COPD* : Epidemiology, Prevalence, Morbidity and Mortality, and Disease Heterogeneity

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Epidemiology, Prevalence, Morbidity and Mortality, and Disease Heterogeneity

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COPD continues to cause a heavy health and economic burden both in the United States and around the world. Some of the risk factors for COPD are well-known and include smoking, occupational exposures, air pollution, airway hyperresponsiveness, asthma, and certain genetic variations, although many questions, such as why < 20% of smokers develop significant airway obstruction, remain. Precise definitions of COPD vary and are frequently dependent on an accurate diagnosis of the problem by a physician. These differences in the definition of COPD can have large effects on the estimates of COPD in the population. Furthermore, evidence that COPD represents several different disease processes with potentially different interventions continues to emerge. In most of the world, COPD prevalence and mortality are still increasing and likely will continue to rise in response to increases in smoking, particularly by women and adolescents. Resources aimed at smoking cessation and prevention, COPD education and early detection, and better treatment will be of the most benefit in our continuing efforts against this important cause of morbidity and mortality.

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Key words: COPD; epidemiology; mortality; prevalence; risk factors

Abbreviations: ATS = American Thoracic Society; DALY = disability-adjusted life-years; ERS = European Respiratory Society; GOLD = Global Obstructive Lung Disease initiative; NHANES = National Health and Nutrition Examination Survey; NHIS = National Health Interview Survey

COPD is characterized by airflow obstruction with related symptoms such as chronic cough, exertion dyspnea, expectoration, and wheeze.[1] These symptoms may occur in conjunction with airway hyperresponsiveness and may be partially reversible. Even though COPD is a nonspecific term referring to a set of conditions that develops progressively as a result of a number of different disease processes, it most commonly refers to patients with chronic bronchitis and emphysema and to a subset of patients with asthma. These conditions can be present with or without significant impairment. COPD has been defined in several different ways, and these different definitions can have a large impact on the population estimates of the burden of disease.[2–5]

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Definitions

Several different definitions exist for COPD. The American Thoracic Society (ATS) has defined COPD as "a disease state characterized by the presence of airflow limitation due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible."[4] The European Respiratory Society (ERS) defined COPD as "reduced maximum expiratory flow and slow forced emptying of the lungs, which is slowly progressive and mostly irreversible to present medical treatment."[3] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classified COPD as "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases"[5] (Fig 1). For these three different definitions, however, the precise classification of airflow limitation, reversibility, and severity of disease varies. In addition, the definitions and diagnoses of chronic bronchitis, emphysema, and asthma also can vary.

Airflow Limitation

Airflow limitation is the slowing of a patient's expiratory airflow, as measured by spirometry, with a persistently low FEV_1 and a low FEV_1/FVC ratio despite treatment. The 1995 ATS definition of COPD did not list a specific level of the FEV_1/FVC ratio for airflow limitation,[4] although a previous ATS document listed an FEV_1/FVC ratio of less than the fifth percentile as evidence of airflow limitation.[6] The 1995 ERS definition for airflow limitation is an FEV_1/slow vital capacity ratio of $< 88\%$ of the predicted value for men and a ratio of $< 89\%$ of the predicted value for women.[3] The GOLD definition for airflow limitation is an FEV_1/FVC ratio of $< 70\%$.[5]

Airflow Limitation Reversibility

Airflow limitation reversibility can be acute, in response to an inhaled bronchodilator, or in response to oral or inhaled corticosteroids.[5,7] The ATS definition of COPD did not specifically define reversibility, although a previous ATS statement classified reversibility as an FEV_1 increase of 200 mL and 12% above baseline FEV_1 for treatment with inhaled bronchodilators.[6] The ERS definition of COPD classifies reversibility as a $> 10\%$ improvement in predicted FEV_1 after a patient receives a bronchodilator.[3] The GOLD definition of COPD classifies reversibility as an FEV_1 increase of 200 mL and a 12% improvement from baseline FEV_1 for treatment with either inhaled corticosteroids or bronchodilators.[5]

The term "partial reversibility" is frequently mentioned but has not been fully defined. In the context of the definitions, this term probably defines patients who in fact have "reversibility" in response to therapy with either

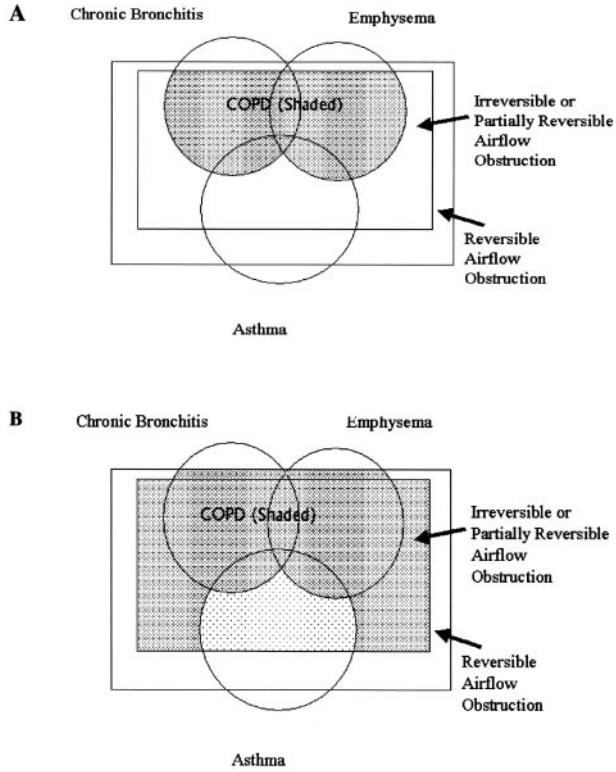

FIGURE 1. Venn diagrams depicting the subsets of disease comprising COPD and the relationships among the subsets. Subset areas are not proportional to actual relative subset sizes. *Top*, *A*: a modified version of the ATS COPD definition is depicted. *Bottom*, *B*: the GOLD COPD definition is depicted.

corticosteroids or a bronchodilator (as defined above), yet their best FEV_1 and FEV_1/FVC ratio classifies them as having airflow limitation.

Disease Severity

Disease severity has typically been determined using the degree of lung function impairment, although the wisdom of this approach has been questioned, with the suggestion that factors such as arterial blood gas levels, time and distance walked, sensation of dyspnea, and body mass index be included in this determination.[8] The ATS criteria classify COPD into the following three stages: stage 1 (FEV_1, $\geq$ 50% of predicted); stage 2 (FEV_1, 35 to 49% of predicted); and stage 3 (FEV_1, $<$ 35% predicted).[4] The ERS criteria classify COPD into the following three stages: mild (FEV_1, $\geq$ 70% of predicted); moderate (FEV_1, 50% to $<$ 80% of predicted); and severe (FEV_1, $<$ 50% of predicted).[3] The GOLD criteria classify COPD into the following three stages: stage 1 (FEV_1, $\geq$ 80% of predicted); stage 2 (FEV_1, 30 to $<$ 80% of predicted); and stage 3 (FEV_1, $<$ 30% of predicted).[5]

Chronic Bronchitis

Chronic bronchitis, which is defined in clinical terms, is the presence of a chronic productive cough for 3 months in each of 2 successive years, provided that other causes of chronic cough have been ruled out.[4] Airway obstruction occurs as a result of varying degrees of inflammation and nonspecific bronchial hyperreactivity associated with chronic bronchitis. Unfortunately, many surveillance systems that attempt to estimate the burden of chronic bronchitis do not have this specific definition and only estimate "physician-diagnosed" chronic bronchitis or recurrent episodes of bronchitis (typically, three episodes) in the previous year.

Emphysema

Emphysema, which is defined in anatomic terms, is defined as the destruction of alveolar walls and the permanent enlargement of the airspaces distal to the terminal bronchioles.[4] The ensuing loss of lung elastic recoil and intralumenal pressure in the terminal airways causes small airways to lose their patency, especially during forced expiratory maneuvers. The collapse of these airways furthermore results in airflow limitation that is independent of exertion. Clinically, the patient experiences progressive dyspnea and variable cough. It is not clear how most clinicians diagnose emphysema. While the use of imaging such as a CT scan would be optimal in the diagnosis of emphysema, it is likely that the majority of cases are diagnosed using different criteria.

Asthma

Asthma, which is defined in physiologic terms, is defined as reversible smooth muscle contraction that narrows the airway lumen, limiting expiratory airflow and resulting in symptoms including wheeze, cough, and exertion dyspnea.[9] The distinguishing feature of asthma is the reversibility of symptoms in response to treatment with inhaled bronchodilators, such as β-agonists, anticholinergic agents, methylxanthines, and corticosteroids.

Prevalence of COPD

As noted above, estimates of the prevalence of COPD are very dependent on the way COPD is defined. In national surveys in the United States, the primary means by which the prevalence of COPD has been determined is by asking adults whether they have had any 1 of 17 respiratory diseases in the past 12 months. Three of the diseases asked about in this list are chronic bronchitis, emphysema, and asthma, with the estimate of COPD prevalence made by adding the cases of chronic bronchitis and emphysema. The National Health Interview Survey (NHIS) is an annually conducted, nationally representative survey of about 40,000 US households.[10] In 1996, the estimated number of adults aged $\geq$ 25 years in the United States with COPD was 10.1 million, or 6.0% of the population. In 1997, the NHIS was redesigned to ask about physician-diagnosed disease, including chronic bronchitis and asthma, and whether the respondent had experienced an attack or episode of this disease in the previous 12 months. Although this change resulted in a 30% decrement in the estimate of asthma prevalence,[11]

there was virtually no change in the prevalence of COPD, with an estimated 10.2 million, or 5.9% of the adult population, reporting having COPD.

There are two main limitations to this survey. First, it is dependent on the proper recognition and diagnosis of COPD by both the study participants and their health-care providers, which would tend to bias the estimates toward there being fewer cases than actually exist. A bias in the opposite direction, however, is that the term "chronic bronchitis" in this survey is not precisely defined and could be interpreted as recurrent episodes of acute bronchitis. The finding that 3 to 4% of children have reported "chronic bronchitis" supports the presence of this potential bias. Second, this survey is not able to validate, through physiologic evaluation, whether airway obstruction is present or absent.

These limitations have been addressed, in part, by a separate nationally representative US study. In the National Health and Nutrition Examination Survey (NHANES) III, a stratified multistage clustered probability design was used to select a representative sample of the civilian, noninstitutionalized US population from 1988 to 1994.[12] Survey participants completed extensive questionnaires at home and received a comprehensive physical examination, including pulmonary function testing, at a specially equipped mobile examination center. Procedures for spirometry testing were based on the 1987 ATS recommendations.[13] With this survey, it is thus possible to determine the presence of airway obstruction, the prevalence of diagnosed COPD, and the estimated prevalence of COPD in the population. The ATS definition of COPD (*ie*, airway obstruction and chronic bronchitis or emphysema) resulted in an estimated national prevalence of 4.8 million adults (2.9% of the adult population), whereas the ERS and GOLD definitions, which are based on the presence of airway obstruction only, resulted in much higher prevalence estimates of 24.2 million adults (14.3% of the adult population) and 23.6 million adults (13.9% of the adult population) with COPD, respectively. An estimated 2.4 million adults (1.4% of the population) have moderate-to-severe airways obstruction, with an FEV_1 of $< 50\%$ of the predicted value. Thus, the majority of the subjects classified as having COPD by ERS and GOLD criteria have mild disease.

A limitation of this survey, and of most similar surveys, is that there was no determination of the reversibility of the airway obstruction. Many studies have investigated airways responsiveness (usually in response to methacholine or another nonspecific irritant), but that investigation typically is performed in a scenario of normal or near-normal lung function. The studies that do exist are often difficult to compare to each other because of differences in the way that reversibility is determined. For example, among participants in the Lung Health Study,[14] 10.9% had at least a 10% improvement in their FEV_1 over baseline in response to an inhaled bronchodilator. That study, however, excluded subjects with FEV_1 values $< 50\%$ of their predicted value and subjects with variability in their FEV_1/FVC ratios.[15] In a clinic-based study of subjects in Denmark (EF Hansen; personal communication; March 7, 2001) that included subjects with FEV_1 values of $< 50\%$ of their predicted values, 60% of 1,095 COPD patients and 64% of asthma patients showed a 15% improvement in their baseline FEV_1 after a 7-day course of treatment with an oral corticosteroid and an inhaled bronchodilator. If, in that study, one defined reversibility as a 10% improvement relative to the predicted FEV_1, only 33% of COPD patients and 49% of asthma patients demonstrated reversibility. In another clinic-based study[16] of subjects ≥ 69 years of age, 31% demonstrated reversibility, which was defined as a 15% improvement (from baseline) in FVC and FEV_1 following treatment with an inhaled bronchodilator. In this study, as in the previous one, subjects with more severe obstruction were more likely to have reversibility but would also be more likely to continue to have diminished lung function after maximum improvement was obtained, thus yielding a classification of "partial reversibility."

The presence of significant reversibility or partial reversibility in patients with COPD,[17] and of nonreversible airflow obstruction in asthma patients,[18] demonstrates that these diseases can coexist. A reduction in the pretreatment FEV_1 as a percentage of the predicted value is an important means of classifying patients with asthma. Patients with values that are $< 60\%$ of the predicted value are classified as having severe, persistent asthma, and those with values of 60 to 80% of the predicted value are classified as having moderate asthma.[9] The relationships among asthma, COPD, and markers of disease severity are discussed below.

Morbidity and Mortality

COPD is a leading cause of disease morbidity and mortality in the United States. The National Center for Health Statistics conducts ongoing surveillance of a number of health indicators nationally. The National Center for Health Statistics collects physician office visit data with the National Ambulatory Medical Care Survey,[19] emergency department visit data and hospital outpatient data with the National Hospital Ambulatory Medical Care Survey,[20] hospitalization data with the National Hospital Discharge Survey,[21,22] and death data with the mortality component of the National Vital Statistics System.[23] We report the number and rate of COPD events in US adults (using *International Classification of Diseases*, ninth revision, clinical modification, codes 490, 491, 492, and 496) in these data sets for the most recent years available.

In 1997, COPD affected 10.2 million adults (5.9% of the adult population). In 1998, COPD was responsible for an estimated 14.2 million ambulatory visits (either to hospital outpatient departments or physician offices), with a resulting rate of 82 visits per 1,000 population. COPD was also responsible for an estimated 1.4 million emergency department visits, with a resulting rate of 83 visits per 10,000 population.

COPD is a leading cause of hospitalization in US adults, particularly in older populations. In 1998, almost 662,000 hospitalizations (1.9% of total hospitalizations) were attributed to COPD. An additional 2,530,000 hospitalizations (7.0% of total hospitalizations) had COPD listed as a contributing cause of the hospitalization. In patients aged

Table 1—*The Estimated Population, Stratified by Reported Lung Disease, With Low Lung Function, and the Percentage of the Population With Low Lung Function and With the Symptoms of Cough, Wheeze, Sputum Production, and Shortness of Breath, Age-Adjusted to All Study Participants

Lung Disease Category	Estimated Population†	Low Lung Function		Cough	Phlegm	Wheeze	SOB	Any Symptom	
		No.	AA, %	AA, %	AA, %	AA, %	AA, %	No.	AA, %
Reported COPD and asthma	2,302	939	29.9	50.8	46.7	80.6	65.0	2,221	94.5
Reported COPD only	5,989	1,791	17.4	33.9	25.6	57.8	48.3	5,110	83.8
Reported asthma only	6,073	1,002	19.2	13.9	11.1	66.9	45.5	4,928	80.6
Reported chronic bronchitis or asthma in the past	7,280	584	8.9	13.7	11.2	29.5	32.7	3,740	52.2
No reported COPD or asthma	147,700	7,204	5.1	7.3	6.9	12.3	19.6	46,280	31.6
Total‡	169,352	11,521	6.8	9.3	8.3	17.6	22.9	62,272	36.8

*All relative SEs are $< 35\%$. Low lung function = FEV_1/FVC ratio < 0.70 and $FEV_1 < 80\%$ of predicted; SOB = shortness of breath; AA = age-adjusted. Table is based on data from NHANES III.[37]

†All population estimate values given as $\times 10^3$.

‡Totals for columns may not add up due to rounding.

55 to 65 years, 65 to 75 years, and ≥ 75 years, COPD was a primary or contributing cause of hospitalization in 14.8%, 19.9%, and 18.2%, respectively, of total hospitalizations. The rate of hospitalizations for COPD (*ie*, with COPD as the primary cause of hospitalization) was 38.3 per 10,000 population in 1998.

Deaths due to or associated with COPD have been increasing steadily in the United States over the past 20 years. While the death rate among men has reached a plateau, the rate among women has continued to increase. In 1998, 54,615 men and 51,377 women died from COPD. From 1995 to 1998, the death rate attributable to COPD among men remained stable at 53.1 deaths per 100,000 population (age-adjusted to the 2000 US population), whereas the death rate attributable to COPD among women increased 9.5% from 29.3 to 32.1 deaths per 100,000 population (age-adjusted to the 2000 US population). One of the limitations of the mortality database is that many decedents with COPD have their death attributed to another cause.[24] In 1998, only 45.4% of the 233,610 decedents with COPD mentioned on their death certificates had this ultimately listed as the underlying cause of death, despite the presence of prospective studies showing that people with COPD listed on their death certificates frequently have severe disease.[25]

COPD is a very costly disease, with estimated direct medical costs in 1993 of $14.7 billion (in US dollars).[26] The estimated indirect costs related to morbidity (*ie*, loss of work time and productivity) and to premature mortality was an additional $9.2 billion, for a total of $23.9 billion. When the indirect and direct medical costs that are attributable to asthma of $12.6 billion are added to this, the total cost of obstructive lung disease (*ie*, COPD and asthma) in the United States is $36.1 billion. Because COPD is frequently not listed as the underlying cause of death or as the primary reason for hospitalization, as noted above, these cost estimates may underestimate the true cost of COPD.

Another manifestation of the importance of COPD is its effect on the burden of disease in a population determined using disability-adjusted life-years (DALYs).[27] In 1996, COPD was estimated to be the eighth leading cause of DALYs among men and the seventh leading cause of DALYs among women.[27] Worldwide, COPD is expected to move up from the 12th leading cause of DALYs in 1990 to the fifth leading cause in 2020.[28]

Disease Heterogeneity

COPD has been long recognized as a heterogeneous disorder or group of disorders, with components of asthma, chronic bronchitis, emphysema, and airflow obstruction all being important parts of the final disease process.[29] The different components of disease heterogeneity in COPD include different mechanisms in development, presentation, and course. Disease heterogeneity in COPD may ultimately provide opportunities for targeted interventions in COPD patients.

Smoking is the dominant risk factor for the development and progression of COPD, however, $< 25\%$ of smokers develop COPD and $> 15\%$ of COPD-related mortality occurs in never-smokers, suggesting that other factors are important. Smoking cessation is the single most important intervention in COPD management, although the best reported cessation rates are still $< 30\%$,[30] indicating that better treatments are needed. α_1-Antiprotease deficiency is an important cause of COPD in a very small percentage of cases.[31] Other undefined genetic factors certainly play important roles in COPD development.[32] The role of infections in both the development and progression of COPD is getting increased attention, including the role of adenoviral infections in patients with emphysema and the role of intracellular infections in patients with asthma.[33–35] Occupational and environmental exposures to various pollutants are also important factors in the development of COPD.[36]

COPD is also heterogeneous in its presentation. Based on data from NHANES III,[37] a significant proportion of patients with severe airflow limitation (*ie*, FEV_1, $< 50\%$ of predicted) may not report symptoms. The symptoms

Table 2—*The Estimated Population, Stratified by Reported Lung Disease, and the Mean Number of Annual Days of Restricted Activity, Bed Confinement, and Work Absence, and the Proportion of Patients Working and With Activity Limitation, Age-Adjusted to All Study Participants

Lung Disease Category	Estimated Population†	Annual Restricted Activity, d	Annual Bed Confinement, d	Annual Work Loss, d	Working, %	Persons With Activity Limitation, %
Reported COPD and asthma	2,100	62.5	31.5	8.2	54	45
Reported COPD only	8,000	31.0	13.1	2.4	56	32
Reported asthma only	6,600	35.4	17.8	0.6	57	35
No reported COPD or asthma	152,000	15.3	6.1	2.9	65	22
Total‡	168,700	17.5	7.2	3.0	64	24

*All relative SEs are < 35%. Table is based on data from NHIS.[10]
†All population estimates × 10^3.
‡Columns may not add up due to rounding.

reported most frequently include wheezing and shortness of breath in 64% and 65% of subjects, respectively, with FEV_1 values < 50% of predicted. COPD has become increasingly recognized as a systemic illness, with effects on nutritional status, muscle wasting, and depression.[38,39] A large proportion of patients probably have components of chronic bronchitis, asthma, and emphysema occurring together. While some of this overlap may be related to misdiagnosis, some of it may be a measure of the presence of reversibility. A better definition of the individuals comprising these groups ultimately may help to tailor better interventions. An indication of disease heterogeneity and reversibility in COPD patients can be obtained by looking at respiratory symptoms, lung function, and activity limitation in subjects who report COPD alone, asthma alone, COPD and asthma together, and neither COPD or asthma.

In the NHANES III,[37] 1.4% of the adult participants reported both COPD and asthma, 3.5% reported COPD only, 3.6% reported asthma only, and 4.3% reported having chronic bronchitis or asthma in the past (Table 1). As can be seen in Table 1, lower lung function and a higher prevalence of respiratory symptoms were reported in subjects who stated that they had both asthma and COPD.

In the 1996 NHIS,[10] 1.2% of the adult participants reported both COPD and asthma, 4.7% reported COPD only, and 3.9% reported asthma only. Table 2 shows that participants reporting both COPD and asthma had more days of restricted activity, bed confinement, and work loss than did participants with asthma or COPD alone or those with neither disease.

It is not clear in these survey data whether the coexistence of COPD and asthma represents the presence of more reversibility or other factors compared to what is seen in subjects reporting only COPD. Other studies, though, have actually measured reversibility with an inhaled bronchodilator, treatment with steroids, or both[17,40,41] and have observed these subjects over time to determine long-term prognosis.

One study[40] found that subjects with increased reversibility had a higher risk of dying from COPD in almost 9 years of follow-up. A second longitudinal study had similar findings when the baseline FEV_1 was used to predict the mortality rate over an 11-year period, but the degree of reversibility did not predict the mortality rate if the best FEV_1 (*ie*, after receiving bronchodilators or steroids) was used in the prediction models.[17] Another study[41] that followed patients over an 11-year period found that the presence of reversibility in conjunction with regular clinic attendance was associated with better survival rates. On the whole, the evidence suggests that the presence of a degree of reversibility, if appropriately detected and treated, may provide improved survival rates in certain patients with COPD. The degree of reversibility may be an important part of designing a plan for disease management.

Conclusion

COPD is a common disease causing a great deal of morbidity and mortality both in the United States and worldwide. Current symptom-based definitions or clinically based definitions of COPD cause the underestimation of the prevalence of actual disease, and we may need to progress to a definition based on objective measurements. Furthermore, the importance of COPD in both deaths and hospitalizations is frequently underestimated. COPD is a systemic and heterogeneous disease, and certain aspects of the heterogeneity of COPD, such as the role of infections or the presence of reversibility, may provide opportunities for targeted interventions. Finally, smoking cessation remains the cornerstone of COPD treatment, yet success rates in the best programs are < 30%,[30] demonstrating that better tailored treatments are needed.

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