Asthma risk factors

Elina Toskala, MD, PhD[1] and David W. Kennedy, MD[2]

Background: **Bronchial asthma is one of the most common chronic diseases in childhood, with a current prevalence of 6% to 9%, but a prevalence that is increasing at an alarming rate. Asthma is a complex genetic disorder with strong environmental influence. It imposes a growing burden on our society in terms of morbidity, quality of life, and healthcare costs. Despite large-scale efforts, only a few asthma genes have been confirmed, suggesting that the genetic underpinning of asthma is highly complex.**

Methods: **A review of the literature was performed regarding atopic and nonatopic asthma risk factors, including environmental risk factors and genetic studies in adults and children.**

Results: **Several environmental risk factors have been identified to increase the risk of developing asthma such as exposure to air pollution and tobaccos smoke as well as occupational risk factors. In addition atopy, stress, and obesity all can increases the risk for asthma in genetically susceptible persons.**

Conclusion: **Asthma represents a dysfunctional interaction with our genes and the environment to which they are exposed, especially in fetal and early infant life. The increasing prevalence of asthma in all age groups indicate that our living environment and immunity are in imbalance with each other reacting with airway inflammation to the environmental exposures and often non-harmful proteins, such as allergens causing the current "asthma and allergy epidemic." Because of the close relationship between asthma and chronic rhinosinusitis, it is important that otolaryngologists have a good understanding of asthma, the etiologic factors associated with disease, and its evaluation and management.**

Key Words:
air pollution; allergens; asthma; atopy; environmental risk factors; epigenetics; genetic risk factors; hygiene hypothesis; microbes; risk factors

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Asthma is a chronic respiratory disorder with a heterogeneous and multifactorial background manifested as episodes of wheezing, coughing, and shortness of breath, with about 75% of the patients having coexisting atopy. It has been estimated that in total, more than 25 million children and adults in the United States have asthma and that globally over 300 million persons suffer from asthma.[1–3] Epidemiological studies have shown that asthma is more prevalent in women than in men and more prevalent among children, especially boys, who have higher prevalence of asthma compared to girls.[4] It is the most common chronic disease of childhood. The prevalence has been increasing at an alarming rate and has more than doubled in last the decade. Over 9 million children in the United States have been diagnosed with asthma, of whom 75% have active disease.[1]

Asthma also has different prevalence among ethnic groups. It is more prevalent among African Americans of all ages (11%) and among African American children (17%) than in any other ethnic group.[4] Furthermore, a disproportionately large number of children with asthma are from low-income families. Asthma is a major cause of work and school absences, and it is the third leading cause of hospitalization of children under the age of 15 years.[1]

Although asthma is usually recognized through the acute episodes of asthma attacks, including wheezing and sometimes irreversible declines in lung function, it has become appreciated that asthma has an important immune system component as well. Roles for many immune cells and mediators have been described. There is a clear connection between asthma and atopy, although this connection is not absolute. Atopic individuals are more prone to developing asthma, and much of the prevalence of asthma can be linked

[1]*Department of Otorhinolaryngology–Head and Neck Surgery, Temple University, Philadelphia, PA;* [2]*Department of Otorhinolaryngology–Head and Neck Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Correspondence to: Elina Toskala, MD, PhD, Department of Otorhinolaryngology–Head and Neck Surgery, Temple University, 3440 N. Broad Str., Kresge West, 3rd Floor, Philadelphia, PA 19140; e-mail: elina.toskala@temple.edu

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to specific allergies.[5] However, not all atopic individuals develop asthma, and not all asthmatics have detectably elevated allergic responses. Dysregulated immunity appears to be important in the development of asthma, with elevated serum immunoglobulin E (IgE) levels, excess release of allergic mediators from mast cells, infiltration of eosinophils into the lungs and inflammation in the airways and with skewed T helper 1 (Th1) and Th2 responses. Reduction of chronic inflammation in the lungs is part of a strategy for long-term control of asthma, through the use of anti-inflammatory agents such as inhaled glucocorticoids.

Both family-based and twin studies indicate that asthma is a complex genetic disorder.[6] Multiple genetic and environmental factors are also known to modulate the clinical expression of the disease and its associated phenotypes—bronchial hyperresponsiveness, atopy, and elevated IgE.[7] Asthma is generally believed to result from gene-environment interactions. There are several well-known risk-factors for developing asthma and these are discussed in this article.

Environmental risk factors

Tobacco

Active smoking has been shown to be risk factor for developing asthma; women who smoke are at particular risk. Interestingly, the prevalence of smokers among asthmatics is almost the same as it is in the general population. It has been shown that it is more difficult to maintain asthma control in smokers with asthma than in nonsmokers with asthma. Altered airway inflammation and corticosteroid insensitivity are thought to be the mechanisms behind the adverse effects of smoking in asthma patients.[8–11]

A number of studies have shown a clear association between smoking and an increased risk of developing asthma.[12–16] This correlation was studied in a large 10-year follow-up study of patients with allergic rhinitis.[17] This study showed that active smoking was strongly predictive of the development of new onset asthma in allergic adults. In addition, this study also showed that there was a dose-response relationship between the effect of smoking exposure and the risk of new onset asthma. Several epidemiological studies have also shown strong a correlation between parental smoking and the development of asthma in children.[18–21] A recent systematic review and meta-analysis of 76 studies examining the effect of exposure to prenatal or postnatal passive smoke reported a 21% to 85% increased risk of incident asthma in children.[20] Similarly, secondhand tobacco smoke (SHS) exposure is also associated with the development of asthma in adolescents and adults.[19] Interestingly, childhood exposure to passive smoke has also been shown to be associated with an increased risk of developing asthma as an adult, with an odds ratio (OR) of 1.9 (95% confidence interval [CI], 1.6 to 3.2).[22] Thus, it seems that the increased risk after being exposed to SHS in childhood can be carried into the adulthood.

SHS exposure is particularly relevant in urban childhood asthma because more than one-half of inner-city U.S. children with asthma live with a smoker at home.[23] Although some studies have reported no effect of SHS exposure on asthma symptoms or asthma-related healthcare use,[24] others have found a clear association between SHS exposure and asthma morbidity in children.[25,26] A recent public smoking ban in the United Kingdom was associated with a marked reduction in childhood asthma hospitalizations, suggesting a causal link between SHS exposure and childhood asthma morbidity.[27]

Pollution

Despite attempts and some successes to improve air quality over the decades, current U.S. national trends suggest that exposure to outdoor and indoor air pollution remains a significant risk factor for both the development of asthma and the triggering of asthma symptoms.[28]

A substantial disparity in asthma prevalence and morbidity among urban children compared to non-urban children has been recognized for more than 2 decades.[29] Because of the nature of urban neighborhoods, pest allergens, such as cockroach and mouse, are present in high concentrations in U.S. urban housing and both of these allergens are linked to asthma morbidity in sensitized children.[30] In addition, there is a growing body of evidence showing that concentrations of many pollutants are higher indoors than outdoors in both U.S. and European urban communities and that exposures to indoor pollutants such as particulate matter (PM) and nitrogen dioxide (NO_2) are independently associated with symptoms in children with asthma.[29] It has been shown that environmental interventions can reduce relevant indoor allergen and pollutant exposures and they are associated with clear improvements in asthma.[31,32] Other modifiable risk factors in urban childhood asthma include dietary and nutritional factors, being overweight, and insufficient vitamin D and folate, all of which have been shown to increase both the risk of asthma and asthma morbidity in children.[33–35]

The best-studied indoor pollutants include airborne PM, NO_2, and SHS. Airborne PM is typically measured in different-sized fractions, so that fine PM is considered PM with an aerodynamic diameter of 2.5 μm or less (PM2.5) and coarse PM is considered PM with an aerodynamic diameter of greater than 2.5 μm and up to 10 μm (PM2.5–10). Both fine and coarse PM comprise PM10. SHS exposure is composed of many substances, which are both particulate and gaseous in nature. SHS contributes predominantly to the fine particle (PM2.5) fraction of airborne PM, and the most commonly measured gaseous component of SHS is airborne nicotine.[30]

It has been shown that the indoor PM concentrations in urban homes is as much as 2 times higher than the concentrations in nonurban homes.[36–40] The most common indoor sources for PM2.5 and PM10 are smoking, sweeping, and stove use. Both indoor PM2.5 and PM2.5–10 exposures are

associated with more asthma symptoms and rescue medication use in urban children with asthma.[37] Additionally, NO_2 is the byproduct of combustion reactions, and homes with gas-powered appliances have higher levels of NO_2 than homes without gas-powered appliances; also, indoor NO_2 levels are higher than outdoor NO_2 levels in urban homes. In many U.S. cities, gas stoves and heat are prevalent, and some families will use their gas stoves and ovens for heat. In contrast to PM, outdoor NO_2 has little to no influence on indoor NO_2 concentrations.[30]

Additional aspect to the problem is that susceptibility to the respiratory effects of exposure to air pollution has been shown to be elevated within overweight patients.[41] It has been reported that overweight or obese children had more asthma symptoms, but not worse lung function or airway inflammation, after higher exposure to fine particulate matter and NO_2 than normal-weight participants across a range of asthma symptoms.[42]

Obesity

In addition to increasing the risks of the respiratory effects of air pollution, obesity alone has a significant impact on asthma risk, phenotype, and prognosis. Epidemiological studies have clearly demonstrated that asthma is more likely to occur in obese patients, and health status is impaired in obese individuals with asthma, with such asthmatics experiencing more symptoms, worse quality of life, increased healthcare use, and increased asthma severity.[43,44]

It has been suggested that immunological mechanisms and increased airway inflammation relevant to both disorders may link asthma and obesity. In addition to increasing the risk of developing asthma, these pathways may also converge to enhance airway inflammation, and skew asthma toward a more difficult-to control phenotype,[45,46] as well as altering response to therapy,[47,48] particularly glucocorticoid (GC) response. However, it has also been shown that obesity can cause dyspnea and asthma symptoms, mechanically reducing lung function without any inflammatory effects. The relationship between obesity and asthma is an important one for additional study.

Occupational risk factors

Work environment is an important potential risk factor for asthmatic patients both as a risk factor in terms of its development, and in terms of disease exacerbation. Occupational asthma (OA) is a form of asthma that is often underdiagnosed and underreported, and when unrecognized can lead to progression of disease and increased morbidity. Traditionally, sensitizers to occupational asthma have been divided into high–molecular weight compounds (HMW) and low–molecular weight compounds (LMW).[49] The most relevant causes of HMW agents include flour dust, enzymes (plant and animal derived), gums, foods, tobacco, rubber-derived proteins, animal-derived and insect-derived allergens, and fish/seafood–derived allergens. The most relevant LMW agents include Western red cedar, polyisocyanates and their polymers, acid anhydrides, metals, and a spectrum of chemical substances.[50,51] The diagnosis of OA has a significant impact on the future employment, health, and the socioeconomics of the worker, but this should be considered in every asthma patients with poor asthma control. It is critical to keep in mind that a careful history of work-related exposures is included in evaluation of a patient with chronic cough, asthma, and allergic rhinitis.[52]

Microbes

Viral and bacterial infections are important factors in asthma pathogenesis, and patients with asthma may be more susceptible to viral and bacterial infections as a result of impaired mucosal and systemic immune defense and atopy. Bacterial colonization of the airway and gut mucosal surfaces seem to play an important part in the defense mechanism, and both host factors and the result of infections contribute to the development and progression of asthma.[53]

Viral infections are the most common cause for upper and lower respiratory tract infections (URTI and LRTI). The most commonly identified viruses causing respiratory tract infections in children are human rhinoviruses (HRVs), respiratory syncytial virus (RSV), influenza and parainfluenza viruses, coronavirus, adenovirus, human metapneumovirus, and bocavirus.[54–56] Several studies have shown that there is an association between early viral LRTIs and the development of childhood wheeze and asthma.[54,57,58] The mechanism of this association is not clear, but potential mechanisms could be that viruses might predispose to the onset of wheeze and asthma, that viral infections merely unmask host factors underlying disease susceptibility, or that viruses might trigger wheeze and asthma and thereby aggravate airway inflammation.[57] The role of the bacterial microbiome in shaping immune responses to viral infections is currently unknown.

In a longitudinal birth cohorts study,[59] viral LRTI during the first 3 years of life was shown to be an independent determinant of wheeze at age 6 years. This risk decreased until age 11 to 13 years and was accompanied by a reduction in forced expiratory volume and increased responsiveness to salbutamol, implying a lasting change in the regulation of airway smooth muscle tone. Another birth cohort study reported that about 13% of childhood asthma cases were attributable to infant LRTIs during the RSV season.[60]

In a recent review by Fuchs and von Mutius,[53] the authors propose a theory for the role of viruses and bacteria in the development of childhood asthma. They identify 4 primary components that could be attributed to the development of asthma: (1) altered airway function and mechanics; (2) impaired mucosal immune responses; (3) impaired systemic immune responses; and (4) atopic sensitization. These components could be formed prenatally depending on the genetic background of the mother and offspring, as well as by maternal environmental exposures during pregnancy, such as tobacco smoke, antibiotic use, infections, and microbial environments.

Hygiene hypothesis

Childhood infections and exposure to certain microbial antigens on the other hand seem to present a strong negative correlation with allergies, and therefore the increase of the allergic burden in the Western world has been frequently related to a decline of childhood infections, giving birth to the "hygiene hypothesis." The hygiene hypothesis is based on large epidemiological data demonstrating an increased incidence of asthma and allergic disease in the industrialized world during the last several decades. During this same time period, the increased use of antibiotics, improved hygiene, and urbanization presumably decreased childhood exposure to previously common infections, diverse environmental microorganisms, and their products.[61,62] These events, suggest an inverse relationship between microbiologic diversity and atopic disease, also known as the hygiene hypothesis. An early and prolonged imbalanced expression of the TH2 allergic phenotype can persist in those without an appropriate TH1-directed response to infection in early life. This is supported by mouse models in which pathogen exposure before allergic sensitization favors decreased airway inflammation, airway hyperresponsiveness, and TH2-related cytokines with allergen re-exposure.[63] Recognition of the human microbiome and its systemic immune-modulatory effects further contribute to the hygiene hypothesis although the hypothesis remains somewhat controversial and more studies are needed to evaluate the role of "hygiene" in the development and prevention of allergic diseases.

One of the important findings from the studies of the hygiene hypothesis is that repeated stimulation of the immune system by pathogens has important role in the development of allergic diseases. Besides a potentially protective role of early exposure to bacterial antigens, it is important to emphasize that exposure to both Gram-negative (LPS) and Gram-positive (superantigen) bacterial antigens in already sensitized individuals may promote inflammatory responses, leading to increased severity of allergic disease and asthma. Several factors, such as the route and the period of exposure, the dose, and the genetic background of each patient determine the outcome of the immune response to the pathogens.[64]

Stress

Current evidence suggests a causal association between chronic psychosocial stress and asthma or asthma morbidity. Recent findings suggest potential mechanisms underlying this association, including changes in the methylation and expression of genes that regulate behavioral, autonomic, neuroendocrine, and immunologic responses to stress. There is also evidence suggesting the existence of susceptibility genes that predispose chronically stressed youth to both posttraumatic stress disorder (PTSD) and asthma.[65]

In a study of more than 1200 (predominantly African American) adults exposed to traumatic events, the authors found implications of the pituitary adenylate cyclase–activating peptide (PACAP)-PAC1 receptor pathway on the pathogenesis of PTSD.[66] In this study both PACAP38 (PACAP peptide containing 38 residues) blood levels and the C allele of a functional single-nucleotide polymorphism (SNP) (rs2267735) in an estrogen-receptor element of the gene for the PAC1 receptor (ADCYAP1R1) were significantly associated with PTSD or more PTSD symptoms in female but not in male subjects.

Genetics of asthma

As discussed in the previous section, asthma is a complex genetic disorder. Several genetic and environmental factors are also known to modulate the clinical expression of the disease and its associated phenotypes. In addition to environmental exposures, genetic factors have an important effect on the inception, severity, and treatment of asthma.

Twin studies have shown that there is a genetic element to asthma susceptibility, with heritability of the condition estimated at between 0.36 and 0.77.[67–70] The first study to link a genetic locus (chromosome 11q13) to asthma was published in 1989.[71] Since then more than 600 candidate genes have been described in more than 1000 publications in relation to asthma or an associated phenotype, such as elevated IgE levels, bronchial hyperresponsiveness, or eosinophilia.

Despite the large number of candidate genes identified for asthma, surprisingly few of these candidate gene discoveries have been rigorously replicated, and many have been examined and failed replication in subsequent studies.[72–74] Genes that have been extensively replicated include the beta2 adrenergic receptor gene,[75–77] as well as genes involving cytokines, receptors, signaling proteins, and transcription factors involved in Th1 and Th2 cell differentiation, such as *IL4*, *IL4RA*, *IFNG*, *IFNGR1*, *STAT6*, *GATA3*, and *TBX21*,[78–85] as well as genes involved in the cellular responses that characterize atopic disease, such as *IL13* and its receptor and the *FCER1B* gene.[86–90]

Over the past decade, genomewide association studies (GWASs) have been used extensively to investigate the genetic bases of common complex diseases, including asthma.[91,92] Before GWAS, many candidate gene studies were performed for asthma susceptibility[93,94]; however, most of the positive associations were not replicated in GWASs, because of differences in either phenotype definition or the populations studied (either in terms of ancestry or environmental exposures), or because of false positives. Approximately 30 GWASs have been reported in different populations in the investigation of chromosomal regions that are linked to asthma and atopy, or related phenotypes such as elevated IgE levels, wheezing, and bronchial hyperresponsiveness. The function of the genes are still incompletely known but the has been shown that polymorphisms of different genes affect the origins of asthma, its severity, and its responses to treatment.

Epigenetics

The epigenetic data regarding asthma and allergic disease has expanded in the last decade. Previously thought of only in terms of cell differentiation, it is now evident that

epigenetic events regulate many processes. With T cell activation, commitment toward an allergic phenotype is tightly regulated by DNA methylation and histone modifications at the Th2 locus control region. When normal epigenetic control is disturbed, either experimentally or by environmental exposures, Th1/Th2 balance can be affected.[95]

Chemical modification of DNA and histone proteins that can be passed down to offspring could have a crucial role in translating environmental interactions into changes in expression of specific disease-related genes. Epigenome-wide association studies are a promising approach through which this interaction can be systematically explored.[96] However, investigators have to be cautious when the direction of causality is unknown, because epigenetic changes could be either a cause or a consequence of disease.[97] Investigation of epigenetic processes (such as CpG methylation and histone modification) and genomewide interaction studies are providing new insights into how environmental and genetic factors interact.

Development of allergy and asthma is determined by interplay between environmental and inherited factors, the later accounting for over one-half of the risk.[98] Interestingly, this is in high contrast with the low fraction of variance in asthma prevalence (4%) that can be accounted for by genetic loci in a large-scale GWAS.[99,100] As with other complex diseases, GWASs have identified common genetic variants that confer susceptibility to asthma but do not account for a large proportion of its heritability. This "missing heritability" of asthma might be explained by unaccounted phenotypic heterogeneity,[101] structural variation (eg, copy number variants),[102] rare genetic variants with strong effects,[103] gene-gene interactions,[104] gene-environment interactions,[105,106] or epigenetic mechanisms, such as DNA methylation[107] or microRNAs.

Conclusion

Asthma is a common disorder with a dramatically increased incidence in the past decades. There are several theories as to why this increase is happening, but the reasons for this epidemic in Westernized nations are not fully known. It seems however, that there is an association with a Th-1–Th-2 imbalance which is affected by decreased and altered microbial exposure, pollution, epithelial microbiome changes, increased obesity, and nutritional factors. Although the genetic aspects of the disease have been widely investigated and many candidate genes identified, epigenetic and environmental factors appear to play a major part in phenotype expression, and additional work is required to further explore the epigenetics of this disease. Because of the close relationship between asthma and chronic rhinosinusitis, especially eosinophilic nasal polyposis, it is important that otolaryngologists and especially rhinologists have a good understanding of asthma, the etiologic factors associated with disease, and its evaluation and management.

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