

Allergic Rhinitis

Environmental Determinants



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KEYWORDS

• Allergic rhinitis • Environment • Allergen • Sensitization • Risk

KEY POINTS

- The prevalence of allergic rhinitis (AR) has risen in developed countries, and the rate of this change suggests environmental, more so than genetic, factors may be responsible.
- Multiple environmental influences significantly impact the prevalence of AR.
- Allergen exposure is an important determinant of AR. There is strong evidence that allergen exposure triggers symptoms in those with established AR. However, the relationship between allergen exposure and the initial development of AR is highly complex and incompletely understood, because some studies suggest allergen exposure in early childhood increases risk of AR, whereas others suggest a protective effect.
- There are several additional environmental factors that may influence the development of AR, including bacterial exposures (hygiene, farm residence, exposure to other children, endotoxin), air pollution, and environmental toxicants.

INTRODUCTION

The prevalence of allergic rhinitis (AR) has been rising globally, and seems to be associated with a Western lifestyle.¹ In Westernized countries, the prevalence of AR increased from the 1870s to the 1950s, whereas it began rising in developing countries in the late 1980s to early 1990s.^{2,3} AR is now estimated to affect approximately 15% of the general population in Westernized countries,³ and accounts for children in the United States missing about 2 million school days each year.⁴

Certain intrinsic host factors seem to be linked to the development of AR. For example, children with comorbid atopic diseases, such as atopic dermatitis, food allergy, and asthma, have a much greater risk of AR, likely as part of the atopic march of childhood.⁵ Family history of AR and other allergic diseases also is significantly

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associated with the development of AR. For instance, a 2015 German birth cohort study found that only parental AR and comorbid early eczema predicted AR up to age 20 years.⁶ The environmental factors assessed in this study did not predict AR; however, other data strongly suggest an environmental link.

Although there is evidence for a strong genetic component to AR and other atopic disorders, these are complex genetic traits, and their inheritance patterns are incompletely understood.⁷ Furthermore, the rapid increase in prevalence of AR during the twentieth century suggests environmental determinants, instead of or perhaps in association with genetic changes, may be the underlying cause. Several of these environmental changes took effect gradually between the late-1800s and mid-1900s in Westernized countries, and are now taking place, often more rapidly and simultaneously, in developing countries.

The manner in which environmental factors interact with underlying genes to lead to atopic disease is complex.⁸ In the case of asthma, more than 100 genes have been implicated, and multiple environmental factors likely interact with each of those gene products. Also, there is growing evidence that specific epigenetic changes associated with environmental exposures may contribute to the risk of allergic disease.^{9,10} As an example, in mouse studies, a maternal diet rich in methyl donors has been linked to increased allergic inflammation in offspring, mediated through DNA methylation.¹⁰ Additional human studies are needed to further explore the role of epigenetic modifications in atopic disorders.

Because environmental changes may underlie much of the rise in AR prevalence, this article examines the evidence underlying key environmental determinants of AR. The role of hygiene as an AR determinant is first examined, then the contributions of allergen exposure, air pollution, climate change, and environmental toxicants to the development of AR are discussed (**Box 1**). Although some of these factors are known to induce symptoms in those with established AR, the primary focus of this article is to examine the evidence for these environmental exposures as risk factors for the development of AR.

IMPROVED HYGIENE AND BACTERIAL EXPOSURE

The “hygiene hypothesis” posits that improvements in hygiene have resulted in decreased exposure to microbes in early life and thereby an increase in the prevalence of allergic disease.¹¹ The sharp increase in AR prevalence in Westernized countries during the late-1800s to mid-1900s did coincide with important improvements in hygiene, including the separation of drinking water from sewage, which led to reductions in enteric diseases.¹² Other hygiene changes during that time included decreased exposure to farm animals and horses as transportation, chlorination of water, and eradication of malaria and helminth infections.

Aside from these hygiene improvements simply coinciding with the rise of AR, several epidemiologic studies have shown an association between AR prevalence and environmental factors that impact bacterial exposure. For example, early childhood exposures to farms and other children have been demonstrated to protect against AR. A 2013 European study demonstrated a combined effect of family size and farm exposure on childhood AR. The prevalence of AR ranged from 2% among farmers’ children with more than two siblings to 12% among children with no farm exposure and no siblings. No effect modification was found between family size and farm exposure, suggesting different biologic mechanisms underlie the protective effects of each.¹³ Additionally, farm exposure in early childhood is associated with life-long protection against AR. In a large-scale Swedish study, living on a farm during the

Box 1**Potential environmental determinants of allergic rhinitis**

Improvements in hygiene

Bacterial exposures

Farm exposure

Family size/exposure to other children

Mode of dishwashing

Cesarean section birth

Early antibiotic exposure

Endotoxin exposure, level and bioactivity

Indoor allergen exposures

Cat, dog, and furry animals

House dust mites

Rodents (mouse and rat)

Mold and indoor dampness

Occupational allergens

Rodents (laboratory workers)

Latex (health care workers)

Guar gum (carpet workers)

Air pollution

Ozone

Traffic pollutants

Climate change

Environmental toxicants

Antimicrobial products

Triclosan

Parabens

first 5 years of life was associated with lower prevalence of AR in all age groups, even the oldest (up to age 75 years). Increasing degree of urbanization was associated with increased prevalence of AR, independent of childhood farm living, suggesting both childhood and adult exposures may affect AR risk.¹⁴ Cleaning practices of pacifiers and dishes have also been linked to risk of allergic disease. Hand dishwashing, compared with machine dishwashing, has been associated in one study with lower prevalence of AR, asthma, and atopic dermatitis at 7 to 8 years of age.¹⁵ In a Swedish birth cohort study, children whose parents cleaned their pacifier by sucking it were less likely to have asthma, eczema, and sensitization (to airborne and food allergens) at age 18 months. Furthermore, the salivary microbiota differed in those children whose parents sucked the pacifier, suggesting the observed clinical effect was driven by altered bacterial exposures.¹⁶

There is growing evidence that the effect of these altered bacterial exposures is mediated through changes in the gut microbiome during infancy. Cesarean section birth and early life antibiotic exposure have been shown to affect the microbiome composition, and are both also associated with increased risk of atopic disease.¹⁷ In a large European birth cohort study, an increase in certain bacteria in fecal samples from 3-week-old infants was associated with heightened risk of allergic disease later in childhood.¹⁸

Multiple studies have examined the role of endotoxin environmental exposure in modulating allergic response to environmental allergens. Endotoxin may represent a specific bacterial product that affects AR risk. This is supported by findings of polymorphisms in the endotoxin signaling pathway, such as in toll-like receptor 4, which

are associated with greater risk of allergic disease.¹⁹ Alternatively, endotoxin may be a marker more generally of certain types of bacterial exposure. Endotoxin is the best studied, but a variety of microbial products serve as innate immune stimulants and may affect risk of allergic disease, such as peptidoglycans, CpGs, and flagellin.²⁰

The relationship between endotoxin exposure and development of allergic disease seems to be complex. Some studies have found correlations between house dust endotoxin level in infancy and the development of AR in high-risk patients.²¹ An inner-city birth cohort study in New York found that endotoxin levels were positively associated with wheeze, but inversely associated with eczema. No relationship was found with development of AR.²² Another birth cohort in Boston similarly found an inverse relationship between endotoxin level and early eczema.²³ More research is needed regarding the elements of endotoxin exposure that modulate risk. For example, a nested case control study of infants at high risk for allergy in Cincinnati demonstrated that higher house dust bioactivity was significantly associated with lower numbers of positive skin prick test results to aeroallergens. There was no relationship of house dust endotoxin level and aeroallergen sensitization, suggesting the immunostimulatory activity of house dust may better predict risk of aeroallergen sensitization than endotoxin levels.²⁴ Finally, there may be a link between endotoxin and respiratory symptoms independent of allergic sensitization. In an occupational mouse allergen exposure study, allergic-type symptoms among workers who were not sensitized to mouse were associated with endotoxin exposure.²⁵

ALLERGEN EXPOSURE

The rise in AR prevalence in Westernized countries coincided with several housing and lifestyle changes that increased indoor allergen exposure. Allergen exposure in susceptible hosts has been implicated in the development of AR; however, data regarding a protective effect of allergen exposure are conflicting. For certain allergens, such as those derived from dust mites, cockroach, mold, and pollens, a linear relationship between exposure and disease seems to exist, but the same is not necessarily true for pet allergens, such as cat and dog. The timing of allergen and bacterial exposures may be the key factor responsible for discrepancies between study findings. In an urban birth cohort at high risk for asthma, cumulative allergen exposure over the first 3 years to cockroach, mouse, and dust mite was associated with sensitization to those allergens at age 3 years.²⁶ In contrast, exposure to these allergens in the first year of life was negatively associated with recurrent wheeze at age 3. Furthermore, the combination of bacterial exposures in dust and higher allergen levels in the first year was the most protective against later wheeze. These findings, although not specifically related to AR, have important implications for the interpretation of conflicting studies of a link between allergen exposure and AR development. Because the first year seems so crucial, cross-sectional studies or even prospective studies in which allergen exposure is captured after the first year of life would be expected to give different results than those that collected exposure in infancy.

Cat/Dog Allergen Exposure

Despite the prevailing theory regarding the natural history of allergen exposure leading to sensitization and disease, several studies have found that early exposure to furry household pets, such as cats and dogs, may decrease the risk of sensitization and atopic disease, thus having a protective effect against allergic disease. A systematic review of recent birth cohort, cross-sectional, and case-control studies concluded that early life cat exposure is likely to protect against allergic disease. However,

findings are inconsistent because a meta-analysis from 11 prospective European birth cohorts found no clear evidence for either a protective or detrimental effect of cat exposure on sensitization.^{27,28}

The relationship between cat allergen exposure and allergic sensitization is complex. Very high levels of cat allergen in homes do not seem to increase the risk of sensitization, and many children who become sensitized to cat do not live in a house with a cat.²⁹ There are many determinants that may contribute to whether an individual exposed to pet allergen becomes sensitized. Some factors are related to the allergen itself, such as its biologic activity, and the timing, variability, and intensity of the exposure.²⁹ With regard to intensity, very high levels of exposure to pet allergen (unlike other allergens) may be tolerogenic. Community prevalence of pets is also important; particularly if there is no pet exposure at home and community prevalence is low, sensitization will unlikely occur. Furthermore, concomitant exposures to other allergens may influence sensitization, but the complexities of these relationships are poorly understood. For example, in New Zealand, where exposure to dust mites and cat in the home is common, cat exposure has little effect on dust mite sensitization. Meanwhile, in Sweden, where dust mites are rare, cat exposure at home is associated with decreased sensitization to other allergens.²⁹

Concomitant exposure to microorganisms may additionally determine whether pet exposure leads to allergic sensitization. Animals carry endotoxin, pollens, or fungal spores, in addition to pet-derived proteins. Dog ownership is linked to increased airborne endotoxin, but cat exposure is not.³⁰ Cats, however, can serve as vectors for other antigens, such as *Staphylococcus aureus*. Dog exposure also alters the house dust microbiome and the fecal microbiome of children. Further studies are needed to determine whether similar effects can occur with other pets, but collectively these findings raise the possibility that animal allergen exposure and sensitization in itself may not be the mechanism by which animal exposure potentiates or prevents AR.

House Dust Mite Exposure

Increasing house dust mite allergen concentrations are associated with risk of allergic sensitization. Some hypothesize that the changes in homes, making them more airtight, warmer, and more humid, and development of an indoor-centric lifestyle have led to increased indoor allergen exposure, particularly dust mites, and associated allergic disease.³¹ Specific changes, such as increased indoor temperature and wall-to-wall carpeting, may have contributed to enhanced dust mite allergen levels because mites thrive in warm, humid environments and are distributed not only in beds, but also carpet and upholstery. Several studies have demonstrated that increased dust mite exposure in young children is associated with sensitization and increased later risk for development of AR.⁴

Rodent Allergen Exposure

The role of rodent allergen in occupational rhinitis and asthma has long been described (discussed later). However, within the past decade, the importance of rodent allergen exposure in inner-city allergic disease has been uncovered. Mouse allergen is present in much greater concentrations in inner-city homes compared with suburban homes, and exposure to mouse allergen in homes has been associated with sensitization. Inner-city children with asthma who are both exposed and sensitized to mouse have significantly worse asthma morbidity.³² In addition, mouse sensitization in early life has been linked with an increased risk of wheeze, rhinitis, and eczema by age 3 years in an inner-city birth cohort, suggesting that it is a risk factor not only for asthma, but other allergic diseases including AR and eczema.³³

Mold Exposure

Both indoor dampness and mold exposure have been explored as potential determinants of AR. Several studies have found an association between mold exposure and asthma in childhood.¹ A 2013 systematic review and meta-analysis examined the association between mold exposure and risk of rhinitis. Prior studies were inconclusive, and this was the first meta-analysis. It concluded that exposure to dampness and mold at home are associated with increased odds of all rhinitis types, including AR. The association was strongest for mold exposure as measured by mold odor, a surrogate marker for microbial volatile organic acids. These findings suggest that interventions to prevent and remediate indoor dampness and mold may reduce risk of rhinitis.³⁴ A longitudinal study of Finnish children also demonstrated that water damage and moisture on household surfaces were consistent determinants of physician-diagnosed AR to a variety of allergens, again suggesting that indoor dampness and mold exposure play a significant role in the development of AR.³⁵

Allergic Occupational Rhinitis

The natural history of occupational rhinitis argues for a disease model of allergen exposure leading to sensitization and then disease. High-molecular-weight allergens or low-molecular-weight allergens bound to proteins (hapten-protein conjugates) can elicit an allergic response.³⁶ Regular exposure to the allergen in occupational settings leads to sensitization and then development of allergic disease, usually within 1 to 3 years of employment. Occupational AR may be associated with ocular symptoms of allergic conjunctivitis, such as itching, tearing, and redness. The same mechanisms are responsible for occupational allergic asthma.

A well-studied example of occupational AR involves exposure to mice among laboratory workers who then progress to develop sensitization and rhinitis. In an observational study, it was noted that by 2 years almost 25% of workers in a mouse facility developed sensitization (positive skin prick test response to mouse).³⁷ Both the level and variability of mouse allergen exposure were found to influence immune responses. Sensitization increased as exposure levels increased until the peak, beyond which the incidence of sensitization declined. In addition, the more variable mouse exposure was over time, the less likely workers were to develop allergic sensitization.

Other examples of allergens that can induce occupational AR include latex in health care workers, guar gum in carpet workers, and psyllium used in laxatives in nurses.³⁸ Occupational rhinitis is covered in more detail elsewhere (See [Grammer LC: Occupational Rhinitis](#), in this issue).

AIR POLLUTION

Individuals with AR have nasal hyperreactivity, rendering them more responsive to airborne irritants. These irritants likely therefore play some role in exacerbating symptoms of AR. Air pollution is known to have an impact on allergic diseases. Some studies suggest that the irritant effect of pollutants potentiates the allergic immune response.³⁹ Pollution may damage the nasal mucosa and impair mucociliary clearance, thereby facilitating the access of inhaled allergens to the cells of the immune system.⁴⁰ Airborne particles, including diesel fuel exhaust, are also able to carry allergens, thus potentially increasing their spread, or the duration of exposure. However, studies have not demonstrated a consistent link between living in regions with higher air pollution and a higher prevalence of AR.⁴¹ The relationships of ozone and traffic pollution to AR are reviewed next.

Ozone

Ground-level ozone is created by chemical reactions between nitrogen oxides and volatile organic compounds in the presence of sunlight. The major sources of nitrogen oxides and volatile organic compounds include emissions from industrial facilities and electric utilities, motor vehicle exhaust, gasoline vapors, and chemical solvents. In challenge studies, ozone has been noted to directly induce inflammation in the nasal mucosa.⁴² It also has been implicated in increasing allergenicity of tree pollens, such as birch.⁴³ In a Korean study, ozone exposure was associated with AR prevalence in children who resided in industrial areas. In addition, ozone exposure was significantly associated with the rate of newly developed sensitization to outdoor allergens, which may explain the mechanism for the related increase in AR prevalence.⁴⁴

Traffic Pollution

Studies of components of traffic pollution have demonstrated varying degrees of association with AR. It is thought that diesel particles and other irritant gases, such as ozone, exert aggravating effects on allergenicity in AR.¹ These particles may potentiate allergenicity through multiple mechanisms including modification of the nasal epithelium, influencing immune response, and increasing the allergenicity of particular antigens. For example, nasal provocation studies in dust mite-sensitive individuals showed that combined challenge with dust mite allergen and diesel exhaust particles led to enhanced mast cell degranulation and increased severity of clinical rhinitis symptoms.⁴⁵ Increased air pollution has also been associated with increased IgE production against common outdoor allergens, such as tree pollen.³⁹

In a Swedish birth cohort study of 2500 children, air pollution exposure was assessed by outdoor concentration of nitrous oxides (a marker of exhaust particles) and particles of less than 10 μm diameter (a marker of road dust). Pollution exposure during infancy was associated with increased risk of pollen sensitization at age 4 years, but exposures after the first year of life were not associated with later aeroallergen sensitization.⁴⁶ Therefore, the timing of pollutant exposure (during infancy) may be a key determinant in the observed increase in allergic sensitization. However, it is unclear if this sensitization leads to later AR. In a recent prospective study of more than 600 children, diesel exhaust particles exposure during infancy was associated with aeroallergen sensitization at ages 2 and 3 years, but not with AR at age 4 years.⁴⁷

CLIMATE CHANGE

There is some evidence that climate factors may indirectly contribute to increased AR symptom severity (through its effects on the previously mentioned factors, such as pollution and pollen allergens), but not necessarily an increase in AR prevalence. A recent analysis found that regional differences in AR prevalence in the United States were related to a variety of climate factors, including humidity, drought, heat, and precipitation.⁴⁸ The highest prevalence was found in Southeastern and Southern states. No association between changes in climate over time and AR prevalence trends has been found. Therefore, more studies are needed to determine what role, if any, climate factors play in development of AR.

Some studies have suggested that global temperature changes may impact AR disease severity through effects on pollens and air pollutants. For example, temperature changes have been linked to longer duration of pollen seasons (such as ragweed), and a resultant increase in pollen allergen levels.¹ Temperature changes may also increase ozone levels, which as discussed previously are associated with enhanced

allergenicity of birch tree pollen.⁴³ There is also some thought that increased temperature potentiates the effect of air pollution as an irritant.

ENVIRONMENTAL TOXICANTS

Environmental toxicants have increasingly been linked to allergic disease. These include antimicrobial agents, such as triclosan and parabens. Using data from the 2003 to 2006 US National Health and Nutrition Examination Survey, one study found that higher urinary levels of triclosan, but not bisphenol A (an endocrine-disrupting compound used in plastics), were associated with significantly greater odds of AR diagnosis in children younger than 18 years.⁴⁹ In another study that used 2005 to 2006 National Health and Nutrition Examination Survey data, urinary levels of triclosan and parabens were associated with increased odds of aeroallergen sensitization.⁵⁰ Similar associations between urinary triclosan and aeroallergen sensitization, and current AR diagnosis, were found in a study of Norwegian children.⁵¹ The mechanisms of the effects of antimicrobials, such as triclosan, on the immune and respiratory systems remain unknown. In a mouse model of asthma, triclosan exposure alone was not observed to be allergenic; however, coexposure with a known allergen (ovalbumin) resulted in enhanced allergic response to that allergen.⁵² Given how commonly antimicrobials are used in Westernized countries, more research is warranted to further examine their potential role in allergic disease.

SUMMARY

Increases in prevalence of AR may be related to a host of environmental factors that interact with underlying genetic predisposition. There is significant evidence that early life bacterial and allergen exposures serve as important environmental determinants of later AR. However, the exact mechanisms by which these exposures modulate AR risk are poorly understood, as evidenced, for example, by the complex relationship between pet allergen exposure and subsequent AR. Less is known about the role, if any, that air pollutants and climate change may play in the prevalence of AR. Further research is needed to delineate the most important environmental determinants of AR and their mechanisms of action, so that future prevention strategies may be devised targeting these environmental factors.

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