TABLE 309-1 RISK FACTORS AND TRIGGERS INVOLVED IN ASTHMA

Endogenous Factors	Environmental Factors
Genetic predisposition	Indoor allergens
Atopy	Outdoor allergens
Airway hyperresponsiveness	Occupational sensitizers
Gender	Passive smoking
Ethnicity	Respiratory infections
Obesity	Diet
Early viral infections	Acetaminophen (paracetamol)
Triggers	
Allergens	
Upper respiratory tract viral infections	
Exercise and hyperventilation	
Cold air	
Sulfur dioxide and irritant gases	
Drugs (β blockers, aspirin)	
Stress	
Irritants (household sprays, paint fumes)	

individuals becoming asthmatic. This observation suggests that some other environmental or genetic factor(s) predispose to the development of asthma in atopic individuals. The allergens that lead to sensitization are usually proteins that have protease activity, and the most common allergens are derived from house dust mites, cat and dog fur, cockroaches (in inner cities), grass and tree pollens, and rodents (in laboratory workers). Atopy is due to the genetically determined production of specific IgE antibody, with many patients showing a family history of allergic diseases.

Genetic Predisposition The familial association of asthma and a high degree of concordance for asthma in identical twins indicate a genetic predisposition to the disease; however, whether or not the genes predisposing to asthma are similar or in addition to those predisposing to atopy is not yet clear. It now seems likely that different genes may also contribute to asthma specifically, and there is increasing evidence that the severity of asthma is also genetically determined. Genetic screens with classical linkage analysis and single-nucleotide polymorphisms of various candidate genes indicate that asthma is polygenic, with each gene identified having a small effect that is often not replicated in different populations. This observation suggests that the interaction of many genes is important, and these may differ in different populations. The most consistent findings have been associations with polymorphisms of genes on chromosome 5q, including the T helper 2 (T_H2) cells interleukin (IL)-4, IL-5, IL-9, and IL-13, which are associated with atopy. There is increasing evidence for a complex interaction between genetic polymorphisms and environmental factors that will require very large population studies to unravel. Novel genes that have been associated with asthma, including *ADAM-33*, and *DPP-10*, have also been identified by positional cloning, but their function in disease pathogenesis is not yet clear. Recent genome-wide association studies have identified further novel genes, such as *ORMDL3*, although their functional role is not yet clear. Genetic polymorphisms may also be important in determining the response to asthma therapy. For example, the Arg-Gly-16 variant in the β_2-receptor has been associated with reduced response to β_2-agonists, and repeats of an Sp1 recognition sequence in the promoter region of 5-lipoxygenase may affect the response to antileukotrienes. However, these effects are small and inconsistent and do not yet have any implications for asthma therapy.

It is likely that environmental factors in early life determine which atopic individuals become asthmatic. The increasing prevalence of asthma, particularly in developing countries, over the last few decades also indicates the importance of environmental mechanisms interacting with a genetic predisposition.

Infections Although viral infections (especially rhinovirus) are common triggers of asthma exacerbations, it is uncertain whether they play a role in etiology. There is some association between respiratory syncytial virus infection in infancy and the development of asthma, but the specific pathogenesis is difficult to elucidate because this infection is very common in children. Atypical bacteria, such as *Mycoplasma* and *Chlamydophila*, have been implicated in the mechanism of severe asthma, but thus far, the evidence is not very convincing of a true association.

The observation that allergic sensitization and asthma were less common in children with older siblings first suggested that lower levels of infection may be a factor in affluent societies that increase the risks of asthma. This "hygiene hypothesis" proposes that lack of infections in early childhood preserves the T_H2 cell bias at birth, whereas exposure to infections and endotoxin results in a shift toward a predominant protective T_H1 immune response. Children brought up on farms who are exposed to a high level of endotoxin are less likely to develop allergic sensitization than children raised on dairy farms. Intestinal parasite infection, such as hookworm, may also be associated with a reduced risk of asthma. Although there is considerable epidemiologic support for the hygiene hypothesis, it cannot account for the parallel increase in T_H1-driven diseases such as diabetes mellitus over the same period.

Diet The role of dietary factors is controversial. Observational studies have shown that diets low in antioxidants such as vitamin C and vitamin A, magnesium, selenium, and omega-3 polyunsaturated fats (fish oil) or high in sodium and omega-6 polyunsaturated fats are associated with an increased risk of asthma. Vitamin D deficiency may also predispose to the development of asthma. However, interventional studies with supplementary diets have not supported an important role for these dietary factors. Obesity is also an independent risk factor for asthma, particularly in women, but the mechanisms are thus far unknown.

Air Pollution Air pollutants, such as sulfur dioxide, ozone, and diesel particulates, may trigger asthma symptoms, but the role of different air pollutants in the etiology of the disease is much less certain. Most evidence argues against an important role for air pollution because asthma is no more prevalent in cities with a high ambient level of traffic pollution than in rural areas with low levels of pollution. Asthma had a much lower prevalence in East Germany compared to West Germany despite a much higher level of air pollution, but since reunification, these differences have decreased as eastern Germany has become more affluent. Indoor air pollution may be more important with exposure to nitrogen oxides from cooking stoves and exposure to passive cigarette smoke. There is some evidence that maternal smoking is a risk factor for asthma, but it is difficult to dissociate this association from an increased risk of respiratory infections.

Allergens Inhaled allergens are common triggers of asthma symptoms and have also been implicated in allergic sensitization. Exposure to house dust mites in early childhood is a risk factor for allergic sensitization and asthma, but rigorous allergen avoidance has not shown any evidence for a reduced risk of developing asthma. The increase in house dust mites in centrally heated poorly ventilated homes with fitted carpets has been implicated in the increasing prevalence of asthma in affluent countries. Domestic pets, particularly cats, have also been associated with allergic sensitization, but early exposure to cats in the home may be protective through the induction of tolerance.

Occupational Exposure Occupational asthma is relatively common and may affect up to 10% of young adults. Over 300 sensitizing agents have been identified. Chemicals such as toluene diisocyanate and trimellitic anhydride, may lead to sensitization independent of atopy. Individuals may also be exposed to allergens in the workplace such as small animal allergens in laboratory workers and fungal amylase in wheat flour in bakers. Occupational asthma may be suspected when symptoms improve during weekends and holidays.

Obesity Asthma occurs more frequently in obese people (body mass index >30 kg/m^2) and is often more difficult to control. Although