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Increasing Prevalence of Allergic Disease and Its Impact on Current Practice

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Abstract

Purpose of Review To summarize the most up-to-date literature on allergic diseases with an emphasis on understanding the increase in prevalence of allergic diseases.

Recent Findings As atopy continues to rise, there is increasing evidence that genetic factors in addition to environmental factors contribute to the development of allergic disease. There is research to support that worsening air pollution and climate change as well as lifestyle changes such as an increase in saturated fats and sugars in the diet, antibiotic use, changes in the gut microbiome, and a shift towards a more sterile, more urbanized environment could all increase the likelihood of developing allergic diseases.

Summary While the options available for management of allergic diseases are increasing and improving, the prevalence of allergic disease continues to rise. Further investigation of how we can influence the changes in our environment leading to increases in atopy as well as the genetics involved is crucial in order to prevent the development of allergic diseases.

Keywords Atopy · Prevalence · Allergic rhinitis · Asthma · Allergic conjunctivitis

Introduction

The past half-century has witnessed an allergy epidemic, with substantial epidemiological data that validate a real and disquieting increase in the prevalence of atopic diseases. These include IgE-mediated allergic rhinitis, conjunctivitis, asthma, food allergies, and atopic dermatitis. This increase in prevalence not only was first recognized in industrialized countries, but is now also problematic in the developing world. This has been attributed to a complex interaction between elements of Westernized lifestyle, such as diet, the hygiene hypothesis, air pollution, climate change, and urbanization. However, there is at present no definitive culprit.

The "atopic march" theorizes that all allergic diseases are related, and refers to the natural history of clinically apparent allergic disease. This often progresses from allergic sensitization in early infancy to atopic eczema in childhood, followed by food allergy, asthma, and allergic rhinitis later in life. While there is a lot of evidence to support some version of this theory, other studies indicate distinct individual phenotypes rather than progressive evolution [1]. What we do know is that all of these atopic diseases appear to be related, and understanding the genetic and environmental factors responsible for their rise is crucial for prevention and treatment. Here, we will focus on reviewing the epidemiology and risk factors for allergic rhinitis, conjunctivitis, and asthma, and implications for diagnosis and management (Fig. 1).

Asthma

Rather than being a single disease, asthma is now considered to be caused by several heterogenous disease entities with common manifestations of wheezing, shortness of breath,

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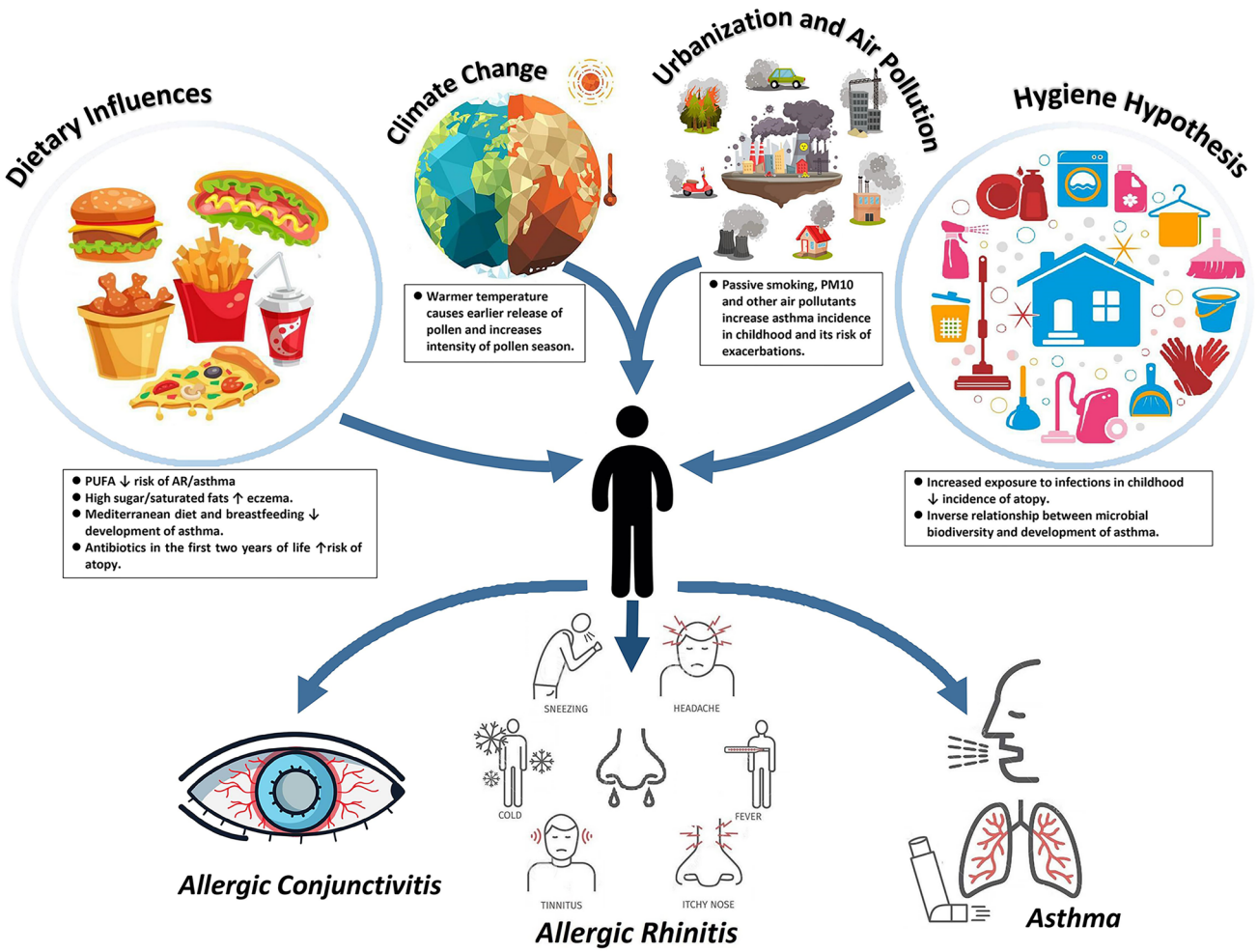

Fig. 1 Factors associated with the increasing prevalence of common allergic conditions

chest tightness, and cough due to chronic airway inflammation [2•]. The prevalence of asthma has markedly increased in the past 50 years and is viewed as a global public health concern. The Global Burden of Disease reported asthma as the most common chronic respiratory disease in 2015, the estimated prevalence being 358 million cases [3]. However, a true assessment of disease burden is confounded by misdiagnosis. Bias in surveillance reports may also over- or underestimate cases. Despite these discrepancies in data collection, it is clear that the incidence and prevalence of asthma have markedly increased in recent years. It is alarming that recent studies describe asthma diagnoses in up to 15–20% of the population in some countries [4]. Further, the World Health Organization extrapolates a further increase in asthma cases by an added 100 million by 2025 [5]. This underscores the need to apply standardized methods to improve the evaluation of longitudinal trends in asthma prevalence.

In the USA, the Center for Disease Control and Prevention (CDC) has executed different surveillance activities to establish asthma burden in terms of occurrence, mortality, and health care utilization. The Vital Statistics System and National Center for Health Statistics (NCHS) surveys are used to collect most of this data. Asthma affects 1–18% of people worldwide according to the 2021 GINA report, about 7.8% of the population in the USA according to the CDC, and affects adults and children equally [6]. Overall, a decline in annual asthma mortality was reported between 1999 and 2016 in the USA [6].

Despite this overall decrease in mortality, children and ethnic minorities experience disproportionate asthma burdens [7•]. It has been long recognized that inner city children are at increased risk for asthma as well as adverse disease outcomes, and these disparities were highlighted in the recent TENOR study [6]. Black race and Puerto Rican ethnicity are clear risk factors, although the weight of influence of socioeconomic factors as opposed to genetic susceptibility remains unknown.

Pediatric findings parallel asthma-related health outcomes in adult populations. In 2015, non-Hispanic blacks had the highest incidence of asthma (10.3%), followed by

non-Hispanic whites (7.8%) [8]. The black population has suffered a nearly 50% increase in diagnosis of asthma over the past decade. This has been associated with a higher rate of asthma mortality that is threefold greater when compared with other races.

Between 5 and 10% of all asthmatics have severe disease with refractory symptoms. Severe asthma accounts for most of disease morbidity and mortality and this is a clear unmet need. Asthma is broadly stratified according to inflammatory endotype as type 2 (eosinophilic) or non-type 2 (non-eosinophilic). A subset of adult-onset type 2 asthma is characterized by a steroid-resistant eosinophilic phenotype [2•]. The majority have comorbid chronic rhinosinusitis with nasal polyps (CRSwNP) that precedes the development of asthma. Patients have prominent sputum and blood eosinophilia despite the absence of atopy that is refractory to glucocorticoid treatment. Some of these patients develop aspirin-exacerbated respiratory disease (AERD), characterized by CRSwNP, asthma, and COX-1 inhibitor-induced respiratory reactions.

Allergic Conjunctivitis

There are many kinds of ocular allergy but the majority of cases are either due to seasonal (SAC) or perennial allergic conjunctivitis (PAC). SAC and PAC are estimated to affect 15–20% of the population. However, an accurate insight into the prevalence of ocular allergy is complicated by multiple factors. Many epidemiologic studies are limited by relying solely on questionnaires rather than objective clinical evidence of allergic disease. Also, most reports do not distinguish specifically between allergic rhinitis and allergic conjunctivitis symptoms. Rather, allergic conjunctivitis is viewed as a secondary manifestation of allergic rhinitis.

The cardinal symptom of ocular allergy is itch. In the absence of itch, another diagnosis for a patient's ocular symptoms should be considered. Other symptoms that can accompany ocular allergy include conjunctival erythema, chemosis, and periorbital edema [11]. The diagnosis of ocular allergy is mostly clinical but skin testing or serum testing for IgE antibodies can help in making the diagnosis.

Ocular allergies are under-reported for various reasons such as symptom variability and increased focus on nasal and other non-ocular allergy symptoms. Therefore, despite the burden of illness associated with allergic conjunctivitis, it is often under recognized and undertreated except when very severe.

The International Study of Asthma and Allergies in Childhood (ISAAC) is a worldwide study established in 1991 that investigates the epidemiology of allergic diseases using the same standardized questionnaire to determine temporal trends in prevalence in different countries. Phase I of ISAAC described the prevalence of allergic conjunctivitis symptoms in two pediatric cohorts: ages 6 to 7 years in 91 centers/38 countries, and ages 13 to 14 years in 155 centers/56 countries. Phase I results reported ocular symptoms in ~ 33 to 50% of children with allergic rhinitis [9].

The Global Asthma Network recently applied the same procedures as ISAAC to survey 45,434 6–7-year-olds and 74,361 adolescents in 27 centers/14 countries [10]. The prevalence of allergic conjunctivitis had decreased slightly from ISAAC Phase III among both pediatric age groups. In another analysis of almost 3,000 patients from the "Alergológica 2015" study, one-third were diagnosed with allergic conjunctivitis that was associated with allergic rhinitis in 88% of cases [12].

Allergic Rhinitis

Allergic rhinitis affects between 10 and 30% of all adults in the USA and other industrialized countries, and as many as 40% of children [13]. In about 80% of cases, AR develops before the age of 20 years and most commonly in early childhood. While the child's immune system evolves through the first and fourth year of life, individuals with an atopic predisposition start to exhibit allergic symptoms associated with an obvious Th2 response to allergen exposure [14]. This is especially prominent among high-risk children in families with atopy affecting both parents. Children in this situation typically develop early-onset symptoms prior to adolescence.

The World Health Organization estimates that 400 million people in the world suffer from allergic rhinitis, with a continued increased in global prevalence as per the ISAAC reports. Allergic rhinitis is among the most common chronic conditions in industrialized countries, and is steadily increasing in prevalence in low- and middle-income countries. Allergic rhinitis is associated with major disability and burden globally, with negative impact on work and school [15], sleep, and decreased participation in outdoor activities among children [16]. The economic effect of allergic rhinitis is similarly substantial due to adverse effects on work productivity [17].

Two large global studies have been conducted between 1990 and 2010 on allergic rhinitis prevalence in children and adults, including ISAAC and the European Community Health Survey (ECRHS) [18]. Similar large studies have not been conducted recently. These studies showed that allergic rhinitis often starts in early life, with a prevalence of > 5% at 3 years. The ISAAC phase III report noted an increase in allergic rhinitis prevalence from 8.5% in children aged 6 to 7 years to 14.6% in the adolescent age group [10]. Overall, the pediatric distribution of allergic rhinitis is more prominent in industrialized countries. The ECRHS study was

conducted in 35 centers and 15 countries. The prevalence of allergic rhinitis in adults aged 20 to 44 ranged from 11.8 in Spain to 46% in Australia [19].

Factors that have been associated with increased prevalence that will be discussed in more detail later include climate change, polluted urban areas, diet, and the microbiome among others. Diagnosis can be made on history and physical exam alone but oftentimes laboratory and/or skin tests can confirm the diagnosis [20].

Factors Contributing to Increase in Allergic Diseases

Air Pollution and Climate Change

Changes in air quality have been theorized to contribute to the increase in allergic disease. One such association is the relationship between nicotine smoke exposure and asthma. A meta-analysis by Burke et al. found that exposure to passive smoking increases the incidence of asthma in children and young adults by at least 20% [21]. Air pollution in general has been linked with severe health outcomes worldwide and was declared to be one of the leading killers of children worldwide by the World Health Organization (WHO) in 2018. In terms of allergic diseases, air pollution has been associated with an increase in asthma exacerbations, as was found in a study that looked at the effects of fine particulate matter ($PM_{2.5}$) on hospital admissions and emergency department visits for asthma [22]. Increasing exposure to $PM_{2.5}$ was associated with sensitization to both aeroallergens and food allergens in another study [23]. A meta-analysis by Orellano et al. found that all pollutants except sulfur dioxide (SO_2) and particulate matter 10 (PM_{10}) were significantly associated with asthma exacerbations in adults and children [24].

Another theory explaining the increasing prevalence of allergic diseases is climate change. Climate change appears to be responsible for increased duration and intensity of pollen seasons [25]. One paper by Manangan et al. found that concentrations of pollen in Atlanta, GA, were increasing and trending towards earlier release [26]. The study used pollen counts for 13 allergenic taxa from 1992 to 2018 and found an overall increase in airborne pollen concentrations. They found that oak pollen was the most abundant and allergenic pollen type and it increased on average 5.2% every year. They also found that for certain kinds of pollen, their seasons were lengthened—increasing exposure overall. The etiology for this trend is thought to be related to climate change, as they found that warmer temperatures were associated with earlier pollen release for certain flora including oak, pine, mulberry, sycamore, and weeds.

Dietary Influences and the Gut Microbiome

Another theory for the increased prevalence of atopic disease involves diet and the gut microbiome. This theory overlaps somewhat with the theory of urbanization/the hygiene hypothesis in some cases, such as in the case of some epidemiological studies that observed lower rates of allergic disease in children that were raised in rural environments linked to exposure to stables as well as raw bovine milk [27]. The Protection Against Allergy Study in Rural Environments (PASTURE) was a study that followed over one thousand children living in rural areas in Europe from birth to age 6 years and found that the risk of developing asthma by age 6 was decreased if there was previous consumption of unprocessed farm milk in comparison to store bought milk [28]. This study concluded that the higher levels of fat content in farm milk, in particular ω-3 polyunsaturated fatty acids, could in part explain this effect. There have also been multiple meta-analyses that have demonstrated reduced risk of asthma development associated with breast feeding [29].

In terms of foods that have been theorized to affect chances of developing atopy, Mediterranean diet was associated with lower odds of both recurrent wheeze and chances of ever developing asthma [29]. The Mediterranean diet is low in saturated fatty acids and rich in fiber, antioxidants, and n-3 polyunsaturated fatty acids (PUFAs). In these diets, n-3 PUFA is usually derived from fish or olive oil. Fatty acids are thought to play a role in the immune response as they are essential components of cells and signaling throughout the body—they are primary components of biological membranes and serve as essential intracellular and extracellular lipid mediators and hormones [30]. There have been studies showing benefit from the early introduction of fish (rich in n-3 PUFA) in reducing the chances of developing allergic rhinitis as well as asthma [30]. On the other hand, higher risk of asthma is reported in populations that consume a diet with a higher ratio of saturated fatty acids as opposed to unsaturated fatty acids [30]. In addition, a study performed in Cape Town, RSA found that compared to children without eczema, children with eczema had a higher daily consumption of total sugar and saturated fat [31].

Not only could the foods consumed be influencing the development of allergic disease, but there have been studies to suggest antibiotic exposure could be a player in the development of atopy. One study by Ni et al. found that the use of antibiotics in the first 12 months of life was significantly associated with lifetime asthma. They did not find this association with allergic rhinitis; however, they did find a significant association between lifetime antibiotics and allergic rhinitis [32]. Another more recent study found that early antibiotic exposure in the first 2 years of life was associated with an increased risk of childhood asthma, allergic rhinitis, atopic dermatitis, and other diseases [33].

Antibiotics can alter the gut microbiome, which is thought to play an important role in predisposition to the development of allergic disease [32]. The results of these studies suggest that the first 2 years of life may be particularly important in stabilizing the gut microbiota. Several clinical research studies link the microbiota of the GI tract, skin, and respiratory tract to allergic disease [27]. By altering the gut microbiome early in life, not only is there a shift in the prevalence of gut microbes but changes are also induced in the production of microbial-derived metabolites like short-chain fatty acids (SCFAs) and other metabolites that interact with immune cells [34]. These metabolites have been associated with decreased inflammation in the lungs of mice. The findings by Arrieta et al. suggest that in humans, the first 100 days of life are a critical window in which gut microbial dysbiosis is linked to asthma and allergic disease [34]. They found reductions in four specific bacteria genera were particularly influential — *Faecalibacetrium*, *Lachnospira*, *Veillonella*, and *Rothia*. Taken together, this information strongly supports the notion that more modern changes in our lifestyles and diet strongly influence the tendency to develop allergic disease.

The Hygiene Hypothesis and Urbanization

The thought behind the hygiene hypothesis is that the more infections someone is exposed to in childhood, the more likely they are to be protected against the development of atopy. In other words, the increase in atopy seen around the world could in part be explained by the overall increase in sanitation and subsequent decrease in infections [35]. One observation that led to the hygiene hypothesis was that children in larger families had a lower incidence of allergic rhinitis and eczema compared to children from smaller families, implying that perhaps larger families were less sanitary and had more exposure to diverse microbiota [27]. Lack of exposure to environmental microorganisms and pathogens is thought to suppress the development of immune tolerance, therefore increasing the risk of atopy [36].

Some literature suggests that exposure to the lipopolysaccharide (LPS) component of the outer membrane of gram-negative bacteria, double-stranded DNA viruses, dendritic cells, and epithelial cells are the key contributors to the hygiene hypothesis [35]. This study proposes that impaired barrier function of the airway respiratory epithelium, as well as downstream epithelial interactions with dendritic cells, can activate immune responses. There are multiple studies that support the hygiene hypothesis by demonstrating how LPS can have protective properties over the development of atopy, including one study by Lin et al. which demonstrated how LPS could attenuate the induction of the pro-allergenic cytokines thymic stromal lymphopoietin (TSLP) and interleukin-33 in respiratory epithelial cells. They found that in comparison to controls (human parechovirus type 1 and toll-like receptor ligand polyI:C) that did stimulate TSLP and IL33, LPS actually reduced their induction [36]. There is some overlap in the hygiene hypothesis and the urbanization hypothesis in regard to the theory that microbial exposure can be protective against atopy.

The theory behind urbanization is that children in urban environments are exposed to less microbial diversity that is thought to be protective against the development of atopy. When studying dust particles in the homes of urban families versus farm homes, richer and more diverse microbial contents were found in farm homes than in their urban counterparts [31]. One case–control study by Mahdavinia et al. sampled dust from the homes of 86 black South African children aged 12–36 months to analyze the bacterial microbiome from dust in the homes of children with and without atopic dermatitis from rural and urban homes. This study found significant differences in the composition and diversity in the dust of the homes of children with and without atopic dermatitis and those that lived in urban versus rural areas [37]. These findings suggest that the composition of house dust could be a factor in the development of atopic dermatitis and possibly influence the development of further atopy. Another study by Birzele et al. demonstrated a significant relationship between environmental microbiota in the development of childhood asthma [38]. This study took DNA from both mattress dust and nasal samples of 86 school aged children and found that there was more bacterial diversity in mattress dust samples from farms and that there was an inverse association between the development of asthma and the bacterial diversity in dust samples and to a lesser extent, nasal samples. These findings reinforce that the microbial environment one inhabits plays an important role that goes beyond mere upper airway colonization in the development of atopic disease.

Genetic Risk Factors

Not only are environmental factors, such as the ones discussed previously, thought to affect the development of allergic disease, but it is also believed that genetic and epigenetic influences also play important roles. As a result of genome-wide association studies (GWAS), which were made available in 2005, many genetic associations with allergic diseases have been found. Overlapping genetic susceptibility loci have been found between multiple allergic diseases. The IL33/IL1RL1 axis and the C11*orf30*/LRR*C32* locus in particular are thought to be important for the development of asthma, atopic dermatitis, allergic sensitization, and blood eosinophil counts [39]. The fact that these allergic diseases have multiple relevant shared genetic loci could further support the theory of the atopic march. Loss-of-function mutations in the filaggrin (FLG) gene has been found to

predispose infants to peanut allergy even when studies controlled for the presence of atopic dermatitis [40]. The association between atopic dermatitis and other allergic conditions such as asthma and allergic rhinitis are not as well defined but one recent GWAS by Ferreira et al. found 99 potential loci that could provide evidence for a shared genetic basis for allergic rhinitis, asthma, and atopic dermatitis [41]. There does also seem to be some variability of important loci depending on ancestry. For example, 17q21, IL1RL1, IL33, and TSLP were found to be important for development of allergic conditions in Caucasian studies whereas PYHIN1 was only found to be important in individuals of African descent [39]. 17q21 has also been found to be significant in Latino populations. More recently, one meta-GWAS study identified 42 genetic loci that were associated with allergic rhinitis alone [42]. To date, there have been many GWAS focusing on asthma. Childhood asthma, severe asthma, and asthma with allergic rhinitis have been found to be linked to the *ORMDL3/GSDMBIZPB2* locus that is found on chromosome 17 [43]. The knowledge of genes associated with allergic conditions continues to expand and with that, hopes of shifting medical practice to a precision medicine model increase but there are still more questions to be answered before the application of omics can be made to patient care.

Clinical Relevance

The increasing prevalence of atopic disease has a direct impact on patient care. Comorbid atopy, such as allergic rhinitis and asthma, are associated with multiple conditions seen in the general otolaryngic practice, such as chronic rhinosinusitis (CRS) and dysphonia. Furthermore, CRS patients with comorbid atopy demonstrate higher rates of disease recalcitrance [44]. While a causal association between atopy and CRS is yet to be established, there is a clear impact on the severity of disease and long-term outcomes following appropriate management.

Conclusion

While there are promising new therapies that have been developed for the management of atopic disease in the recent years, their prevalence continues to rise. There is therefore an urgent need to tackle this burden using a strategic and multipronged approach. Several risk factors are implicated in the development of various phenotypes of atopic disease. Further research is needed to establish the precise role of individual environmental factors that contribute to atopy in order to shift medical practice focus on primary prevention strategies for allergic disease. It is also important to implement public health measures such as improvement of air quality standards to prevent and improve allergic disease.

Compliance with Ethical Standard

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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