Clinical reviews in allergy and immunology

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The role of air pollutants in atopic dermatitis

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Activity Objectives

1. To review the major environmental pollutants.
2. To understand that exposure to pollutants is associated with development and exacerbation of atopic dermatitis (AD).
3. To describe the possible biologic mechanisms responsible for the role that pollutants play in AD.

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Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease and a growing health concern, especially in children, because of its high prevalence and associated low quality of life. Genetic predisposition, environmental triggers, or interactions between them contribute to the pathophysiology of AD. Therefore, it is very important to identify and control risk factors from the environment in susceptible subjects for successful treatment and prevention. Both indoor and outdoor air pollution, which are of increasing concern with urbanization, are well-known environmental risk factors for asthma, whereas there is relatively little evidence in AD. This review highlights epidemiologic and experimental data on the role of air pollution in patients with AD. Recent evidence suggests that a variety of air pollutants, such as environmental tobacco smoke, volatile organic compounds, formaldehyde, toluene, nitrogen dioxide, and particulate matter, act as risk factors for the development or aggravation of AD. These air pollutants probably induce oxidative stress in the skin, leading to skin barrier dysfunction or immune dysregulation. However, these results are still controversial because of the low number of studies, limitations in study design, inaccurate assessment of exposure and absorption, and many other issues. Further research about the adverse effects of air pollution on AD will help to expand our understanding and to establish a better strategy for the prevention and management of AD. (J Allergy Clin Immunol 2014;134:993-9.)

Key words: *Air pollution, atopic dermatitis, environmental tobacco smoke, volatile organic compounds, formaldehyde, toluene, particulate matter*

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease mostly occurring in early childhood. According to Phases I and III of the International Study of Asthma and Allergies in Childhood, the prevalence of eczema in children aged 6 to 7 years and 13 to 14 years is still increasing in both developing and developed countries.[1] The natural course of AD over time varies considerably, largely depending on severity and atopic sensitization.[2,3] Moreover, many children with AD have asthma or allergic rhinitis as they grow older.[4-6] Because of its high prevalence and progression into respiratory allergies, AD is one of the major medical problems in children.

The pathogenesis of AD involves both skin barrier defects and immunologic dysregulation.[7] The epidermal barrier is found in the stratum corneum, the outermost part of the epidermis, in which corneocyte layers are locked by corneodesmosomes and embedded

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Abbreviations used
AD: Atopic dermatitis
CGI: 5′-CpG island
CO: Carbon monoxide
DNP: Dinitrophenylhydrazone
ETS: Environmental tobacco smoke
NO_2: Nitrogen dioxide
NO_x: Nitrogen oxide compound
OR: Odds ratio
PM: Particulate matter
$PM_{2.5}$: Particulate matter with a diameter of 2.5 μm or less
PM_{10}: Particulate matter with a diameter of 10 μm or less
ROS: Reactive oxygen species
TRPA-1: Transient receptor potential ankyrin 1
TRPV-1: Transient receptor potential vanilloid 1
TSLP: Thymic stromal lymphopoietin
VOC: Volatile organic compound

in a lipid-enriched intercellular matrix.[8] In particular, the cornified envelope of corneocytes plays an important role in maintaining the structural integrity of the skin barrier and is composed of various structural proteins, such as loricrin, involucrin, filaggrin, and small proline-rich proteins.[8] It is hypothesized that primary impairment of the skin barrier and subsequent penetration of allergens causes the development of AD, which is known as the "outside-inside" hypothesis. Examples are loss-of-function mutations of genes encoding structural proteins, such as filaggrin, or barrier damage induced by washing with soap and detergents.[8-10] Conversely, prior immunologic predisposition induces skin barrier defects, resulting in the development of AD, which is the so-called "inside-outside" hypothesis. Indeed, increased expression of T_H2-type cytokines, such as IL-4 and IL-13, downregulates the expression of epidermal proteins, including filaggrin, loricrin, and involucrin, leading to skin barrier defects in patients with AD.[11-13]

Many studies also have focused on the role of environmental factors in worsening symptoms in patients with pre-existing AD. Pruritus and eczema can be exacerbated by aeroallergens, such as house dust mites, animal dander, and pollens.[14-16] AD can be complicated by skin infections, such as *Staphylococcus aureus* and herpes simplex virus.[17-19]

Cases of AD have been classified as intrinsic and extrinsic according to the presence of specific IgE against environmental allergens.[20,21] Intrinsic AD has been considered a distinct phenotype that is not caused by exposure to allergens but induced by different causes.[22,23] In contrast, a new hypothesis about the natural history of AD has proposed that intrinsic AD might be the first manifestation of extrinsic AD before sensitization is induced by inhalant or food allergens.[7] No matter which hypothesis is true, it is obvious that there are causative factors other than allergens and that these factors should be identified for the prevention of AD.

Genes, environmental factors, or interactions between them are known to be responsible for the development of AD. There is little doubt that the recent increase in the prevalence of AD is attributed to increased exposure to a variety of triggers in our environment rather than abrupt genetic alterations. Environmental factors are also likely to aggravate AD by causing further damage to the skin barrier or immune responses. Among a number of environmental triggers, indoor and outdoor air pollutants have been considered potential risk factors for the development or exacerbation of AD. Although it is very important to identify and control environmental risk factors for the successful treatment or prevention of AD, investigations to elucidate the role of air pollution in patients with AD remain a challenge.

OUTDOOR AND INDOOR AIR POLLUTANTS

Air pollutants are various substances in the air that can have hazardous effects on human health. They exist in either a particulate or gaseous form and are classified as primary or secondary pollutants. Major primary pollutants include sulfur oxide compounds, nitrogen oxide compounds (NO_x), carbon monoxide (CO), volatile organic compounds (VOCs), particulate matter (PM), toxic metals (eg, lead and mercury), ammonia, and radioactive pollutants, such as radon. Secondary pollutants are formed from primary pollutants in the atmosphere through chemical and photochemical reactions. Examples are ground-level ozone, nitrogen dioxide (NO_2), sulfuric acid, and smog.

Air pollutants are present everywhere and can originate from either indoor or outdoor sources. Outdoor air pollutants make up a complex mixture found in ambient air. They come from many sources, being of both natural and man-made origin. Natural sources include wildfires, volcanoes, biologic decay, and dust storms. Of more concern are man-made air pollutants from motor vehicles, biomass burning, and stationary sources, such as power plants, manufacturing facilities, and waste incinerators. Sulfur dioxide, CO, and NO_2 are typical outdoor air pollutants from fuel combustion or motor vehicle emission. Ozone is formed from a chemical reaction between VOCs and NO_2 in the presence of sunlight and causes health problems. PM is a mixture of particles with various chemical compositions and physical properties. It is classified according to its size, which is the primary determinant of where the particles can be deposited in the human body, as particulate matter with a diameter of 10 μm or less (PM_{10}), particulate matter with a diameter of 2.5 μm or less ($PM_{2.5}$), and particulate matter with a diameter of 0.1 μm or less. Diesel exhaust is another example of a traffic-related outdoor air pollutant that is known to have a harmful effect on patients with allergic diseases.[24,25]

On the other hand, indoor environments have a range of air pollutants from sources that include tobacco smoke, stoves, construction materials, furniture, and electronic devices. Allergens and biologic materials, such as house dust mites, animal dander, mold spores, and bacteria, are the sources of biologic pollutants that are found ubiquitously indoors. From a health perspective, concerns regarding indoor air pollution are increasing because people spend most of their time indoors in their homes, schools, and public buildings. Indoor air pollutants include VOCs, PM, and combustion pollutants, such as sulfur dioxide, CO, and NO_2. Benzene, toluene, ethylbenzene, xylene, formaldehyde, and many other compounds are VOCs commonly found at home or in other buildings. Indoor PM originates partly from the outside, depending on the degree of ventilation of the building, whereas there are many indoor sources of PM as well. The concentration of indoor air pollutants is influenced by a subject's lifestyle, socioeconomic status, and cleaning frequency.

The risk of air pollution is represented as a function of the hazard of the pollutant and the extent of exposure. The route of exposure to air pollutants is mainly through inhalation, ingestion, and skin contact. Prenatal exposure might affect the development of the fetus through the transplacental route.[26-28] The extent of exposure to air pollutants in a subject is determined by the concentration at the point of contact and the duration of exposure. Numerous