The most extensively studied and most significant aspect of lung function decline is that of the forced expiratory volume in 1 second (FEV$_1$), for two reasons. First, the FEV$_1$ is the most reproducible lung function test and therefore is best adapted to the assessment of large groups of people. Second, excessive decline of FEV$_1$ is the hallmark of obstructive lung disease, especially chronic obstructive pulmonary disease (COPD), and most studies of age-related decline in lung function have been done in this context. For this reason we confine our discussion to decline of FEV$_1$.

**DECLINE OF FEV$_1$ IN NORMAL SUBJECTS**

In normal adults, the FEV$_1$ declines with age. Whether this is a result of changes intrinsic to the lung or a response to inhalants with adverse effects on the lung is unknown and probably unknowable. The rate of decline in normal subjects, that is, people who have never smoked and do not have respiratory symptoms, has been estimated in both cross-sectional and longitudinal studies. Cross-sectional studies have largely been used for the development of normal values; the most recent and probably the best of these is that of Hankinson and colleagues, who studied a random sample of the U.S. population. Table 59-1 shows illustrative examples of annual decline of FEV$_1$ from these data. Generally, decline increased with age, although this was not the case in African American and Mexican American males, and decline was larger in men than in women.

In general, longitudinal studies of FEV$_1$ decline in normal subjects agree with cross-sectional estimates, although agreement is not entirely consistent. In particular, Burrows and colleagues found that FEV$_1$ tended to plateau in early adulthood, beginning to decline in the mid-thirties in both sexes. Longitudinal studies, by definition, examine data from a particular cohort and measure events occurring during the study, whereas cross-sectional studies examine the effects of events that occurred before the study, so failure to have exact agreement is explicable.

**CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

COPD is defined as chronic airways obstruction that cannot be completely reversed with therapy and is not explained by another more specific pathology. In the developed world, it is strongly related to smoking. COPD includes three specific pathologies: chronic bronchitis, peripheral airways disease, and emphysema. Chronic bronchitis is usually defined as cough and sputum present more than 3 months of the year for 2 consecutive years and is accompanied by pathologic changes in large airways. Peripheral airways disease involves obstruction of bronchioles. Emphysema is defined as destruction of peripheral lung units with loss of gas-exchanging area. Chronic bronchitis, peripheral airways disease, and emphysema are all related to tobacco use, and all three are present in many but not all patients with severe COPD. Peripheral airways disease and emphysema cause chronic airways obstruction, but this is not necessarily true of chronic bronchitis. Although related to smoking, most heavy smokers do not develop clinically apparent COPD, so there must be additional determinants or risk factors. Most information on decline of FEV$_1$ is related to the development of COPD and risk factors involved, and this is the context for the remainder of this chapter.

**RELATIONSHIP TO ASTHMA**

Asthma is also characterized by airways obstruction but is regarded as different from COPD because asthma and COPD generally present different clinical pictures, have different epidemiologic features, and have different natural histories. On the other hand, some asthmatics pursue an unremitting course and some develop nonreversible airways obstruction, but the mechanisms involved in the chronic obstruction of asthma probably differ from those in smoking-related COPD.

Some patients with progressive airways obstruction and significant smoking histories resemble asthmatics in that they demonstrate substantial reversibility of their obstruction with inhaled bronchodilators. It has not been shown that these individuals differ in any important way from COPD patients with less reversibility, and it should be noted that reversibility is not a very reproducible test.

**NATURAL HISTORY OF COPD**

COPD is commonly characterized as an abnormally rapid decline in FEV$_1$ in response to inhaled toxins: in the developed world, by far the most important of these is tobacco smoke. Figure 59-1 shows a model of the effects of smoking.
on lung function, adapted from the classic work of Fletcher and colleagues and validated in many subsequent studies. The decline in FEV is shown as linear functions starting at age 30 years. Disability occurs at a value of 1.5 to 2.0 L and severe disability at 1.0 L. In the average nonsmoker, FEV declines at a rate approximating 30 mL/yr, so disability does not occur during the normal life span. In the average smoker, the FEV declines approximately twice as fast, at a rate of about 60 mL/yr, and disability will not occur until quite late in life. A subgroup of smokers is unusually “sensitive” to the effects of tobacco smoke and declines much more rapidly, at rates of 100 mL/yr and more. These people develop severe disability in late middle age. This “sensitive” subgroup is thought to consist of 15 to 20% of all smokers.

The effect of smoking cessation in middle age is also illustrated in Figure 59-1. With cessation, the rate of decline reverts to that of the normal nonsmoker. This effect was observed in people who spontaneously quit smoking and in a randomized trial of smoking cessation. Smoking cessation in middle age will either prevent or greatly delay the onset of symptomatic disease (see Figure 59-1). Once disability has developed, the benefit of cessation is not as clear.

**RISK FACTORS FOR ACCELERATED DECLINE OF FEV**

**AIRWAYS HYPERREACTIVITY**

In the 1960s Dutch investigators proposed that the degree of airways reactivity was an important determinant of the development of COPD. According to this argument, smokers with highly reactive airways would be much more likely to develop chronic airways obstruction than would those with less reactivity. The “Dutch hypothesis” proved difficult to test for several reasons. First, airways hyperreactivity is a hallmark of asthma, and Dutch investigators tended to lump together patients with asthma and those with COPD, so many Dutch studies of the influence of airways reactivity included asthmatics. Second, it was clear that the degree of airways reactivity was inversely proportional to the FEV in people with airways obstruction and that the reactivity might be a consequence rather than a cause of the obstruction. For this reason, cross-sectional studies of reactivity in people with COPD were of little value in testing the Dutch hypothesis.

Prospective studies of the influence of airways reactivity on the rate of decline of lung function have been carried out in a number of populations at relatively low risk of symptomatic COPD and indicated that reactivity did predict decline. However, the Lung Health Study provided the best support for the Dutch hypothesis. In nonasthmatic smokers aged 35 to 59 years with a ratio of FEV to forced vital capacity (FVC) <0.70, the degree of methacholine responsiveness was the second most important predictor (after smoking status) of subsequent decline in FEV. Reactivity was strongly interactive with smoking; in continuing smokers it had a powerful effect on decline, whereas it had much less effect in people who stopped smoking.

**ATOPY**

Two manifestations of atopy have been thought to be risk factors for loss of lung function and, by implication, for COPD. These are serum total immunoglobulin E (IgE) levels and skin test reactivity to common allergens. Both are associated with asthma and airways hyperreactivity in healthy people. Of the two, IgE levels have received the most attention. Smoking is also associated with increased IgE levels. Given the associations of IgE levels with both smoking and asthma, it is not surprising that the IgE level is inversely related to lung function in cross-sectional studies. However, most longitudinal studies of lung function have not found a relationship between IgE levels and rate of decline of lung function in smokers. IgE is probably not a risk factor for the development of smoking-related COPD.

If asthmatics are excluded, atopy as assessed by skin tests is apparently not related to decline in lung function in either smokers or nonsmokers.
**Episodes of Acute Bronchitis: Exacerbations**

The “British hypothesis” explaining the pathogenesis of COPD was that chronic bronchitis predisposed individuals to repeated episodes of respiratory tract infection and that these episodes led to irreversible lung damage and airways obstruction.\(^1\) The hypothesis rested on the observation that many COPD patients had chronic cough and sputum production associated with periodic chest infections occurring prior to the onset of dyspnea and disability. Further, even when clinically stable, these patients had bacteria in their sputum that were similar to those recovered during acute episodes.

The landmark study of Fletcher and colleagues tested the British hypothesis by evaluating 792 male London transit workers (both smokers and nonsmokers) for 8 years, with regular assessment of sputum, chest infections, and FEV\(_1\).\(^7\) They found that neither symptomatic chronic bronchitis nor chest infections correlated with the decline of lung function. Acute chest infections were more common in people with chronic bronchitis but did not relate to the development of chronic airways obstruction. Their results were confirmed by other long-term studies.\(^19\)

For many years, it was thought that the presence or absence of chronic bronchitis with or without acute episodes had no long-term effect on the course of the disease, although exacerbations undeniably caused short-term decreases in lung function and were important causes of hospitalization and death. However, two carefully done long-term studies have demonstrated that the rate of decline of FEV\(_1\) is higher in smokers with chronic cough and sputum production than in those without symptomatic chronic bronchitis.\(^20,21\)

Recently, new light has been shed on the problem. Seemungal and colleagues carefully followed a cohort of COPD patients, characterizing their exacerbations, including peak flows measured before, during, and after the illness.\(^22\) Not all patients recovered completely. Indeed, in about 7% of patients peak flows were lower 90 days after an exacerbation than they were before. Thus, exacerbations may have a long-term deleterious effect on lung function in COPD. Retrospective analysis of data from the Lung Health Study may have a long-term deleterious effect on lung function in exacerbation than they were before. Thus, exacerbations about 7% of patients peak flows were lower 90 days after an exacerbation than they were before. Thus, exacerbations may have a long-term deleterious effect on lung function in COPD. Retrospective analysis of data from the Lung Health Study supported this argument.\(^23\) Participants were asked at annual visits if they had seen a doctor for bronchitis, pneumonia, influenza, or chest colds. Positive responses were classified as lower respiratory infections (LRIs). Participants with chronic cough and sputum production had about twice as many LRIs as those without. People who quit smoking had fewer LRIs than those who continued. In continuing smokers, a single LRI was associated with a loss of 7 mL of FEV\(_1\) during the year of the event, and there was a clear dose-response effect, with more LRIs associated with greater losses. This was true whether or not chronic cough and sputum production were present. In people who stopped smoking, LRIs had no effect on the rate of decline of FEV\(_1\). Thus, exacerbations of symptoms had a long-term negative effect on lung function, which would be significant if several episodes occurred per year.

**Sex**

COPD has been considered to be largely a disease of men; this sex distribution reflected differences in smoking habits between men and women, and as the prevalence of female smokers has increased over the last 50 years, so has the prevalence of COPD in women. There is little question that the COPD prevalence in women will continue to increase in the foreseeable future.

If sex were an independent risk factor for COPD, men and women with the same smoking habits would develop COPD at different rates. The effect of smoking on sex-specific lung function has been examined on a number of occasions with conflicting results. The Lung Health Study followed a substantial number of women with airways obstruction, and data from 11 years of follow-up have recently been examined to look for sex-specific functional differences.\(^24\) Among continuing smokers, rates of decline of FEV\(_1\) were quite similar between sexes when expressed as a percentage of the predicted normal value (Table 59-2). Men were heavier smokers than women, so these results could be interpreted as indicating that women might be more sensitive than men to cigarette smoke, but differences are probably minor and are not evident given sex-related differences in smoking habit.

**Genetic or Hereditary Risk Factors**

The observation that only 15 to 20% of smokers develop COPD is a strong indication that genetically controlled susceptibility to the disease may be involved in the development of COPD. Familial aggregation has been documented in COPD; more cases than expected have been found in the families of index cases. However, it has been difficult to separate the presumed hereditary effect from the sharing of environmental exposures or lifestyle. In North America, the effects of familial aggregation and heredity on lung function were examined in a number of cross-sectional studies. Heritability was estimated as the proportion of the variance in lung function owing to hereditary factors. Most such studies showed such an influence.\(^25\) Only a modest effect of family history has been shown in longitudinal analysis,\(^26\) probably because of methodological problems in conducting such studies that tend to dilute associations. Lung function must be hereditary to some extent, but the effect is difficult to quantify.

The only genetic factor that is strongly correlated with the development of COPD is that of the homozygous ZZ phenotype of α\(_1\)-antitrypsin (AAT) deficiency.\(^27\) Although this phenotype is associated with the premature development of severe emphysema, it leads to substantially reduced life expectancy largely in smokers; the effects in people who

<table>
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<tr>
<th></th>
<th>Women</th>
<th>Men</th>
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<tr>
<td></td>
<td>N ( FEV_1 % ) predicted</td>
<td>N ( FEV_1 % ) predicted</td>
<td></td>
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<tr>
<td>Sustained quitter</td>
<td>253 -0.05</td>
<td>462 -0.27</td>
<td>&lt;.0001</td>
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<tr>
<td>Intermittent quitter</td>
<td>906 -0.86</td>
<td>1,423 -0.88</td>
<td>.697</td>
</tr>
<tr>
<td>Continuous smoker</td>
<td>396 -1.31</td>
<td>644 -1.27</td>
<td>.532</td>
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\( FEV_1 \) = forced expiratory capacity in 1 second.
never smoked and in those not exposed to environmental hazards are relatively small.28 Because the ZZ phenotype is rare, it accounts for only a small proportion of individuals with COPD. Among heterozygous AAT phenotypes, only the more common MZ and SZ phenotypes might interact with smoking and environmental exposure to produce the disease; however, the evidence for their role is not consistent. Sandford and colleagues reviewed seven case-control studies that showed a 1.5 to 5.0 times higher risk of COPD in carriers of some alleles have been characterized as likely to have emphysema.39

Heme Oxygenase-1 Heme Oxygenase-1 (HO-1) is a lung antioxidant. Carriers of some alleles have been characterized as likely to have emphysema.39

Tumor Necrosis Factor Alpha Tumor necrosis factor alpha (TNF-α) is a multifunctional cytokine, a proinflammatory mediator that is released by epithelial cells and macrophages. The bulk of the evidence does not support a role for TNF-α polymorphisms with rapid decline of FEV1,35

Interleukin 1 Interleukin 1 (IL-1), which exists in two forms, is a proinflammatory cytokine associated with airways disease. Both the IL-1β (IL-1β) form and the IL-1 receptor antagonist (IL-1RN) have naturally occurring genetic polymorphisms. Although specific genotypes were not associated with rapid decline of lung function, the distribution of IL-1β and IL-1RN haplotypes differed between smokers with rapid decline and those without.40

OCCUPATIONAL EXPOSURES

It has long been known that occupational exposure to dusts can be associated with symptoms and abnormalities of lung function. However, assessments of the contribution of occupational exposures to the rapid decline of FEV1 and COPD have been difficult and often inconclusive. It should also be noted that over the past 30 years, the levels of occupational exposure to a variety of dusts have decreased as a result of legislation aimed at workers’ protection, so the current applicability of much of the data in older workers is questionable.

Cross-sectional studies have repeatedly shown occupational exposure to mineral dusts to be associated with chronic cough and sputum production and reductions in lung function.41 Longitudinal studies of workers exposed to mineral dusts have also shown deleterious effects. Both coal miners and hard rock miners have higher rates of lung function loss than control subjects after correction for the effects of smoking.42,43 The most recent estimates in coal miners indicate a risk that is at most one-half that imposed by smoking.44,45

Other occupational dust exposures have been associated with increased loss of lung function over time. A particularly well-documented instance is cotton dust exposure in textile workers,46 and relatively low levels of cotton dust exposure may interact with smoking, in that exposure-related loss of lung function was evident only in smokers.47 In cross-sectional studies, dust exposure has had a more pronounced effect on lung function than exposure to gases and fumes, but the latter were associated with relatively minor deficits.48

In summary, it is likely that occupation-related exposures to dusts and, to some extent, noxious fumes and gases accelerate loss of lung function. With the possible exception of people exposed to cadmium, which causes emphysema in animal models, and a previous generation of coal miners, it is unlikely that occupational exposure alone causes much COPD, at least in Europe and North America.
**AIR POLLUTION**
Adverse effects of ambient air pollution on health have been recognized for a long time. There is good evidence that current pollutants, derived from the combustion of fossil fuels, photochemical reactions, and automotive exhaust, are associated with excess mortality and hospitalizations.\(^48\) Rises in pollution levels have been associated with exacerbations of asthma and COPD.

It is, however, less well established whether chronic exposure to air pollution affects the decline of FEV\(_1\). This is owing to difficulties in interpreting cross-sectional studies, in conducting appropriate longitudinal studies, in estimating personal exposure levels in large numbers of individuals, and in controlling the effects of potential confounders, such as smoking. In addition, people are frequently exposed to several air pollutants concurrently. The issue has been intensely studied with inconsistent results, in that specific pollutants had varying effects or effects that varied with the age or sex of the people exposed. Two very large American studies found that FEV\(_1\) was lower in people exposed to oxides of nitrogen, ozone, and particulates after adjustment for confounding variables.\(^49,50\) The effects were small compared with those of smoking.

**ENVIRONMENTAL TOBACCO SMOKE**
Environmental tobacco smoke (ETS) is other people’s cigarette smoke and contains most of the toxins that the original smoker inhaled. It is difficult to estimate ETS exposure in other than a semiquantitative way, such as the number of smokers in the immediate environment and the fraction of time in the suspect environment. Most studies compare nonsmokers who are exposed to smokers with those who are not. There is an increased risk of dying from emphysema or bronchitis in nonsmoking women exposed to ETS but not in men.\(^51\) Most other evidence relating ETS and lung function has been obtained from cross-sectional studies comparing FEV\(_1\) between ETS-exposed and nonexposed nonsmokers. The results of these studies are inconsistent but taken together indicate that long-term exposure to ETS is associated with a decrease of approximately 0.1 L, too small to cause clinical illness.

**INDOOR AIR POLLUTION**
Indoor air pollution may be an important determinant of health because people spend a substantial proportion of their life indoors and because, under some circumstances, pollutant levels can be very high. Evidence from developing countries is accumulating to suggest that smoke from wood and other biomass fuels may be an important determinant of airflow obstruction. This is typified by a recent study from Mexico.\(^52\)

**CHILDHOOD CONDITIONS**
Events in childhood could predispose to reduced lung function in adults by a number of mechanisms. It is extremely difficult to study childhood influences on a disease that develops gradually and becomes apparent only in late adult life, and no such longitudinal studies are available. Nevertheless, the influences of childhood respiratory infections and exposures to ETS have been intensely investigated. To summarize, both appear to cause small reductions in lung function, at least in children. Although these changes per se are not large enough to pose a credible COPD risk factor, it is conceivable that these childhood events increase the susceptibility of smokers to tobacco products.

A specific and promising hypothesis regarding childhood infection and COPD has emerged from the work of Hogg, who demonstrated that pieces of the adenoviral genome were commonly present in autopsied lung specimens from smokers with and without COPD.\(^53\) This genetic material was presumably due to previous infection with this agent that might have occurred during childhood. They also demonstrated that the E1A viral segment is present much more often in smokers with airways obstruction than in those without and have developed evidence that this viral segment could be a cause of chronic inflammation.

**DIETARY FACTORS**
Three groups of dietary factors have been investigated as potential contributors to chronic obstructive disease: (1) antioxidants, (2) \(\omega-3\) fatty acids, and (3) electrolytes. Such studies are plagued with methodological problems, and the resulting evidence is far from conclusive but is worthy of consideration because dietary factors apply to large populations.

**Antioxidants** Cross-sectional studies have related the estimated intake of specific antioxidants to the FEV\(_1\). In several, higher intake of vitamin C was associated with slightly higher values of FEV\(_1\). Similar but less consistent associations have been developed for vitamin E and \(\beta\)-carotenoid intake.

**\(\omega-3\) Fatty Acids** \(\omega-6\) Fatty acids are proinflammatory; \(\omega-3\) fatty acids, largely derived from fish, are protective. People who eat fish regularly tend to have a slightly higher level of FEV\(_1\) than those who do not.

**Electrolytes** There are some studies suggesting that bronchial responsiveness is higher in people with a higher intake of sodium, and a higher intake of magnesium may have a protective effect. Bronchial reactivity is associated with rapid decline of FEV\(_1\) in smokers.

**SUMMARY AND CONCLUSIONS**
Lung function—FEV\(_1\)—declines in normal people, but the decline is so slow that they do not develop dyspnea in the absence of disease. Tobacco smoking causes accelerated decline of FEV\(_1\), the hallmark of COPD. However, only a minority of smokers develop symptomatic COPD, so other “host factors” must be involved, and several have been identified. Airways reactivity, as assessed by methacholine, is associated with relatively rapid loss of lung function in smokers, as is repeated respiratory infection. It is well known that homozygous ZZ \(\alpha_1\)-antitrypsin deficiency combined with smoking causes severe, premature COPD, and the role of other genes is under intense investigation. Results are promising but not conclusive. Occupational exposure to
certain dusts is also associated with accelerated loss of lung function. Other putative risk factors, including ambient air pollution, environmental tobacco smoke, and dietary components, are probably not important. At present it is still impossible to predict which smokers will develop symptomatic COPD.

REFERENCES


