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Chronic Obstructive Pulmonary Disease: Epidemiology and Evaluation

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Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction with breathing-related symptoms such as chronic cough, exertional dyspnea, expectoration, and wheeze.[1] These symptoms may occur in conjunction with airway hyperresponsiveness and may be partially reversible. Although COPD is a nonspecific term referring to a set of conditions that develop progressively as a result of a number of different disease processes, it most commonly refers to chronic bronchitis and emphysema and a subset of patients with asthma. These conditions can be present with or without significant physical impairment. Despite being a very common disease and the fourth leading cause of death in the United States,[2] COPD often is a silent and unrecognized disease, particularly in its early phases.[3]

This article, the first of a 2-part series on COPD, reviews the epidemiology, clinical presentation, evaluation, and diagnosis of patients with COPD. The recently published Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for the classification of COPD are discussed. The importance of spirometry in identifying patients in the early stages of the disease is stressed. The second article in the series will use a case-based approach to review the management of COPD.

GOLD CRITERIA FOR COPD

Several different definitions have existed for COPD.[4,5] The recently published and widely accepted definition from GOLD defines 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."[6]

Airflow limitation is the slowing of expiratory airflow as measured by spirometry, with a persistently low forced expiratory volume in 1 second (FEV_1) and a low FEV_1/forced vital capacity (FVC) ratio despite treatment.[5] The GOLD definition for airflow limitation is an FEV_1/FVC ratio of less than 70%.[6,7] Airflow limitation reversibility can occur spontaneously, in response to an inhaled bronchodilator, or in response to oral or inhaled corticosteroids.[5–8] The GOLD definition of COPD classifies reversibility as an FEV_1 increase of 200 mL and 12% improvement above baseline FEV_1 following administration of either inhaled corticosteroids or bronchodilators. **Figure 1** depicts a spirometric tracing representative of a patient with COPD compared with a normal tracing.

The term *partial reversibility* describes patients who in fact have "reversibility" in response to administration of either corticosteroids or a bronchodilator, yet their best FEV_1 and FEV_1/FVC ratio classifies them as having airflow limitation.

Severity of COPD has typically been determined using the degree of lung function impairment, although the wisdom of this approach has been questioned recently, with the suggestion that other signs and symptoms, such as arterial blood gases values, body mass index, timed walking distance, and the sensation of dyspnea, be included in this determination.[5,9] The GOLD criteria classify COPD into 4 stages based primarily on lung function impairment (**Table 1**): Stage I ($FEV_1 \geq 80\%$ predicted), Stage IIA (FEV_1 50%–79% of predicted), Stage IIB (FEV_1 30%–49% of predicted) and Stage III ($FEV_1 < 30\%$ of predicted).[6,7] Additionally, GOLD lists a stage 0 level of disease, which describes persons who have normal lung function yet report respiratory symptoms such as chronic cough or sputum production.

Previous definitions of COPD differentiated between chronic bronchitis, asthma, and emphysema, acknowledging that there is frequently overlap between these disease entities. The GOLD definition of COPD does not differentiate between chronic bronchitis and emphysema but does note that although asthma and COPD can coexist,[3] the largely reversible airflow limitation in asthma merits different therapeutic

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approaches than the largely irreversible airflow limitation of COPD.

EPIDEMIOLOGY

Prevalence of COPD

In national surveys in the United States, the primary means by which the prevalence of COPD has been determined has been 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 18 years and older in the United States with COPD was 11.9 million.[11]

The NHIS estimates for COPD have 2 important limitations. First, these estimates depend upon the proper recognition and diagnosis of COPD by both the study participants and their health care providers. This would tend to bias the estimates toward counting 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 "chronic bronchitis" has been reported in 3% to 4% of children supports the presence of this potential bias. The second limitation is that this survey is not able to validate, through physiologic evaluation, whether airway obstruction is present or absent.

These limitations were addressed, in part, by a separate nationally representative US survey. In the Third 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 through 1994.[12] Survey participants completed extensive questionnaires in their homes, and received a comprehensive physical examination, including pulmonary function testing, at specially equipped mobile examination centers. Procedures for spirometric testing were based on the 1987 American Thoracic Society recommendations.[13]

The NHANES III survey made it possible to determine the presence of airway obstruction, the prevalence of diagnosed COPD, and the estimated prevalence of COPD in the population of the United States. The application of the GOLD definition of COPD to the survey data resulted in an estimated national prevalence of 23.6 million adults or 13.9% of the adult population.[3] An estimated 2.4 million adults, or 1.4% of the adult population, have moderate to severe airway obstruction, with an FEV_1 of less than 50% of the predicted value.[3] Thus, the majority of the subjects classified as having COPD by GOLD criteria (roughly 90%) have stage I or IIA disease. These data demonstrate that a large proportion of US adults with COPD are undiagnosed. Overall, 63% of the study population with evidence of COPD never had a diagnosis of lung disease, including 44% of subjects with an FEV_1 less than 50% of the predicted value.[3]

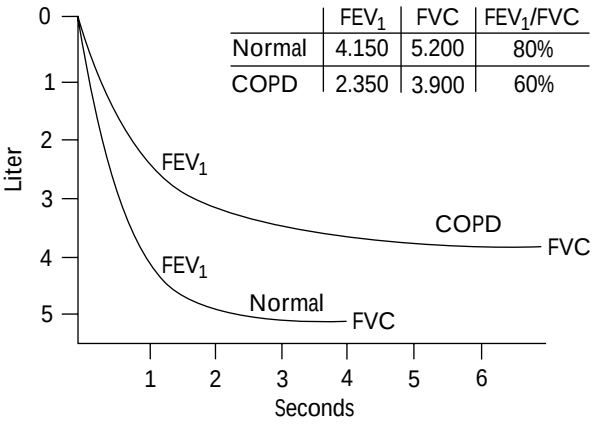

Figure 1. Normal spirogram and spirogram typical of patients with mild to moderate chronic obstructive pulmonary disease. Calculation of FEV_1, FVC, and FEV_1/FVC ratio is also shown. Reprinted from Management of COPD, component 1: Assess and monitor disease. In: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO workshop report. Global Initiative for Chronic Obstructive Lung Disease. Available at http://www.goldcopd.com/workshop/ch5p1.html. Accessed 5 September 2001.

A limitation of this survey—and most similar surveys—is that there was no determination of the reversibility of the airway obstruction, which is part of the GOLD definition of COPD.[6] Many studies have looked at airway responsiveness (usually in response to methacholine or another nonspecific irritant), but that evaluation typically is done 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, 10.9% of patients with diagnosed mild COPD had at least a 10% improvement in their FEV_1 over their baseline FEV_1 in response to an inhaled bronchodilator.[14] That study, however, excluded subjects with FEV_1 values of less than 50% of

Table 1. Classification of Chronic Obstructive Pulmonary Disease by Severity

Stage	Characteristics*
0: at risk	Normal spirometry Chronic symptoms (cough, sputum production)
I : mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ of predicted With or without chronic symptoms
IIA: moderate COPD	$FEV_1/FVC < 70\%$ $50\% \text{ of predicted} \leq FEV_1 < 80\%$ of predicted With or without chronic symptoms
IIB: moderate COPD with the potential for severe exacerbations	$FEV_1/FVC < 70\%$ $30\% \text{ of predicted} \leq FEV_1 < 50\%$ of predicted With or without chronic symptoms
III: severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ of predicted *or* $< 50\%$ of predicted plus the presence of respiratory failure† or clinical signs of right heart failure

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

*All FEV_1 values refer to the postbronchodilator FEV_1.

†Respiratory failure defined as $PaO_2 < 60$ mm Hg with or without $PaCO_2 > 50$ mm Hg while breathing air at sea level.

Adapted with permission from Pauwels RA, Buist AS, Calverley PM, et al. 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;163:1257.

their predicted value as well as subjects with variability in their FEV_1/FVC ratios.[15] In a clinic-based study of subjects with COPD who were aged 69 years and older, 31% demonstrated reversibility, defined as a 15% improvement (from baseline) in FVC and FEV_1 following administration of an inhaled bronchodilator.[16] In this latter study, 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 being classified as having "partial reversibility."

The presence of significant reversibility or partial reversibility in patients with COPD[17] and nonreversible airflow obstruction in asthma patients[18] demonstrates that these diseases can coexist or, alternatively, that there is overlap and imprecision in the ways that these diseases are clinically diagnosed.

Morbidity and Mortality

COPD is a leading cause of disease morbidity and mortality in the United States. The National Center for Health Statistics (NCHS) conducts ongoing surveillance of several health indicators nationally. The NCHS collects physician office visit data using the National Ambulatory Medical Care Survey,[19] emergency department visit data and hospital outpatient data using the National Hospital Ambulatory Medical Care Survey,[20] hospitalization data using the National Hospital Discharge Survey,[21,22] and death data using the mortality component of the National Vital Statistics System.[23] The following data include the number and rate of COPD events in adults in the United States (using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], codes 490, 491, 492 and 496) in these data sets for the most recent years available.

In 1998, COPD was responsible for an estimated 14.2 million ambulatory visits (to either hospital outpatient departments or physician offices), with a resulting rate of 82 visits per 1,000 population.[19,20] COPD was also responsible for an estimated 1.4 million emergency room visits, with a resulting rate of 83 visits per 10,000 population.[20]

COPD is a leading cause of hospitalization in US adults, particularly in older populations. In 1998, almost 662,000 hospitalizations, or 1.9% of total hospitalizations, were attributed to COPD.[22] The rate of COPD hospitalizations (as the primary cause of hospitalization) was 38.3 per 10,000 population in 1998.[22]

Deaths due to or associated with COPD have been steadily increasing in the United States over the past 20 years. While the death rate among men has plateaued, the rate among women has continued to

(continued on page 27)

(from page 24)

Table 2. Key Indicators for Considering a Diagnosis of Chronic Obstructive Pulmonary Disease*

Indicator	Characteristics
Chronic cough	Present intermittently or every day Often present throughout the day; seldom only nocturnal
Chronic sputum production	Any pattern of chronic sputum production may indicate COPD
Dyspnea that is:	Progressive (worsens over time) Persistent (present every day) Described by the patient as "increased effort to breath," "heaviness," "air hunger," or "gasping" Worse on exercise Worse during respiratory infections
History of exposure to risk factors, especially:	Tobacco smoke Occupational dusts and chemicals Smoke from home cooking and heating fuels

COPD = chronic obstructive pulmonary disease.

*Consider COPD and perform spirometry if any of these indicators are present. These indicators are not diagnostic by themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD.

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increase. In 1998, 54,615 men and 51,377 women died of COPD.[23] From 1995 to 1998, the rate of death attributable to COPD among men remained stable at 53.1 per 100,000 population (age-adjusted to the year 2000 US population), whereas the rate of death attributable to COPD among women increased 9.5%, from 29.3 to 32.1 per 100,000 (age-adjusted to the year 2000 US population). One of the limitations of using the mortality component of the National Vital Statistics System is that it is based on the underlying cause of death as reported on the death certificate; however, many decedents with COPD listed on the death certificate have their death attributed to another cause.[24] The significance of COPD as a contributor to death is undefined when it is present with diseases more likely to be attributed as the underlying cause of death, such as myocardial infarction or lung cancer.[25]

COPD is a very costly disease, with estimated direct medical costs in 1993 of $14.7 billion.[26] The estimated indirect costs related to morbidity (loss of work time and productivity) and premature mortality is an additional $9.2 billion, for a total of $23.9 billion.[26] Because COPD may be present but not listed as the underlying cause of death or the primary reason for hospitalization, these cited 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). DALYs for a disease or condition are calculated as the sum of the years of life lost due to premature mortality in the population and the years of life lost due to disability.[27] In 1996, COPD was estimated to be the eighth leading cause of DALYs among US men and the seventh leading cause of DALYs among US women.[27] Worldwide, COPD is expected to move up from being the twelfth leading cause of DALYs in 1990 to the fifth leading cause in 2020.[28]

Gender Differences

Smoking-related diseases such as COPD and lung cancer are continuing to increase among women in the United States, while they have plateaued or are decreasing among men.[24,29] Some evidence has emerged that compared with men at a similar level of tobacco smoking, women may be more likely to develop COPD[30] or that the severity of COPD in women may be increased.[31] In the Lung Health Study, which evaluated patients with mild COPD, more women than men demonstrated increased airway responsiveness, although this difference was thought to be related to airway caliber rather than gender.[14] Adult women are more likely to both develop and die of asthma than are men.[32–34] In NHANES III, whereas women reported more physician-diagnosed COPD and asthma than men, men and women had similar rates of decreased lung function, and a similar proportion of both men and women with

Table 3. Differential Diagnosis of Chronic Obstructive Pulmonary Disease

Diagnosis	Suggestive Features*
COPD	Onset in mid-life Symptoms slowly progressive Long smoking history Dyspnea during exercise Largely irreversible airflow limitation
Asthma	Onset early in life (often in childhood) Family history of asthma Symptoms vary from day to day Symptoms worse at night/early morning Allergy, rhinitis, or eczema also present Largely reversible airflow limitation
Congestive heart failure	Fine basilar crackles on auscultation Chest radiograph shows dilated heart, pulmonary edema Pulmonary function testing indicate volume restriction, not airflow limitation
Bronchiectasis	Large volumes of purulent sputum Commonly associated with bacterial infection Coarse crackles on auscultation Chest radiograph/CT scans show bronchial dilatation, bronchial wall thickening
Tuberculosis	Onset may occur at all ages Chest radiograph shows lung infiltrate or nodular lesions Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Onset at younger age, nonsmokers May have history of rheumatoid arthritis or fume exposure Chest CT on expiration shows hypodense areas
Diffuse panbronchiolitis	Most patients are male and nonsmokers Almost all patients have chronic sinusitis Chest radiograph and high resolution CT show diffuse small centrilobular nodular opacities and hyperinflation

COPD = chronic obstructive pulmonary disease; CT = computed tomography.

*These features tend to be characteristic of the respective diseases, but do not occur in every case. For example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than cigarette smoking); asthma may develop in adults and even elderly patients.

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low lung function had undiagnosed lung disease.[3] The current evidence is inadequate to determine whether women who smoke are more likely to develop COPD or have more severe COPD than men, although this question is being studied by various groups.

RISK FACTORS AND ETIOLOGY

Smoking is the dominant risk factor for the development and progression of COPD; however, not all smokers develop COPD, and COPD does occur in persons who have never smoked,[1] suggesting that other factors are important in the etiology of COPD. α_1-Antitrypsin deficiency is an important cause of COPD in a very small percentage of cases.[35] Other undefined genetic factors certainly play an important role in COPD development.[36] The role of infections in both the development and progression of COPD is receiving increased attention, including the role of adenoviral infections in emphysema and the role of intracellular infections (eg, mycoplasma) in asthma.[37–39] Occupational and environmental exposures to various pollutants (eg, particulate matter, agricultural dusts) are also important factors in the development of COPD.[40]

CLINICAL PRESENTATION

COPD is heterogeneous in its presentation. Based on data from NHANES III, 44% of patients with severe airflow limitation (FEV_1 < 50% of predicted) may not report symptoms.[3] Among patients with severe airflow limitation who do report symptoms, the symptoms reported most frequently include wheezing (64%) and shortness of breath (65%).

In recent years, COPD has been increasingly recognized as a systemic illness, with effects on nutritional status, muscle wasting, and depression.[41,42] A large proportion of patients probably have components of chronic bronchitis, asthma, and emphysema occurring together. Although some of this overlap may be related to misdiagnosis, some of it may be a measure of the presence of airflow limitation reversibility. Better defining individuals in these groups may ultimately help tailor better interventions.

Key indicators for considering a diagnosis of COPD are listed in **Table 2**. These indicators are either the presence of symptoms (chronic cough, chronic sputum production, or dyspnea) or a history of smoking or exposure to occupational dusts or chemicals. Spirometry with an evaluation of bronchodilator response is then needed to establish a diagnosis of COPD. Based on data from NHANES III, at least 67% of the adult US population would have at least 1 of these indicators present.[3] The proportion of the US

Table 4. Evaluation and Work-Up of Chronic Obstructive Pulmonary Disease

Procedure	Comments
	Evaluation for all subjects with suspected COPD
History and physical examination	Should include the following: Exposure to risk factors Past history of asthma or allergic disease Family history of COPD Presence of comorbid diseases Effect of disease on patient's life, including ability to work and mental health status Possibility for reducing risk factors, especially smoking cessation
Spirometry and bronchodilator response	FEV_1 and FVC should be measured, and the FEV_1/FVC ratio calculated, both before and after an inhaled bronchodilator. COPD severity (*see* Table 1) is assessed using the postbronchodilator lung function.
	Evaluation for subjects with confirmed moderate COPD*
Glucocorticosteroid reversibility testing	Pulmonary function testing after a long-term (6–12 week) course of inhaled glucocorticosteroids, with reversibility present if FEV_1 increases at least 200 mL and 15% above baseline as compared to baseline.
Chest radiograph	Seldom diagnostic in COPD, but useful to rule out other diagnoses Computed tomography scans may be helpful in the presence of atypical findings on the chest radiograph
Arterial blood gas measurement	Should be performed in patients with $FEV_1 < 40\%$ of predicted or with clinical signs suggestive of respiratory failure (cyanosis or ankle swelling) or right heart failure. $PaO_2 < 60$ mm Hg with or without $PaCO_2 > 50$ mm Hg while breathing air at sea level suggests COPD-related respiratory failure.
α_1-Antitrypsin deficiency screening	Indicated in patients who develop COPD at a young age (< 45 years) or who have a strong family history of COPD

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

*Moderate COPD = FEV_1/FVC < 70% and FEV_1 < 80% of predicted after bronchodilator response.

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population that has had pulmonary function testing is unknown but is thought to be very low. To address this problem, the National Lung Health Education Program (NLHEP) has been developed to educate both the public and physicians about the importance of COPD[43] and to promote spirometry in primary care physician offices.[44] NLHEP recommends that smokers older than 45 years and people with respiratory symptoms (eg, chronic cough, wheezing, dyspnea on exertion) have office-based spirometry performed.[44] Abnormal findings on the office-based spirometry should be followed up with diagnostic-quality spirometry, including the determination of reversibility.

DIAGNOSIS AND EVALUATION

The evaluation of a patient with suspected COPD is oriented toward establishing the correct diagnosis and, once this has occurred, determining the extent of the impairment such that therapy can be appropriately targeted.

The differential diagnosis of COPD is listed in **Table 3**. While some of the other diagnoses listed are rare in the United States (eg, diffuse panbronchiolitis, obliterative bronchiolitis), others, such as asthma and congestive heart failure, are quite common. In addition, in underdeveloped regions of the world, bronchiectasis and tuberculosis continue to be very important and prevalent diseases.

Components in the evaluation of COPD are listed in **Table 4**. Every patient with suspected COPD should undergo a thorough history and physical examination. The history should pay particular attention to the following: exposure to risk factors; past history of asthma or allergic disease; family history of COPD;

presence of comorbid diseases; effect of disease on the patient's life, including ability to work and mental health status; and possibilities for reducing risk factors, especially smoking cessation.[6] The physical examination is rarely diagnostic in COPD because most physical abnormalities do not occur until the advanced stages of the disease. Physical examination findings in patients with advanced disease include wheezing, prolonged expiration, decreased breath sounds, and an increased anterior-posterior diameter of the chest.

Pulmonary function testing, with assessment of response to a bronchodilator, is a critical part of the evaluation of suspected COPD. Whereas most patients with COPD can be managed by a primary care physician, patients with moderate or severe COPD should be evaluated by a specialist.

Once the diagnosis of moderate or severe COPD has been established, further testing, including glucocorticosteroid responsiveness, chest radiograph, arterial blood gas determination, and screening for α_1-antitrypsin deficiency may be indicated based on the patient's history and/or clinical findings.

Treatment of COPD depends largely on the severity of the disease and will be covered in the second article in this series.

CONCLUSION

COPD is a common disease that is a leading cause of morbidity and mortality both in the United States and worldwide. Most—but not all—cases of COPD are attributable to smoking. Although its incidence among men has plateaued, it continues to increase among women. COPD, particularly in its early stages, is underdiagnosed in the United States. An increased awareness among physicians of the prevalence of mild COPD and the importance of spirometry in screening for and diagnosing the disease is important in combating the disease. **HP**

REFERENCES

1. Rennard SI. COPD: overview of definitions, epidemiology, and factors influencing its development [review]. Chest 1998;113(4 Suppl):235S–41S.
2. Benson V, Marano MA. Current estimates from the National Health Interview Survey, 1995. Vital Health Stat 10 1998;199:193.
3. Mannino DM, 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;160:1683–9.
4. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. [Review]. Am J Respir Crit Care Med 1995;152(5 Pt 2):S77–121.
5. Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995;8:1398–420.
6. Pauwels RA, Buist AS, Calverley PM, et al. 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;163:1256–76.
7. World Health Organization. The GOLD global strategy for the management and prevention of COPD. Available at http://www.goldcopd.com. Accessed 13 August 2001.
8. Dirksen A, Christensen H, Evald T, et al. Bronchodilator and corticosteroid reversibility in ambulatory patients with airways obstruction. Dan Med Bull 1991;38: 486–9.
9. Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54:581–6.
10. National Health Interview Survey: research for the 1995–2004 redesign. Vital Health Stat 2 1999;126:1–119.
11. Adams PF, Hendershot GE, Marano MA. Current estimates from the National Health Interview Survey, 1996. National Center for Health Statistics. Vital Health Stat 10 1991;200:93.
12. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–94. Series 1: programs and collection procedures. Vital Health Stat 1 1994;32:1–407.
13. Standardization of spirometry—1987 update. Statement of the American Thoracic Society. Am Rev Respir Dis 1987;136:1285–98.
14. 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;150:956–61.
15. Enright PL, Johnson LR, Connett JE, et al. Spirometry in the Lung Health Study. 1. Methods and quality control. Am Rev Respir Dis 1991;143:1215–23.
16. Chang JT, Moran MB, Cugell DW, Webster JR, Jr. COPD in the elderly. A reversible cause of functional impairment. Chest 1995;108:736–40.
17. Hansen EF, Phanareth K, Laursen LC, et al. Reversible and irreversible airflow obstruction as predictor of overall mortality in asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159(4 Pt 1): 1267–71.
18. Ulrik CS, Backer V. Nonreversible airflow obstruction in life-long nonsmokers with moderate to severe asthma. Eur Respir J 1999;14:892–6.
19. Slusarcick AL, McCaig LF. National Hospital Ambulatory Medical Care Survey: 1998 outpatient department summary. Adv Data 2000;317:1–23.

20. McCaig LF. National Hospital Ambulatory Medical Care Survey: 1998 emergency department summary. Adv Data 2000;313:1–23.
21. Dennison C, Pokras R. Design and operation of the National Hospital Discharge Survey: 1988 redesign. Vital Health Stat 1 2000;39:1–42.
22. Popovic JR, Kozak LJ. National hospital discharge survey: annual summary, 1998. Vital Health Stat 13 2000; 148:1–194.
23. Murphy SL. Deaths: final data for 1998. Natl Vital Stat Rep 2000;48:1–105.
24. 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(3 Pt 1):814–8.
25. Camilli AE, Robbins DR, Lebowitz MD. Death certificate reporting of confirmed airways obstructive disease. Am J of Epidemiol 1991;133:795–800.
26. Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. Chest 2000;117(2 Suppl):5S–9S.
27. Michaud CM, Murray CJ, Bloom BR. Burden of disease—implications for future research. JAMA 2001;285:535–9.
28. Lopez AD, Murray CC. The global burden of disease, 1990–2020. Nat Med 1998;4:1241–3.
29. Tanoue LT. Cigarette smoking and women's respiratory health. Clin Chest Med 2000;21:47–65.
30. 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; 162:2152–8.
31. Carter R, Nicotra B, Huber G. Differing effects of airway obstruction on physical work capacity and ventilation in men and women with COPD. Chest 1994;106: 1730–9.
32. de Marco R, Locatelli F, Sunyer J, Burney P. Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. Am J Respir Crit Care Med 2000;162:68–74.
33. Moorman JE, Mannino DM. Increasing U.S. asthma mortality rates: who is really dying? J Asthma 2001; 38:65–71.
34. Mannino DM, Homa DM, Pertowski CA, et al. Surveillance for asthma—United States, 1960–1995. Mor Mortal Wkly Rep CDC Surveill Summ 1998;47:1–27.
35. Snider GL. Molecular epidemiology: a key to better understanding of chronic obstructive lung disease. Monaldi Arch Chest Dis 1995;50:3–6.
36. Silverman EK, Speizer FE. Risk factors for the development of chronic obstructive pulmonary disease [review]. Med Clin North Am 1996;80:501–522.
37. Hogg JC. Chronic bronchitis: the role of viruses. Semin Respir Infect 2000;15:32–40.
38. Kraft M, Cassell GH, Henson JE, et al. Detection of Mycoplasma pneumoniae in the airways of adults with chronic asthma. Am J Respir Crit Care Med 1998;158: 998–1001.
39. Hegele RG, Hayashi S, Hogg JC, Pare PD. Mechanisms of airway narrowing and hyperresponsiveness in viral respiratory tract infections. Am J Respir Crit Care Med 1995;151:1659–64.
40. Becklake MR. Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease. Am Rev Respir Dis 1989;140(3 Pt 2):S85–S91.
41. Aguilaniu B, Goldstein-Shapses S, Pajon A, et al. Muscle protein degradation in severely malnourished patients with chronic obstructive pulmonary disease subject to short-term total parenteral nutrition. JPEN J Parenter Enteral Nutr 1992;16:248–54.
42. Keele-Card G, Foxall MJ, Barron CR. Loneliness, depression, and social support of patients with COPD and their spouses. Public Health Nurs 1993;10:245–51.
43. Strategies in preserving lung health and prevention COPD and associated disease: The National Lung Health Education Program (NLHEP) [review]. Chest 1998;113(2 Suppl):1235–635.
44. Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: a consensus statement from the National Lung Health Education Program. Chest 2000;117:1146–61.