Asthma and COPD

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Abstract

Asthma and chronic obstructive pulmonary disease (COPD) are clinically important in older adults because like heart failure, they are common causes of chronic shortness of breath, which reduces the quality of life by limiting an individual's activity. In developed countries, about 4% of older adults have been diagnosed with asthma and another 4% have been diagnosed with COPD, but the prevalence is doubled for each of these chronic respiratory diseases when objective tests are performed. COPD has become the fourth leading cause of death in some developed countries. COPD onset occurs almost exclusively in older age due to the cumulative effects of cigarette smoking in genetically-susceptible individuals. An upper respiratory viral infection commonly leads to the initial diagnosis of asthma at any age. About half of older adults with asthma have allergic triggers, compared to about 90% of asthmatic children. Exacerbations with dyspnea, wheezing and cough are the major morbidity of asthma and COPD, which limits activity, reduces quality of life and increases health care utilization and costs. In older adults as in younger adults, the most effective prevention for both asthma and COPD is smoking cessation.

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Abbreviations

BHR	Bronchial Hyper-Responsiveness
BNP	B-type natriuretic peptide
CHF	Chronic Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
DLCO	Carbon Monoxide Diffusing Capacity
FEV1	Forced Expiratory Volume
FVC	Forced Vital Capacity
hMPV	Human Metapneumovirus
IgE	Immunoglobulin E
LLN	Lower Limit of the Normal range
MIP	Maximal Inspiratory Pressure
NHANES	National Health and Nutrition Examination Survey
Pre-BD	Prior to inhalation of a Bronchodilator
Post-BD	After inhalation of a Bronchodilator
RSV	Respiratory Syncytial Virus
TENOR	The Epidemiology and Natural History of Asthma study
US	United States

24.1 Introduction

Asthma, chronic obstructive pulmonary disease (COPD) and chronic heart failure are clinically important in older adults because they are common causes of chronic shortness of breath (dyspnea), which reduces quality of life by limiting activity. An older adult with any of these diseases is more likely to experience morbidity (exacerbations and hospitalization) and mortality. Asthma and COPD both cause airway narrowing, which can be detected by spirometry testing. While asthma can start during any decade of life, COPD only develops after decades of cigarette smoking and so is very rare before 40 years of age. It is important to distinguish between asthma, COPD and heart failure because the interventions differ; treatment for asthma is more successful and the prognosis is much better. About 20% of older adults with any one of these causes of dyspnea will also have one of the others (co-morbid conditions).

24.2 Definitions

The definitions of asthma and COPD are based on symptoms, self-reported diagnosis, and/or the testing of pulmonary function using spirometry. Asthma is defined as episodic and reversible airways obstruction. COPD is defined as chronic and irreversible airways obstruction. Other chronic conditions can also cause dyspnea. We define two of these here to distinguish them from asthma and COPD. The definition of chronic bronchitis is based on a history of a chronic cough (productive of sputum or not) which has been present for at least 2 years. Epidemiologic studies use a standardized set of questions to define chronic bronchitis; no objective tests are needed. Emphysema is a term used to describe the irreversible destruction of lung tissue, which is detected using a breathing test called carbon monoxide diffusing capacity (DLCO) or by high-resolution CT scans of the lungs that show reduced lung density or holes in the lungs (blebs or bullae). Overlap amongst the above chronic lung disease phenotypes does occur since decades of cigarette smoking can cause any one or all of them (asthma, chronic airway obstruction, chronic bronchitis and emphysema).

24.3 Spirometry

Airway obstruction is reliably detected in older adults through the use of a spirometer [1]. The study participant is coached to take as deep a breath as possible and then blow into the

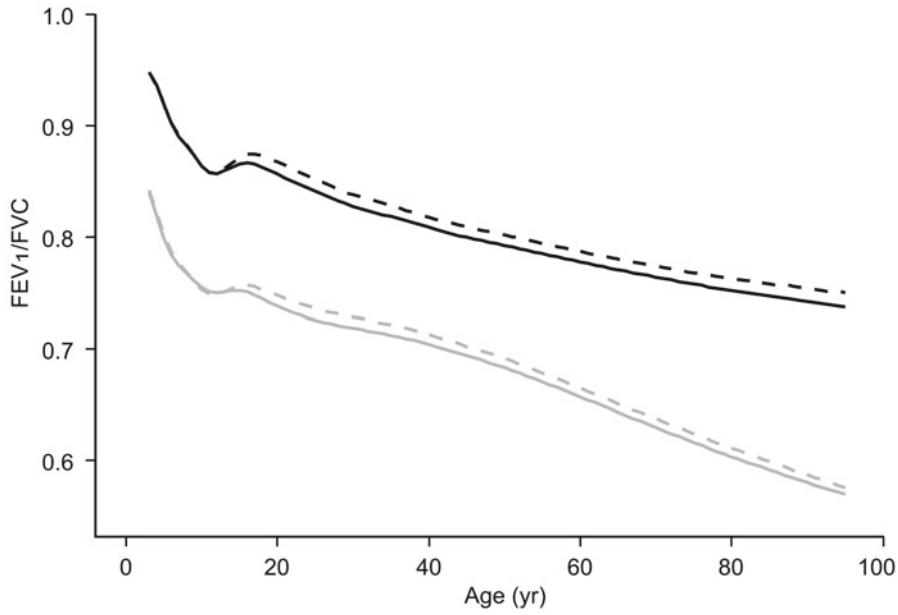

Fig. 24.1 The predicted (*black lines*) and the lower limit of the normal range (LLN, *grey lines*) for FEV1/FVC—which defines airway obstruction—decrease with age. The values for females (*dashed lines*) are slightly higher than for men (*solid lines*)

spirometer mouthpiece as quickly as possible for at least 6 s. The volume of air forcefully exhaled during the first second is called the forced expiratory volume (FEV1) and the total amount of air exhaled is called the forced vital capacity (FVC) (measured in liters). Healthy middle-aged adults can exhale about 75% of their air in the first second, so the ratio of their FEV1/FVC is about 0.75. Smokers who have developed COPD have a permanently reduced capacity to exhale rapidly, so their FEV1 and their FEV1/FVC fall below the lower limit of the normal range (LLN).

Almost all clinical and epidemiological definitions of COPD are based on a low FEV1/FVC in a patient with COPD risk factors. However, the LLN for this ratio has been controversial. The pulmonary function standards committee of the American Thoracic Society [2]—the largest and most influential pulmonary professional society—recommends using the fifth percentile LLNs from spirometry reference equations from the healthy, never-smoking subset of participants from the National Health and Nutrition Examination Survey (NHANES) III for use throughout North America [3]. The mean and LLN for the FEV1/FVC from this study (and from most studies of lung function in healthy population-based samples) decrease with aging. So the LLN for this ratio is about 0.75 for young adults and falls to about 0.60 for adults ≥85 years of age (Fig. 24.1). In the year 2000, an industry-sponsored, international group of key opinion leaders published and began extensive worldwide promotion of a COPD clinical practice guideline which defined COPD as a FEV1/FVC ratio <0.70 (a fixed threshold) after inhaling a fast-acting bronchodilator (post-BD). Many COPD guidelines developed for individual countries quickly adopted this definition. However, compared to the use of an age-adjusted LLN, the use of this fixed threshold to define COPD greatly increases the apparent prevalence of COPD in population-based samples of healthy older adults [4]. The vast majority of patients given a diagnosis of COPD in clinical settings present with symptoms; however, in population-based studies which included spirometry, half of adults with severe airway obstruction did not report respiratory symptoms. Therefore, epidemiologic studies with spirometry should base the COPD prevalence only on spirometry results.

Spirometers designed in the 1960s collected exhaled air in a container for measurement of the

Fig. 24.2 An older woman blowing forcefully into a spirometer for 6 s. Due to COPD, her FEV1 is only 0.35 l (very severe airway obstruction) and she has required continuous oxygen therapy (2 l per minute to maintain her oxygen saturation above 90%) during the past decade. Note the nasal prongs which deliver the supplemental oxygen. She kindly gave us written permission to publish this 2012 photo of her

vital capacity (Fig. 24.2). Since tall people can exhale up to two gallons of air, these devices were bulky and heavy. During the 1990s, flow-sensing spirometers, many of which are hand-held and battery-powered, replaced the older devices. The American Thoracic Society provides standards for the accuracy of spirometers and spirometry procedures [2].

24.4 Differentiating Asthma from COPD and Chronic Heart Failure (CHF)

One difference between asthma and COPD is that the airway obstruction of patients who have asthma is more likely to quickly respond to an inhaled bronchodilator medication (such as albuterol, also called salbutamol). Amongst individuals who have asthma, the majority of asthma is mild and intermittent. There is no airway obstruction between asthma exacerbations (which are usually triggered by an upper respiratory viral infection). Therefore, in epidemiological surveys, participants with mild asthma usually have normal spirometry tests (no airway obstruction). Those with moderate or poorly-controlled asthma have some degree of airway obstruction, but their lung function returns toward the normal range (due to increased FEV1) within 10 min post-BD (Fig. 24.3). For those who report asthma-like symptoms, if their spirometry results improve into the normal range post-BD, COPD is ruled out and the probability of asthma is greatly increased.

In spirometry testing, CHF causes a small decrease in the FVC, but there is no airway obstruction [5]. CHF causes an increase in blood levels of B-type natriuretic peptide (BNP), while BNP levels are normal in patients who have asthma or COPD. Echocardiography shows left heart failure in CHF and right heart failure (i.e., cor pulmonale) in very severe COPD, but electrocardiography is normal in asthma (Table 24.1).

The agency which funds the majority of pulmonary research in the United States (US), the Lung Division of the National Heart, Lung and Blood Institute, made asthma a high priority in the 1980s–1990s, so standardization of asthma definitions was advanced for both reporting purposes and clinical practice guidelines. However, the emphasis was on the control of asthma in children. Although the US Centers for Disease Control and Prevention reported that the majority of asthma deaths occurred in older adults [6], very little asthma research (observational or intervention) was done in this age group. Around the year 2000, the Lung Division shifted its major research funding and disease awareness programs to COPD, a disease almost exclusively of older adults. Still, controversy exists regarding the definitions of asthma and COPD in older adults.

24.4.1 Controversy in Defining Asthma and COPD

Older adults who have respiratory symptoms and airway obstruction that remains post-BD are

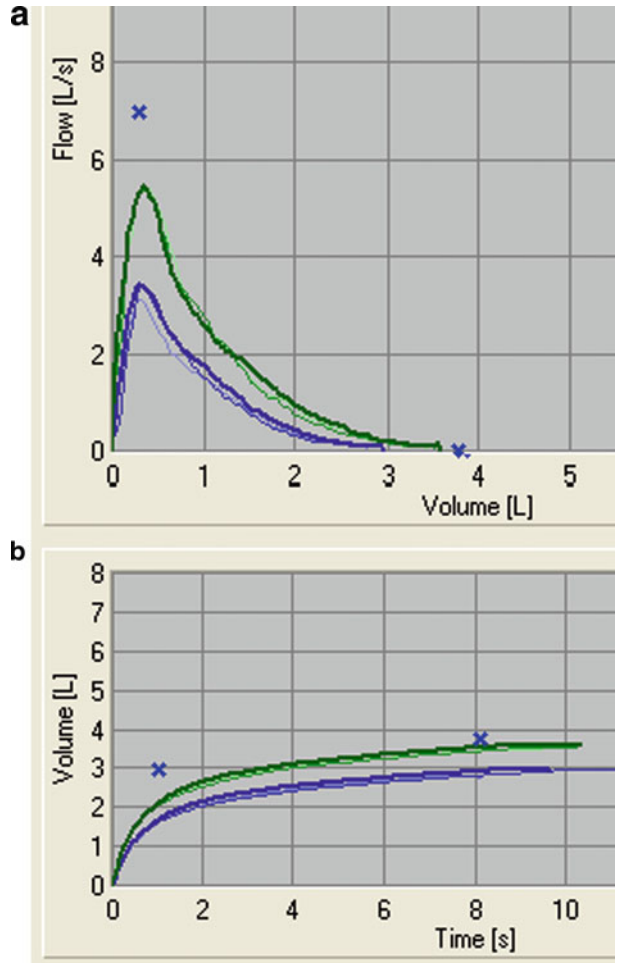

Fig. 24.3 Spirometry graphs from a 75-year-old man with asthma. The *top graph* (**a**) shows flow-volume curves with the characteristic bowl-shape of airway obstruction. The *bottom graph* (**b**) shows traditional volume-time curves, from which the FEV1 and FVC are measured. The man's FEV1 was 1.5 l (from the pre-bronchodilator smaller curve); his FVC was 3.0 l; and his FEV1/FVC was only 0.50, confirming airway obstruction. The small *x-marks* indicate the predicted normal values. Ten minutes after inhaling a bronchodilator (albuterol), his FEV1 increased to 2.0 l (about 33% larger) and his FVC increased to about 3.7 l. If he had been a smoker with COPD, his bronchodilator response would have been much smaller (usually less than 0.25 l)

classified by some studies as having asthma and by others as having COPD. Asthma has to be defined on the basis of a physician diagnosis, but in the future, there should be some consideration of a reversibility of chronic obstruction. Some investigators use smoking status to classify the respiratory disease of those with post-BD airway obstruction (never smokers as having asthma or ever smokers as having COPD). Large epidemiological surveys of adults have demonstrated that about one-third of participants who have mild airway obstruction before inhaling a fast-acting bronchodilator (pre-BD) do not have airway obstruction post-BD. However, the majority of studies of chronic lung disease in adults do not take the time to perform post-BD spirometry (since it takes 15–20 min).

A chronic cough is a very common feature in smokers who have developed COPD, so some studies wrongly include people with a chronic cough or chronic bronchitis under their definition of COPD. However, even in adult smokers, there

Table 24.1 Tests to differentiate asthma, chronic obstructive pulmonary disease, and chronic heart failure

Test	Asthma	Chronic obstructive pulmonary disease	Chronic heart failure
Spirometry	Reversible obstruction	Fixed obstruction	Low FVC (restriction)
Chest x-ray	Hyperinflation	Hyperinflation	Increased vascularity
BNP	Normal (<100)	Normal (<100)	High (>500)
Echocardiography	Normal	Normal	Low ejection fraction

Abbreviations: *BNP* B-type natriuretic peptide (pg/mL), *FVC* forced vital capacity

are many other causes for a chronic cough (e.g., rhinosinusitis, gastro-esophageal reflux and asthma), so large COPD misclassification rates result when an objective measurement of airway obstruction is not performed.

The definition of asthma for epidemiological surveys is less controversial than for COPD [7, 8]. For diagnosis of asthma, most studies of adults rely on participant recollection of a physician diagnosis of asthma, using a set of standardized questions. Study participants may also be asked to list their breathing medications or to bring them to a study visit. Objective measurements of the bronchial hyper-responsiveness (BHR) and eosinophilic airway inflammation of asthma are available [9], but they have not come into widespread use due to the time needed to perform the BHR measurement (45–60 min for a methacholine or mannitol inhalation challenge test) and the expense of exhaled nitric oxide analyzers. Also, as discussed above, a spirometry test only detects moderate or poorly-controlled asthma.

A physician diagnosis of asthma underestimates the true prevalence of asthma because many people do not seek medical attention for what they consider to merely be "a cold that goes to my chest" [10]. However, the morbidity that is experienced by older adults who have recurrent, intermittent episodes of wheezing with shortness of breath but no diagnosis of asthma is similar to those who have a diagnosis of asthma.

24.4.2 Implications of Disease Definitions

As with other common chronic diseases for which expensive drugs are available, the exact definition of the disease has large financial implications (for the payors and sometimes for the individual patients). The market for medications that control airway obstruction greatly expands when definitions for disease extend into the normal range and when clinical practice guidelines call for early detection and treatment of more mild disease. Currently, there is no evidence that early detection and treatment changes the natural history of COPD.

24.5 Prevalence and Incidence

Two large population-based studies of adults from many countries have provided good estimates of the prevalence of COPD based on post-BD spirometry measurements [11, 12] (Fig. 24.4). The prevalence of COPD in the moderate range (50–90% predicted FEV1) in men and women ≥60 years of age ranges from 3 to 6% (depending on the country). The prevalence of severe COPD (FEV1 below 50% predicted) is only about 1%. However, COPD is now the fourth leading cause of death in the US [13].

Population-based samples of older adults have provided estimates of the prevalence of asthma in adults ≥60 years of age [14, 15]. Using a large community-based cohort of individuals >65 years of age in the US, the CHS defined *definite* asthma as positive responses to the questions: "Has a physician ever told you that you have asthma?" and "Do you still have asthma?" *Probable* asthma was defined as a history of wheezing in the past year associated with chest tightness or breathlessness. Excluding smokers and those with a diagnosis of congestive heart failure, 4% of individuals had definite asthma and 4% had probable asthma [16]. Among current smokers, 11% had definite asthma and 14% had probable asthma. The age of asthma onset was spread approximately evenly among decades, with 25% reporting onset before age 20 and 27% after age 60.

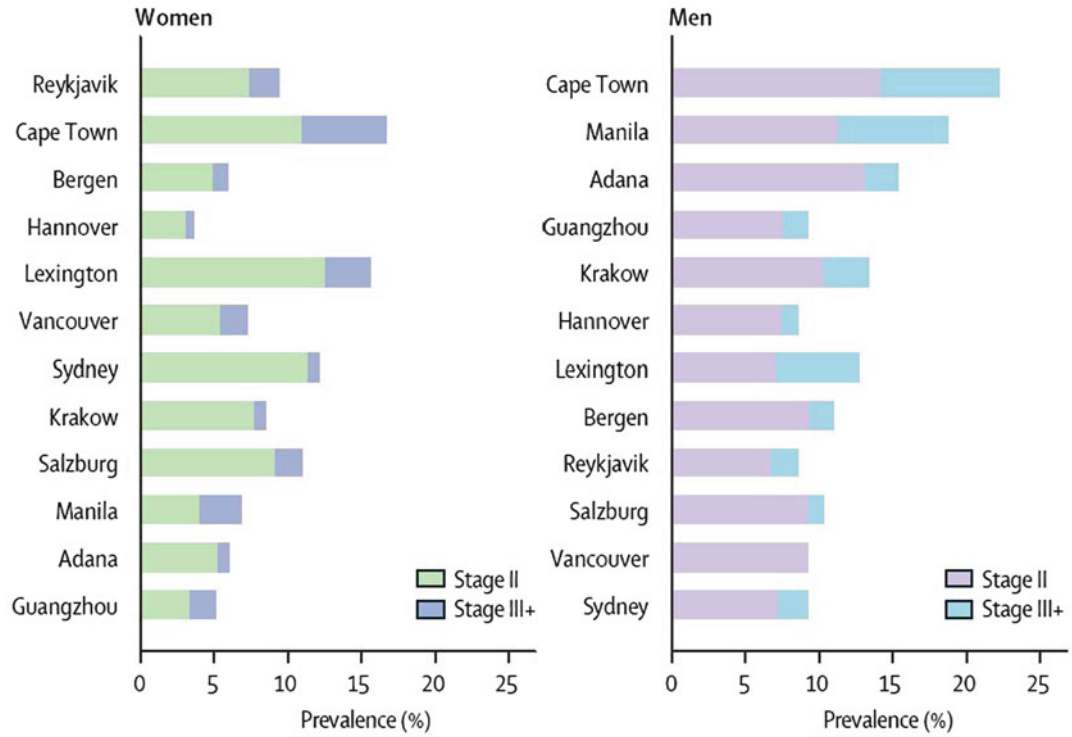

Fig. 24.4 Prevalence rates for mild-moderate COPD in women (**a**) and men (**b**) ages 40–90 from 12 different countries. Stage II is mild-moderate with post-bronchodilator FEV1 between 50 and 80% of predicted. Individuals with severe stage III+ COPD have an FEV1 below 50% of predicted. Predicted FEV1 values are based on height, age and gender (Results are from the BOLD study [11]). No adjustment was made for predicted FEV1 for African race in Cape Town, South Africa or Lexington, Kentucky

In the US, the National Health Interview Survey asks questions regarding lifetime history of asthma, current asthma prevalence, and asthma attacks in the last 12 months [17]. For all age groups, asthma prevalence has been steadily increasing since 1980. For example, the prevalence of current asthma in those aged 65 and above rose from 6.0% in 2001 to 7.0% in 2004. For those ≥65 years of age, asthma is consistently more prevalent in women than in men. In 2003, 3.3% of women over age 65 reported an asthma attack during the previous 12 months, compared to 1.7% of older men. The National Center for Health Statistics tracks data on physician encounters for asthma. Using this data, the National Ambulatory Care Survey reported that those ≥65 years of age have the second-highest rate of outpatient office visits for asthma after preschool children, but do not have significantly different rates for emergency room visits compared to other adult age groups [18]. The 65+ age group accounts for a greater proportion of hospitalizations (23%) than the size of its population (13%) would indicate, and has higher asthma mortality rates than do young adults [6].

24.6 Risk Factors

24.6.1 Age

Within the age range of 65–95, the risk of the clinical appearance of asthma or COPD does not increase appreciably with age. Allergic asthma commonly begins in childhood, but it can begin at any age. Older patients who have asthma often note the onset of asthma after age 60, usually associated with a serious cold or influenza [16].

In contrast, age is a risk factor for COPD since it develops very slowly, with the onset of dyspnea upon exertion prompting a diagnosis in the fifth or sixth decade of life. After age 85, the prevalence of COPD falls, probably due to mortality from other smoking-related diseases.

Aging is a cause of decreased lung function in older adults. Lung function grows with height in childhood and adolescence, reaches a peak in the 20s or early 30s then declines linearly throughout adulthood. FVC starts at 4–5 l in young adults (depending on height and gender) then declines by about one-third of a liter per decade. On average, the functional reserve of the lungs continues to slowly erode throughout older age, even in healthy individuals who have never smoked and had no measurable environmental exposures. The FEV1 declines at a somewhat faster rate than the FVC (largely due to a loss of lung tissue elasticity), so the FEV1/FVC also declines with aging. Age-related impairments in respiratory physiology become most problematic during maximal exercise or in an episode of acute lung injury (e.g., pneumonia), as well as in individuals who already have a reduced ventilatory reserve due to lung disease.

24.6.2 Gender

For a given exposure history (such as pack-years of smoking), women and men have a roughly equivalent risk of developing COPD [19–21]. Older women are more likely than older men to have asthma-like symptoms and to report dyspnea upon exertion (even after adjustment for other risk factors).

24.6.3 Genetic Risk

Studies have identified some racial differences in susceptibility to asthma and COPD. However, large projects have had only limited success in determining the exact set of genetic polymorphisms that are responsible for increased susceptibility for developing these chronic airway diseases [22]. African-Americans are more likely to have a genetic polymorphism that increases their risk of asthma (at all ages) and reduces the effectiveness of the long-acting bronchodilators which are commonly used to control asthma (inhaled beta-agonists). Amongst Hispanics, a greater percentage of African ancestry correlates with lower FVC and a greater risk of asthma and asthma severity [23]. On the other hand, African-American women are less susceptible to the risk that cigarette smoking will cause COPD [19].

24.6.4 Smoking

About one in five people who begin smoking before age 20 will slowly develop COPD. About 90% of clinically-important COPD is caused by smoking. The respiratory system has a very large functional reserve, so decades of slow loss in lung function usually occurs (as in COPD caused by cigarette smoking) before shortness of breath prompts the individual to seek medical attention [24]. Smoking also increases the risk of asthma (at all ages) and continued smoking makes asthma more difficult to control because smoking reduces the effectiveness of inhaled corticosteroid therapy.

24.6.5 Viruses

All of the common respiratory viruses have been associated with asthma and COPD exacerbations: respiratory syncytial virus (RSV), parainfluenza viruses, coronaviruses, human metapneumovirus (hMPV) and rhinoviruses. Wheezing is a common symptom in older adults who are infected with any respiratory virus, particularly with RSV and hMPV, and 7 percent of adults who are hospitalized with RSV pneumonia will have a discharge diagnosis of asthma [25].

24.6.6 Allergies

Many risk factors for asthma in young and middle-aged adults have been identified. Most remain as risk factors for asthma in older adults. In the CHS cohort, 58% of older-adult asthmatics

reported the most common trigger of an asthma exacerbation to be an upper respiratory viral infection (upper respiratory infection, common cold or influenza), while 30% reported that contact with animals caused their asthma to worsen. Two-thirds reported seasonal worsening.

About 50% of older adults with asthma have allergic triggers, compared to about 90% of asthmatic children. The Epidemiology and Natural History of Asthma (TENOR) study compared the natural history of asthma in younger and older patients [26]. The older patients had lower total immunoglobulin E (IgE) levels, fewer positive skin prick tests and less concomitant allergic rhinitis or atopic dermatitis. There is also evidence for an age-related decline in skin-prick test responses to allergens; however, older adults who have greater levels of IgE remain more likely to have allergic rhinitis and asthma [27].

24.6.7 Environmental Risk Factors

A few epidemiologic studies have suggested an association between short-term worsening of outdoor air pollution and emergency department or hospital admissions for asthma in older adults [28]. Decades of exposure to severe outdoor air pollution may increase the risk of at least mild COPD in older ages [29]. Like the skin, the lungs have a very large surface area which is directly exposed to the environment. Inflammatory responses to these exposures usually promote long-term health, but they can also cause long-term damage in a susceptible subset of individuals, damage which often accumulates decade-by-decade. Occupational exposures to inhaled dusts, fumes, smoke and chemicals increase the risk of chronic airway obstruction which persists into older age [30]. Decades of exposure to second-hand smoke, or to smoke from cooking with biomass fuels in developing countries, increases the risk of chronic bronchitis [31]. It remains unknown whether these environmental exposures also cause clinically-important COPD because almost all studies used pre-BD FEV1/FVC <0.70 to define COPD, which caused high false-positive rates for airway obstruction.

24.7 Dyspnea, the Primary Outcome of Asthma and COPD

Older adults with asthma or COPD frequently have respiratory symptoms such as chronic cough, phlegm and wheezing, all caused by their chronic airway inflammation [32]. Reduced lung function causes shortness of breath which limits their activity, reduces the quality of their lives and prompts them to utilize health care during exacerbations (visit emergency departments, sometimes leading to hospitalizations) [33]. This morbidity, along with the drugs prescribed for their dyspnea, is expensive [34–36].

Dyspnea is the most distressing feature of chronic lung disease and is a leading cause of disability and healthcare utilization [37]. In the CHS cohort, dyspnea upon exertion was 1.6-fold more likely to be present in patients diagnosed with asthma than in those without the diagnosis [16]. Asthma had a significant impact on quality of life, with 35% of older adults who have definite or probable asthma reporting a fair or poor health status compared to 17% of older adults who do not have asthma. Depression, restless sleep and daytime sleepiness were substantially more common in those with asthma.

Dyspnea may be considered an imbalance between ventilatory capacity and ventilatory demand. Increased ventilatory demand is commonly caused by comorbid conditions such as heart failure, anemia, obesity and peripheral vascular disease. The ability of the chest wall to expand easily is reduced by osteoporosis (vertebral compression, kyphosis and scoliosis) and osteoarthritis.

Very severe COPD and CHF (but not asthma) commonly cause skeletal muscle weakness (sarcopenia). Respiratory muscle weakness is a major factor that causes respiratory failure in COPD and pneumonia. The strength of the diaphragm, which is the primary breathing muscle, can be measured by a simple pressure meter. Maximal inspiratory pressure (MIP) ranges from 20 (very low) to 150 cm of water (normal), and is the best index of respiratory muscle strength [38]. MIP is an independent predictor of all-cause, cardiovascular and respiratory death in older adults [39].

24.8 Prevention

The most effective primary and secondary prevention for asthma and COPD after age 65 is the same as for middle age: smoking cessation. About half of older adults who have asthma and about one-third of those who have COPD are current smokers. Smoking cessation, both in middle age and older ages, is the only intervention that has been proven to slow the progression of COPD (thereby altering the natural history of the disease). Smoking cessation has been proven to make asthma respond better to inhaled corticosteroids, thus improving asthma control, and has been proven to prolong the life of those with COPD. The chronic cough and phlegm production of COPD will improve with successful smoking cessation, but the loss of lung function and emphysema are not reversible. The cough may get worse for a few weeks, but the degree of dyspnea on exertion tends to remain.

Influenza and pneumococcal vaccinations reduce asthma and COPD exacerbation rates [40]. It is likely that avoiding exposure to young children who have upper respiratory infections also reduces the risk of exacerbations, but no clinical trials have studied the benefit of avoiding exposure to these young children.

Another prevention method for asthma and COPD is avoiding the inhalation of respiratory irritants (e.g., smoke, fumes, dusts chemicals), which cause airway inflammation that persists for several hours after inhalation. This temporary inflammation increases coughing and phlegm from the lower airways. It also causes nasal congestion, leading to mouth breathing which bypasses the heating, humidification and dust removal of nasal passages which naturally protects the lower airways (in the lungs).

24.9 Summary

Asthma, COPD and heart failure are clinically important in older adults because they are common causes of dyspnea, which reduces the quality of life by limiting activity. In developed countries, about 4% of older adults have been diagnosed with asthma and another 4% with COPD. Epidemiologic studies use standardized questionnaires to determine the presence of asthma and post-BD spirometry to detect and verify COPD. An upper respiratory viral infection commonly leads to the initial diagnosis of asthma in older adults. About 90% of COPD is due to the cumulative effects of cigarette smoking in genetically-susceptible individuals. About half of older adults with asthma have allergic triggers. Periodic exacerbations with dyspnea, wheezing and cough are the major morbidity of asthma and COPD. Both conditions are associated with a higher risk of death. In older adults, the most effective prevention for both asthma and COPD is smoking cessation.

References

1. Camhi SL, Enright PL (2000) How to assess pulmonary function in older adults. J Respir Dis 21:395–400
2. Miller MR, Hankinson J, Brusasco V et al (2005) Standardisation of spirometry. Eur Respir J 26(2):319–338
3. Stanojevic S, Wade A, Stocks J et al (2008) Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 177:253–260
4. Swanney MP, Ruppel G, Enright PL et al (2008) Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. Thorax 63(12):1046–1051
5. Hawkins NM, Petrie MC, Jhund PS et al (2009) Heart failure and COPD: diagnostic pitfalls and epidemiology. Eur J Heart Fail 11:130–139
6. Moorman JE, Mannino DM (2001) Increasing U.S. asthma mortality rates: who is really dying? J Asthma 38:65–71
7. NHLBI (National Heart, Lung and Blood Institute National Institute of Health) (2008) National asthma education and prevention program: expert panel report 3- guidelines for the diagnosis and management of asthma. NIH Publication 08–4051, Bethesda, MD
8. Pekkanen J, Pearce N (1999) Defining asthma in epidemiological studies. Eur Respir J 14:951–957
9. Scichilone N, Messina M, Battaglia S et al (2005) Airway hyper-responsiveness in the elderly: prevalence and clinical implications. Eur Respir J 25:364–375
10. Bellia V, Battaglia F, Catalano N et al (2003) Aging and disability affect misdiagnosis of COPD in elderly asthmatics: the SARA study. Chest 123:1066–1072
11. Buist AS, McBurnie MA, Vollmer WM et al; for the BOLD Collaborative Research Group (2007) International variation in the prevalence of COPD (the

BOLD Study): a population-based prevalence study. Lancet 370(9589):741–750
12. Menezes AM, Perez-Padilla R, Jardim JR et al; for the PLATINO Team (2005) Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet 366:1875–1881
13. Jemal A, Ward E, Hao Y et al (2005) Trends in the leading causes of death in the United States, 1970–2002. JAMA 294(10):1255–1259
14. King MJ, Hanania NA (2010) Asthma in the elderly: current knowledge and future directions. Curr Opin Pulm Med 16:55–59
15. Parameswaran K, Hildreth AJ, Chadha D et al (1998) Asthma in the elderly: underperceived, underdiagnosed and undertreated; a community survey. Respir Med 92:573–577
16. Enright PL, McClelland RL, Newman AB et al (1999) Underdiagnosis and undertreatment of asthma in the elderly. Chest 116:603–613
17. Moorman JE, Rudd RA, Johnson CA et al (2007) National surveillance for asthma–United States, 1980–2004. MMWR Surveill Summ 56:1–54
18. Cherry DK, Burt CW, Woodwell DA (2001) National ambulatory medical care survey: 1999 summary. Adv Data Vital Health Stat (CDC) 322:1–36. http://www.cdc.gov/nchs/about/major/ahcd/adata.htm
19. Vollmer WM, Enright PL, Pedula KL et al (2000) Race and gender differences in the effects of smoking on lung function. Chest 117(3):764–772
20. Camp PG, O'Donnell DE, Postma DS (2009) Chronic obstructive pulmonary disease in men and women: myths and reality. Proc Am Thorac Soc 6(6):535–538
21. Lopez Varela MV, Montes de Oca M, Halbert RJ et al; PLATINO Team (2010) Sex-related differences in COPD in five Latin American cities: the PLATINO study. Eur Respir J 36(5):1034–1041
22. Smolonska J, Wijmenga C, Postma DS et al (2009) Meta-analyses on suspected chronic obstructive pulmonary disease genes: a summary of 20 years' research. Am J Respir Crit Care Med 180(7):618–631
23. Kumar R, Seibold MA, Aldrich MC et al (2010) Genetic ancestry in lung-function predictions. N Engl J Med 363(4):321–330
24. Higgins MW, Enright PL, Kronmal RA et al (1993) Smoking and lung function in elderly men and women: the Cardiovascular Health Study. JAMA 21:2741–2748
25. Proud D, Chow CW (2006) Role of viral infections in asthma and chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol 35:513–518
26. Slavin RG, Haselkorn T, Lee JH et al (2006) Asthma in older adults: observations from the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study. Ann Allergy Asthma Immunol 96:406–414
27. Katial R, Zheng W (2007) Allergy and immunology of the aging lung. Clin Chest Med 28:663–672
28. Selgrade MK, Lemanske RF Jr, Gilmour MI et al (2006) Induction of asthma and the environment: what we know and need to know. Environ Health Perspect 114(4):615–619
29. Abbey DE, Burchette RJ, Knutsen SF et al (1998) Long-term particulate and other air pollutants and lung function in nonsmokers. Am J Respir Crit Care Med 158:289–298
30. Blanc PD, Torén K (2007) Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update. Int J Tuberc Lung Dis 11(3):251–257
31. Salvi S, Barnes PJ (2010) Is exposure to biomass smoke the biggest risk factor for COPD globally? Chest 138(1):3–6
32. Jones PW, Quirk FH, Baveystock CM et al (1992) A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis 145:1321–1327
33. Chapman KR, Mannino DM, Soriano JB et al (2006) Epidemiology and costs of COPD. Eur Respir J 27:188–207
34. Bauer BA, Reed CE, Yunginger JW et al (1997) Incidence and outcomes of asthma in the elderly. A population-based study in Rochester, Minnesota. Chest 111:303–310
35. Blanchette CM, Gutierrez B, Ory C et al (2008) Economic burden in direct costs of concomitant chronic obstructive pulmonary disease and asthma in a Medicare advantage population. J Manag Care Pharm 14:176–185
36. Zeiger RS, Hay JW, Contreras R et al (2008) Asthma costs and utilization in a managed care organization. J Allergy Clin Immunol 121:885–892
37. ATS: American Thoracic Society (1999) Dyspnea: mechanisms, assessment, and management. A consensus statement. Am J Respir Crit Care Med 159:321–340
38. Enright PL, Kronmal RA, Schenker M et al (1994) Correlates of respiratory muscle strength, and maximal respiratory pressure reference values in the elderly. Am Rev Respir Dis 149:430–438
39. van der Palen J, Rea TD, Manolio TA et al (2004) Respiratory muscle strength and the risk of incident cardiovascular events. Thorax 59(12):1063–1067
40. Simonsen L, Taylor RJ, Viboud C et al (2007) Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis 7:658–666