pharmacological and non-pharmacological treatments.[9]

Occupational exposures

Occupational exposures, including organic and inorganic dusts, chemical agents and fumes, are an under-appreciated environmental risk factor for COPD.[18,94] Individuals with exposure to inhalation of high doses of pesticides have a higher incidence of respiratory symptoms, airways obstruction and COPD.[95,96] A study of the population-based UK biobank cohort identified occupations including sculptors, gardeners and warehouse workers that were associated with an increased COPD risk among never-smokers without asthma.[97] A cross-sectional observational study demonstrated that self-reported exposure to workplace dust and fumes is associated with not only increased airflow obstruction and respiratory symptoms, but also more emphysema and gas trapping, as assessed by computed tomography scan, in both men and women.[98] An analysis of the large U.S. population-based National Health and Nutrition Examination Survey III survey of almost 10,000 adults aged 30-75 years estimated the fraction of COPD attributable to workplace exposures was 19.2% overall, and 31.1% among never-smokers.[99] These estimates are consistent with a statement published by the American Thoracic Society that concluded that occupational exposures account for 10-20% of either symptoms or functional impairment consistent with COPD.[100] The risk from occupational exposures in less regulated areas of the world is likely to be much higher than reported in studies from Europe and North America.

Air pollution

Air pollution typically consists of particulate matter (PM), ozone, oxides of nitrogen or sulfur, heavy metals, and other greenhouse gases, is a major worldwide cause of COPD, responsible for approximately 50% of the attributable risk for COPD in low- and middle-income countries (LMICs).[101] In never smokers, air pollution is the leading known risk factor for COPD.[102] The respiratory risk of air pollution to individuals is dose-dependent with no apparent “safe” thresholds. Even in countries with low ambient air pollution levels, chronic exposure to PM2.5 and nitrogen dioxides significantly impairs lung growth in children,[103] accelerates lung function decline in adults and increases the risk for COPD, especially among those with additional risk factors for COPD.[104] Poor air quality from air pollution also increases the risk of COPD exacerbations, hospitalizations and mortality.[105,106] Thus, reduction in both indoor and outdoor air pollution is a key goal in the prevention and management of COPD.

Genetic factors

A significant familial risk of airflow obstruction has been observed in people who smoke and are siblings of patients with severe COPD,[107] suggesting that genetics (in combination with environmental risk factors) could influence this susceptibility. The best documented genetic risk factor for COPD are mutations in the SERPINA1 gene that leads to the hereditary deficiency of α-1 antitrypsin (AATD),[108] a major circulating inhibitor of serine proteases. Although AATD deficiency is relevant to only a small part of the world’s population, it illustrates the interaction between genes and environmental exposures that predispose an individual to COPD. A systematic review of 20 studies in European populations found AATD PiZZ genotypes in 0.12% of COPD patients (range 0.08-0.24%), and a prevalence ranging from 1 in 408 in Northern Europe to 1 in 1,274 in Eastern Europe.[109]

There has been a long-standing controversy concerning the risk of heterozygotes (MZ and SZ) for the development of COPD. This has largely reflected acquisition bias but is of critical importance due to the large numbers of such individuals worldwide[110] who may potentially benefit from augmentation therapy. Recent careful sibling studies[111,112] indicated no increased risk in these heterozygotes in the absence of smoking although lung function was reduced in smokers compared to MM siblings. This likely reflects the presence of low concentrations of the Z AAT protein rather than an absolute lack of it[113] and is not an indication for augmentation therapy (discussed in more detail in **Chapter 3**).

To date, hundreds of genetic variants associated with reduced lung function and risk of COPD have been identified,