males with mild COPD [59]. Notably, sex differences in this group of individuals with established COPD were not significant with respect to the influence of hyperresponsiveness on lung function decline. Conversely, females have a greater degree of hyperresponsiveness to methacholine irrespective of pulmonary function [60]. Thus, it is still possible that the enhanced severity of hyperresponsiveness in females may contribute to their greater susceptibility to cigarette smoke and other environmental risk factors that influence pulmonary function.

Airway size is another factor possibly contributing to differences between sex susceptibility to the effects of cigarette smoke. Between males and females at a young age, differences

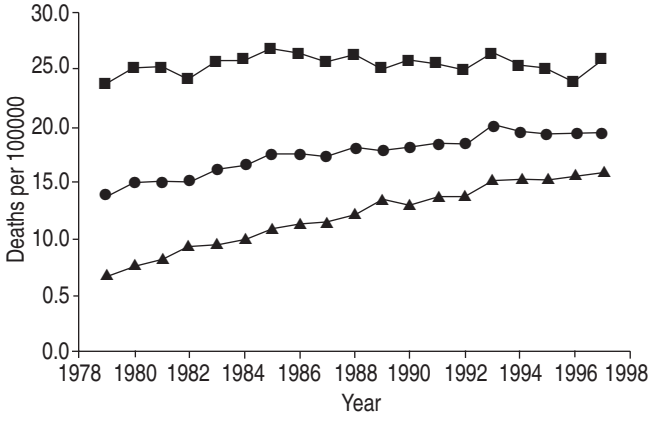


Fig. 4. – Mortality due to chronic obstructive pulmonary disease (COPD). Female mortality from COPD has increased steadily in the USA over the last several decades, largely as a result of their increased cigarette smoking. ■: male; ●: total; ▲: female. Adapted from data from [51].

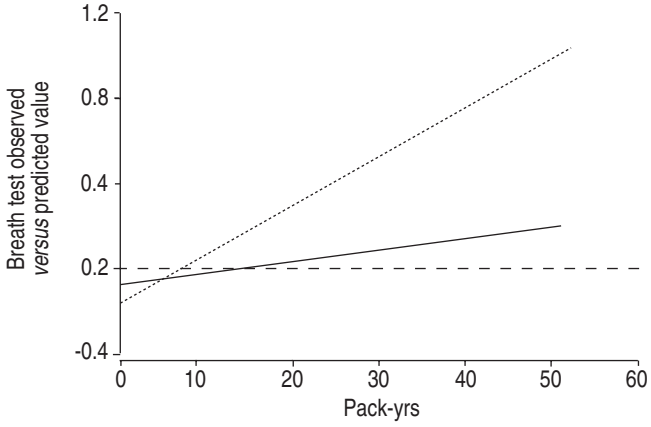


Fig. 5. – Slope of Phase III of the single breath nitrogen test: differences in females (·····) and males (—). Females have more severe small airway disease than males for a similar level of cigarette smoking. Reproduced from [56] with permission.

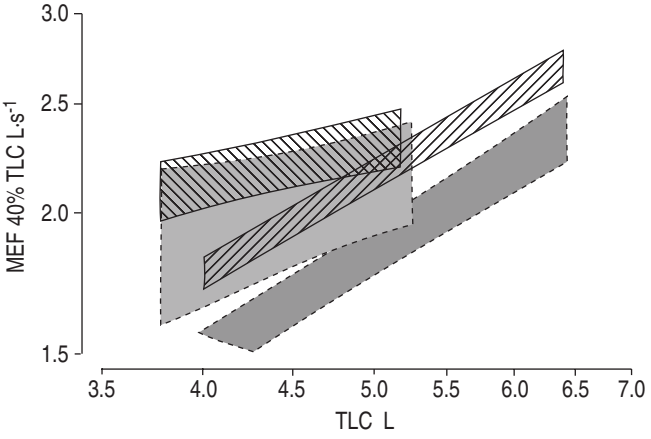


Fig. 6. – Growth of lungs and airways in young males and females aged 13–17.5 yrs. Females have larger airways in relation to lung size than males. Males demonstrated more pronounced airway growth compared with females, resulting in airways equal to or larger than those in females with the same lung volume. This figure shows longitudinal change of log maximal expiratory flow (MEF) *versus* change of total lung capacity (TLC) based on individual slopes and intercepts. 90% Confidence bands for symptomatic males (▒), asymptomatic males (▨), symptomatic females (■) and asymptomatic females (▨) are shown. Reproduced from [61] with permission.

already exist that may account for the enhanced effect of smoking in females. Young females have larger airways in relation to lung size than young males [61] and specific airway resistance is lower at any given height in females (fig. 6). Thus, relevant to the development of COPD, smoke particles may impact males and females differently.

## Genetics

Most COPD is not secondary to $\alpha_1$-antitrypsin deficiency, the only currently proven genetic risk for this disease [62, 63]. Instead, most COPD represents the expression of a complex genetic disease, resulting from an interaction between host and environmental factors [64]. Most studies of COPD genetics have focused upon intermediate phenotypes and pulmonary function parameters. Twin studies have shown that the concordance of lung function was larger in monozygotic than in dizygotic twins [65]. In a cohort of individuals with COPD, SILVERMAN *et al.* [66] studied 104 first-degree relatives of 44 probands with severe, early-onset COPD. First-degree relatives of probands had significantly lower FEV1 and FEV1/FVC ratios when compared with controls having similar smoking histories. Reduced spirometry in first-degree relatives was found in current or exsmokers only [66]. These reports suggest both familial aggregation of COPD (independent of protease inhibitor type) and the importance of gene-by-environment interactions between cigarette smoke and still unidentified genetic influences. Recent publications have found multiple genetic loci involved in spirometric phenotypes associated with COPD [65, 67–70]. The variability in gene-to-gene and gene-by-environment interactions, both in the susceptibility and the progression of COPD, constitutes the challenge of dissecting the genetics of COPD.

## Environmental risk factors

Cigarette smoke is the most important environmental challenge that influences lung function decline and the development of COPD. The dose/effect relationship between cigarette smoke and lung function decline depends upon when an individual is exposed. Among those smokers already with a low FEV1, lung injury and decrease in lung function secondary to cigarette smoking is more impressive. In the Lung Health Study [42], middle-aged smokers who continued smoking for 5 yrs had further losses of FEV1 of several hundred millilitres. Importantly, however, COPD has been identified in nonsmokers as well, with 4% of males and 5% of females reporting physician-diagnosed COPD. Therefore, other related environmental risks are important contributors. Occupational and air pollution exposures may result in the development of an obstructive phenotype [71, 72], and environmental awareness and control should be an ancillary feature addressed in minimising patient risk for the development and progression of COPD.

## Risk for disease exacerbation

It is still debatable whether exacerbations of COPD constitute a risk factor for accelerated decline in lung function [73]. However, exacerbations constitute a large individual burden and have a dramatic impact on the quality of life and need for healthcare [74]. Risk factors for exacerbations have not been studied extensively, although a wide variety have been proposed. Bacterial [75, 76] and viral [77] infections are important factors that influence exacerbations of COPD. Exacerbation may be manifest as increased sputum production with the development of purulent features and increased dyspnoea. In one study, daily wheeze and bronchitic symptoms contributed to a higher frequency of exacerbation [74]. KESSLER *et al.* [78] reported that risk factors for hospitalisation included a low body mass index and poor performance on a 6-min walk test, but gas exchange impairment and pulmonary and haemodynamic dysfunction were the most important risks. Importantly, one study suggests that many patients ultimately hospitalised with COPD exacerbation have modifiable characteristics that impact on susceptibility (such as lack of influenza vaccination, improper use of medications, ongoing cigarette smoke exposure) [79]. These deficiencies in outpatient management may be addressed to help limit disease exacerbation. In this same study, previous hospital admissions, lower FEV1 and underprescription of long-term oxygen therapy were independently associated with a higher risk of admission for a COPD exacerbation [79]. Longitudinal studies are urgently needed to assess relevant determinants of COPD-related exacerbations and hospitalisation.

## Disease outcome measurement

Despite the understanding of the host susceptibility factors, COPD diagnosis remains a challenge. Frequently, COPD is diagnosed only when the disease has already progressed. It is not possible to measure lung tissue damage or small airway disease at an early stage. This early stage is precisely when a person should be warned about the negative effects of environmental stimuli and when a physician could intervene to limit the progression of these changes in lung tissue and airway walls.

COPD is defined physiologically on the basis of pulmonary function level, and spirometry has become the primary endpoint for clinical trials. Although knowledge is increasing [80, 81], relatively little is known about the inflammatory processes in COPD. Unlike other diseases, where there are viable biomarkers to monitor the inflammatory process, COPD lacks established intermediate phenotypes that can be utilised to track the disease progression and serve as surrogate markers and outcome variables in clinical trials. This is a tremendous problem both for determining the

economic and social burdens of COPD, as well as determining efficacy and effectiveness in clinical studies. One such monitoring tool may be induced sputum or exhaled air condensate. Sputum eosinophilia appears to be present in some individuals with COPD and has been associated with a better oral corticosteroid response [82]. To date, no study has investigated prospectively whether this can be utilised in clinical practice to assess inhaled steroid responders. It has been well established that exhaled hydrogen peroxide ($H_2O_2$) is increased in patients with COPD [83]. One study investigated the effect of 600 mg *N*-acetylcysteine (NAC) on exhaled air condensate with $H_2O_2$ and lipid peroxidation products [83]. After 9 and 12 months of treatment, the NAC group exhaled 23-fold and 26-fold less $H_2O_2$ than those who received placebo. No significant effect of NAC administration on lipid peroxidation products was noted over the whole treatment period. These results indicate that long-term oral administration of NAC attenuates $H_2O_2$ formation in the airways of COPD subjects and provides support for the antioxidant action of the drug. However, further studies are necessary to estimate the clinical significance of this finding [84].

One other potential biomarker of COPD is high-resolution computed tomography (HRCT), which harnesses the anatomical and pathological features of COPD together with cutting-edge technology. In fact, refinement of this technique may prove useful in addressing the presence of risk for lung obstruction before spirometric abnormalities develop. SANDERS *et al.* [85] and SANTIS *et al.* [86] showed that 68–80% of smokers had demonstrable evidence of emphysema on HRCT in the presence of normal spirometry. Although HRCT as a clinical technique is still being developed, it may provide a much-needed link between the anatomy and physiology and allow for earlier recognition and management of disease susceptibility factors.

Finally, COPD is a heterogeneous disease. Some patients with COPD have evidence of bronchitis in the airway wall. Others have small and almost undetectable airway disease with conventional pulmonary function testing and others may have a loss of elasticity in lung tissue. It is clear that these disease characteristics suggest different underlying disease processes. Continuing to consider these disparate groups as one group may obscure risk factors for disease development or progression. In grouping these different phenotypes, a clear understanding of the variable expression of COPD is lost. Consequently, the opportunity to select adequate measures to address the underlying differences is also lost. Therefore, better tools are needed to assess the various aetiological and pathogenic aspects of COPD. The goals are to slow and, ultimately, to prevent the development of emphysema.

## Comorbidities

In general, COPD has its onset in individuals during their 60s and 70s. Smoking, which is the major risk factor for COPD, is also a risk factor for atherosclerosis, cancer and coronary artery disease, and thus the potential for severe and significant comorbidities influencing the course and natural history of COPD is substantial. Most studies have been unable to characterise the COPD population accurately with regard to their comorbidities. Subsequently, the influence of these comorbidities on the results of clinical trials and the natural history of disease progression is poorly understood.

## Conclusions

COPD is a major public health problem. Although reliable physiological testing can define disease severity and occurrence, this testing is not uniformly applied to high-risk populations. There are major uncertainties with regard to diagnoses based on symptoms because symptoms that mark the susceptible adult are usually not remembered or reported at the time of disease onset. An additional major concern is diagnostic misclassification. Risk factors other than smoking, such as airway hyperresponsiveness and atopy/allergy, need to be studied further, as do sex and genetic differences that may impact susceptibility.

Finally, investigators lack repeatable, reliable markers of airway inflammation and burden of disease, independently of spirometric testing that would allow monitoring of disease progression and effects of therapy in clinical trials. High-resolution computed tomography may provide a much-needed biomarker for use in chronic obstructive pulmonary disease investigations, but its role has still to be established. Most chronic obstructive pulmonary disease presents in older individuals with other diseases and thus assessment of the impact of comorbid conditions on the natural history of chronic obstructive pulmonary disease are urgently needed to place this disease in better context. The future clinical agenda for chronic obstructive pulmonary disease research will depend on the ability to solve these problems.

## References


1. National Heart, Lung and Blood Institute. Morbidity and Mortality Chartbook. Bethesda, National Institutes for Health, National Heart, Lung and Blood Institute, 2000.
2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; 349: 1498–1504.
3. US Surgeon General. The health consequences of smoking: obstructive lung disease. Washington DC, US Dept of Health and Human Services, 1984.
4. Burrows B, Knudson RJ, Cline MG, Lebowitz MD. Quantitative relationships between cigarette smoking and ventilatory function. *Am Rev Respir Dis* 1977; 115: 195–205.
5. Viegi G, Pedreschi M, Pistelli F, *et al.* Prevalence of airways obstruction in a general population: European Respiratory Society vs American Thoracic Society definition. *Chest* 2000; 117: Suppl. 2, 339S–345S.
6. Hurd S. International efforts directed at attacking the problem of COPD. *Chest* 2000; 117: Suppl. 2, 3366S–3368S.
7. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS and on behalf of the GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001; 163: 1256–1276.
8. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152: S77–S120.
9. Thurlbeck WM. Aspects of chronic airflow obstruction. *Chest* 1977; 72: 341–349.
10. Gelb AF, Hogg JC, Muller NL, *et al.* Contribution of emphysema and small airways in COPD. *Chest* 1996; 109: 353–359.
11. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): Executive Summary. *Respir Care* 2001; 46: 798–825.
12. Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 2002; 166: 329–332.
13. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BGJ.

Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993; 15: 75–88.
14. Mannino SM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med* 2000; 160: 1683–1689.
15. Zielinski J, Bednarek M. Early detection of COPD in a high-risk population using spirometric screening. *Chest* 2001; 119: 731–736.
16. Renwick DS, Connolly MJ. Prevalence and treatment of chronic airways obstruction in adults over the age of 45. *Thorax* 1996; 51: 164–168.
17. van den Boom G, van Schayck CP, van Mollen MP, *et al.* Active detection of chronic obstructive pulmonary disease and asthma in the general population. Results and economic consequences of the DIMCA program. *Am J Respir Crit Care Med* 1998; 158: 1730–1738.
18. Pena VS, Miravitlles M, Gabriel R, *et al.* Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. *Chest* 2000; 118: 981–989.
19. Dickenson JA, Meaker M, Searle M, Ratcliffe G. Screening older patients for obstructive airways disease in a semi-rural practice. *Thorax* 1999; 54: 501–505.
20. O′Connor GT, Sparrow D, Weiss ST. A prospective longitudinal study of methacholine airway responsiveness as a predictor of pulmonary-function decline: The Normative Aging Study. *Am J Respir Crit Care Med* 1995; 152: 87–92.
21. Weiss ST, Ware JH. Overview of issues in the longitudinal analysis of respiratory data. *Am J Respir Crit Care Med* 1996; 154: S208–S211.
22. Yunginger JW, Reed CE, O′Connell EJ, Melton L Jr, O′Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma. Incidence rates of 1964–1983. *Am Rev Respir Dis* 1992; 146: 888–894.
23. Gold DR, Tager IB, Weiss ST, Tosteson TD, Speizer FE. Acute lower respiratory illness in childhood as a predictor of lung function and chronic respiratory symptoms. *Am Rev Respir Dis* 1989; 140: 877–884.
24. Mannino DM, Homa DM, Pertowski CA, Ashizawa A, Nixon LL. Surveillance for asthma--United States, 1960–1995. Center for Disease Control Surveillance Summary. *Morb Mortal Wkly Rep* 1998; 47: 1–27.
25. Ozbay B, Urzun K, Arslan H, Zehir I. Functional and radiological impairment in women highly exposed to indoor biomass fuels. *Respirology* 2001; 6: 255–258.
26. Perez-Padilla R, Regalado J, Vedal S, *et al.* Exposure to biomass smoke and chronic airway disease in Mexican women. A case-control study. *Am J Respir Crit Care Med* 1996; 154: 701–706.
27. Pandey MR. Domestic smoke pollution and chronic bronchitis in a rural community of the hill region of Nepal. *Thorax* 1984; 39: 337–339.
28. Amoli K. Bronchopulmonary disease in Iranian housewives chronically exposed to indoor smoke. *Eur Respir J* 1998; 11: 659–663.
29. Silverman EK, Speizer FE. Risk factors for the development of chronic obstructive pulmonary disease. *Med Clin North Am* 1996; 80: 501–522.
30. Weiss ST. Atopy as a risk factor for chronic obstructive pulmonary disease: epidemiological evidence. *Am J Respir Crit Care Med* 2000; 162: S134–S136.
31. Dodge RR, Burrows B. The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. *Am Rev Respir Dis* 1980; 122: 567–575.
32. Chapman KR, Tashkin DP, Pye DJ. Gender bias in the diagnosis of COPD. *Chest* 2001; 119: 1691–1695.
33. Feenstra TL, van Genugten ML, Hoogenveen RT, Wouters EF, Rutten-van Molken MP. The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. *Am J Respir Crit Care Med* 2001; 164: 590–596.
34. Barbee RA, Kaltenborn W, Lebowitz MD, Burrows B. Longitudinal changes in allergen skin test reactivity in a community population sample. *J Allergy Clin Immunol* 1987; 79: 16–24.
35. Frew AJ, Kennedy SM, Chan-Yeung M. Methacholine responsiveness, smoking, and atopy as risk factors for accelerated FEV1 decline in male working populations. *Am Rev Respir Dis* 1992; 146: 878–883.
36. Taylor RG, Joyce H, Gross E, Holland F, Pride NB. Bronchial reactivity to inhaled histamine and annual rate of decline in FEV1 in male smokers and ex-smokers. *Thorax* 1985; 40: 9–16.
37. Gottlieb DJ, Sparrow D, O′Connor GT, Weiss ST. Skin test reactivity to common aeroallergens and decline of lung function. The Normative Aging Study. *Am J Respir Crit Care Med* 1996; 153: 561–566.
38. Rijcken B, Schouten JP, Weiss ST, Speizer FE, van der Lende R. The association of airways responsiveness to respiratory symptom prevalence and to pulmonary function in a random population sample. *Bull Eur Physiopathol Respir* 1987; 23: 391–394.
39. Hospers JJ, Postma DS, Rijcken B, Weiss ST, Schouten JP. Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. *Lancet* 2000; 356: 1313–1317.
40. O′Connor GT, Sparrow D, Weiss ST. The role of allergy and nonspecific airway hyperresponsiveness in the pathogenesis of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140: 225–252.
41. Rijcken B, Schouten JP, Xu X, Rosner B, Weiss ST. Airway hyperresponsiveness to histamine associated with accelerated decline in FEV1. *Am J Respir Crit Care Med* 1995; 151: 1377–1382.
42. Tashkin DP, Altose MD, Connett JE, Kanner RE, Lee WW, Wise RA. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. The Lung Health Study Research Group. *Am J Respir Crit Care Med* 1996; 153: 1802–1811.
43. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000; 343: 1902–1909.
44. Sherrill DL, Lebowitz MD, Knudson RJ, Burrows B. Longitudinal methods for describing the relationship between pulmonary function, respiratory symptoms and smoking in elderly subjects: The Tucson Study. *Eur Respir J* 1993; 6: 342–348.
45. Sherman CB, Xu X, Speizer FE, Ferris BG Jr, Weiss ST, Dockery DW. Longitudinal lung function decline in subjects with respiratory symptoms. *Am Rev Respir Dis* 1992; 146: 855–859.
46. Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. *Am J Respir Crit Care Med* 1996; 153: 1530–1535.
47. Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Relation of ventilatory impairment and of chronic mucus hypersecretion to mortality from obstructive lung disease and from all causes. *Thorax* 1990; 45: 579–585.
48. Rennard S, Decramer M, Calverley PM, *et al.* Impact of COPD in North America and Europe in 2000: Subjects′ perspective of Confronting COPD International Survey. *Eur Respir J* 2002; 20: 799–805.
49. Xu X, Rijcken B, Schouten JP, Weiss ST. Airways responsiveness and development and remission of chronic respiratory symptoms in adults. *Lancet* 1997; 350: 1431–1434.
50. Jansen DF, Schouten JP, Vonk JM, *et al.* Smoking and airway hyperresponsiveness especially in the presence of blood eosinophilia increase the risk to develop respiratory

symptoms: a 25-year follow-up study in the general adult population. *Am J Respir Crit Care Med* 1999; 160: 259–264.
51. Centers for Disease Control and Prevention. National Center for Health Statistics. Publications and information products. http://www.cdc.gov/nchs/products/elec_prods/subject/mortucd.htm#desciption. Last updated June 18 2002. Accessed February 2003.
52. Mannino DM, Brown C, Giovino GA. Obstructive lung disease deaths in the United States from 1979 through 1993. An analysis using multiple-cause mortality data. *Am J Respir Crit Care Med* 1997; 156: 814–818.
53. Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur Respir J* 1997; 10: 822–827.
54. Xu X, Weiss ST, Rijcken B, Schouten JP. Smoking, changes in smoking habits, and rate of decline in FEV1: new insight into gender differences. *Eur Respir J* 1994; 7: 1056–1061.
55. Silverman EK, Weiss ST, Drazen JM, *et al.* Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 2152–2158.
56. Chen Y, Horne SL, Dosman JA. Increased susceptibility to lung dysfunction in female smokers. *Am Rev Respir Dis* 1991; 143: 1224–1230.
57. Leynaert B, Bouquet J, Henry C, Liard R, Neukirch F. Is bronchial hyperresponsiveness more frequent in women than in men? A population-based study. *Am J Respir Crit Care Med* 1997; 156: 1413–1420.
58. Tracey M, Villar A, Dow L, Coggon D, Lampe FC, Holgate ST. The influence of increased bronchial responsiveness, atopy, and serum IgE on decline in FEV1. A longitudinal study in the elderly. *Am J Respir Crit Care Med* 1995; 151: 656–662.
59. Kanner RE, Connett JE, Altose MD, *et al.* Gender difference in airway hyperresponsiveness in smokers with mild COPD. The Lung Health Study. *Am J Respir Crit Care Med* 1994; 150: 956–961.
60. Paoletti P, Carrozzi L, Viegi G, *et al.* Distribution of bronchial responsiveness in a general population: effect of sex, age, smoking, and level of pulmonary function. *Am J Respir Crit Care Med* 1995; 151: 1770–1777.
61. Merkus PJ, Borsboom GJ, van Pelt W, *et al.* Growth of airways and air spaces in teenagers is related to sex but not to symptoms. *J Appl Physiol* 1993; 75: 2045–2053.
62. Laurell CB, Eriksson S. The electrophoretic alpha-1-globulin pattern of serum in $alpha_1$-antitrypsin deficiency. *Scand J Clin Lab Invest* 1963; 15: 132–140.
63. Erikkson S. Studies in alpha 1-antitrypsin deficiency. *Acta Med Scand Suppl* 1965; 432: 1–85.
64. Sandford AJ, Pare PD. Genetic risk factors for chronic obstructive pulmonary disease. *Eur Respir J* 1997; 10: 1380–1391.
65. Sandford AJ, Pare PD. Genetic risk factors for chronic obstructive pulmonary disease. *Clin Chest Med* 2000; 21: 633–643.
66. Silverman EK, Chapman HA, Drazen JM, *et al.* Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease: Risk to relatives for airflow obstruction and chronic bronchitis. *Am J Respir Crit Care Med* 1998; 157: 1770–1778.
67. Silverman EK. Genetics of chronic obstructive pulmonary disease. *Novartis Found Symp* 2001; 234: 45–58.
68. Hoidal JR. Genetics of COPD: present and future. *Eur Respir J* 2001; 18: 741–743.
69. Silverman EK, Palmer LJ, Mosley JD, *et al.* Genomewide linkage analysis of quantitative spirometric phenotypes in severe early-onset chronic obstructive pulmonary disease. *Am J Hum Genet* 2002; 70: 1229–1239.
70. Silverman EK. Genomewide linkage analysis of severe, early onset chronic obstructive pulmonary disease: airflow obstruction and chronic bronchitis phenotypes. *Hum Mol Genet* 2002; 11: 623–632.
71. Becklake MR. Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140: S85–S91.
72. Korn RJ, Dockery DW, Speizer FE, Ware JH, Ferris BG Jr. Occupational exposures and chronic respiratory symptoms: A population-based study. *Am Rev Respir Dis* 1987; 136: 298–304.
73. Sluiter HJ, Blokzijl EJ, van Dijl W, van Haeringen JR, Hilvering C, Steenhuis EJ. Conservative and respiratory treatment of acute respiratory insufficiency in patients with chronic obstructive lung disease. A reappraisal. *Am Rev Respir Dis* 1972; 105: 932–943.
74. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418–1422.
75. Monso E, Ruiz J, Rosell A, *et al.* Bacterial infection in chronic obstructive pulmonary disease: a study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995; 152: 1316–1320.
76. Soler N, Torres A, Ewig S, *et al.* Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998; 157: 1498–1505.
77. McHardy VU, Inglis JM, Calder MA, *et al.* A study of infective and other factors in exacerbations of chronic bronchitis. *Br J Dis Chest* 1980; 74: 228–238.
78. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 158–164.
79. Garcia-Aymerich J, Barreiro E, Farrero E, Marrades RM, Morera J, Anto JM. Patients hospitalized for COPD have a high prevalence of modifiable risk factors for exacerbation (EFRAM study). *Eur Respir J* 2000; 16: 1037–1042.
80. Jeffrey PK. Structural and inflammatory changes in COPD: a comparison with asthma. *Thorax* 1998; 53: 129–136.
81. Barnes PJ. Mechanisms in COPD: differences from asthma. *Chest* 2000; 117: Suppl. 2, 10S–14S.
82. Brightling CE, Pavord ID. Eosinophilic bronchitis - what is it and why is it important? *Clin Exp Allergy* 2000; 30: 4–6.
83. Dekhuijzen PN, Aben KK, Dekker I, *et al.* Increased exhalation of hydrogen peroxide in patients with stable and unstable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 154: 813–816.
84. Kasielski M, Nowak D. Long-term administration of N-acetylcysteine decreases hydrogen peroxide exhalation in subjects with chronic obstructive pulmonary disease. *Respir Med* 2001; 95: 448–456.
85. Sanders C, Nath PH, Bailey WC. Detection of emphysema with computed tomography. Correlation with pulmonary function tests and chest radiography. *Invest Radiol* 1988; 23: 262–266.
86. Santis G, Hodson ME, Strickland B. High resolution computed tomography in adult cystic fibrosis patients with mild lung disease. *Clin Radiol* 1991; 44: 20–22.