

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:	Dinitrophenylhydrazine
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, down-regulates 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 (NO₂), 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 NO₂ are typical outdoor air pollutants from fuel combustion or motor vehicle emission. Ozone is formed from a chemical reaction between VOCs and NO₂ 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 (PM₁₀), 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 NO₂. 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

environmental pollutants exposed to the skin permeate the epidermal barrier and could enter the systemic circulation through capillaries in the dermis.²⁹ These compounds evaporate from the surface of the skin, bind to the stratum corneum, penetrate into the epidermis, or become metabolized. In this process the structural and functional integrity of the epidermal barrier seems to be directly damaged at the sites of contact or impaired through indirect pathways, such as increased inflammation. However, there are still many difficulties in investigating the role of air pollution in patients with AD. Further effort is needed to determine the best way to assess the extent of dermal exposure to indoor and outdoor air pollutants in each subject. Moreover, the amount of dermal absorption of the pollutants should be estimated in order to evaluate their effect on the skin, because the extent of absorption differs from that of dermal exposure and is influenced by many other factors, such as the components of the pollution, exposure concentrations, surface area exposed, and permeability coefficient.

AIR POLLUTANTS ASSOCIATED WITH DEVELOPMENT OF AD

A number of cross-sectional studies have shown that air pollution influences the prevalence of AD. In a study involving 4907 French children (9-11 years of age) residing at their current address for 3 years or longer, lifetime eczema was significantly associated with 3-year averaged concentrations of PM₁₀, NO₂, NO_x, and CO³⁰; adjusted odds ratios (ORs) were 1.13, 1.23, 1.06, and 1.08, respectively. A study of 7030 children aged 6 to 13 years demonstrated a positive correlation between AD and maternal smoking during pregnancy, in the first year after birth, or both (OR, 2.06).³¹ A history of living in a newly built house during the first year of life was positively correlated with AD in schoolchildren.³² In a nested case-control study comprising 198 cases and 202 control subjects aged 3 to 8 years, eczema symptoms in children were associated with the concentration of butyl benzyl phthalate in dust collected from their bedrooms.³³ However, in these cross-sectional studies there was a selection bias by misclassification because the diagnosis of AD was based simply on reports from the patients or their parents and was not confirmed by a physician. In addition, because of the limitations of study designs, a causal relationship could not be proved. For example, CO and NO_x might be surrogate indicators of traffic-related air pollution rather than causes that provoke eczema symptoms, although they were positively associated with eczema.

Birth cohort studies are more advantageous than cross-sectional studies in determining causal relationships. Two birth cohort studies in the Munich metropolitan area revealed strong positive associations between the distance to the nearest main road and eczema.³⁴ It was also found that NO₂ exposure was positively associated with doctor-diagnosed eczema (OR, 1.18). In a German birth cohort study involving 2536 children, redecorating activities, such as painting, floor covering, and new furniture, before birth and in the first year of life were associated with the development of AD during the study period of 6 years (OR, 1.95).³⁵ Prenatal exposure to VOCs or environmental tobacco smoke (ETS) is likely to induce a T_H2-dominant immune status or the development of AD after birth.^{28,36-39} Prenatal exposure to PM_{2.5} in combination with postnatal exposure to ETS might increase the risk of eczema in infants (OR, 2.39).⁴⁰ In this study the estimated incidence rate ratio for eczema symptoms was 1.55 (95% CI, 0.99-2.44) when infants

had high exposure to prenatal PM_{2.5} and postnatal ETS. In the urban US birth cohort study, exposure to butyl benzyl phthalate during pregnancy was associated with eczema development at 2 years of age.²³ Birth cohort studies suggest that both indoor and outdoor air pollution are risk factors for the development of AD. However, these studies were observational and limited in exposure assessment. Available evidence is still too scarce to confirm whether the development of AD can be caused by exposure to air pollutants during the prenatal and postnatal periods.

AIR POLLUTANTS ASSOCIATED WITH AGGRAVATION OF AD

Most cases of AD develop in infants and young children, 60% occurring during the first year of life and up to 85% occurring before the age of 5 years.⁴¹ Thus, recurrent or persistent eczema symptoms in older children or adolescents are partly explained by the failure to avoid triggers in the environment. Numerous cross-sectional studies with large study populations revealed an association between exposure to air pollutants and current eczema. For example, a nationwide survey of middle school students in Taiwan involving 317,926 children demonstrated that flexural eczema was positively associated with exposure to traffic-related air pollutants, such as CO and NO_x.⁴² In a study using a dispersion model, eczema symptoms in the previous year were significantly associated with benzene, PM₁₀, NO_x, and CO exposure in 9- to 11-year-old children.³⁰ There was an association between AD severity and indoor remodeling activities, such as painting ($P = .004$), floor covering ($P = .001$), and wallpapering ($P = .002$).⁴³ However, definitive results suggesting that air pollution aggravates AD symptoms could not be obtained from these studies when a variety of confounders that could have exacerbated eczema symptoms were considered.

In a prospective study to evaluate the clinical effects of outdoor air pollution on skin symptoms in children with AD, 22 patients were followed on a regular basis for 18 months.⁴⁴ In this study, concentrations of outdoor PM₁₀, PM_{2.5}, toluene, and total VOCs were higher on days when the patients had symptoms of AD than on days when they reported no symptoms. Analysis with a generalized linear mixed model revealed that a 1-ppb increase in benzene concentration was associated with a 27.38% increase in AD symptoms. A 1-ppb increase in total VOC concentration was related to a 25.86% increase in AD symptoms on the following day. Although the effect was small, an increased PM₁₀ concentration by 1 $\mu\text{g}/\text{m}^3$ was significantly associated with a 0.44% increase in AD symptoms on the following day.

The effect of PM on AD was also investigated in a longitudinal study of 41 schoolchildren aged 8 to 12 years.⁴⁵ For 67 consecutive days, daily symptom scores were recorded, and daily PM concentrations were measured on the rooftop of the school building. By using linear regression analysis, it was found that the itching score was significantly associated with the concentrations of ambient ultrafine particles with a diameter less than 0.1 μm but not of larger particles, after adjustment for confounding factors, such as age, sex, height, SCORAD index, commuting time, and temperature.

A causal relationship between air pollution and aggravation of AD symptoms was directly investigated by using a provocation test. Eberlein-König et al⁴⁶ evaluated the effect of formaldehyde or NO₂ on AD after short-term exposure in a single-blind study. Adults with AD and control subjects were exposed to formaldehyde, NO₂, or room air in a climate chamber for 4 hours. Patients and control subjects were not identical in each exposure. The authors found

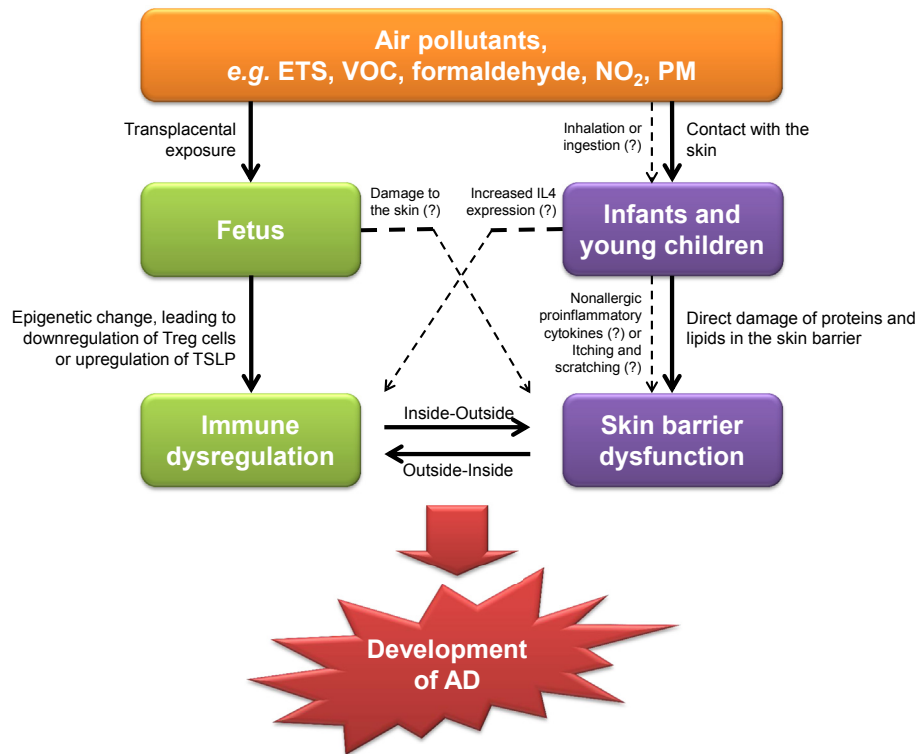


FIG 1. A proposed mechanism by which exposure to air pollutants affects the development of AD. For example, transplacental exposure to ETS during pregnancy causes epigenetic changes, such as upregulation of microRNA-223 or hypomethylation of the TSLP gene *CGI*. These changes reduce the number of regulatory T cells or increase the expression of TSLP protein, leading to T_H2 polarization. Postnatally, the skin is directly contacted by a variety of air pollutants, which produce ROS and reactive nitrogen species. This oxidative stress leads to damage to proteins and lipids in the epidermis, subsequently resulting in skin barrier dysfunction. Prior immunologic dysregulation or T_H2 polarization induces skin barrier dysfunction and vice versa. Damage from air pollution could occur in a normal fetus, an infant, or a young child who is at the developmental stage or in a subject with genetic predisposition. Another route of exposure to air pollutants might be through inhalation or ingestion. Animal experiments and *in vitro* studies suggest that release of nonallergic proinflammatory cytokines, induction of itching and subsequent scratching, or an increase in the expression of IL-4 possibly contributes to the development of AD. Although transplacental exposure to air pollutants might directly impair the skin barrier in a fetus, there has been no evidence thus far.

that exposure to formaldehyde and NO_2 increased transepidermal water loss in patients with AD, whereas exposure to room air did not.

The effect of VOCs on the skin was examined in a double-blind crossover study.⁴⁷ In this study, 12 adults with AD and 12 healthy control subjects were exposed to Der p 1 on their forearm and subsequently to a mixture of VOCs on their whole body in a chamber for 4 hours. It was demonstrated that VOCs increased transepidermal water loss in patients with AD 48 hours after exposure and that dermal blood flow was enhanced by prior exposure to Der p 1. These studies indicate that skin barrier function in patients with AD is impaired by exposure to formaldehyde, NO_2 , or VOCs. More data on human exposure studies are required to confirm the hazardous effect of air pollution on AD.

POSSIBLE MECHANISMS

Air pollutants are considered one of the potential risk factors for the development of AD, although the exact biologic mechanisms remain unclear. Air pollutants, through the production of

reactive oxygen species (ROS) and reactive nitrogen species, lead to damage of proteins, lipids, and DNA.^{48,49} In the skin, exposure to environmental pollutants causes imbalance between oxidants and antioxidants, and this oxidative stress has been implicated in the aggravation of AD in various ways. The skin barrier appears to be directly damaged by oxidative stress initiated by external pollutants. In a study of 75 adults with AD, the biopsied skin samples were analyzed by using the spectrophotometric assay of dinitrophenylhydrazine (DNP) to measure the content of carbonyl moieties, a marker of oxidative protein damage. In this study, DNP formation increased significantly in AD lesions and was correlated with AD severity. It was also noted that immunohistochemical staining of DNP was more intense in the superficial layers of the stratum corneum than in the lower layers, indicating that oxidative damage might be attributed to exposure to environmental oxidants, such as air pollutants and solar radiation. The authors concluded that increased ROS generated from environmental pollution and solar UV light can induce oxidative protein damage in the stratum corneum, resulting in skin barrier dysfunction and aggravation of AD.⁵⁰ Exposure of human

keratinocytes to cigarette smoke through the production of hydrogen peroxide induced modification, translocation, and degradation of scavenger receptor B1, a protein that plays an important role in cholesterol trafficking and thereby contributes to the permeability barrier.⁵¹ Dermal exposure to m-xylene induced pathologic changes and increased expression of IL-1 α and inducible nitric oxide synthase in a rat model.⁵²

In animal experiments, oxidative stress in the skin seems to elicit itching and scratching, even in nonatopic animals. Repeated painting of formaldehyde on the skin of 8-week-old BALB/c mice caused ear swelling and infiltration of inflammatory cells. This was related to the increased expression of IL-4 and transient receptor potential vanilloid 1 (TRPV-1) mRNAs, whereas this response was significantly suppressed by subcutaneous administration of capsazepine, a TRPV-1 antagonist.⁵³ In a study using male adult CD1 mice (8-10 weeks of age) and C57BL/6 wild-type and *Trpv1* and transient receptor potential ankyrin 1 (*Trpa1*) knockout mice, intradermal hydrogen peroxide or tert-Butyl hydroperoxide provoked itching through a TRPA-1-dependent but histamine- and TRPV-1-independent pathway.⁵⁴ An *in vivo* study of the mercuric chloride-induced T_H2-mediated autoimmune syndrome in the Brown Norway rat revealed that antioxidant desferrioxamine treatment suppressed IL-4 gene expression.⁵⁵ These animal studies are suggestive of the possibility that oxidative stress and redox imbalance might develop or aggravate AD by triggering pruritus or enhancing T_H2 polarization. Another mechanism for oxidative stress-induced skin inflammation appears to be the COX-2 pathway. Exposure of human skin keratinocytes (HaCaT cells) to cobalt chloride caused the production of ROS, upregulation of COX-2 expression, and phosphorylation of nuclear factor κ B, resulting in increased secretion of IL-6 and IL-8.⁵⁶

Recent evidence demonstrates that prior alteration of immune status by exposure to air pollutants during the fetal period is related to the development of AD. In a subgroup of 85 neonates randomly selected from a birth cohort study, cord blood T-cell functions and concentrations of VOCs over a period of 4 weeks after birth in children's dwellings were evaluated.³⁷ In this study, an increased percentage of IL-4-producing T cells was found in children exposed to naphthalene (OR, 2.9) and methylcyclopentane (OR, 3.3). In addition, there was a significant association between exposure to tetrachloroethylene and a reduced percentage of IFN- γ -producing T cells (OR, 4.9). These results suggest that maternal exposure to VOCs during pregnancy might affect the immune status of the newborn child. In a prospective German birth cohort study, prenatal exposure to tobacco smoke reduced regulatory T-cell numbers at birth, predisposing the babies to an atopy-prone immune status and the development of AD during the first year of life.³⁶ It was also demonstrated that a low number of regulatory T cells in maternal and cord blood might have effects lasting as long as 3 years and was associated with upregulation of maternal and cord blood microRNA-223.²⁸ A Taiwanese birth panel study showed that the methylation status of the thymic stromal lymphopoietin (TSLP) gene 5'-CpG island (CGI) in cord blood was significantly associated with exposure to tobacco smoke during pregnancy (OR, 3.17) and with AD at 2 years of age (OR, 2.32).³⁸ An increased cotinine level in cord blood was associated with hypomethylation of TSLP 5'-CGI, leading to increased expression of the TSLP protein and subsequent AD development. However, neither of the studies clarified which component of tobacco smoke was responsible for these epigenetic changes.

Collectively, these studies indicate that prenatal exposure to air pollutants, especially tobacco smoke, is likely to be linked to the development of AD through immune dysregulation, which might be mediated by microRNA and DNA methylation. Future studies are needed to elucidate how air pollutants induce epigenetic changes and whether genes responsible for T_H2 polarization are the only ones with expression altered by these changes.

The potential health risks posed by air pollution depend not only on the extent of exposure or composition of the pollutants but also on the susceptibility of the host. Because genetic factors modify the effects of environmental risk factors, the interaction between genes and air pollution might play a role in the pathogenesis of AD. For example, a case-control study of 34 children with AD and 106 control subjects without AD from a Taiwanese birth cohort revealed that a glutathione-S-transferase (*GST*) gene polymorphism (*GSTM1* null genotype) significantly increased the risk of AD in children with cord blood cotinine levels of 0.1 ng/mL or greater (OR, 5.21).³⁹ This study indicates that polymorphism in a gene responsible for antioxidant function might predispose the host to the development of AD when combined with exposure to oxidative stress.

Another example is mutation of the filaggrin gene. In a Danish birth cohort study, filaggrin null mutations were associated with dermatitis at exposed areas, whereas there was no predilection site in children with the wild-type gene.⁵⁷ This suggests that children with mutations in genes encoding structural proteins of the skin barrier are susceptible to AD when exposed to environmental triggers, such as climate change or contact with irritants. Of note, most patients with AD have skin barrier defects in the absence of known genetic mutations, which indicates that AD might occur as a result of exposure to environmental factors alone in a subgroup of patients. In particular, the skin of infants and children in the developmental stage seems to be more vulnerable to damage by air pollutant exposure because infants and children have immature skin barrier function and probably immature detoxification pathways.^{8,58} This might explain why the prevalence of AD is increasing worldwide, even though there is no evidence of abrupt genetic alterations. Further investigation is needed to identify hosts who are susceptible to air pollution. The proposed mechanisms by which air pollution affects the development of AD are summarized in Fig 1.

CONCLUSION

The environmental factors that induce the development of AD must be identified and avoided for disease prevention. In children with pre-existing AD, it is critical to find environmental triggers to exacerbate AD symptoms, because AD should be managed with strict avoidance of various aggravating factors as well as appropriate skin care and reduction of inflammation. There is growing evidence that air pollution might act as an important environmental risk factor in the development or aggravation of AD. However, a limited number of studies have been done, and many issues still remain to be elucidated. For example, it is essential to identify the major components responsible for the disease, the extent of exposure required to induce pathophysiologic changes, the factors that determine a subject's susceptibility, and the exact mechanism by which air pollutants affect the skin barrier or immune status. Further research is needed to examine the role of air pollutants in AD. This will help to expand our understanding and establish a better strategy for primary, secondary, and tertiary prevention of AD.

What do we know?

- Air pollution is of increasing concern with urbanization and acts as a risk factor for asthma, whereas there is relatively little evidence of its role as a risk factor for AD.
- Birth cohort studies demonstrated that perinatal exposure to air pollutants, such as ETS, VOCs, PM, and phthalate, are associated with the development of AD.
- Longitudinal studies and challenge tests suggest that AD symptoms are aggravated by exposure to a variety of air pollutants, including benzene, VOCs, PM, formaldehyde, and NO₂.
- Prenatal exposure to air pollutants, especially tobacco smoke, is likely to be linked to the development of AD through immune dysregulation, which might be mediated by microRNA and DNA methylation.
- The skin barrier appears to be directly damaged by oxidative stress initiated by external pollutants.

What is still unknown?

- It is not known what pollutants are mainly responsible for AD. For example, ETS, VOCs, and PM each represents a mixture of various pollutants. It is necessary to assess the hazard of each component of these pollutants.
- We do not know how much exposure to air pollutants is required to induce pathophysiologic changes in the skin.
- We need to investigate the factors that determine a subject's susceptibility. There might be hosts with susceptible genes or at the developmental stage who are likely to have AD because of exposure to air pollutants.
- The exact biologic mechanisms by which air pollutants affect the skin barrier or immune status remain unclear. Although perinatal exposure to air pollution is related to epigenetic changes and subsequent development of AD, it is not known how these changes (ie, upregulation of microRNA and decreased DNA methylation) are induced and whether the expression of genes for T_H2 polarization are altered selectively or preferentially.
- There are no human data to show that release of nonallergic proinflammatory cytokines, induction of itching and subsequent scratching, or an increase in the expression of IL-4 contributes to the development of AD, as was demonstrated in animal experiments and *in vitro* studies.
- It is not known whether exposure to air pollutants through inhalation or ingestion can affect skin barrier dysfunction.

REFERENCES

- Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR. International Study of Asthma and Allergies in Childhood (ISAAC) Phase One and Three Study Groups. Is eczema really on the increase worldwide? *J Allergy Clin Immunol* 2008;121:947-54.e15.
- Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004;113:925-31.
- Ricci G, Patrizi A, Baldi E, Menna G, Tabanelli M, Masi M. Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006;55:765-71.
- Kapoor R, Menon C, Hoffstad O, Bilker W, Leclerc P, Margolis DJ. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. *J Am Acad Dermatol* 2008;58:68-73.
- van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. *J Allergy Clin Immunol* 2007;120:565-9.
- Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet* 2008;372:1058-64.
- Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483-94.
- Cork MJ, Danby SG, Vasilopoulos Y, Hadgraft J, Lane ME, Moustafa M, et al. Epidermal barrier dysfunction in atopic dermatitis. *J Invest Dermatol* 2009;129:1892-908.
- Barnes KC. An update on the genetics of atopic dermatitis: scratching the surface in 2009. *J Allergy Clin Immunol* 2010;125:16-31, e1-11.
- McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. *J Allergy Clin Immunol* 2013;131:280-91.
- Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, De Benedetto A, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol* 2007;120:150-5.
- Kim BE, Leung DY, Boguniewicz M, Howell MD. Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6. *Clin Immunol* 2008;126:332-7.
- Howell MD, Fairchild HR, Kim BE, Bin L, Boguniewicz M, Redicz JS, et al. Th2 cytokines act on S100A11 to downregulate keratinocyte differentiation. *J Invest Dermatol* 2008;128:2248-58.
- Tupker RA, De Monchy JG, Coenraads PJ, Homan A, van der Meer JB. Induction of atopic dermatitis by inhalation of house dust mite. *J Allergy Clin Immunol* 1996;97:1064-70.
- Darsow U, Laifauji J, Kerschenlohr K, Wollenberg A, Przybilla B, Wuthrich B, et al. The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. *Allergy* 2004;59:1318-25.
- Seidenari S, Giusti F, Pellacani G, Bertoni L. Frequency and intensity of responses to mite patch tests are lower in nonatopic subjects with respect to patients with atopic dermatitis. *Allergy* 2003;58:426-9.
- Leung DY, Harbeck R, Bina P, Reiser RF, Yang E, Norris DA, et al. Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis. Evidence for a new group of allergens. *J Clin Invest* 1993;92:1374-80.
- Bunikowski R, Mielke ME, Skarabis H, Worm M, Anagnostopoulos I, Kolde G, et al. Evidence for a disease-promoting effect of *Staphylococcus aureus*-derived exotoxins in atopic dermatitis. *J Allergy Clin Immunol* 2000;105:814-9.
- Beck LA, Boguniewicz M, Hata T, Schneider LC, Hanifin J, Gallo R, et al. Phenotype of atopic dermatitis subjects with a history of eczema herpeticum. *J Allergy Clin Immunol* 2009;124:260-9, e1-7.
- Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol* 2006;118:152-69.
- Flohr C, Johansson SG, Wahlgren CF, Williams H. How atopic is atopic dermatitis? *J Allergy Clin Immunol* 2004;114:150-8.
- Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832-6.
- Just AC, Whyatt RM, Perzanowski MS, Calafat AM, Perera FP, Goldstein IF, et al. Prenatal exposure to butylbenzyl phthalate and early eczema in an urban cohort. *Environ Health Perspect* 2012;120:1475-80.
- Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet* 2014;383:1581-92.
- Peden D, Reed CE. Environmental and occupational allergies. *J Allergy Clin Immunol* 2010;125(suppl):S150-60.
- Herbstman JB, Tang D, Zhu D, Qu L, Sjödin A, Li Z, et al. Prenatal exposure to polycyclic aromatic hydrocarbons, benzo[a]pyrene-DNA adducts, and genomic DNA methylation in cord blood. *Environ Health Perspect* 2012;120:733-8.
- Auten RL, Gilmour MI, Krantz QT, Potts EN, Mason SN, Foster WM. Maternal diesel inhalation increases airway hyperreactivity in ozone-exposed offspring. *Am J Respir Cell Mol Biol* 2012;46:454-60.

28. Herberth G, Bauer M, Gasch M, Hinz D, Roder S, Olek S, et al. Maternal and cord blood miR-223 expression associates with prenatal tobacco smoke exposure and low regulatory T-cell numbers. *J Allergy Clin Immunol* 2014;133:543-50.
29. Morgan DL, Cooper SW, Carlock DL, Sykora JJ, Sutton B, Mattie DR, et al. Dermal absorption of neat and aqueous volatile organic chemicals in the Fischer 344 rat. *Environ Res* 1991;55:51-63.
30. Penard-Morand C, Raheison C, Charpin D, Kopferschmitt C, Lavaud F, Caillaud D, et al. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. *Eur Respir J* 2010;36:33-40.
31. Yi O, Kwon HJ, Kim H, Ha M, Hong SJ, Hong YC, et al. Effect of environmental tobacco smoke on atopic dermatitis among children in Korea. *Environ Res* 2012;113:40-5.
32. Lee JY, Seo JH, Kwon JW, Yu J, Kim BJ, Lee SY, et al. Exposure to gene-environment interactions before 1 year of age may favor the development of atopic dermatitis. *Int Arch Allergy Immunol* 2012;157:363-71.
33. Bornehag CG, Sundell J, Weschler CJ, Sigsgaard T, Lundgren B, Hasselgren M, et al. The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. *Environ Health Perspect* 2004;112:1393-7.
34. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Kramer U, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med* 2008;177:1331-7.
35. Herbarth O, Fritz GJ, Rehagen M, Richter M, Roder S, Schlink U. Association between indoor renovation activities and eczema in early childhood. *Int J Hyg Environ Health* 2006;209:241-7.
36. Hinz D, Bauer M, Roder S, Olek S, Huehn J, Sack U, et al. Cord blood Tregs with stable FOXP3 expression are influenced by prenatal environment and associated with atopic dermatitis at the age of one year. *Allergy* 2012;67:380-9.
37. Lehmann I, Thielke A, Rehagen M, Rolle-Kampczyk U, Schlink U, Schulz R, et al. The influence of maternal exposure to volatile organic compounds on the cytokine secretion profile of neonatal T cells. *Environ Toxicol* 2002;17:203-10.
38. Wang JJ, Chen SL, Lu TP, Chuang EY, Chen PC. Prenatal smoke exposure, DNA methylation, and childhood atopic dermatitis. *Clin Exp Allergy* 2013;43:535-43.
39. Wang JJ, Guo YL, Lin TJ, Chen PC, Wu YN. GSTM1, GSTP1, prenatal smoke exposure, and atopic dermatitis. *Ann Allergy Asthma Immunol* 2010;105:124-9.
40. Jedrychowski W, Perera F, Mauger U, Mrozek-Budzyn D, Miller RL, Flak E, et al. Effects of prenatal and perinatal exposure to fine air pollutants and maternal fish consumption on the occurrence of infantile eczema. *Int Arch Allergy Immunol* 2011;155:275-81.
41. Kay J, Gawkrödger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994;30:35-9.
42. Lee YL, Su HJ, Sheu HM, Yu HS, Guo YL. Traffic-related air pollution, climate, and prevalence of eczema in Taiwanese school children. *J Invest Dermatol* 2008;128:2412-20.
43. Lee JH, Suh J, Kim EH, Cho JB, Park HY, Kim J, et al. Surveillance of home environment in children with atopic dermatitis: a questionnaire survey. *Asia Pac Allergy* 2012;2:59-66.
44. Kim J, Kim EH, Oh I, Jung K, Han Y, Cheong HK, et al. Symptoms of atopic dermatitis are influenced by outdoor air pollution. *J Allergy Clin Immunol* 2013;132:495-8.e1.
45. Song S, Lee K, Lee YM, Lee JH, Lee SI, Yu SD, et al. Acute health effects of urban fine and ultrafine particles on children with atopic dermatitis. *Environ Res* 2011;111:394-9.
46. Eberlein-König B, Przybilla B, Kuhl P, Pechak J, Gebefugi I, Kleinschmidt J, et al. Influence of airborne nitrogen dioxide or formaldehyde on parameters of skin function and cellular activation in patients with atopic eczema and control subjects. *J Allergy Clin Immunol* 1998;101:141-3.
47. Huss-Marp J, Eberlein-König B, Breuer K, Mair S, Ansel A, Darsow U, et al. Influence of short-term exposure to airborne Der p 1 and volatile organic compounds on skin barrier function and dermal blood flow in patients with atopic eczema and healthy individuals. *Clin Exp Allergy* 2006;36:338-45.
48. Bowler RP, Crapo JD. Oxidative stress in allergic respiratory diseases. *J Allergy Clin Immunol* 2002;110:349-56.
49. Pastore S, Korkina L. Redox imbalance in T cell-mediated skin diseases. *Mediators Inflamm* 2010;2010:861949.
50. Niwa Y, Sumi H, Kawahira K, Terashima T, Nakamura T, Akamatsu H. Protein oxidative damage in the stratum corneum: Evidence for a link between environmental oxidants and the changing prevalence and nature of atopic dermatitis in Japan. *Br J Dermatol* 2003;149:248-54.
51. Sticozzi C, Belmonte G, Pecorelli A, Arezzini B, Gardi C, Maioli E, et al. Cigarette smoke affects keratinocytes SRB1 expression and localization via H2O2 production and HNE protein adducts formation. *PLoS One* 2012;7:e33592.
52. Gunasekar PG, Rogers JV, Kabbur MB, Garrett CM, Brinkley WW, McDougall JN. Molecular and histological responses in rat skin exposed to m-xylene. *J Biochem Mol Toxicol* 2003;17:92-4.
53. Saito A, Tanaka H, Usuda H, Shibata T, Higashi S, Yamashita H, et al. Characterization of skin inflammation induced by repeated exposure of toluene, xylene, and formaldehyde in mice. *Environ Toxicol* 2011;26:224-32.
54. Liu T, Ji RR. Oxidative stress induces itch via activation of transient receptor potential subtype ankyrin 1 in mice. *Neurosci Bull* 2012;28:145-54.
55. Wu Z, Holwill SD, Oliveira DB. Desferrioxamine modulates chemically induced T helper 2-mediated autoimmunity in the rat. *Clin Exp Immunol* 2004;135:194-9.
56. Yang C, Ling H, Zhang M, Yang Z, Wang X, Zeng F, et al. Oxidative stress mediates chemical hypoxia-induced injury and inflammation by activating NF-kappaB-COX-2 pathway in HaCaT cells. *Mol Cells* 2011;31:531-8.
57. Carson CG, Rasmussen MA, Thyssen JP, Menne T, Bisgaard H. Clinical presentation of atopic dermatitis by filaggrin gene mutation status during the first 7 years of life in a prospective cohort study. *PLoS One* 2012;7:e48678.
58. Nikolovski J, Stamatas GN, Kollias N, Wiegand BC. Barrier function and water-holding and transport properties of infant stratum corneum are different from adult and continue to develop through the first year of life. *J Invest Dermatol* 2008;128:1728-36.