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17

CHRONIC RESPIRATORY DISEASES

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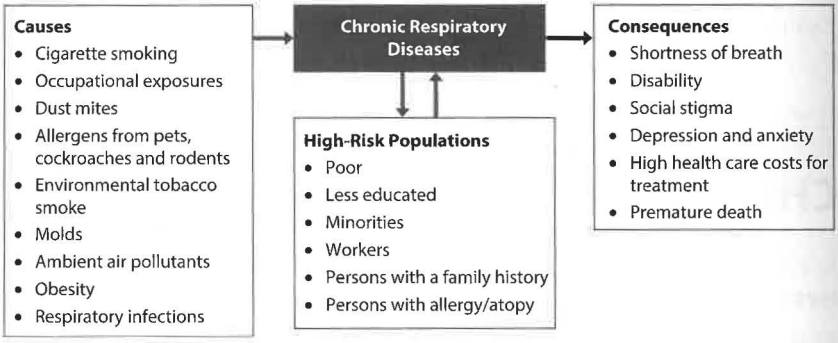
Introduction

Chronic respiratory diseases include a broad range of conditions marked by variability in the range of symptoms, causative and exacerbating factors, and diagnostic criteria. The "upstream" causes and "downstream" consequences of chronic respiratory diseases are complex, and related to the specific type of disease (Figure 17-1). According to the Centers for Disease Control and Prevention's (CDC's) National Center for Health Statistics, chronic lower respiratory diseases were the third leading cause of death in the United States in 2013, responsible for 5.7% of U.S. deaths (Xu et al. 2016). Hospitalization is a frequent adverse outcome of a chronic respiratory disease diagnosis, with the average duration of a hospitalization of 4.5 days for chronic bronchitis and 3.6 days for asthma in 2010 (CDC 2012a). Population-based national health surveys have found that approximately 12% of adults reported obstructive lung disease, including chronic bronchitis, emphysema, and asthma in 2014 (Blackwell and Lucas 2015).

Significance

The primary consequence of chronic respiratory diseases that contributes to morbidity is dyspnea, or pathologic breathlessness (Stulberg and Adams 2000). Depending on the severity, dyspnea may result in restrictions ranging from inability to climb stairs to constant breathlessness and difficulty in sleeping. Effects of dyspnea include impaired respiratory tract clearance mechanisms, excessive mucus production, and reduced lung capacity, which likely contribute to more frequent, severe, and prolonged acute viral and bacterial respiratory



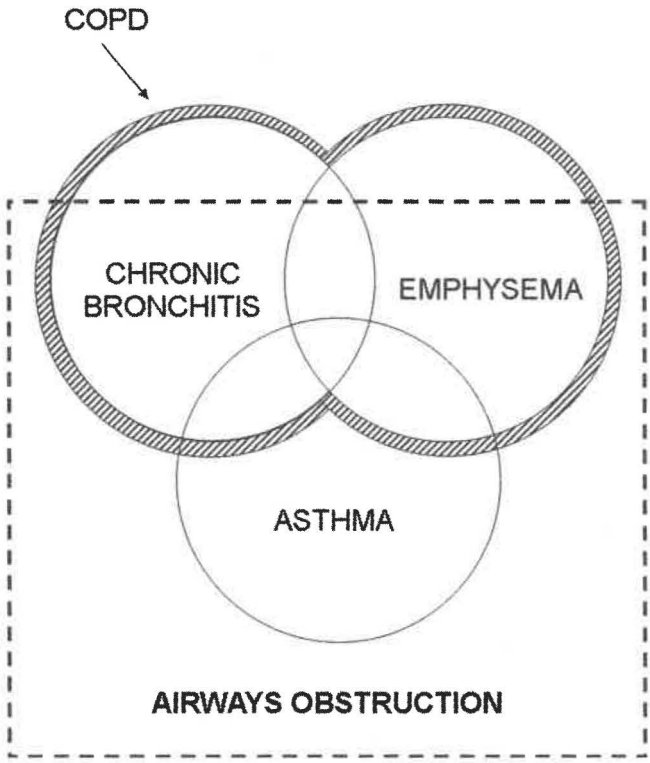
Source: Adapted from Anderson and Werner (2010).

Figure 17-1. Chronic Respiratory Diseases: Causes, Consequences, and High-Risk Groups

infections (Mahler and Meija 1999). Dyspnea is also a common clinical feature in chronic nonpulmonary conditions such as heart disease, obesity, and muscular diseases. Cough, chest pain, excessive phlegm or sputum production, wheezing, and coughing of blood (or hemoptysis) are other commonly observed symptoms of respiratory disease (Mason et al. 2000). As is the case for dyspnea, these symptoms can manifest variously in different respiratory and nonrespiratory disorders.

Among the challenges of describing symptoms commonly observed in respiratory disease is that terminology can differ greatly among clinicians describing similar patterns of respiratory impairment. The use of the term chronic obstructive pulmonary disease (COPD) can describe sets of symptoms that are alternately described as chronic bronchitis, emphysema, or asthma; as such, assigning a definition based on clinical, physiologic, or pathologic criteria may be problematic (Figure 17-2). Clinicians may also use the term COPD to describe nonspecific respiratory symptoms in cases in which airflow impairment may be either absent or present. The *International Classification of Diseases (ICD)*-9 and -10 codes and the definitions used in this chapter are presented in Table 17-1.

Both cystic fibrosis (CF) and sleep apnea are chronic diseases affecting multiple systems with principal effects on the respiratory system. Cystic fibrosis is an inherited disease characterized by the production of abnormally thick and sticky mucus, resulting in respiratory infections and pancreatic obstruction, and is a major source of severe chronic lung disease in children and an increasingly important cause of morbidity and mortality from chronic lung disease in young adults (Boucher et al. 2000). Obstructive sleep apnea is characterized by



Source: Based on Snider (1988).
Note: Chronic obstructive pulmonary disease (COPD) includes patients with chronic bronchitis and emphysema, and a subset of patients with asthma. Patients with COPD found outside the box for airways obstruction would have clinical or radiographic features of chronic bronchitis or emphysema.

Figure 17-2. Schema of Chronic Obstructive Pulmonary Disease (COPD)

sleep-disordered breathing associated with daytime symptoms, such as excessive sleepiness, and intermittent upper respiratory tract obstruction (Caples et al. 2005). The condition has been estimated to be present in 3% to 7% of men and 2% to 5% of women (Punjabi 2008).

Pathophysiology

The diagnostic tests and associated criteria for definition differ among various chronic respiratory diseases. Chronic bronchitis is diagnosed by clinical signs and reported symptom history, whereas asthma and other forms of COPD are

Table 17-1. Definitions of Specific Chronic Respiratory Diseases

Disease	*ICD-9*	*ICD-10*	Definition
Asthma	493	J45–J46	Reversible airway obstruction with airway inflammation and increased airways responsiveness to a variety of stimuli.
Bronchitis[a]	490–491	J40–J42	Excessive tracheobronchial mucus production associated with narrowing of the bronchial airways and cough.
Emphysema[a]	492	J43	Alveolar destruction and associated airspace enlargement.
Other chronic obstructive pulmonary diseases	491.21–491.22, 493.2, 496	J44	Asthma with chronic obstructive pulmonary disease and other chronic airway obstruction.
Cystic fibrosis	277.00, 277.01	E84	Genetic disease with exocrine gland dysfunction resulting in pancreatic insufficiency, chronic progressive lung disease, and elevated sweat chloride production.
Bronchiectasis	494	J47	Bronchial wall destruction.
Pneumoconioses (and other externally induced alveolar diseases)	500–504, 506.4, 507.1, 507.8, 515, 516.3	J60–J67	Dust-, fume- or mist-induced pneumoconiosis or lung injury (not immunologically mediated).
Sleep apnea	780.51, 780.53, 780.57	G47.3	Repetitive cessation of breathing during sleep.

Note: ICD-9=International Classification of Diseases, Ninth Revision; ICD-10=International Classification of Diseases, Tenth Revision.

[a]Bronchitis and emphysema are the major conditions falling under the classification of chronic obstructive pulmonary disease.

diagnosed by clinical evaluation and spirometric tests of lung function (GINA 2015; GOLD 2016). Emphysema is defined in histopathologic terms (i.e., study of lung tissue) and is diagnosed with certainty only with lung biopsy or autopsy, although computerized axial tomography (CT) scanning of the chest can be informative. A further complication is that the symptoms of gastroesophageal reflux, a digestive condition, can occasionally be similar to those of various airways diseases, and the two conditions are often confused (Guill 1995).

One manifestation of the occupation-related pneumoconioses, or dust-induced lung conditions, is a fibrotic response to deposition of inorganic material. Diagnosis requires an exposure history and x-ray assessment (ILO 2002). In a heterogeneous group of lung disorders, interstitial lung diseases, the chest x-ray, and occasionally CT of the chest can assist in the evaluation and monitoring of disease status and are used in conjunction with other methods of assessing respiratory function, such as spirometry.

Spirometric testing is simple and inexpensive and is a sensitive and noninvasive method of assessing obstructive lung diseases as well as different fibrotic or restrictive lung diseases. Spirometry measures the expired volume as a function of time. Forced vital capacity (FVC) and forced expiratory volume in the first one second (FEV1) are less variable than many other tests of lung function (Gold 2000a). Using the FVC or FEV1, or the ratio of FEV1 to FVC, lung disorders can be categorized into those with airflow obstruction (ratio of FEV1 to FVC less than 0.75) or restriction (FVC less than 80% of predicted) or into mixed disorders (decreases in both FEV1 to FVC ratio and FVC).

In addition to spirometry, other lung function tests can include measurement of total lung capacity, functional residual capacity, carbon monoxide diffusing capacity, and cardiopulmonary exercise testing. Assessment of lung function following bronchoprovocation with methacholine or histamine may indicate airway hyperreactivity and is sometimes performed if asthma is suspected but spirometry is inconclusive.

The chest radiograph is of most help in the clinical evaluation of chronic lung diseases. However, its role in the screening or epidemiologic study of lung diseases is limited by expense, feasibility, and technical considerations. A uniform method of chest radiograph interpretation has been developed by the International Labour Office (ILO) for use in selected clinical settings (e.g., disability assessment for occupational lung disease) and for research purposes (ILO 2002; ILO 2011). The system categorizes opacities and pleural changes on the chest radiograph by their shape, size, location, and density (ILO 2002; ILO 2011). Physicians who obtain additional training in ILO interpretation of the chest x-ray and pass an examination are called B readers. Methods similar to the ILO scheme for the chest x-ray have been developed for standardized interpretation of CT images of the chest (Tamura et al. 2015).

This chapter not only discusses the two major chronic lung diseases, asthma and COPD, but also includes shorter descriptions of a variety of occupationally induced chronic lung diseases, including coal workers'

pneumoconiosis, silicosis, asbestosis, byssinosis, and occupational asthma; lung diseases associated with exposure to organic dusts; a diverse group of diseases resulting in fibrosis of the lung (i.e., interstitial lung disease); CF; and obstructive sleep apnea.

ASTHMA

According to results of the 2014 National Health Interview Survey, approximately 7.7% of the general population currently has asthma (current prevalence), and 12.9% have received a diagnosis of asthma during their lifetime (lifetime prevalence; CDC 2016a). Although much effort has been made in recent years to develop standardized diagnostic criteria for asthma, estimates of asthma prevalence continue to vary with different data collection approaches, such as self-reported and physician-reported data. International asthma prevalence estimates vary widely, ranging from less than 2% in Nepal to 16% in Isle of Man (GINA 2015). In 2013, 3,630 people in the United States died from asthma (Xu et al. 2016).

Significance

Asthma was responsible for an estimated 17.3 million ambulatory care visits in 2010, including visits to physician offices, emergency departments, and hospital outpatient departments (CDC 2012b). Appropriate medical management may limit the degree to which asthma affects productivity of children and adults; however, asthma remains a significant cause of missed days of work or school. In 2013, U.S. children missed an estimated 13.8 million days of school because of asthma (CDC 2013).

Pathophysiology

Historically, asthma has been classified into two categories: allergic or atopic (extrinsic) and nonallergic or nonatopic (intrinsic) asthma. Atopy is defined as the capacity to produce abnormal amounts of immunoglobulin E (IgE) in response to environmental allergen exposure. Between the two categories, asthma appears to be more commonly classified as allergic in children than in adults (Pearce et al. 1999; Knudsen et al. 2009). However, many individuals have asthmatic responses that are characteristic of both categories and the basis for

this classification has been under question. The introduction of newer information about the role of genetics in asthma and observations of higher IgE levels in patients of all age groups has added weight to the proposal of a unifying hypothesis for both types of asthma (White and Kaliner 1991; Meyers et al. 2004).

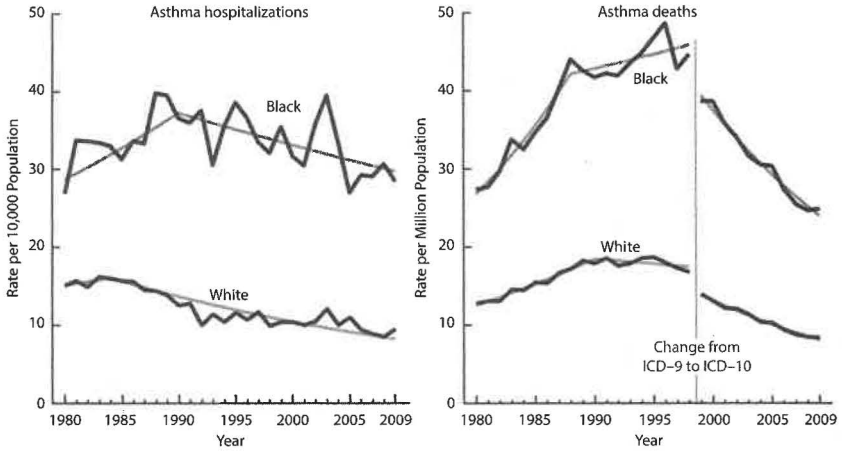
Asthma primarily manifests itself in the airways, and patients with asthma show evidence of mucosal edema, epithelial disruption, infiltration with inflammatory cells, and excessive amounts of mucus in airways (Boushey et al. 2000). The development of the changes responsible for airway obstruction and hyperresponsiveness is primarily attributable to inflammatory responses in the airways of patients. In allergic asthma, IgE–antigen complexes bind to the membranes of various connective tissue cells, causing the release of signaling chemical agents responsible for an asthmatic response. Positive response to skin test batteries for common allergens is more prevalent among those with extrinsic asthma than those with intrinsic asthma, and more common among people with asthma as a category than among people without asthma (Pearce et al. 1999).

Symptoms of asthma, such as intermittent wheezing or shortness of breath triggered by specific environmental exposures or exercise, frequently appear in children before the age of five years. About 50% of adults who were diagnosed with asthma as children no longer have the condition, with about half of these becoming totally symptom-free (Barbee and Murphy 1998). Conversely, about one fourth of childhood asthma cases persist with a similar degree of severity into adulthood, and the remaining one fourth may experience a temporary cessation in symptoms, with symptoms returning in adulthood (Sears 1991).

Descriptive Epidemiology

High-Risk Populations

Although there is a range of factors that are useful for describing the distribution of asthma and asthma-related adverse health outcomes among populations, the most important determinants of asthma and related morbidity and mortality are race/ethnicity, age, and sex. Racial disparities for asthma are found for a range of endpoints, most notably prevalence, mortality, and hospitalizations (Figure 17-3). Data from the 2014 National Health Interview Survey found significantly higher values of current asthma prevalence for non-Hispanic African Americans than for non-Hispanic whites (9.9% vs. 7.6%;



Source: Reprinted from Moorman et al. (2012).

Note: Population-based rates age-adjusted to the 2000 standard population. Rates based on asthma as the first-listed diagnosis or as the underlying cause of death. Straight lines show the modeled trend estimated by Joinpoint. Inflection points represent a change in the annual percent change.

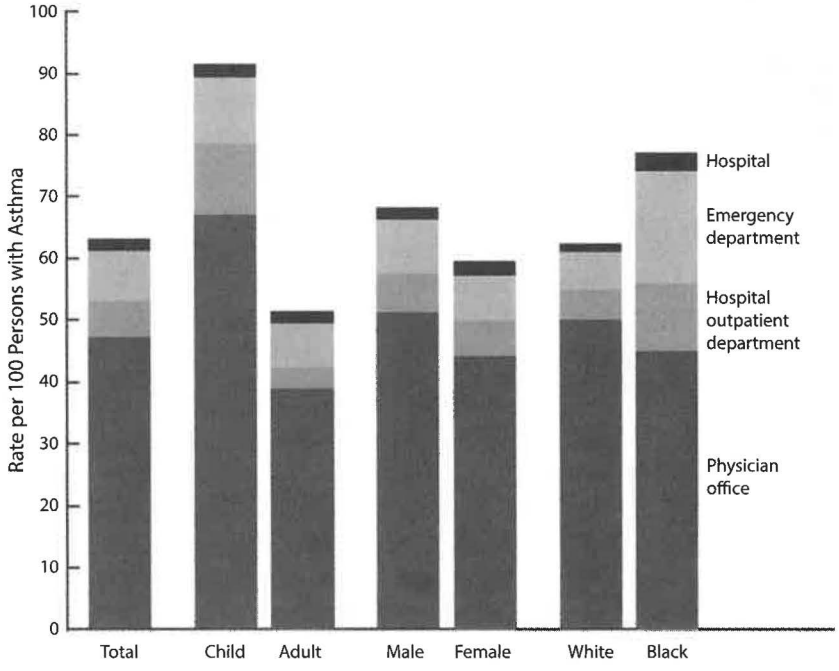
Figure 17-3. Asthma Hospitalization Rates and Asthma Death Rates (Population-Based), by Race, United States, 1980–2009

CDC 2016a). When the data were limited to children, the disparity was even more striking (13.4% vs. 7.6%; CDC 2016a). Across all race groups, Hispanic ethnicity is not associated with higher asthma prevalence. As a subset of the Hispanic population, however, those of Puerto Rican descent have an asthma prevalence rate of 16.5% for all age groups and 23.5% among children. Asthma prevalence tends to be higher in children than adults. Data from the 2014 National Health Interview Survey show similar prevalence among white children and adults (7.6%) but higher prevalence among children versus adults for African Americans (13.4% vs. 9.9%), and among Hispanics (8.5% vs. 6.7%; CDC 2016a).

For health care utilization, rates of inpatient hospitalization and emergency department use related to asthma are significantly higher for African Americans than for whites. In 2010, the inpatient hospitalization rate for asthma among African Americans was 29.9 per 10,000 population compared to 8.7 per 10,000 for whites (CDC 2016b). The emergency department visit rate for asthma among African Americans and whites per 10,000 population was 182.1 and 51.0, respectively, in 2009 (Moorman et al. 2012). Differences in asthma

health care utilization for persons with current asthma by age, sex, and race are depicted in Figure 17-4 (Moorman et al. 2012). Rates for the population with asthma take into account differences in asthma prevalence among demographic groups. In 2014, the asthma mortality rate for non-Hispanic African Americans was three times higher compared to that for non-Hispanic whites (2.5 vs. 0.9 per 1,000,000 population, respectively; CDC 2015).

Among the striking features of the epidemiology of asthma is the observed trend by which prevalence shifts according to sex among age groups. By sex, asthma prevalence is higher in boys than in girls (Moorman et al. 2012). In 2014, asthma prevalence among boys and girls was 10.1% and 7.0%, respectively (CDC 2016a). Among adults, however, this trend is reversed, with 2014 asthma prevalence rates for men and women of 5.1% and 9.6%, respectively



Source: Reprinted from Moorman et al. (2012).
Note: Crude risk-based rates (per 100 persons with current asthma) are presented.

Figure 17-4. Asthma Physician Office Visit, Hospital Outpatient Department, Emergency Department and Hospitalization Rates by Age, Sex, and Race: United States, Average Annual 2007–2009

(CDC 2016a). This trend is borne out in health care utilization rates (inpatient admissions, emergency department visits, and ambulatory care visits) and for mortality rates. No clear explanation for this observation has emerged.

The degree to which the racial disparity in asthma prevalence and adverse health outcomes can be explained by socioeconomic differences is a subject of some controversy. Factors such as access to high-quality health care and housing conditions are likely to account for some of the racial disparities seen with asthma. Some ecologic studies of national databases indicate that controlling for family income can diminish or decrease the racial difference in asthma prevalence (Weitzman et al. 1992; Smith et al. 2005), whereas others have found that racial and ethnic disparities in asthma prevalence and health care utilization persist after accounting for income and other socioeconomic factors (Bhan et al. 2015; Law et al. 2011).

As described earlier, approximately 30% to 50% of the general population can be classified as atopic, and most asthmatics fall into this category (Pearce et al. 1999). Because of growing knowledge that atopy is strongly influenced by genetics, it follows that some aspects of asthma development may be under genetic control. Indeed, those with a family history of asthma have long been known to be at increased risk for developing the disease (Burke et al. 2003).

Geographic Distribution

Data from the National Health Interview Survey from 2008 to 2010 suggest that regional differences exist in the United States for asthma prevalence. Based on standard U.S. census regions, asthma prevalence is highest in the Northeast (8.8%), followed by the Midwest (8.7%), West (8.0%), and South (7.6%; Moorman et al. 2012). Average annual emergency department visit rate estimates for the period 2007 to 2009 are highest in the Northeast (10.2 per 100 persons with current asthma), followed by the South (8.7), Midwest (8.0), and West (5.5; Moorman et al. 2012).

Time Trends

Although the range of data sources available for asthma surveillance has changed over time, observed increases in patient encounter measures for asthma have been predicated by increased asthma prevalence in recent decades (Moorman et al. 2012). Based on survey responses regarding whether a family member had asthma in the past 12 months, asthma prevalence increased from 3.1% in 1980 to 5.5% in 1996, an increase of 3.8% per year. This increase occurred among all age,

sex, and race subgroups. Although changes in survey questions make comparisons from 1997 to 2000 with newer national prevalence data problematic, current asthma prevalence rates increased from 7.3% in 2001 to 8.4% in 2010, an increase of 1.5% per year. Data on asthma mortality suggest that death rates increased from 1980 through 1989, remained stable from 1989 to 1998, and have declined by 4.9% per year from 1999 to 2009 (Moorman et al. 2012).

Seasonal trends have been consistently exhibited for both asthma morbidity and mortality. Asthma hospitalization rates reflect a seasonal variation whereby the highest rates occur in early spring and early fall, and rates are lowest in the summer (Weiss 1990). Studies on asthma mortality have suggested that asthma mortality in children and young adults may peak in summer, whereas mortality among older adults peaks in winter. Potential explanations for this observed seasonality include plant allergens, acute respiratory infections, cold weather, and air pollution. For school-age children, the onset of school in September has been found to contribute to increased emergency department visits for asthma (Silverman et al. 2005).

Causes

Modifiable Risk Factors

The bulk of the published literature on asthma epidemiology and risk factors has focused on the identification of asthma triggers—specific exposures that often precipitate symptoms in individuals with asthma. Common asthma triggers include dust mites, allergens from pets, cockroaches and rodents, secondhand smoke, molds, ambient air pollutants, cold conditions, and exercise (GINA 2015). There are, by contrast, relatively few conclusive findings about what risk factors contribute to the development of the condition itself, and the factors that cause asthma remain largely unidentified (Taussig et al. 2003).

As discussed in the previous section, atopic individuals are more likely to be diagnosed with asthma than others, and atopy is a significant risk factor for developing asthma. One study found that most people with asthma are atopic (Arbes et al. 2007). Although the relationship to atopy suggests that there is a strong genetic component among the factors related to the etiology of asthma, environmental factors appear to play a role as well. One longitudinal study in children found that although IgE levels in umbilical cord blood were not predictive of subsequent development of asthma, IgE blood levels in blood

samples taken at age one year were predictive (Martinez et al. 1995). This finding suggests that exposures within the first year of life may be substantial contributors to the risk of developing asthma in childhood.

Although exposures to dogs and cats in the home can be an asthma trigger for some people with asthma, results from studies on the effect of the presence of dogs and cats in the home environment on the development of asthma have been mixed. One longitudinal study found a decreased likelihood for developing wheezing among children without maternal asthma in homes with one or more indoor dogs, but no effect related to cats in the home (Remes et al. 2001). Another study found increased likelihood of cat sensitization and development of severe asthma among children reporting the presence of cats in the home before the age of two years (Melen et al. 2001).

Although breast-feeding practices in childhood may also affect the risk of developing asthma in children, the results of studies on this question have also been mixed. In one longitudinal study, atopic children with asthmatic mothers were more likely to have asthma if they were exclusively breast-fed as infants (Wright et al. 2001). In the same study, however, exclusive breast-feeding was associated with reduced likelihood of recurrent wheeze in the first two years of life regardless of atopy status or whether the child's mother had asthma.

Secondhand smoke has clearly been established as a risk factor for asthma exacerbations (Chilmonczyk et al. 1993; Witorsch and Witorsch 2000). There is also increasing evidence that exposure to secondhand smoke may contribute to the development of asthma, both in adults and children (Gold 2000b; Jaakkola et al. 2003). For children, the risk associated with secondhand smoke may be confounded by effects of maternal smoking that may have been incurred during pregnancy.

The relationship between asthma and obesity has received increased attention in recent years. Because obesity is associated with a generalized increase in inflammatory response, a causal role in asthma has been postulated (Beuther et al. 2006). Increased incidence of asthma and poorer asthma control have been observed at higher rates among people with elevated body mass index (BMI) values (Akinbami and Fryar 2016). In children, the impact of obesity on incident asthma was shown to be more pronounced among girls than boys (Gold et al. 2003). Because of the possibility that reduced physical activity among people with asthma could contribute to the likelihood of obesity, the relationship between asthma and obesity is likely to be complex in nature.

Ambient air pollutants have been shown to be important asthma triggers (GINA 2015). Associations between asthma and exposure to ozone and

particulate matter have been commonly observed, but other pollutants such as nitrogen dioxide and volatile organic compounds, and community traffic density and proximity to heavily traveled roads have also been found to be associated with adverse asthma-related health outcomes (Sarnat and Holguin 2007). The role of air pollution in the development of asthma is less certain. In a study of southern California schoolchildren, residence within 75 meters of a major road was found to be associated with increased risk of lifetime asthma, with effects more pronounced in girls than in boys (McConnell et al. 2006). Incidence of asthma was also associated with traffic-related air pollution exposure from roadways near homes and schools (McConnell et al. 2010). Among school-age children active in sports, incidence of asthma was found to be higher in children living in communities with high ozone concentrations than among other children (McConnell et al. 2002).

Population-Attributable Risk

The development of asthma clearly appears to be related to both genetic and environmental factors. As such, quantifying the relative contribution of genetics and environment is a difficult proposition. Specific genes related to atopy and asthma development have begun to be identified (Ober and Yao 2011). Although it appears increasingly apparent that some specific environmental factors play a role in asthma development, there is a substantial amount of variability among individuals with asthma as to the triggers causing exacerbations. It is likely that the list of environmental and occupational exposures that may contribute to the development will be highly individual-specific as well.

Evidence-Based Interventions

Prevention

Because of the considerable uncertainty about how specific genetic and environmental factors contribute to the development of asthma at both the individual and population levels, there are few clear recommendations to offer by way of preventing the development of asthma. For potentially susceptible populations, such as siblings and children of people with asthma, there may be benefit in extending environmental control measures applied to the individual with asthma (such as limiting exposure to pests and mold) to other members of the household. For example, dust mites can be effectively controlled by encasing

mattresses and pillows in airtight covers, washing bedding every week, and removing wall-to-wall carpeting, especially in bedrooms. Given the increased evidence regarding secondhand smoke and air pollutants as contributors to developing asthma, public policy efforts to ban smoking in public places and establish appropriate air pollutant restrictions for ozone and particulate matter may have benefit in reducing future asthma incidence and prevalence.

Rather than focus on poorly informed efforts on asthma prevention, public health activity on asthma has focused primarily on means by which individuals with asthma can reduce or eliminate exacerbations that may pose a threat to a patient's health or limit his or her quality of life. This has been done by promoting regular interaction with appropriate health care providers, providing and disseminating guidance about appropriate use of controller medications to patients and health care providers, and by educating patients about the nature of asthma as a chronic disease and how to identify and avoid asthma triggers that may cause exacerbations. Because secondhand smoke is a known asthma trigger, efforts to discourage tobacco use in homes and other indoor environments or focusing smoking cessation efforts on people with asthma and their families may be worthwhile approaches to consider. Because influenza may have a considerable impact on asthma-related morbidity, it is recommended that people with asthma obtain a yearly flu shot. Whether people with asthma constitute a risk category on par with the elderly or other groups for targeting flu shots when resources are scarce remains an open question (Bueving et al. 2005). Exposure to ambient airborne particulates and irritants has been associated with asthma exacerbations and increased inpatient hospitalization and emergency department visit rates for asthma. In addition to efforts to decrease ambient concentrations of these pollutants, state and national public health alerts are issued when pollution concentrations exceed standards and could pose a threat to sensitive populations, including people with asthma.

Screening

Because effective management can minimize the frequency and severity of asthma exacerbations, applying a proper diagnosis to individuals who have asthma is an important step in controlling the disease and reducing asthma-related adverse health outcomes. However, mild to moderate cases of asthma may be difficult to diagnose, especially among young children. In such cases,

symptoms can often be confused with recurrent respiratory infections or bronchitis, and, as such, may not be recognized as a chronic condition.

Because of its impact on school attendance, as a major cause of hospitalization in children, and the preventable nature of asthma-related morbidity, the notion of population-based screening for asthma has received much attention as a potential intervention. Many organizations, including the American Thoracic Society, have refrained from endorsing such screening efforts because of the lack of evidence that such approaches result in measurable improvements in health outcomes (Gerald et al. 2007). Population-based screening may be most effective in areas where there is likely to be a high prevalence of undiagnosed asthma and where access to high-quality care is likely to be available for newly diagnosed patients.

Treatment

The primary goal of asthma treatment is to control the condition and minimize exacerbations to avoid adverse asthma-related health outcomes. Most asthma medications can be described as controller medications or reliever (rescue) medications (GINA 2015). Controller medications are generally taken daily on a long-term basis to achieve control of inflammation. Common types of controller medications include inhaled corticosteroids such as fluticasone, leukotriene modifiers such as montelukast, and long-acting β2-agonists such as salmeterol. Reliever medications act quickly to address bronchoconstriction. These include rapid-acting β2-agonists and systemic glutocorticosteroids. Frequent use of reliever medications (e.g., on a daily basis) may signify that a patient's asthma is not being well controlled and his or her treatment plan should be re-evaluated. Some medications in both classes are not recommended as stand-alone therapies, but are generally prescribed only when other controller medications are included in the patient's therapy plan.

Examples of Evidence-Based Interventions

Over the past decade, substantial effort has been made in designing, implementing, and evaluating public health interventions to address asthma. Common objectives for intervention efforts include educating patients about asthma, controlling exposure to triggers in the home and work environments, and enhancing communication across different parts of the health care system

about patients with asthma. Sites where interventions have been implemented to address asthma include health care facilities (clinics, hospitals, and emergency departments), pharmacies, homes, schools, and workplaces. The focus of such interventions has ranged from patients and parents to teachers and health care providers, and effective programs have taken approaches such as modifying the home environment during pregnancy to reduce the likelihood of developing asthma in childhood (Custovic et al. 2001), assessing the quality of patients' interaction with pharmacists (Barbanel et al. 2003), and ensuring that health education messages are culturally appropriate for patients (Brotanek et al. 2007).

Reducing exposure to secondhand smoke through state smoke-free policies has been associated with a lower risk of asthma health care utilization (Mackay et al. 2010; Millett et al. 2013). A systematic review of public health interventions for asthma found that skills-based asthma self-management education is effective for both children and adults (Labre et al. 2012). Furthermore, a Guide to Community Preventive Services review indicated that home-based, multi-trigger, multi-component environmental interventions are effective in children and demonstrate a modest return on investment (Guide to Community Preventive Services 2012). Guidelines have been established for asthma management and prevention at both the national and international levels, setting the stage for more uniform practices for the evaluation, dissemination, and adaptation of effective public health interventions for asthma (GINA 2015; NHLBI 2007).

Areas of Future Research

Risk factors for the development of childhood asthma have not been fully assessed, and further work to develop appropriate animal models for asthma research is needed (Coleman 1999). Longitudinal cohorts of asthma patients are recommended to further understand the origins of asthma and the relationships between exposures and developmental changes over the lifespan (Levy et al. 2015). A broader description of the genetic determinants of asthma will help enable the identification of high-risk individuals for whom particular interventions to prevent asthma might be recommended. Although effective medications for asthma control exist, there remain concerns about long-term side effects, such as growth restrictions in children, for which more data are required. Although home-based multicomponent interventions to reduce

exposure to asthma triggers in the home have been shown to be effective in children with asthma, the evidence demonstrating effectiveness for adults with asthma remains tenuous (Guide to Community Preventive Services 2012). Further data on the effectiveness of such interventions for adults with asthma would be of great benefit.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) has been defined as a disease chiefly marked by airway obstruction that is not fully reversible (Rabe et al. 2007). The condition is usually progressive in nature and is associated with an abnormal inflammatory response of the lungs to noxious particles and gases (Shapiro et al. 2000). Conditions such as chronic bronchitis and emphysema that are obstructive in nature are frequently grouped together under the broader heading of COPD. Because there can be a significant overlap of symptoms and manifestations of different forms of COPD, distinctions among the various diagnoses within the broader COPD category can be difficult to make successfully.

Significance

In National Health Interview Survey findings from 2007 to 2009, self-reported prevalence for chronic bronchitis (in the past 12 months) or emphysema (lifetime) was estimated at 5.1% (Akinbami and Liu 2011). Findings from the Behavioral Risk Factor Surveillance System indicate that 6.3% of adults in the United States reported having been given a diagnosis of COPD by a physician or other health professional (CDC 2012c). For adults aged 40 to 79 years, population projections based on spirometry data from physical examinations from the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2010 place the prevalence of mild and moderate obstructive pulmonary disease between 10.2% and 20.9% (Tilert et al. 2013). These findings suggest that prevalence estimates based on self-reported data may significantly underestimate actual COPD prevalence. Inpatient hospitalization rates in the United States for COPD of 33.4 (women) and 31.6 (men) per 10,000 population were observed in 2010 (Ford et al. 2013), with a national mortality rate for that year of 63.1 per 100,000 population. For all health endpoints related to COPD, however, imprecise and variable definitions make the quantification of prevalence, morbidity, and mortality difficult.

An estimate of the economic costs of COPD in the United States was placed at $36 billion—including $32.1 billion for direct medical costs and $3.9 billion for absenteeism (Ford et al. 2015). Primary payers of direct costs included Medicare (51%), Medicaid (25%), and private insurance (18%).

In addition to being a common primary diagnosis for hospitalization, COPD is a common comorbidity for inpatient hospitalizations. It was found to be present as a comorbid condition in 12% of hospital discharge records (Merrill and Elixhauser 2005).

Pathophysiology

Initial pathologic changes of COPD occur in the proximal and peripheral airways, lung parenchyma, and pulmonary vasculature (Hogg 2004). These pathologic changes consist of inflammatory responses and associated increases in goblet cell number and mucous gland size. This inflammation appears to be an amplification of normal inflammatory responses to toxic gases and particulates. This response is most commonly observed as ongoing exposure to tobacco smoke (Rabe et al. 2007).

Emphysema is best characterized by the destruction of the bronchioles, alveolar ducts, and alveoli that constitute gas exchange air spaces. The mechanism for this destruction is inflammatory in nature, most commonly resulting from ongoing exposure to tobacco smoke (Shapiro et al. 2000). The chief physiological result in emphysema is the obstruction of expiratory airflow and reduced gas transfer capacity. It is increasingly recognized that elastases play an important role in the pathophysiology of emphysema. Elastases are enzymes that digest and degrade elastin, an elastic substance that supports the structure of the lungs. It is theorized that exposure to toxic gases and particulates alters the balance between proteinase and antiproteinase activity in the lungs, resulting in the degradation of lung tissue that leads to the symptoms of emphysema (Shapiro et al. 2000).

In adults, the onset of COPD often begins with a moderate decline in lung function capacity before age 50 years. In many cases, COPD would be observable by spirometry, but medical attention may not be sought until symptoms such as dyspnea are observed. Among smokers, a characteristic cough may provide early evidence of the onset of COPD. In the typical case, the decline in lung function accelerates after the age of 50 years (Shapiro et al. 2000; GOLD 2016). As the disease progresses, the damage to the lung ultimately results in

inadequate oxygen delivery. Chronic obstructive pulmonary disease is a common comorbid condition among patients presenting with cardiovascular disease and a range of other systemic conditions.

Descriptive Epidemiology

High-Risk Populations

Although describing the epidemiological burden of COPD is complicated by variable diagnostic criteria and differences between self-reported data and results from physical examinations, certain groups are at greater risk for COPD than others. Smokers and ex-smokers constitute the most distinct high-risk group for COPD, and the prevalence of tobacco smoking is the best predictor of COPD prevalence across the globe (GOLD 2016). The prevalence of COPD also increases with age, especially after the age of 40 years (Halbert et al. 2006). This increase in risk with age is attributable to both increased cumulative tobacco smoke exposure among smokers and a generally observed decline in lung function with age across populations. While the U.S. death rate from COPD remained steady among women from 1999 to 2010, it decreased moderately for men over the same period (from 88 per 100,000 to 74 per 100,000; Ford et al. 2013). Although observed COPD prevalence by sex closely follows expectations based on patterns of tobacco smoking, decline in lung function consistent with COPD appears to be more strongly affected by smoking in women than in men (Connett et al. 2003). Improvements in lung function upon tobacco cessation also appear to be greater among women than among men.

A small number of patients with COPD have a deficiency of the protein alpha-1 antitrypsin. The genetic variation leading to this deficiency is seen most commonly in whites of Scandinavian descent, and is estimated to be present in some degree in roughly one of every 2,500 to 5,000 newborns in Western Europe (Fregonese and Stolk 2008). This protein acts to inhibit the destructive capabilities of the white blood cell elastase responsible for degradation of lung tissue, and deficiencies of alpha-1 antitrypsin have been associated with emphysema. Other high-risk groups may be defined based on low birthweight, respiratory infections in childhood, and occupational exposure to dusts (described later in this chapter). In addition, there is some evidence that physician-diagnosed asthma increases one's risk of developing the irreversible airway obstruction seen in COPD (Silva et al. 2004).

Geographic Distribution

By state, COPD mortality rates tend to be higher in some parts of the West and South, including Appalachia. Mortality data from 2010 showed the highest age-adjusted COPD mortality rates among adults aged 25 years and older in Oklahoma (102.6 per 100,000 population), West Virginia (95.1), Kentucky (90.7) and Wyoming (89.6), whereas the lowest rates were found in Hawaii (24.8 per 100,000), the District of Columbia (37.7), and Connecticut (43.6; Ford et al. 2013). Although comparison with state-specific smoking-attributable mortality rates explains COPD mortality rates for Appalachian states, it does not explain elevated rates in Western states (Weinhold 2000). Although theories regarding population migration, ambient air pollutants, and diagnostic differences have been postulated, this discrepancy has yet to be fully explained.

Time Trends

Unlike the period of 1990 to 1998, when COPD prevalence increased among women in the United States (Mannino et al. 2002), COPD prevalence was largely stable over the period 1999 to 2010 (Ford et al. 2013). Declines were seen over this period for COPD inpatient hospitalizations and Medicare hospital discharge claims overall, among men, and among enrollees aged 65 to 74 years (Ford et al. 2013).

Causes

Modifiable Risk Factors

The most commonly encountered risk factor for the development of COPD is cigarette smoking. This risk is dose-related, and factors such as age of starting to smoke, total pack-years smoked, and current smoking status are all predictive of COPD mortality (GOLD 2016). As has been increasingly found for other smoking-related health outcomes, exposure to secondhand smoke may also contribute to the risk of developing COPD (Eisner et al. 2005). Further study has indicated that exposure to secondhand smoke in childhood is associated with COPD and related respiratory symptoms in adulthood (Johannessen et al. 2012).

Occupational exposure to organic and inorganic dusts and fumes may contribute to the development of COPD (Trupin et al. 2003; Blanc et al. 2009).

In an analysis of data from the NHANES, occupations found to be associated with an increased risk of developing COPD included records processing and construction trades workers (Hnizdo et al. 2002). There is growing literature that indoor pollution from the burning of biomass in poorly ventilated dwellings can contribute to the development of COPD, especially in developing countries (Ezzati 2005; Orozco-Levi et al. 2006; Hu et al. 2010). Although outdoor air pollution can contribute to COPD exacerbations, its role in the development of COPD remains unclear.

Population-Attributable Risk

Cigarette smoking is by far the most commonly encountered risk factor for COPD, and estimates of the fraction of cases attributable to smoking range from 45% to 90% (Marsh et al. 2006). The American Thoracic Society concluded that the population-attributable fraction of COPD attributable to cigarette smoking is no more than 80% (Eisner et al. 2010). Estimates for the population-attributable fraction for secondhand smoke in the home and work environments have been derived to account for 9% and 7% of COPD cases, respectively (Eisner et al. 2005). Other factors for which quantifiable fractions of COPD may be derived include occupational exposures, exposure to biomass smoke, and exposure to traffic and outdoor air pollutants (Eisner et al. 2010).

Evidence-Based Interventions

Prevention

Because of the primacy of tobacco smoking as a risk factor for COPD, prevention of tobacco smoking is the single most important preventive activity to reduce the burden of COPD. Because the effect of tobacco smoking on COPD is dose-related, any reduction in smoking may bring about a reduction in related COPD morbidity. When a smoker quits, the age-related rate of decline in FEV1 can approach the rate of lung function decline in never smokers, but it does not return to the level of lung function seen in never smokers.

For individuals exposed to multiple risk factors, the effect of the collective set of risk factors appears to be additive. As such, identifying individuals with multiple risk factors, such as smoking and occupational exposures, may provide an important avenue for COPD prevention.

Screening

Because interventions aimed at reducing harmful exposures can be effective in slowing the progression of COPD, early detection of disease is beneficial for patients. The primary mode of screening for COPD is to measure airflow obstruction with spirometry or peak airflow measurement. Because there is a large population that may be in the early stages of COPD without being aware of it, increasing awareness of the relationship between symptoms such as chronic cough and excessive sputum production and COPD may increase the fraction of patients who are appropriately diagnosed with COPD. Broad population-based screening should be limited to individuals at high risk for developing COPD, such as cigarette smokers. Screening for genetic markers for alpha-1 antitrypsin deficiency is available and is recommended for individuals for whom a genetic predisposition to the deficiency is suspected as well as infants displaying unusual hepatic symptoms (de Serres and Blanco 2006; Fregonese and Stolk 2008).

Treatment

The most effective treatment for COPD is to avoid exposure to causative and exacerbatory agents, such as cigarette smoke, workplace dusts, and ambient air pollutants. Once COPD has been diagnosed, the objectives of disease management are to relieve symptoms, improve exercise tolerance and health status, and prevent and treat complications and exacerbations (GOLD 2016). A range of medications, such as inhaled bronchodilators and glucocorticosteroids, can help alleviate some of the symptoms of COPD. When the progression of disease results in decreased blood oxygen, supplemental oxygen therapy has been shown to increase survival (Shapiro et al. 2000). Pulmonary rehabilitation efforts such as exercise training and breathing retraining have been shown to decrease dyspnea, increase exercise tolerance, and improve patients' quality of life (GOLD 2016). Surgical approaches, such removal of emphysematous lung or lung transplantation, can be effective in increasing survival in selected circumstances. Pneumococcal and influenza vaccination are recommended for people diagnosed with COPD (GOLD 2016).

Examples of Evidence-Based Interventions

Effective tobacco prevention and control efforts (as discussed in Chapter 7) represent the most important avenue for interventions achieving a reduction in

the burden of COPD. Policies prohibiting tobacco smoking in workplaces such as taverns and restaurants are now commonplace in the United States and may decrease exposures that can precipitate COPD exacerbations.

Governmental agencies such as the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA) have established enforceable occupational exposure limits to reduce harmful workplace exposures that may contribute to COPD development. The Environmental Protection Agency (EPA) and various state and local agencies have adopted emissions limits for ambient air pollutants. Public health and environmental agencies routinely issue alerts when air pollutant levels exceed guidelines to advise individuals with COPD and other high-risk groups to avoid activities that may increase the risk of an exacerbation.

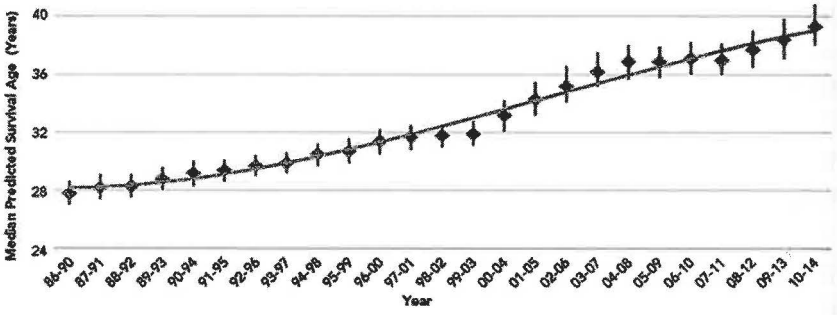
Areas of Future Research

Although the primary risk factors for COPD are well established, differences in regional COPD mortality rates that remain unexplained by tobacco smoking patterns may offer an opportunity to better understand the epidemiology of COPD. Additional studies of the cellular basis of COPD and identification of more sensitive and specific biochemical, genetic, and molecular markers of COPD may lead to better approaches for the diagnosis and control of COPD (Petty and Weinmann 1997; Thomashow et al. 2014). Additional epidemiologic studies assessing the interaction between cigarette smoking and exposures from environmental and occupational sources may aid in assessing the relative efficacy of various avenues for intervention. Longitudinal epidemiology studies may help identify and quantify risk factors that contribute to the development of COPD, either independently or in tandem with established COPD risk factors.

CYSTIC FIBROSIS

Significance

Cystic fibrosis is an inherited disease characterized by the production of abnormally thick and sticky mucus resulting in respiratory infections and pancreatic obstruction, and is a major source of severe chronic lung disease in children and an increasingly important cause of morbidity and mortality from chronic lung disease in young adults (Boucher et al. 2000). Although CF continues to result



Source: Reprinted with permission from CFF (2015).
Note: Cystic fibrosis patients under care at CF Foundation–accredited care centers in the United States, who consented to have their data entered.

Figure 17-5. Median Predicted Survival Age for Individuals with Cystic Fibrosis, 1986–2014 (Five-Year Intervals)

in premature death from its effects on the respiratory, gastrointestinal, and endocrine systems, major strides in screening and treatment in recent decades have improved patient outcomes and survival for patients with CF (Figure 17-5; Strausbaugh and Davis 2007; MacKenzie et al. 2014). There are an estimated 30,000 patients in the United States with CF, and the current median projected survival for patients born and diagnosed with CF in 2010 is estimated at 37 years for female and 40 years for male patients (MacKenzie et al. 2014).

Pathophysiology

The primary genetic defect associated with CF affects a transmembrane conductance regulator protein that acts as a chloride channel. This genetic defect has been localized to chromosome seven, and more than 1,500 specific mutations have been identified and recorded. Levels of the functional regulator protein are substantially reduced in patients with CF, affecting ion transport in sweat ducts, airways, pancreatic ducts, and elsewhere. The severity and level of organ involvement in CF is directly related to tissue levels of the protein. The primary manifestation of CF in the respiratory tract is abnormally thick and copious mucus in the airways that impairs microbial and mucociliary clearance. This often contributes to progressive cycles of respiratory infection and inflammation (Strausbaugh and Davis 2007; Flume and Van Devanter 2012). Impaired ion transport may result in depletion of periciliary liquid on airway surfaces,

resulting in impaired clearance by both cough and ciliary mechanisms (Boucher 2004). As more patients survive into adulthood, extrarespiratory effects such as CF-induced diabetes and fibrotic and cirrhotic liver disease are increasingly observed. Lung disease, however, remains the primary cause of morbidity and mortality from CF.

Descriptive Epidemiology

High-Risk Populations

Cystic fibrosis is among the most common lethal genetic defects affecting whites in the United States. Incidence varies greatly in the United States on the basis of ethnicity, with incidence at 1 in 3,200 births for whites, 1 in 15,000 births for African Americans, and 1 in 31,000 births for Asian Americans (Orenstein et al. 2000). It is inherited in an autosomal recessive fashion, and the estimates of the prevalence of the heterozygous form in individuals of Northern European descent ranges from 2% to 4% (Tsui and Buchwald 1991; Schulz et al. 2006). Individuals with the heterozygous form are not affected with CF.

A review of CF mortality records from 10 countries found that the median age of death was consistently highest in the United States. Although increases in life span were observed in all 10 countries over time, all 10 showed a shorter life span for women with CF than for men with CF (Fogarty et al. 2000).

Causes

Risk for developing CF is based on genetics. However, there are several classes of specific mutations within the target gene that can lead to the condition, and there are observed differences in disease severity associated with the different classes (Strausbaugh and Davis 2007). Among patients with CF, decrease in FEV1 and use of nutritional intervention have been established as markers for mortality risk (Kerem et al. 1992; Belkin et al. 2004).

Evidence-Based Interventions

Prevention

Aside from genetic counseling and education for prospective parents, the prevention of CF is a difficult proposition. Gene therapy approaches, whereby

copies of the normal *CFTR* gene could be incorporated and expressed in affected cells, remain a promising line of inquiry. The approach in this regard would be to place a copy of the gene for normal transmembrane conductance regulator protein in affected cells, resulting in production of the normal protein. Although clinical trials have shown some early success, many hurdles remain to the use of gene therapy approaches in routine treatment of CF (Griesenbach and Alton 2012).

Screening

Newborn screening for CF is now undertaken in all 50 states. The most common method used for screening is measurement of immunoreactive trypsinogen on dried blood spots, followed by direct gene analysis approach for confirmation. Among the reported benefits of early screening is the ability to begin nutritional interventions that may reduce the risk of growth failure and prolonged vitamin deficiency that can be associated with CF (Castellani 2003; Dunn et al. 2011).

SLEEP APNEA

Significance

Sleep apnea is a chronic condition characterized by recurrent episodes of partial or complete collapse of the upper airway during sleep (Punjabi 2008). It is one of the leading causes of excessive daytime sleepiness in adults, and contributes to the development of conditions such as hypertension and cardiovascular disease. Obstructive sleep apnea is the most common form of the condition. In obstructive sleep apnea, airflow is restricted because of occlusion at the oropharyngeal level, which leads to arousal and obstruction relief. The observed arousal does not always lead to complete awakening, but may interfere with sleep efficiency and contribute to daytime sleepiness.

Pathophysiology

Apnea is defined as a total cessation of airflow; hypopnea occurs when there is a decrease in airflow at the nose and mouth (Caples et al. 2005). A small number of apnea and hypopnea events occur in all people during sleep; the number of apneas and hypopneas considered abnormal depends on the population being tested and indications for testing. The frequency with which airflow reductions

occur is termed the apnea–hypopnea index. The index is used as a quantitative characterization of the severity of sleep apnea (Caples et al. 2005). An apnea–hypopnea index of five or more is indicative of mild sleep apnea, whereas an index value of 15 or more indicates sleep apnea of moderate severity.

Depending on the severity of the condition, sleepiness may be observed during passive activities such as reading or, in more severe cases, activities such as operating motor vehicles. Aside from daytime sleepiness, commonly observed symptoms of sleep apnea include snoring, poor memory, and impaired psychomotor function (Young et al. 2002).

Descriptive Epidemiology

High-Risk Populations

Estimates of the prevalence of obstructive sleep apnea can vary greatly depending on the methodology used. Because obtaining an assessment of an individual's apnea–hypopnea index requires an overnight visit to an appropriate sleep laboratory, data to support measurements of the prevalence of obstructive sleep apnea can be scarce. Available data from population-based studies place the prevalence of sleep apnea in the range of 5% to 7% for men and 2% to 5% for women (Punjabi 2008). However, because of the intensive nature of the assessment needed to diagnose sleep apnea, it is thought that the majority of cases of sleep apnea go undiagnosed (Young et al. 1997).

Obstructive sleep apnea has been implicated as a contributor to the development of a range of conditions, including hypertension, and cardiovascular and cerebrovascular diseases (Young et al. 2002). Specific outcomes such as acute myocardial infarction incidence and mortality (He et al. 1988; Hung et al. 1990) and stroke (Mooe et al. 2001) have been observed at increased levels among people with sleep apnea. Injury-related outcomes observed with increased frequency in people with sleep apnea include motor vehicle crashes and occupational injuries (Young et al. 2002). In one study, individuals with sleep apnea were found to be about 2.5 times more likely to have had an automobile accident than individuals without the syndrome (Karimi et al. 2015).

Causes

Factors contributing to the development of obstructive sleep apnea include age, excess body weight, smoking, alcohol consumption, nasal congestion, and

habitual snoring (Wetter et al. 1994; Young et al. 2002; Punjabi 2008). Other factors for which a causative role is suspected include certain craniofacial features and hypothyroidism.

Evidence-Based Interventions

Screening

Certain features of obstructive sleep apnea, such as its high prevalence and its low recognition as a public health problem, have generated interest in using screening approaches to address the condition. Applying screening approaches to certain occupational populations such as long-distance truck drivers and hazardous duty personnel may be warranted (Baumel et al. 1997). Concern about public safety led to the issuance of specific screening recommendations for sleep apnea in commercial motor vehicle operators (Hartenbaum et al. 2006). Validated screening tools such as the STOP-Bang questionnaire (Chung et al. 2008; Chung et al. 2013) have been developed for application in identifying surgical patients at risk for postoperative complications as a result of undiagnosed sleep apnea.

Examples of Evidence-Based Interventions

The use of continuous positive airway pressure (CPAP) via a nasal mask is a well established and effective means of therapy for obstructive sleep apnea (Caples et al. 2005). Certain oral appliances worn overnight may be useful in some cases. In some cases where the habitual use of CPAP does not improve the condition, surgical options to remove soft palate tissue may be considered.

Addressing known risk factors such as body weight has been shown to reduce apnea–hypopnea index in affected patients, and population-based weight reduction interventions may address diagnosed and undiagnosed cases of obstructive sleep apnea. Increased awareness of sleep apnea as a focus for attention in primary care settings and referral of individuals with suspected cases of sleep apnea to sleep specialists may help reduce the burden of this condition.

INTERSTITIAL LUNG DISEASE

Interstitial lung disease refers to diseases that manifest in the interstitium, which includes the spaces between the pulmonary capillary cells and the pulmonary alveoli, the connective tissue surrounding blood vessels and bronchi,

and the connective tissue of the pleura. Specific descriptors of this category of disease include pulmonary fibrosis, alveolitis, and pneumonitis. Although exposure to occupational dusts and fumes can be associated with this form of disease, most cases of interstitial lung disease cannot be attributed to occupational exposures (Coultas et al. 1994). Non-occupational contributors to this class of disease include medications, therapeutic radiation exposure, infections, and toxic gas inhalations (Raghu et al. 2004).

During the initial assessment of individuals with interstitial lung disease, it is important to look for connective tissue disease or malignancy, and to consider medication use, symptom duration, and the history of exposure to different organic and inorganic dusts. Progressive dyspnea is the most common presenting complaint. Pulmonary function testing, although it may show abnormalities with a restrictive defect with decreased FVC, is more helpful in following the course of the disease than in the initial diagnostic evaluation. The location and type of opacities on the chest radiograph can be helpful in diagnosing interstitial lung diseases (Coultas et al. 1994). A lung biopsy is sometimes required if the diagnosis remains in doubt or if the disease process is severe or rapidly progressive.

Descriptive Epidemiology

Aside from specific agents and processes described elsewhere in this chapter, literature on the epidemiology of interstitial lung diseases is scarce. Diagnosis of interstitial lung disease can often be a diagnosis of exclusion. In many cases, a diagnosis of idiopathic interstitial fibrosis may be applied in the absence of a thorough investigation of occult occupational exposures. In a population-based registry in an urban county, the prevalence of interstitial lung disease in adults aged older than 18 years was 80.9 per 100,000 population in men, and 67.2 per 100,000 population in women (Mannino et al. 1996). Occupational and environmental causes were the most frequent in men (20.8 per 100,000) with idiopathic pulmonary fibrosis as the second-most-likely diagnosis (20.2 per 100,000). In women, pulmonary fibrosis was the most common diagnosis (14.3 per 100,000 individuals) with idiopathic pulmonary fibrosis second (13.2 per 100,000 individuals; Mannino et al. 1996). In a retrospective cohort study of idiopathic pulmonary fibrosis using health plan records from 1996 to 2000, national U.S. prevalence and incidence rates were estimated at 14.0 and 6.8 per 100,000, respectively (Raghu et al. 2006).

Causes

Risk factors for developing many of the interstitial lung diseases remain poorly understood. An autopsy study on the risk factors for idiopathic pulmonary fibrosis found that laundry workers, barbers, beauticians, painters, production metalworkers, and production woodworkers were at greater risk for developing the disease (Scott et al. 1990). Other studies on environmental factors and idiopathic pulmonary fibrosis have found increased odds ratios for exposure to wood dust, textile dust, metal dust, agricultural dust, and damp, moldy environments (Hubbard et al. 1996; Mapel et al. 1996; Baumgartner et al. 1997; Taskar and Coultas 2008). Smoking has been found to be a risk factor for idiopathic pulmonary fibrosis in several studies (Scott et al. 1990; Hubbard et al. 1996; Baumgartner et al. 1997). In a case–control study, a history of having ever smoked increased the risk for idiopathic pulmonary fibrosis by 60% (Hubbard et al. 1996).

Occupational exposure to artificial food flavorings such as butter flavoring (diacetyl) applied to many different food products such as microwave popcorn has been associated with bronchiolitis obliterans (CDC 2007). Exposure to diacetyl and other diketones has been observed from the commercial grinding and roasting of unflavored coffee beans (Gaffney et al. 2015). These findings highlight the need for vigilance as the use of synthetic chemicals use evolves to new settings and the need to establish and maintain surveillance for illness associated with emerging industries and product use.

Evidence-Based Interventions

For interstitial lung diseases that develop from inhaling organic or inorganic dusts or fumes, limiting or avoiding the exposure will minimize or prevent the disease. Because of the important therapeutic benefits of medications and radiation therapy, addressing these exposures as risk factors for interstitial lung disease is difficult. For many of the interstitial diseases, treatment is primarily supportive, treating the complications of respiratory and right heart failure. Preventive care should include influenza and pneumococcal vaccines. Public health surveillance and clinician reporting of unusual diseases associated with occupational exposures is critical to early identification of emerging problems when intervention has the greatest potential for interrupting the emergence of disease.

OCCUPATIONAL LUNG DISEASES

This section covers coal workers' pneumoconiosis, silicosis, asbestosis, byssinosis, occupational asthma, and organic dust–related lung disease.

Significance

It is estimated that, in 1999, 14 occupational illnesses generated $14.5 billion of health expenditures, including $2.2 billion attributed to COPD and $1.5 billion to asthma (Leigh et al. 2003). One of the most common occupational lung diseases, occupational chronic bronchitis (see COPD earlier in the chapter), along with the symptom of cough, is the least specific response to occupational exposures and is often the first indication of work-related pulmonary pathology. Given a sufficient dose and duration of exposure, nearly all respirable agents can contribute to the development or aggravation of chronic lung diseases. It is not uncommon to have multiple occupational lung diseases present in the same workforce or even the same person. This is especially true for occupational bronchitis and occupational asthma.

Many chronic occupational lung diseases are defined by the agent associated with the specific disease and often named after the agent (i.e., silica inhalation causes silicosis, asbestos fiber inhalation causes asbestosis). Several distinct pathological processes have been associated with exposure to specific respirable dusts present in the occupational environment. Only a few of these diseases result from acute exposures. Most, especially pneumoconiosis, result from multiple years of exposure and are associated with an important hallmark of the disease process known as the "disease latency period." This means that disease does not appear immediately, and typically at least 10, and commonly 20 or more, years pass between first exposure and the recognition of clinical disease. Some of these diseases may first appear and even progress many years after exposure has ended.

Occupational dusts are classified as either inorganic (e.g., coal dust, silica, asbestos) or organic (e.g., cotton dust, grain dust, mold spores). The respiratory conditions associated with most inorganic dusts are called pneumoconioses and result from the direct effect of the dust on lung tissue. Chest x-ray is the primary diagnostic tool used to identify these diseases. Guidelines on how to classify chest radiographs for persons with pneumoconioses have been published by the World Health Organization ILO since 1950. These guidelines

describe and codify the radiographic abnormalities of the pneumoconioses in a simple, reproducible manner by using two sets of standard comparison films. The guidelines were issued in 1971 and 1980, revised in 2000, and published in 2002 (ILO 2002). In 2011, the ILO revised the guidelines to extend the classification to use with digital radiographic images (ILO 2011).

From 1968 to 2010, a total of 145,750 deaths from pneumoconiosis were recorded among U.S. residents (NIOSH 2016a). The U.S. OSHA has established national permissible exposure limits for all inorganic dusts associated with disease. Diseases resulting from exposure to most organic dusts are immunologically mediated. One exception to this latter classification is the condition related to cotton dust exposure; cotton dust is organic, but the condition is probably not immunologically mediated and is related to endotoxins present in the cotton dust.

Cigarette smoking increases the risk of lung disease in occupationally exposed workers. In most cases, the disease risks are additive—that is, the total disease risk is the sum of the risk from cigarette smoking and the risk from the occupational exposure. An exception to this is the multiplicative risk between asbestos exposure and cigarette smoking in the occurrence of lung cancer (discussed in Chapter 2).

The following sections briefly describe some important occupation-related chronic lung diseases.

COAL WORKERS' PNEUMOCONIOSIS

Coal workers' pneumoconiosis (CWP), first described in 1831 in a British coal miner, is known as black lung disease and is identified by a pattern of x-ray abnormalities and an exposure history. Through greater mechanization, coal production has increased while the workforce has declined. However, greater mechanization has led to dustier conditions. In 2013, there were approximately 123,000 coal mining sector employees in the United States.

Between 1968 and 2010, 73,849 U.S. deaths occurred with coal workers' pneumoconiosis noted on the death certificates. Deaths have significantly declined from a high of 2,870 in 1972 to 486 in 2010. For the decade from 1990 to 1999, more than three fourths of all CWP decedents were residents of Pennsylvania, West Virginia, Virginia, and Kentucky. Pennsylvania alone accounted for about half of all CWP deaths in this period (NIOSH 2016a). Mining machine operators had the highest proportionate mortality ratio among occupations (NIOSH 2016a). Although CWP has declined in the United States, the threat of CWP has significantly increased in

developing countries seeking inexpensive sources of energy and where dust control measures are often rudimentary and regulatory frameworks ineffective. Since the enactment of the U.S. Black Lung Compensation Program in 1969, through 2004, approximately $41 billion has been paid for CWP benefits. In 2012, 52,296 beneficiaries received $376,497,000 in benefits (NIOSH 2016b).

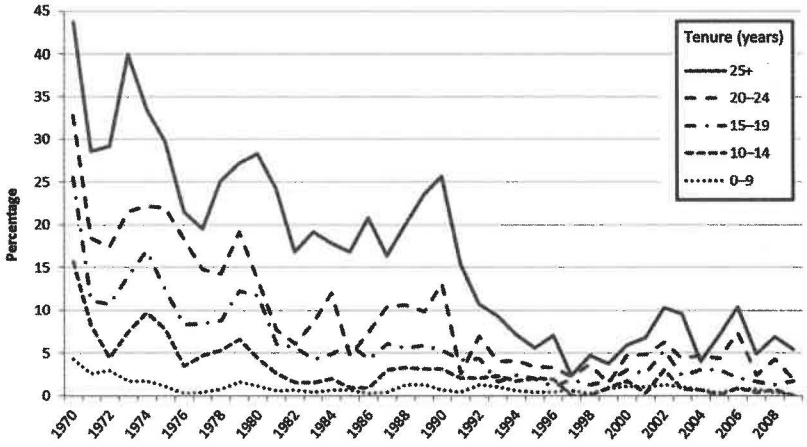
Descriptive Epidemiology

The prevalence of CWP increases with increasing exposure to coal dust. In studies of CWP, years of mining are often used as a surrogate for dust exposure because information on dust exposure for individual miners is rarely complete.

Coal workers' pneumoconiosis is classified as simple CWP if rounded opacities less than one centimeter are seen on the chest radiograph (ILO opacities "p," "q," or "r"; ILO 2002). It is typical for the opacities to first appear in the upper lung fields of the chest x-ray and then to progress to involve all lung fields. The National Study of Coal Workers' Pneumoconiosis is maintained by NIOSH. Data from that ongoing surveillance program shows that, among U.S. underground coal miners with 25 or more years of mining surveyed between 1973 and 1978, 34% had simple CWP. The prevalence of simple CWP declined to 4% during survey years 1996 to 1999 (NIOSH 2004). It is uncommon in simple CWP for the radiographic abnormalities to progress after the individual has left the dusty environment.

Complicated CWP, often described as massive progressive fibrosis, is often preceded by recurrent infection, especially tuberculosis. Radiographically, it is defined as small opacities and the presence of large opacities (greater than one centimeter) on the chest x-ray. Data from the national study suggest that the incidence of both simple and complicated CWP is declining, largely attributed to dust standards in mines being enforced, but may be increasing among younger individuals. In addition, although CWP prevalence in working coal miners declined substantially from 1970 to 1994, it increased from 1995 to 2006 (Figure 17-6; Attfield et al. 2009; NIOSH 2016b).

Chronic exposure to coal dust can lead to the development of COPD, even in the absence of radiographic changes (Oxman et al. 1993). Coal miners with COPD have increased rates of dyspnea, cough, and phlegm production. The magnitude of the deficit in lung function attributable to chronic coal dust exposure is between 150 and 450 milliliters over an average lifetime of work in a coal mine, with a smaller percentage of individuals having deficits of greater than one liter (Lewis et al. 1996).



Source: Reprinted from NIOSH (2016b).

Figure 17-6. Percentage of Examined Underground Miners with Coal Workers' Pneumoconiosis (International Labour Office [ILO] Category 1/0+) by Tenure in Mining, 1970–2009

Causes

Coal workers' pneumoconiosis is related to the total dust burden in the lungs. The type of coal (known as coal rank, which is determined by the carbon content of the coal) is also important; the higher the rank, the greater the disease risk and dust biologic activity. Anthracite coal has the highest rank, followed by bituminous, subbituminous, and lignite. Coal workers' pneumoconiosis is caused by respirable coal mine dust (generally defined as dust particles less than five microns in aerodynamic diameter). Usually, 10 or more years of exposure to coal dust must have elapsed before CWP can be diagnosed by a chest x-ray. Coal dust also may contain other harmful mineral dusts, such as silica dust, which increase the risk of other chronic lung diseases such as silicosis. The radiographic appearance of silicosis can be indistinguishable from CWP. The risk of CWP diagnosed by x-ray increases with the higher rank of coal, in part explaining the higher occurrence in miners from the eastern coal-producing regions of the United States compared to western areas. Miners who work underground, where dust control is problematic, are at higher risk than aboveground or surface miners.

Risk factors for the development of COPD in coal miners are the duration and extent of dust exposure, previous dust exposure, and the presence of

other risk factors for obstructive lung disease, especially cigarette smoking. The average lifetime coal dust exposure among coal miners with symptoms of chronic lung disease was found to result in a loss in lung function equivalent to that associated with smoking 20 cigarettes per day over a lifetime (Lewis et al. 1996). Coal miners working in jobs with higher silica exposure, such as surface coal mine drillers, are at higher risk for the development of COPD.

Evidence-Based Interventions

Coal workers' pneumoconiosis can best be prevented by reducing coal dust exposure in mines and the workplace, comprehensive industrial hygiene monitoring to measure dust suppression, educating workers about disease risk and safe work practices, and, when excessive exposure circumstances are unavoidable, providing respiratory protection. Medical monitoring of coal miners is required, and periodic chest radiographs are intended to identify individuals who have CWP in its preliminary phases, thus enabling them to avoid further exposure and possibly preventing the disease's progression to more advanced stages. The use of the ILO pneumoconiosis grading system is critically important to allow quantification of changes over time and assessment of progression.

The Federal Coal Mine Health and Safety Act passed in 1969 and its amendments set limits on the amount of worksite respirable coal dust in the United States. For coal dust with less than 5% silica, the standard is 2 milligrams per cubic meter of air (mg/m^3). Although there is evidence that the current dust standards have contributed to the decrease in the occurrence of CWP, the MSHA monitoring data from the 1980s through 1999 show little change in the level of coal dust exposure exceedances. More than 8% of the 794,000 samples exceeded the permissible exposure limit. In 1995, NIOSH adopted a recommended exposure level of 1 mg/m^3, which was adopted because of concerns that the current standard did not protect against other lung conditions. Between 1995 and 2003, one fourth of coal mine dust exposures recorded by MSHA exceeded the recommended exposure level (NIOSH 2016b).

SILICOSIS

Silicons comprise almost 28% of the earth's crust. It is the crystalline forms that are most toxic. It exists as five polymorphs, the most common being quartz. Silica has many industrial applications. Occupational exposures occur

worldwide, and although the disease is decreasing in the developed countries, it is increasing in developing countries. In the United States, excessive exposures continue and are most frequently found in small operations that are seldom visited by regulatory agencies. Chronic inhalation of respirable particles of crystalline silica is the cause of silicosis. Like CWP, silicosis is characterized by a predominance of small, rounded x-ray abnormalities predominantly in the upper lung fields indicative of fibrosis. The histopathologic hallmark is the formation of silicotic nodules containing birefringent particles. Also like CWP, silicosis can be divided into simple silicosis and complicated silicosis, or progressive massive fibrosis, based on the size of the opacities on the chest x-ray.

Unlike CWP, silicosis is also characterized as acute, accelerated, or chronic. Fortunately, acute silicosis is uncommon today and occurs after high levels of exposure as can occur in silica flour mills or in the now-outlawed use of silica for sandblasting. It is defined as silicosis that appears in less than five years from first exposure. The acute form is often life-threatening and characterized by pulmonary edema, accumulation of proteinaceous fluid within alveoli, and interstitial inflammation. The most common form of the disease is chronic silicosis, which is defined as silicosis that appears 10 or more years after first exposure.

In its initial phases, the disease is not associated with declines in lung function, although cough and phlegm production are common. Chronic exposure to silica dust can also result in COPD, even without the x-ray manifestations of silicosis (Hnizdo and Vallyathan 2003). The disease may slowly progress over 20 to 40 years to the point of respiratory failure. Individuals with silicosis are at increased risk of developing tuberculosis (Snider 1978). On the basis of analyses of nine studies showing increased rates of lung cancer, silica is now categorized as a probable human carcinogen by the International Agency for Cancer Research (Smith et al. 1995; IARC 1997; IARC 19972012). Although deaths in the United States attributed to silicosis have decreased from more than 1,000 per year before 1971 to less than 200 in the late 1990s (NIOSH 2016a), an estimated 2,000 cases of silicosis are diagnosed each year in the United States (Weeks et al. 1991).

Descriptive Epidemiology

Hazardous exposure to respirable silica occurs in many different occupational settings including surface and underground mining of ores containing silica,

surface drilling, ceramics manufacturing, stone cutting, construction, silica flour mills, foundries, cement production, abrasive manufacturing and use, and sandblasting. In 2013, when OSHA proposed a revised silica standard, they estimated that approximately 2.2 million workers were currently exposed to respirable crystalline silica including 1.85 million workers in the construction industry and 320,000 workers in general industry and maritime workplaces (OSHA 2016), As with CWP deaths, silicosis listed as a cause of death on a death certificate has declined from more than 1,000 annual deaths in the 1960s to less than 200 per year in the 1990s and to 101 in 2010 (NIOSH 2016a). Pennsylvania alone accounted for nearly 18% of all reported silicosis deaths from 1990 to 1999. Construction and mining industries accounted for more than one third of deaths from silicosis during that same period. Short-stay, nonfederal hospital-reported discharges listing silicosis decreased from approximately 6,000 per year in 1970 to 1,000 in 2000 (NIOSH 2016b).

The prevalence of nonfatal silicosis in the United States is unknown. There are no national registries for the disease, and only a few states have surveillance requirements. By extrapolating from national mortality data, the Michigan state-based surveillance system and capture–recapture methodology estimated that from 1987 through 1996, 3,600 to 7,300 cases of silicosis occurred annually (Rosenman et al. 2003). The U.S. Department of Labor estimated in 1980 that 59,000 of the workers who were then exposed to silica would eventually develop silicosis (Bates et al. 1992).

Silicosis is most prevalent among workers involved in the dry drilling or grinding of rock with high silica content and other activities that generate large quantities of respirable particles. Largely reflecting the exposed workforce, silicosis is nine times more common in men than in women and more common among African American than white males. The most common industrial environments where silicosis occurs among men are mines, foundries, quarries, and silica flour mills (NIOSH 2016b). Among women, silicosis occurs most commonly in the ceramics industry.

Causes

Silicosis is caused by acute or chronic inhalation of crystalline silica, which is present in quartz. A more toxic form of silica may be produced when quartz is heated or with freshly fractured quartz particles (Vallyathan et al. 1995). Foundry workers who are in occupations involving both heating and grinding

quartz may be at greater risk of silicosis. A disturbing trend has been the continuing occurrence of silicosis deaths in young adults (aged 15–44 years) and reports of new occupations and tasks that place workers at risk for silicosis, such as fabricators and installers of quartz-containing engineered stone products and most recently workers employed to extract natural gas by hydraulic fracturing exposed to the silica used in that process (Mazurek et al. 2015).

Evidence-Based Interventions

The most effective method for preventing silicosis is primary prevention—eliminating exposure to respirable silica—and, in settings where silica dust occurs, verifying exposure reduction and maintenance through an industrial hygiene monitoring program. A secondary line of defense is worker education and training, use of protective equipment, and regulatory inspections and enforcement of existing work site standards. The OSHA regulatory exposure limits for silica concentrations in the work environment were 0.1 mg/m^3 from 1989 to 1993. In 1993, this limit was modified (and effectively raised) based on a formula with a default limit of 5 mg/m^3 that is reduced as the silica content in a dust sample increases. NIOSH and American Conference of Governmental Industrial Hygienists (ACGIH) recommended an exposure limit of 0.05 mg/m^3. Under development by OSHA since 2013, a revised silica standard became effective on June 23, 2016, reduces the permissible exposure limit for respirable crystalline silica to 50 micrograms per cubic meter of air, averaged over an eight-hour shift. It is estimated to prevent nearly 900 cases of silicosis each year and 600 deaths per year (OSHA 2016). As with medical screening for conditions associated with other inorganic dusts, x-ray screening may identify individuals who have minimal disease, enabling these people to avoid additional exposure and possibly preventing progression to more advanced phases.

ASBESTOSIS

There are four main types of commercially used asbestos fiber—chrysotile (serpentine mineral), and the amphibole minerals amosite, crocidolite, and anthophyllite. Another fibrous amphibole, tremolite, is a frequent contaminant of chrysotile ores as well as vermiculite. An estimated 27,500,000 workers were exposed to asbestos between 1940 and 1979 (American Thoracic Society 2004a). Asbestos was widely used in construction materials, especially those

used for insulation and acoustical products in many public, residential, and commercial buildings.

Most uses of asbestos have been eliminated and many countries, but not the United States, have banned all use of asbestos (Collegium Ramazzini 2011). Although its use in Europe, United States, and many other countries has significantly decreased, the mining production of asbestos has been growing. Raw fiber continues to be used in less-developed countries (LaDou 2004). Current concerns in the United States focus on the potential for exposure to widely distributed, in-place asbestos-containing materials. The risk of adverse health effects from these sources of asbestos to workers or to building occupants depends on many factors, most specifically the status of the material—whether it is releasing asbestos fibers into the indoor environment, whether it is frequently disturbed, and how well contained fiber releases are from maintenance activities.

Adverse health effects from exposure to asbestos include pleural effusions, pleural thickening, and plaques with and without calcification, malignant mesothelioma, lung cancer, and asbestosis. Of these, asbestosis is the most prevalent chronic lung condition. Approximately 107,000 asbestos-related deaths (from cancer or other diseases) occur worldwide each year (Collegium Ramazzini 2016). For each year since 1998, asbestosis deaths outnumbered CWP deaths, displacing CWP as the most frequent type of pneumoconiosis death.

In its early stages, asbestosis is often clinically characterized by dry rales, or whistling or crackling noises, at the end of each inspiration. Often, clinical signs and pulmonary function abnormalities appear before chest x-ray abnormalities become apparent. Eventually, diffuse fibrosis can result in decreased lung capacity, decreased gas exchange, and severe shortness of breath. The x-ray abnormalities evident in people with asbestosis are predominantly small, irregular opacities in the lower lung fields (ILO "s," "t," and "u"). In addition, pleural thickening or pleural plaques, often with calcification, can occur alone or in combination with asbestosis. Unlike CWP or silicosis, asbestosis deaths were increasing, from fewer than 100 in 1968 to more than 1,250 in 1999, but between 2000 and 2010, U.S. death numbers leveled out at around 1,400 deaths per year (NIOSH 2016a).

Descriptive Epidemiology

In various surveys, between 6% and 40% of asbestos textile or insulation workers have detectable x-ray lung abnormalities. Results from the NHANES

indicate that 2.3% of U.S. men and 0.2% of U.S. women have pleural thickening upon chest x-ray (Rogan et al. 1987). In a study of 17,800 insulation workers in the United States, asbestosis was identified as the cause of death in 7% of the workers who died (Selikoff et al. 1979; Markowitz et al. 2013).

Asbestos had thousands of uses, each of which presented the possibility of exposure. Occupations and workers at risk span the life cycle of asbestos from removal from the ground to product manufacturing to installation of products to maintenance and removal, and finally disposal. Although most uses of asbestos in newly manufactured products in the United States have been eliminated, today's exposure threats come from the long life of asbestos-containing products still present in building materials, which may pose a risk to workers during maintenance, repair, renovation, and demolition. A long latency period usually exists between exposure and the development of asbestosis resulting in current cases seen today being a result of the legacy of exposures in the 1940s to 1970s (Selikoff and Lee 1978).

Causes

Asbestosis is caused by exposure to airborne asbestos fibers. The magnitude of the risk of asbestosis depends on both the duration and the intensity of the exposure to asbestos dust. The more intense and prolonged the exposure, the greater the risk of developing the disease. Brief, but very heavy exposure can also cause the disease.

Asbestos is unique among the pneumoconiosis-causing agents. Nonoccupational exposure to family members of workers bringing dust home on their clothes and those living in residences near mines and manufacturing facilities using asbestos have been associated with the occurrence of asbestos-associated disease (Anderson et al. 1976; NIOSH 1995). Most recently, an environmental disaster was identified in Libby, Montana, where a large vermiculite mine and processing facility had been operating since the mid-1920s. The facility closed in 1990 and the community health impacts of the vermiculite asbestiform amphibole present in concentrations as high as 26% have been investigated. Six hundred and ninety-four decedents were identified as having at least one asbestos-related cause of death and residing within the study area boundary. Workers, family members of workers, and community residents had significant excesses of asbestos-associated disease (Naik et al. 2016).

Evidence-Based Interventions

Asbestosis can be prevented by eliminating exposure to asbestos. New asbestos-containing product manufacturing has been largely eliminated from the work environment in the United States and the European Union countries, but its release from existing materials must be controlled. Containment of asbestos in buildings may be initially less expensive than removal; however, containment is only a temporary solution, because product aging and deterioration will continue and ongoing maintenance and repair can result in a further release of asbestos and eventual enforced removal under U.S. EPA regulations. National legislation requires accreditation of contractors who work with asbestos and training for asbestos abatement workers to ensure safety as well as to prevent "bystander" exposure. Safe work practices include identifying materials that contain asbestos; implementing rigorous operating procedures, such as wetting asbestos-containing materials; and wearing a self-contained breathing apparatus.

X-ray and pulmonary function screening may also help in protecting workers. Results from these examinations can encourage the workers to avoid additional exposure, make them more aware of the need for strict work practices, and encourage them to participate in special health surveillance programs.

BYSSINOSIS

Byssinosis is both an acute and chronic airways disease caused by exposure to cotton dust. The acute phase of byssinosis is sometimes called "Monday morning syndrome," in which chest tightness or shortness of breath occurs when workers return to cotton dust exposure following a weekend or days off. Symptoms usually resolve the second day. Progression of the disease is characterized by chronic cough and a decline in lung function. After more than 10 years of exposure, overall pulmonary function is often seen to decline. Byssinosis is similar in pathology to chronic bronchitis. A grading system has been developed for byssinosis (Bouhuys et al. 1977). In the United States, approximately 500,000 workers are potentially at risk for byssinosis (Glindmeyer et al. 1991; Lai and Christiani 2013), although the disease is rarely fatal, claiming fewer than 10 lives per year between 1995 and 2005 (NIOSH 2016a).

Descriptive Epidemiology

It is estimated that more than 60 million people worldwide work in the textile or clothing industry and are at risk for developing byssinosis. The prevalence of byssinosis varies from a few percent to as high as 47% in some surveys (Zuskin et al. 1991). In 1970, it was estimated that approximately 35,000 workers in the cotton textile mills had byssinosis (Glindmeyer et al. 1991). Since regulation of cotton dust began in 1978, the degree of lung function impairment in cotton textile workers may have decreased (Glindmeyer et al. 1991). There is no evidence of sex or race differences in risk of developing byssinosis.

Causes

Byssinosis results from exposure to the dust of cotton, flax, or hemp. Much has been learned about the causal agent of byssinosis, but the precise etiology is still being investigated. Evidence supports that it is not the cotton itself that is the causal agent but a bacterial endotoxin present in cotton dust (Rylander 2002; Shi et al. 2010). Among cotton workers, the risk is highest among workers involved in the initial stages of processing: opening, picking, carding, stripping, and grinding raw cotton.

Evidence-Based Interventions

The best way to prevent byssinosis is to avoid exposure to cotton dust. Cotton dust concentrations in the workplace must be kept below OSHA's permissible exposure level. A technique known as "cotton washing" is effective but may not be feasible on a large scale. Employers must treat the acute phase of byssinosis as a sentinel health event, using it as an opportunity to reduce exposure among other workers with early symptoms.

OCCUPATIONAL ASTHMA

Although the incidence of occupational respiratory diseases already discussed in this chapter is decreasing, occupational asthma is increasing and is rapidly becoming the most common occupational lung disorder in the developed countries (ATS 2004b). Work-related asthma includes occupational asthma and asthma aggravated by work or the work environment, and is characterized by episodes of bronchoconstriction, airway inflammation, and

airway hyperresponsiveness to agents or conditions present in the work environment (Tarlo 2016). Primary occupational asthma is distinguished from exacerbations of existing asthma by the presence of a workplace sensitizing agent or acute exposure event and diagnosis by a specific case definition (Beach et al. 2007). The overall prevalence of occupational asthma varies from region to region with estimates for the United States ranging between 10% and 23% of all adults with asthma (ATS 2004b). In the United States, it was estimated that 15% of all asthma cases in the 1978 Social Security Disability Survey were occupationally related (Smith et al. 1989). Between 50% and 90% of individuals with occupational asthma will continue to have symptoms even after being removed from the source of the exposure (Blanc 1987).

In diagnosing occupational asthma, it is important to establish the presence of airflow obstruction (Tarlo et al. 2008). If the preliminary spirometry is normal, a repeat test, following inhalation challenge with methacholine or histamine, may be indicated. It may be difficult to establish that asthma is caused by an occupational exposure. The fact that initial symptoms may occur only at home or after work can be misleading (Blanc 1987). To document a change in airflow obstruction related to work, it may be helpful to measure the peak expiratory flow rate several times a day for two to three weeks. Skin testing with the suspected compound may also be of diagnostic value in selected cases. Specific inhalation challenge with the suspected compound is not routinely performed because it is expensive, time-consuming, not widely available, and carries the risk of a potentially serious reaction (Alberts and Brooks 1992; Tarlo et al. 2008).

Reactive airways dysfunction syndrome occurs hours after a single exposure to high levels of irritant gases and results in cough, wheezing, and shortness of breath (Tarlo et al. 2008). Reactive airways dysfunction syndrome is not usually considered a form of occupational asthma because there is no latency period between the exposure and the development of symptoms. In occupational asthma, symptoms usually do not appear until a few weeks to as long as several years after the first exposure (Alberts and Brooks 1992). Byssinosis is another condition that may be confused with occupational asthma.

Descriptive Epidemiology

Several mechanisms have been identified that are associated with the development of work-related asthma; they include the following: sensitization; reactive airways dysfunction syndrome (associated with a single, high exposure to

irritant agents with onset of symptoms within hours); nonimmunologic airway irritation of preexisting asthma; and poor indoor environments with biologic contaminants (ATS 2004b; Tarlo et al. 2008). Agents are classified as high-molecular-weight compounds or low-molecular-weight compounds (Chan-Yeung and Malo 1999).

The high-molecular-weight compounds are proteins, polysaccharides, and peptides, which induce an allergic response by stimulating the production of specific IgE and sometimes IgG antibodies. Depending on the level of exposure, the prevalence of asthma from these compounds can be high. Asthma has been reported in 3% to 30% of animal handlers; 10% to 45% of workers exposed to biologic enzymes that are used, for example, in laundry detergents and other cleaning agents; 20% of bakers; and in 70% of flight crews dispersing sterile irradiated screwworm flies (Blanc 1987).

Examples of the low-molecular-weight compounds are isocyanates, wood dusts, metals, and drugs (Chan-Yeung 1990). An allergic response involving IgE occurs less frequently in the development of asthma from the low-molecular-weight compounds than from the high-molecular-weight compounds. Work-related asthma has been reported in 4% of workers exposed to the dust of western red cedar (Chan-Yeung et al. 1982), in 5% to 10% of workers exposed to toluene diisocyanate, in 29% to 40% of workers using epoxy resins, and in 70% of workers exposed to platinum salts in such processes as metallurgy and photography (Mapp et al. 2005).

Causes

Several groups have developed and applied criteria to characterize chemicals as asthmagens (AOEC 2008; Crewe et al. 2016). The AOEC list was updated in 2015 and designated 327 substances as asthma agents. Among these 173 (52.9%) were coded as sensitizers, and 113 (34.6%) proposed as sensitizers but not yet reviewed (Rosenman and Beckett 2015).

Materials having known or suspected allergic properties account for the majority of cases of occupational asthma. The risk of developing occupational asthma is usually related to the magnitude of exposure for many agents including western red cedar, toluene diisocyanate, baking products, and colophony fumes from soldering (Blanc 1987). Atopy, or allergy, is an important risk factor for developing asthma from the high-molecular-weight compounds but not for the low-molecular-weight compounds (Beach et al. 2007).

The risk for persistent symptoms in workers diagnosed with occupational asthma was examined in 125 western red cedar workers (Chan-Yeung et al. 1982). All workers who remained at work continued to have symptoms. Among workers who left the work, those who were older, had a longer duration of exposure, and had a longer duration of symptoms were at higher risk for having persistent symptoms. Workers who develop toluene diisocyanate–related asthma and continue to be exposed to the compound have been found to have continued deterioration in pulmonary function.

Evidence-Based Interventions

The only way to prevent occupational asthma is to avoid work and work sites where exposure to certain levels of agents occurs. Thus, it is important for facility managers to know what agents in their plant have been associated with asthma and to inform their workers and establish work practices that maintain exposures below known sensitization levels (Spagnolo et al. 2015). Material safety data sheets need to include information on components that may cause or exacerbate asthma. Workers need to be educated and trained on proper handling of materials and avoiding spills. Improved ventilation and the use of respirators when exposures are likely can decrease the risk of disease.

When sensitization occurs, often the only remedy for the affected worker is a transfer from the area of exposure. In cases where transfer is not possible, it is debatable whether the worker should be allowed to continue working with the suspected compound, even when protective measures are instituted (ATS 2004b; Tarlo et al. 2008). Deaths have been recorded when sensitized individuals have been re-exposed at the workplace. Desensitization before exposure has not been shown to be effective (Weeks et al. 1991).

ORGANIC DUST–RELATED LUNG DISEASE

A variety of chronic lung conditions can develop following short-term or long-term exposure to organic dusts (hypersensitivity pneumonitis) or toxic gases such as nitrogen oxides produced from the storage or decay of organic material (silo fillers disease). Although agricultural workers are most frequently impacted (Bang et al. 2006), as with occupational asthma, there are more than 200 agents known to cause hypersensitivity pneumonitis and among them industrial chemicals such as metal-working fluids (Kreiss and Cox-Ganser 1997).

In 2003, OSHA estimated that, in 1996, 92,000 grain elevator and 68,000 grain mill employees working in approximately 5,200 grain elevator firms and 1,500 grain mill firms were impacted by the OSHA (2003) grain dust standard. Grain dust is a mixture of different grains, bacteria and fungus, mites, inorganic material, and herbicides and pesticides. Grain-handlers' disease, caused by inhaling grain dust, is characterized by a drop in lung function over a work shift and by changes that persist over a harvest season (James et al. 1986). Chronic grain dust exposure can result in chronic cough, phlegm, wheezing, and dyspnea, and a permanent decline in lung function. Pulmonary fibrosis may occur but is uncommon in workers with chronic grain dust exposure (James et al. 1986).

Farmer's lung is caused by inhaling spores from moldy hay and is characterized by repeated attacks of fever, chills, malaise, coughing, and breathlessness (do Pico 1992). The condition is a type of hypersensitivity pneumonitis or extrinsic allergic alveolitis that results from inhaling many different organic dusts. Most commonly, thermophilic *Actinomyces* or other fungi are present. Testing patient serum for specific precipitating antibodies can help identify which organisms or agents may be contributing to the disease. In a well-controlled research setting, inhalation chamber challenges have been used to identify offending agents. Such testing is not a routine practice. The chronic form occurs in fewer than 5% of patients who develop the acute form of the disease (Speizer 1981). Lung function is abnormal in patients with the chronic form of the disease, with a decline in the FVC and a diffuse fibrosis on the chest x-ray.

Descriptive Epidemiology

Hypersensitivity pneumonitis is a rare disease with an increasing incidence and little is known about the distribution of the disease outside the agricultural sector (Bang et al. 2006; Spagnolo et al. 2015). Some of the increase may be attributable to changes in agricultural practices and the movement to large-scale production of livestock in confined feeding operations (Van Essen and Auvermann 2005). Symptoms are often similar to asthma, COPD, and bronchitis, and initial acute attacks are often mistaken for pneumonia. No single clinical or laboratory test exists to establish the diagnosis. Chronic lung disease from inhaling of grain dust is probably more common, but relatively little is known about its epidemiologic patterns.

Causes

Those at risk for the disease from inhaling biologically active organic dusts include farmers, grain handlers, wood workers, bird breeders, mushroom workers, and animal handlers, including workers who clean pens and handle laboratory animals (Bang et al. 2006). Environments where water-based machining fluids are used have also been associated with hypersensitivity pneumonitis, probably because of aerosolization of bacteria or fungi growing in the fluids (Kreiss and Cox-Ganser 1997).

Evidence-Based Interventions

Agricultural dusts are regulated in the United States; the NIOSH has proposed a limit of 4 mg/m^3 for grain dust. The concern over dust levels in grain handling facilities has, in part, been because of the risk of explosions (OSHA 2003). Improved design of grain elevators and livestock confinement spaces, proper ventilation, and education of farmworkers and rescue services can reduce the risk from dust and toxic gases (Speizer 1981). Self-contained breathing devices should be worn by workers entering closed or poorly ventilated spaces or tanks containing liquid manure. Diseases caused by molds can be minimized by proper grain storage techniques. A critical factor in control of disease is worker knowledge of the circumstances in which exposures are likely to occur so that preventive precautions can be taken.

Resources

American Lung Association, http://www.lungusa.org

Centers for Disease Control and Prevention, http://www.cdc.gov

- Agency for Toxic Substances and Disease Registry, http://www.atsdr.cdc.gov
- Case Studies in Environmental Medicine, http://www.atsdr.cdc.gov/csem/csem.html
- National Asthma Control Program, http://www.cdc.gov/asthma
- National Institute for Occupational Safety and Health, http://www.cdc.gov/niosh
- Toxicological Profiles, http://www.atsdr.cdc.gov/substances/index.asp
- Work-Related Lung Disease Surveillance System, http://wwwn.cdc.gov/eworld/Set/Work-Related_Respiratory_Diseases/88

Cystic Fibrosis Foundation, http://www.cff.org

Environmental Protection Agency (asthma and indoor environments), http://www.epa.gov/asthma

Global Initiative for Chronic Obstructive Lung Disease, http://www.goldcopd.com

National Heart, Lung, and Blood Institute, http://www.nhlbi.nih.gov

- Guidelines for the Diagnosis and Management of Asthma (EPR-3), http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines
- Lung disease information for patients and the general public, http://www.nhlbi.nih.gov/health/public/lung/index.htm

National Sleep Foundation (obstructive sleep apnea), http://www.sleepfoundation.org

Suggested Reading

Chen JC, Mannino DM. Obstructive, occupational, and environmental diseases. Worldwide epidemiology of chronic obstructive pulmonary disease. *Curr Opin Pulm Med.* 1999;5(2):93–99.

Levy BS, Wagner GR, Rest KM, Weeks JL, eds. *Preventing Occupational Disease and Injury.* 2nd ed. Washington, DC: American Public Health Association; 2005.

Moorman JE, Akinbami LJ, Bailey CM, et al. National surveillance of asthma: United States, 2001–2010. National Center for Health Statistics. *Vital Health Stat.* 2012;3(35):1–58.

Morgan MT. *Environmental Health.* 3rd ed. Florence, KY: Brooks Cole; 2003.

Office of Disease Prevention and Health Promotion, Department of Health and Human Services. Healthy People 2020: respiratory diseases. Available at: https://www.healthypeople.gov/2020/topics-objectives/topic/respiratory-diseases. Accessed April 15, 2016.

Speizer FE, Horton S, Batt J, Slutsky AS. Respiratory diseases of adults. In: Jamison DT, Breman JG, Measham AR, et al., eds, *Disease Control Priorities in Developing Countries.* 2nd ed. New York, NY: Oxford University Press; 2006:681–694.

References

Akinbami LJ, Fryar CD. Asthma prevalence by weight status among adults: United States, 2001–2014. *NCHS Data Brief.* 2016;(239):1–8.

Akinbami LJ, Liu X. Chronic obstructive pulmonary disease among adults aged 18 and over in the United States, 1998–2009. *NCHS Data Brief.* 2011;(63):1–8.

Alberts W, Brooks S. Advances in occupational asthma. *Clin Chest Med.* 1992;13(2): 281–302.

American Thoracic Society. Diagnosis and initial management of nonmalignant disease related to asbestos. *Am J Respir Crit Care Med.* 2004a;170(6):691–715.

American Thoracic Society. Guidelines for assessing and managing asthma risk at work, school, and recreation. *Am J Respir Crit Care Med.* 2004b;169(7):873–881.

Anderson HA, Daum SM, Lilis R, Fischbein AS, Selikoff IJ. Household-contact asbestos neoplastic risk. *Ann N Y Acad Sci.* 1976;271:311–323.

Anderson HA, Werner M. Chronic respiratory diseases. In: Remington PL, Brownson RC, Wegner MV, ed. *Chronic Disease Epidemiology and Control.* 3rd ed. Washington, DC: American Public Health Association; 2010:470.

Arbes SJ, Gergen PJ, Vaughn B, Zeldin DC. Asthma cases attributable to atopy: results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol.* 2007;120(5):1139–1145.

Association of Occupational and Environmental Clinics (AOEC). Revised protocol: Criteria for designating substances as occupational asthmagens on the AOEC list of exposure codes. Washington, DC: AOEC; 2008.

Attfield MD, Bang KM, Petsonk EL, Schleiff PL, Mazurek JM. Trends in pneumoconiosis mortality and morbidity for the United States, 1968–2005, and relationship with indicators of extent of exposure. *J Phys Conf Ser.* 2009;151:012051.

Bang K, Weissman D, Pinheiro G, Antao V, Wood J, Syamlal G. Twenty-three years of hypersensitivity pneumonitis mortality surveillance in the United States. *Am J Ind Med.* 2006;49(12):997–1004.

Barbanel D, Eldridge S, Griffiths C. Can a self-management programme delivered by a community pharmacist improve asthma control? A randomized trial. *Thorax.* 2003; 58(10):851–854.

Barbee R, Murphy S. Natural history of asthma. *J Allergy Clin Immunol.* 1998;102(4 pt 2): S65–S72.

Bates D, Gotsch A, Brooks S, Landrigan P, Hankinson J, Merchant J. Prevention of occupational lung disease. *Chest.* 1992;102(3 suppl):257S–276S.

Baumel M, Maislin G, Pack A. Population and occupational screening for obstructive sleep apnea: are we there yet? *Am J Respir Crit Care Med.* 1997;155(1):9–14.

Baumgartner K, Samet J, Stidley C, Colby T, Waldron J. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 1997;155(1):242–248.

Beach J, Russell K, Blitz S, et al. Systematic review of the diagnosis of occupational asthma. *Chest.* 2007;131(2):569–578.

Belkin NA, Henig NR, Singer LG, et al. Risk factors for death of patients with cystic fibrosis awaiting lung transplantation. *Am J Respir Crit Care Med.* 2004;173(6):659–666.

Beuther D, Weiss S, Sutherland E. Obesity and asthma. *Am J Respir Crit Care Med.* 2006;174(2):112–119.

Bhan N, Kawachi I, Glymour MM, Subramanian SV. Time trends in racial and ethnic disparities in asthma prevalence in the United States from the Behavioral Risk Factor Surveillance System (BRFSS) study (1999–2011). *Am J Public Health.* 2015;105(6):1269–1275.

Blackwell DL, Lucas JW. Tables of summary health statistics for US adults: 2014. National Health Interview Survey. 2015. Available at: http://www.cdc.gov/nchs/nhis/SHS/tables.htm. Accessed August 30, 2016.

Blanc P. Occupational asthma in a national disability survey. *Chest.* 1987;92(4):613–617.

Blanc PD, Iribarren C, Trupin L, et al. Occupational exposures and the risk of COPD: dusty trades revisited. *Thorax.* 2009;64(1):6–12.

Boucher R. New concepts of the pathogenesis of cystic fibrosis lung disease. *Eur Respir J.* 2004;23(1):146–158.

Boucher R, Knowles M, Yankaskas J. Cystic fibrosis. In: Mason R, Murray J, Broaddus V, Nadel J, eds. *Murray and Nadel's Textbook of Respiratory Medicine.* Philadelphia, PA: WB Saunders Co; 2000.

Bouhuys A, Schoenberg J, Beck G, Schilling R. Epidemiology of chronic lung disease in a cotton mill community. *Lung.* 1977;154(3):167–186.

Boushey H, Corry D, Fahy J, Burchard E, Woodruff P. Asthma. In: Mason R, Murray J, Broaddus V, Nadel J, eds. *Murray and Nadel's Textbook of Respiratory Medicine.* Philadelphia, PA: WB Saunders Co; 2000.

Brotanek J, Grimes K, Flores G. Leave no asthmatic child behind: the cultural competency of asthma education. *Ethn Dis.* 2007;17(4):742–748.

Bueving H, Thomas S, Wouden J. Is influenza vaccination in asthma helpful? *Curr Opin Allergy Clin Immunol.* 2005;5(4):65–70.

Burke W, Fesinmeyer M, Reed K, Hampson L, Carlsten C. Family history as a predictor of asthma risk. *Am J Prev Med.* 2003;24(2):160–169.

Caples S, Gami A, Somers V. Obstructive sleep apnea. *Ann Intern Med.* 2005;142(3):187–197.

Castellani C. Evidence for newborn screening for cystic fibrosis. *Paediatr Respir Rev.* 2003;4(4):278–284.

Centers for Disease Control and Prevention (CDC). Fixed obstructive lung disease among workers in the flavor-manufacturing industry—California 2004–2007. *MMWR Morb Mortal Wkly Rep.* 2007;56(16):389–393.

Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. National Hospital Discharge Survey, 2010. 2012a. Available at: http://www.cdc.gov/nchs/data/nhds/2average/2010ave2_firstlist.pdf. Accessed April 10, 2016.

Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. National Ambulatory Medical Care Survey, 2010 and National Hospital Ambulatory Medical Care Survey, 2010. 2012b. Available at: http://www.cdc.gov/nchs/ahcd/ahcd_products.htm. Accessed August 30, 2016.

Centers for Disease Control and Prevention (CDC). Chronic obstructive pulmonary disease among adults—United States, 2011. *MMWR Morb Mortal Wkly Rep.* 2012c;61(46): 938–943.

Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. National Health Interview Survey. Asthma stats: asthma-related missed school days among children aged 5–17 years. 2013. Available at: http://www.cdc.gov/asthma/asthma_stats/aststatchild_missed_school_days.pdf. Accessed August 30, 2016.

Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. Compressed Mortality File 1999–2014 on CDC WONDER online database. 2015. Available at: http://wonder.cdc.gov/cmf-icd10.html. Accessed April 16, 2016.

Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). National Health Interview Survey, 2014. 2016a. Available at: http://www.cdc.gov/asthma/nhis/2014/data.htm. Accessed August 30, 2016.

Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. National Hospital Discharge Survey, 2010. 2016b. Available at: http://www.cdc.gov/asthma/most_recent_data.htm. Accessed April 16, 2016.

Chan-Yeung M. Clinician's approach to determine the diagnosis, prognosis, and therapy of occupational asthma. *Med Clin North Am.* 1990;74(3):811–822.

Chan-Yeung M, Lam S, Koener S. Clinical features and natural history of occupational asthma due to western red cedar (*Thuja plicata*). *Am J Med.* 1982;72(3):411–415.

Chan-Yeung M, Malo J. Natural history of occupational asthma. In: Bernstein I, Chan-Yeung M, Malo J, Bernstein D, eds. *Asthma in the Workplace.* 2nd ed. New York, NY: Marcel Dekker; 1999.

Chilmonczyk B, Salmun L, Megathlin K, et al. Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. *N Engl J Med.* 1993;328(23):1665–1669.

Chung F, Yang X, Liao P. Predictive performance of the STOP-Bang score for identifying obstructive sleep apnea in obese patients. *Obes Surg.* 2013;23(12):2050–2057.

Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Clin Sci.* 2008;12:87–89.

Coleman R. Current animal models are not predictive for clinical asthma. *Pulm Pharmacol Ther.* 1999;12(2):87–89.

Collegium Ramazzini. Asbestos is still with us: repeat call for a universal ban. *Am J Ind Med.* 2011;54(2):168–173.

Collegium Ramazzini. The 18th Collegium Ramazzini statement: the global health dimensions of asbestos and asbestos-related diseases. *Scand J Work Environ Health.* 2016;42(1):86–90.

Connett J, Murray R, Buist S, et al. Changes in smoking status affect women more than men: results of the Lung Health Study. *Am J Epidemiol.* 2003;157(11):973–979.

Coultas D, Zumwalt R, Black W, Sobonya R. Epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med.* 1994;150(4):967–972.

Crewe J, Carey R, Glass D, et al. A comprehensive list of asthmagens to inform health interventions in the Australian workplace. *Aust N Z J Public Health.* 2016;40(2):170–173.

Custovic A, Simpson B, Simpson A, Kissen P, Woodcock A. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during the first year of life: a randomized trial. *Lancet.* 2001;358(9277):188–193.

Cystic Fibrosis Foundation (CFF). Cystic Fibrosis Foundation patient registry 2014 annual data report. Bethesda, MD: CFF; 2015.

de Serres F, Blanco I. Estimating the risk for alpha 1-antitrypsin deficiency among COPD patients: evidence supporting targeted screening. *COPD.* 2006;3(3):133–139.

do Pico G. Hazardous exposure and lung disease among farm workers. *Clin Chest Med.* 1992;13(2):311–328.

Dunn CT, Skrypek MM, Powers ALR, Laguna TA. The need for vigilance: the case of a false-negative newborn screen for cystic fibrosis. *Pediatrics.* 2011;128(2):e446.

Eisner MJ, Anthonisen N, Coultas N, et al. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2010;182(5):693–718.

Eisner M, Balmes J, Katz P, Trupin L, Yelin E, Blanc P. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. *Environ Health*. 2005;4(1):7–11.

Ezzati M. Indoor air pollution and health in developing countries. *Lancet*. 2005; 366(9480):104–106.

Flume PA, Van Devanter DR. State of progress in treating cystic fibrosis respiratory disease. *BMC Med*. 2012;10:88.

Fogarty A, Hubbard R, Britton J. International comparison of median age at death from cystic fibrosis. *Chest*. 2000;117(6):1656–1660.

Ford ES, Croft JB, Mannino DM, Wheaton AG, Zhang X, Giles WH. COPD surveillance—United States, 1999–2011. *Chest*. 2013;144(1):284–305.

Ford ES, Murphy LB, Khavjou O, Giles WH, Holt JB, Croft JB. Total and state-specific costs of CPOD among adults aged ≥18 years in the United States for 2010 and projections through 2020. *Chest*. 2015;147(1):31–45.

Fregonese L, Stolk J. Hereditary alpha-1-antitrypsin deficiency and its clinical consequences. *Orphanet J Rare Dis*. 2008;3:16.

Gaffney SH, Abelman A, Pierce JS, et al. Naturally occurring diacetyl and 2,3-pentanedione concentrations associated with roasting and grinding unflavored coffee beans in a commercial setting. *Toxicol Rep*. 2015;2:1171–1181.

Gerald L, Sockrider M, Grad R, et al. An official ATS workshop report: issues in screening for asthma in children. *Proc Am Thorac Soc*. 2007;4(2):133–141.

Glindmeyer H, Lefante J, Jones R, Rando R, Abdel Kader H, Weill H. Exposure-related declines in the lung function of cotton textile workers. *Am Rev Respir Dis*. 1991; 144(3 pt 1):675–683.

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2015. Available at: http://ginasthma.org. Accessed August 30, 2016.

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2016. Available at: http://goldcopd.org. Accessed August 30, 2016.

Gold W. Pulmonary function testing. In: Mason R, Murray J, Broaddus V, Nadel J, eds. *Murray and Nadel's Textbook of Respiratory Medicine*. Philadelphia, PA: WB Saunders Co; 2000a.

Gold D. Environmental tobacco smoke, indoor allergens, and childhood asthma. *Environ Health Perspect*. 2000b;108(suppl 4):643–651.

Gold D, Damokosh A, Dockery D, Berkey C. Body-mass index as a predictor of incident asthma in a prospective cohort of children. *Pediatr Pulmonol.* 2003;36(6): 514–521.

Griesenbach U, Alton EW. Progress in gene and cell therapy for cystic fibrosis lung disease. *Curr Pharm Des.* 2012;18(5):642–662.

Guide to Community Preventive Services. Asthma control: home-based multi-trigger, multicomponent interventions. 2012. Available at: http://www.thecommunityguide.org/asthma/multicomponent.html. Accessed February 2, 2016.

Guill M. Respiratory manifestations of gastroesophageal reflux in children. *J Asthma.* 1995;32(3):173–179.

Halbert R, Natoli J, Gano A, Badamgarav E, Buist A, Mannino D. Global burden of COPD: systemic review and meta-analysis. *Eur Respir J.* 2006;28(3):523–532.

Hartenbaum N, Collop N, Rosen I, et al. Sleep apnea and commercial motor vehicle operators: statement from the joint task force of the American College of Chest Physicians, American College of Occupational and Environmental Medicine, and the National Sleep Foundation: executive summary. *J Occup Environ Med.* 2006;48(suppl):1–3.

He J, Kryger M, Zorick F, Conway W, Roth T. Mortality and apnea index in obstructive sleep apnea: experience in 385 male patients. *Chest.* 1988;94(1):9–14.

Hnizdo E, Sullivan P, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol.* 2002;156(8):738–746.

Hnizdo E, Vallyathan V. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. *Occup Environ Med.* 2003;60(4):237–243.

Hogg J. Pathophysiology of airflow limitation in chronic obstructive respiratory disease. *Lancet.* 2004;364(9435):709–721.

Hu G, Zhou Y, Tian J, et al. Risk of COPD from exposure to biomass smoke: a meta-analysis. *Chest.* 2010;138(1):20–31.

Hubbard R, Lewis S, Richards K, Britton J, Johnston I. Occupational exposure to metal or wood dust and aetiology of cryptogenic alveolitis. *Lancet.* 1996;347(8997): 284–289.

Hung J, Whitford E, Parsons R, Hillman D. Association of sleep apnoea with myocardial infarction in men. *Lancet.* 1990;336(8710):261–264.

International Agency for Research on Cancer (IARC). Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Silica, some silicates, coal dust, and para-aramid fibres. Lyon, France: IARC; 1997.

International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100C: A review of human carcinogens: arsenic, metals, fibres, and dusts. IARC, World Health Organization. 2012. Available at: http://monographs.iarc.fr/ENG/Monographs/vol100C/index.php. Accessed August 30, 2016.

International Labour Office (ILO). Guidelines for the use of ILO International Classification of Radiographs of Pneumoconioses. Occupational safety and health series (no. 22). Geneva, Switzerland: ILO; 2002.

International Labour Office (ILO). Guidelines for the use of ILO International Classification of Radiographs of Pneumoconioses. Occupational safety and health series (no. 22). Geneva, Switzerland: ILO; 2011.

Jaakkola M, Piipari R, Jaakkola N, Jaakkola J. Environmental tobacco smoke and adult-onset asthma: a population-based incident case–control study. *Am J Public Health*. 2003;93(12):2055–2060.

James A, Cookson W, Buters G, et al. Symptoms and longitudinal changes in lung function in young seasonal grain handlers. *Br J Ind Med*. 1986;43(9):587–591.

Johannessen A, Bakke PS, Hardie JA, Eagan TM. Association of exposure to environmental tobacco smoke in childhood with chronic obstructive pulmonary disease and respiratory symptoms in adults. *Respirology*. 2012;17(3):499–505.

Karimi M, Hedner J, Häbel H, Nerman O, Grote L. Sleep apnea related risk of motor vehicle accidents is reduced by continuous positive airway pressure: Swedish Traffic Accident Registry data. *Sleep*. 2015;38(3):341–349.

Kerem E, Reisman J, Corey M, Canny G, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med*. 1992;326(18):1187–1191.

Knudsen TB, Thomsen SF, Nolte H, Backer V. A population-based clinical study of allergic and non-allergic asthma. *J Asthma*. 2009;46(1):91–94.

Kreiss K, Cox-Ganser J. Metalworking fluid-associated hypersensitivity pneumonitis: a workshop summary. *Am J Ind Med*. 1997;32(4):423–432.

Labre MP, Herman EJ, Dumitru GG, Valenzuela KA, Cechman CL. Public health interventions for asthma: an umbrella review, 1990–2010. *Am J Prev Med*. 2012;42(4):403–410.

LaDou J. The asbestos cancer epidemic. *Environ Health Perspect*. 2004;112(3):285–290.

Lai PS, Christiani DC. Long-term respiratory health effects in textile workers. *Curr Opin Pulm Med.* 2013;19(2):152–157.

Law HZ, Oraka E, Mannino DM. The role of income in reducing racial and ethnic disparities in emergency room and urgent care center visits for asthma—United States, 2001–2009. *J Asthma.* 2011;48(4):405–413.

Leigh J, Yasmeen S, Miller T. Medical costs of fourteen occupational illnesses in the United States in 1999. *Scand J Work Environ Health.* 2003;29(4):304–313.

Levy BD, Noel PJ, Freemer MM, et al. Future research directions in asthma: an NHLBI working group report. *Am J Respir Crit Care Med.* 2015;192(11):1366–1372.

Lewis S, Bennett J, Richards K, Britton J. A cross-sectional study of the independent effect of occupation on lung function in British coal miners. *Occup Environ Med.* 1996;53(2):125–128.

Mackay D, Haw S, Ayres JG, Fischbacher C, Pell JP. Smoke-free legislation and hospitalizations for childhood asthma. *N Engl J Med.* 2010;363(12):1139–1145.

MacKenzie T, Gifford AH, Sabadosa KA, et al. Longevity of patients with cystic fibrosis in 2000 and 2010 and beyond: survival analysis of the Cystic Fibrosis Foundation patient registry. *Ann Intern Med.* 2014;161(12):233–241.

Mahler D, Meija R. Dyspnea. In: Mason R, Murray J, Broaddus V, Nadel J, eds. *Murray and Nadel's Textbook of Respiratory Medicine.* Philadelphia, PA: WB Saunders Co; 1999.

Mannino D, Etzel R, Parrish R. Pulmonary fibrosis deaths in the United States, 1979–1991. An analysis of multiple-cause mortality data. *Am J Respir Crit Care Med.* 1996;153(5): 1548–1552.

Mannino D, Homa D, Akinbami L, Ford E, Redd S. Chronic obstructive pulmonary disease surveillance—United States, 1971–2000. *MMWR Surveill Summ.* 2002;51(6):1–16.

Mapel D, Samet J, Coultas D. Corticosteroids and the treatment of idiopathic pulmonary fibrosis. *Chest.* 1996;110(4):1058–1067.

Mapp C, Boschetto P, Maestrelli P, Fabbri L. Occupational asthma. *Am J Respir Crit Care Med.* 2005;172(3):280–305.

Markowitz SB, Stephen M, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer: new findings from the North American insulator cohort. *Am J Respir Crit Care Med.* 2013;188(1):90–96.

Marsh S, Aldington S, Shirtcliffe P, Weatherall M, Beasley R. Smoking and COPD: what really are the risks? *Eur Respir J.* 2006;28(4):883–884.

Martinez F, Wright A, Taussig L, Holberg C, Halonen M, Morgan W. Asthma and wheezing in the first six years of life. *N Engl J Med.* 1995;332(3):133–138.

Mason R, Murray J, Broaddus V, Nadel J, eds. *Murray and Nadel's Textbook of Respiratory Medicine.* Philadelphia, PA: WB Saunders Co; 2000.

Mazurek JM, Patricia L, Schleiff PL, Wood JM, Hendricks SA, Weston A. Update: silicosis mortality—United States, 1999–2013. *MMWR Morb Mortal Wkly Rep.* 2015;64(23):653–654.

McConnell R, Berhane K, Gilliland F, et al. Asthma in exercising children exposed to ozone: a cohort study. *Lancet.* 2002;359(9304):386–391.

McConnell R, Berhane K, Yao L, et al. Traffic, susceptibility and childhood asthma. *Environ Health Perspect.* 2006;114(5):766–772.

McConnell R, Islam T, Shankardass K, et al. Childhood incident asthma and traffic-related air pollution at home and school. *Environ Health Perspect.* 2010;118(7):1021–1026.

Melen E, Wickman M, Nordvall S, van Hage-Hamsten M, Lindfors A. Influence of early and current environmental exposure factors on sensitization and outcome of asthma in pre-school children. *Allergy.* 2001;56(7):646–652.

Merrill C, Elixhauser A. *Hospitalization in the United States, 2002: HCUP Fact Book No. 6.* Rockville, MD: Agency for Healthcare Research and Quality; 2005.

Meyers D, Larj M, Lange L. Genetics of asthma and COPD: similar results for different phenotypes. *Chest.* 2004;126(2 suppl):105–110.

Millett C, Lee JT, Laverty AA, Glantz SA, Majeed A. Hospital admissions for childhood asthma after smoke-free legislation in England. *Pediatrics.* 2013;131(2):e485–e501.

Mooe T, Franklin K, Holmström K, Rabben T, Wiklund U. Sleep-disordered breathing and coronary artery disease: long-term prognosis. *Am J Respir Crit Care Med.* 2001;164(10):1910–1913.

Moorman JE, Akinbami LJ, Bailey CM, et al. National surveillance of asthma: United States, 2001–2010. National Center for Health Statistics. *Vital Health Stat.* 2012;3(35):1–58.

Naik SL, Lewin M, Young R, Dearwent SM, Lee R. Mortality from asbestos-associated disease in Libby, Montana 1979–2011. *J Expo Sci Environ Epidemiol.* 2016; Epub ahead of print March 30, 2016.

National Heart, Lung, and Blood Institute (NHLBI). Guidelines for the diagnosis and management of asthma: National Asthma Education and Prevention Program Expert Panel Report 3. Bethesda, MD: NHLBI, National Institutes of Health; 2007.

National Institute for Occupational Safety and Health (NIOSH). Report to Congress: Workers' Home Contamination Study conducted under the Workers' Family Protection Act. Cincinnati, OH: NIOSH; 1995.

National Institute for Occupational Safety and Health (NIOSH). *Worker Health Chartbook—2004*. Cincinnati, OH: NIOSH; 2004.

National Institute for Occupational Safety and Health (NIOSH). National Occupational Respiratory Mortality System (NORMS). 2016a. Available at: http://webappa.cdc.gov/ords/norms.html. Accessed April 11, 2016.

National Institute for Occupational Safety and Health (NIOSH). Work-Related Lung Disease Surveillance System (eWoRLD). 2016b. Available at: http://wwwn.cdc.gov/eworld/Set/Work-Related_Respiratory_Diseases/88. Accessed April 11, 2016.

Ober C, Yao T-C. The genetics of asthma and allergic disease: a 21st century perspective. *Immunol Rev.* 2011;242(1):10–30.

Occupational Safety and Health Administration (OSHA). Grain handling facilities standard. *Fed Regist.* 2003;68:12301–12303.

Occupational Safety and Health Administration (OSHA). Occupational exposure to respirable crystalline silica. 2016. Available at: https://www.federalregister.gov/articles/2016/03/25/2016-04800/occupational-exposure-to-respirable-crystalline-silica. Accessed August 30, 2016.

Orenstein D, Rosenstein B, Stern R. Diagnosis of cystic fibrosis. In: Orenstein D, Rosenstein B, Stern R, eds. *Cystic Fibrosis Medical Care*. Philadelphia, PA: Lippincott, Williams and Wilkins; 2000:21–54.

Orozco-Levi M, Garcia-Aymerich J, Villar J, Ramirez-Sarmiento A, Anto J, Gea J. Wood smoke exposure and risk of chronic obstructive pulmonary disease. *Eur Respir J.* 2006;27(3):542–546.

Oxman A, Muir D, Shannon H, Stock S, Hnizdo E, Lange H. Occupational dust exposure and chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1993;148(1):38–48.

Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax.* 1999;54(3):268–272.

Petty T, Weinmann G. Building a national strategy for the prevention and management of and research in chronic obstructive pulmonary disease. *JAMA.* 1997;277(3):246–253.

Punjabi NM. Epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc.* 2008;5(2):136–143.

Rabe K, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: gold executive summary. *Am J Respir Crit Care Med.* 2007;176(6):532–555.

Raghu G, Nyberg F, Morgan G. The epidemiology of interstitial lung disease and its association with lung cancer. *Br J Cancer.* 2004;91(suppl 2):S3–S10.

Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2006;174(7):810–816.

Remes S, Castro-Rodriguez J, Holberg C, Martinez F, Wright A. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol.* 2001;108(4):509–515.

Rogan W, Gladen B, Ragan N, Anderson H. US prevalence of occupational pleural thickening: a look at chest x-rays from the First National Health and Nutrition Examination Survey. *Am J Epidemiol.* 1987;126(5):893–900.

Rosenman K, Reilly M, Henneberger P. Estimating the total number of newly-recognized silicosis cases in the United States. *Am J Ind Med.* 2003;44(2):141–147.

Rosenman KD, Beckett WS. Web based listing of agents associated with new onset work-related asthma. *Respir Med.* 2015;109(5):625–631.

Rylander R. Endotoxin in the environment: exposure and effects. *J Endotoxin Res.* 2002;8(4):241–252.

Sarnat J, Holguin F. Asthma and air quality. *Curr Opin Pulm Med.* 2007;13(1):63–66.

Schulz S, Jakubiczka S, Kropf S, Nickel I, Muschke P, Kleinstein J. Increased frequency of cystic fibrosis transmembrane conductance regulator gene mutations in infertile males. *Fertil Steril.* 2006;85(1):135–138.

Scott J, Johnston I, Britton J. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. *BMJ.* 1990;301(6759):1015–1017.

Sears M. Epidemiological trends in bronchial asthma. In: Kaliner M, Barnes P, Persson C, eds. *Asthma: Its Pathology and Treatment.* New York, NY: Marcel Dekker; 1991:1–49.

Selikoff I, Hammond E, Seidman H. Mortality experience of insulation workers in the United States and Canada, 1943–1976. *Ann N Y Acad Sci.* 1979;330:91–116.

Selikoff I, Lee D, eds. *Asbestos and Disease.* New York, NY: Academic Press; 1978.

Shapiro S, Snider G, Rennard SI. Chronic bronchitis and emphysema. In: Mason R, Murray J, Broaddus V, Nadel J, eds. *Murray and Nadel's Textbook of Respiratory Medicine.* Philadelphia, PA: WB Saunders Co; 2000.

Shi J, Mehta AJ, Hang J, et al. Chronic lung function decline in cotton textile workers: roles of historical and recent exposures to endotoxin. *Environ Health Perspect.* 2010;118(11):1620–1624.

Silva G, Sherrill D, Guerra S, Barbee R. Asthma as a risk factor for COPD in a longitudinal study. *Chest.* 2004;126(1):59–65.

Silverman R, Ito K, Stevenson L, Hastings H. Relationship of fall school opening and emergency department asthma visits in a large metropolitan area. *Arch Pediatr Adolesc Med.* 2005;159(9):818–823.

Smith A, Castellan R, Lewis D, Matte T. Guidelines for the epidemiologic assessment of occupational asthma. *J Allergy Clin Immunol.* 1989;84(5 pt 2):794–805.

Smith A, Lopipero P, Barroga V. Meta-analysis of studies of lung cancer among silicotics. *Epidemiology.* 1995;6(6):17–24.

Smith LA, Hatcher-Ross JL, Wertheimer R, Kahn RS. Rethinking race/ethnicity, income, and childhood asthma: racial/ethnic disparities concentrated among the very poor. *Public Health Rep.* 2005;120(2):109–116.

Snider D. Relationship between tuberculosis and silicosis. *Am Rev Respir Dis.* 1978;118(3):455–460.

Snider GL. Chronic bronchitis and emphysema. In: Murrary JF, Nadel JA, eds. *Textbook of Respiratory Medicine.* Philadelphia, PA: WB Saunders Company; 1988:1069–1106.

Spagnolo P, Rossi G, Cavazza A, et al. Hypersensitivity pneumonitis: a comprehensive review. *J Investig Allergol Clin Immunol.* 2015;25(4):237–250.

Speizer F. Epidemiology of environmentally-induced chronic respiratory disease. *Chest.* 1981;80(1 suppl):21S–23S.

Strausbaugh S, Davis P. Cystic fibrosis: a review of epidemiology and pathobiology. *Clin Chest Med.* 2007;28(2):279–288.

Stulberg M, Adams L. Symptoms of respiratory disease and their management. In: Mason R, Murray J, Broaddus V, Nadel J, eds. *Murray and Nadel's Textbook of Respiratory Medicine.* Philadelphia, PA: WB Saunders Co; 2000.

Tamura T, Suganuma N, Hering KG, et al. Relationships (I) of international classification of high-resolution computed tomography for occupational and environmental respiratory diseases with the ILO international classification of radiographs of pneumoconioses for parenchymal abnormalities. *Ind Health.* 2015;53(3):260–270.

Tarlo SM. Update on work-exacerbated asthma. *Int J Occup Med Environ Health.* 2016;29(3):369–374.

Tarlo SM, Balmes J, Balkissoon R, et al. American College of Chest Physicians. Diagnosis and management of work-related asthma: American College of Chest Physicians Consensus Statement. *Chest.* 2008;134(3 suppl):1S–41S.

Taskar V, Coultas D. Exposures and idiopathic lung disease. *Semin Respir Crit Care Med.* 2008;29(6):670–679.

Taussig L, Wright A, Holberg C, Halonen M, Morgan W, Martinez F. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol.* 2003;111(4):661–675.

Thomashow BM, Walsh JW, Malanga EDF. The COPD Foundation: celebrating a decade of progress and looking ahead to a cure. *J COPD F.* 2014;1(1):4–16.

Tilert T, Dillon C, Paulose-Ram R, Hnizdo E, Doney B. Estimating the US prevalence of chronic obstructive pulmonary disease using pre- and post-bronchodilator spirometry: the National Health and Nutrition Examination Survey (NHANES) 2007–2010. *Respir Res.* 2013;14:103.

Trupin L, Earnest G, San Pedro M, et al. Occupational burden of chronic obstructive respiratory disease. *Eur Respir J.* 2003;22(3):462–469.

Tsui LC, Buchwald M. Biochemical and molecular genetics of cystic fibrosis. *Adv Hum Genet.* 1991;20(153–266):311–312.

Vallyathan V, Castronova V, Pack D, et al. Freshly fractured quartz inhalation leads to enhanced lung injury and inflammation. *Am J Respir Crit Care Med.* 1995;152(3): 1003–1009.

Van Essen S, Auvermann B. Health effects from breathing air near CAFOs for feeder cattle or hogs. *J Agromedicine.* 2005;10(4):55–64.

Weeks J, Levy B, Wagner G, eds. *Preventing Occupational Disease and Injury.* Washington, DC: American Public Health Association; 1991.

Weinhold B. Death out West: the link to COPD. *Environ Health Perspect.* 2000;108(8):A350.

Weiss K. Seasonal trends in US asthma hospitalizations and mortality. *JAMA.* 1990;263(17):2323–2328.

Weitzman M, Gortmaker S, Sobol A, Perrin J. Recent trends in the prevalence and severity of childhood asthma. *JAMA.* 1992;268(19):2673–2677.

Wetter D, Young T, Bidwell T, Safwan Badr M, Palta M. Smoking as a risk factor for sleep-disordered breathing. *Arch Intern Med.* 1994;154(19):2219–2224.

White M, Kaliner M. Mast cells and asthma. In: Kaliner M, Barnes P, Persson C, eds. *Asthma: Its Pathology and Treatment.* New York, NY: Marcel Dekker; 1991:409–440.

Witorsch R, Witorsch P. Review: environmental tobacco smoke and respiratory health in children: a critical review and analysis of the literature from 1969 to 1998. *Indoor Built Environ.* 2000;9(5):246–264.

Wright A, Holberg C, Taussig L, Martinez F. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax.* 2001;56(3):192–197.

Xu JQ, Murphy SL, Kochanek KD, Bastian BA. Deaths: final data for 2013. *Natl Vital Stat Rep.* 2016;64(2):1–119.

Young T, Blustein J, Finn L, Palta M. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep.* 1997;20(8):608–613.

Young T, Peppard P, Gottlieb D. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med.* 2002;165(9):1217–1239.

Zuskin E, Ivankovic D, Schachter E, Witek T II. Ten-year follow-up study of cotton textile workers. *Am Rev Respir Dis.* 1991;143(2):301–305.