

# *Fifty percent of all those with atopic dermatitis develop other allergic symptoms within their first year of life and probably as many as 85% of patients experience an onset below 5 years of age*

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## **Atopic Dermatitis: Global Epidemiology and Risk Factors**

by S. Nutton

### **Key insights**

Atopic dermatitis often begins in early childhood and is the first step in the so-called 'atopic march'. This concept summarizes the natural history of atopic manifestations, which typically begin with atopic dermatitis in early childhood followed by the development of other allergic disorders in later life. The onset of atopic dermatitis in childhood often foreshadows the later development of asthma and/or allergic rhinitis (hay fever).

### **Current knowledge**

Atopic dermatitis has a complex etiology, whereby genetic and immune mechanisms act in concert with environmental factors to influence the manifestations of the disease. Genetic mutations in epidermal barrier proteins (such as filaggrin) have recently been shown to affect skin barrier function. The presence of food sensitization and allergies is also predictive of severe atopic dermatitis. The inter-country variations and urban-rural gradient in disease prevalence suggest that environmental factors act in concert with intrinsic genetic factors to drive disease progression.

### **Practical implications**

Breastfeeding is a protective factor; for infants who cannot be breastfed, the use of clinically proven partially or extensively hydrolyzed whey formulas is preferable to cow's milk formulas. Encouraging results have been obtained with the use of pre-



The progression of atopic manifestations is known as the 'atopic march'. This begins with atopic dermatitis in early childhood and is usually followed by other allergic disorders such as allergic rhinitis and asthma.

and probiotics to modulate the gut flora, although the data are still in the exploratory phase and need further study. Finally, protecting the skin barrier is an important strategy for prevention, particularly in children who have mutations in the skin barrier genes and in those who show early signs of skin barrier impairment.

### **Recommended reading**

Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ: Atopic dermatitis and the atopic march revisited. *Allergy* 2014;69:17–27.

# Atopic Dermatitis: Global Epidemiology and Risk Factors

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## Key Messages

- Atopic dermatitis (AD) is a common inflammatory skin disease posing a significant burden on health-care resources and patients' quality of life.
- AD usually starts in early childhood and can be the initial step of the so-called 'atopic march'.
- The prevalence of AD is as high as 20% in children in some countries and continues to increase, affecting now not only developed countries but also low-income countries.
- AD is a complex disease, and the relationship between allergy and AD (allergy being a cause and/or an exacerbating factor of AD) is still debated.
- Genetics has recently been shown to be an important risk factor for AD, and the strongest association so far with the gene encoding filaggrin has raised the recent interest in the role of skin barrier impairment in the development of AD.
- Environmental factors and specifically exposure to microbes are also recognized to play a role in the development of the disease.
- AD is a multifactorial disease presenting with different endophenotypes.
- The prevention of AD should start as soon as possible (possibly even in utero), targeting both skin barrier, immune/allergy and environmental aspects.

## Key Words

Atopic dermatitis · Atopic march · Skin barrier defect · Immune dysregulation · Genetics · Environment

## Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease posing a significant burden on health-care resources and patients' quality of life. It is a complex disease with a wide spectrum of clinical presentations and combinations of symptoms. AD affects up to 20% of children and up to 3% of adults; recent data show that its prevalence is still increasing, especially in low-income countries. First manifestations of AD usually appear early in life and often precede other allergic diseases such as asthma or allergic rhinitis. Individuals affected by AD usually have genetically determined risk factors affecting the skin barrier function or the immune system. However, genetic mutations alone might not be enough to cause clinical manifestations of AD, and it is merely the interaction of a dysfunctional epidermal barrier in genetically predisposed individuals with harmful effects of environmental agents which leads to the development of the disease. AD has been described as an allergic skin disease, but today, the contribution of allergic reactions to the initiation of AD is challenged, and it is proposed that allergy is rather a consequence of AD in subjects with a concomitant underlying atopic constitution. Treatment at best achieves symptom control rather than cure; there is thus a strong need to identify alternatives for disease prevention.

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## Introduction

Atopic dermatitis (AD), also called atopic eczema, is a common chronic or recurrent inflammatory skin disease and affects 15–20% of children [1] and 1–3% of adults worldwide. It is characterized by acute flare-ups of eczematous pruritic lesions over dry skin.

AD usually starts in early childhood and may represent the initial step of the so-called ‘atopic march’ (fig. 1) which represents the natural history of atopic manifestations, characterized by a typical sequence of atopic diseases in childhood preceding the development of other allergic disorders later in life [2–4]. Fifty percent of all those with AD develop other allergic symptoms within their first year of life and probably as many as 85% of the patients experience an onset below 5 years of age. Patients usually outgrow the disease in late childhood as around 70% of the patients with a disease onset during childhood have a spontaneous remission before adolescence. However, early childhood AD is often the initial indication that a child may later develop asthma and/or allergic rhinitis (hay fever) [5].

Symptoms of AD include patches of skin that are red or brownish, dry, cracked or scaly skin and itchy skin, especially at night. In infants, eczema usually appears as tiny bumps on the cheeks, while older children and adults often experience rashes on the knees or elbows (often in the folds of the joints), on the backs of the hands or on the scalp.

AD poses a significant burden on health-care resources [6–8] and patients’ quality of life (mainly because of sleep deprivation due to itchiness, employment loss, time to care and financial costs) [9–12]. As a consequence, there has been a heightened interest in the identification of environmental risks and protective factors.

## Epidemiology

The prevalence of AD is estimated to be 15–20% in children and 1–3% in adults, and the incidence has increased by 2- to 3-fold during the past decades in industrialized countries.

Some of the most valuable AD prevalence and trend data have come from the International Study of Asthma and Allergies in Childhood (ISAAC). This is the biggest (close to 2 million children in 100 countries) and only allergy study that has taken a truly global approach. The strength of the study is the use of a uniformly validated methodology allowing a direct comparison of results between pediatric populations all over the world (<http://isaac.auckland.ac.nz/index.html>).

The study revealed that over 20% of children are affected by AD in some countries, but that the prevalence varies greatly throughout the world. For the age group 6–7 years, data showed that the prevalence of AD ranged from 0.9% in India to 22.5% in Ecuador, with new data showing high values in Asia and Latin America. For the age group 13–14 years, data showed prevalence values ranging from 0.2% in China to 24.6% in Columbia. A prevalence over 15% was found in 4 of 9 regions studied including Africa, Latin America, Europe (1 center in Finland) and Oceania [13].

***Over 20% of children are affected by AD in some countries, but the prevalence varies greatly throughout the world.***

Importantly, the latest available data (Phase Three of the ISAAC study) [14] showed that while AD seems to have reached a plateau in the countries with the highest prevalence such as the UK and New Zealand, AD continues to increase in prevalence, specifically in young children (age 6–7 as compared to age 13–14 years) and in low-income countries, such as Latin America or South East Asia which have emerged as regions of a relatively high prevalence in the follow-up data [15] (fig. 2).

## Immune Mechanisms

The immune response observed during the course of AD is characterized by a biphasic inflammation. A Th2-biased immune response (IL-4, IL-13, TSLP and eosinophils) is predominant in the initial and acute phase of AD, while in chronic AD skin lesions, a Th1/Th0 dominance has been described (IFN- $\gamma$ , IL-12, IL-5 and GM-CSF) [16].

In addition, regulatory T cells and the innate immune system in the skin are altered [17]. The innate immune system represents the first line of defense against infections. In AD, a decrease in the antimicrobial peptides (one component of the skin innate immune system) has been observed and may explain the susceptibility to infections in AD patients [18]. Specifically, lesional and healthy skin of AD patients is frequently colonized with *Staphylococcus aureus* which exacerbates or aggravates skin lesions [19].

## Allergy and AD

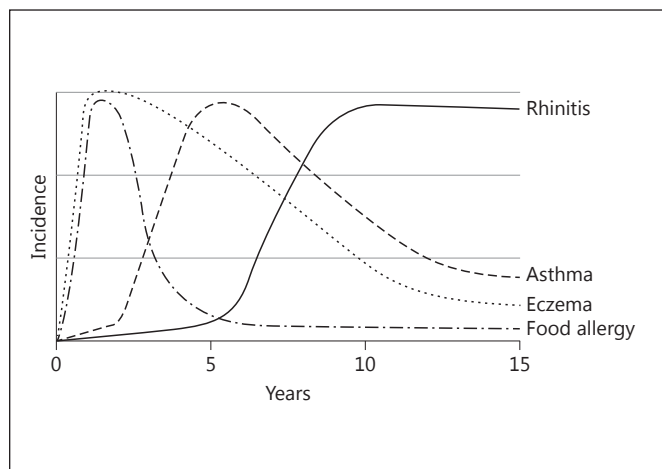
Presence of food sensitization and allergy earlier in life predicts a prognosis of severe AD. Around 50–70% of children with an early onset of AD are sensitized to one or more allergens. These are mainly food allergens (cow's milk, hen's egg and peanuts being the foods most frequently involved) [20] but also house dust mite, pollen and pets. Food allergy is actually much more common in children with AD with an association that ranges from 20 to 80% but is more accepted around 30%.

The relationship between food allergy and AD is complex and can be viewed from different perspectives. It has been proposed recently that food allergy may not have such an important impact on the initiation of AD. In most cases, rather than being a cause of AD ('inside-out hypothesis': the skin lesions of AD are a consequence of the inflammatory response to allergens), food allergy would be co-associated with AD or would be an exacerbating factor for AD [21]. Food allergies have indeed clinical manifestations on the skin and in the gastrointestinal and respiratory systems. Cutaneous reactions can be diverse, but only some of them will exacerbate AD, and they usually manifest as a late event. Skin reactions can anyway lead to excessive scratching and indirect exacerbation of preexisting eczema.

## Genetic Factors

The role of genetics as an important risk factor for AD has first been found in observation studies, describing a positive parental history in AD patients, and in twin studies, showing a higher concordance rate in monozygotic twins compared to dizygotic twins [22]. Then, genetic linkage analysis as well as association studies identified several genes linked to either epidermal function or the immune system.

The recent discovery of the common loss-of-function variants in the *FLG* gene (encoding the epidermal barrier protein filaggrin) and their strong association with AD [23] has led to a heightened interest in the role of skin barrier impairment in the development of AD, allergic sensitization and also food and respiratory allergies. Filaggrin has a crucial role in skin barrier integrity. It is an important epidermal protein that is needed for the formation of the corneocytes as well as the generation of intracellular metabolites which contribute to stratum corneum hydration and pH of the skin. Ten percent of the westernized population and 50% of AD patients carry mutations in the *FLG* gene, and 20 mutations in the *FLG* gene have been described so far.



**Fig. 1.** Incidence of different types of atopy by age: AD is considered as the first manifestation of the atopic march. Reproduced from Barnettson and Rogers [2] with permission from the BMJ Publishing Group Ltd.

Other skin-related genes such as *SPINK5/LEKT1* have also been identified as being associated with AD [24, 25], and, in addition, different tissue-specific patterns of DNA methylation have been identified as first evidence for the relevance of epigenetic modifications in AD.

Altogether, these data have raised the recent interest in the role of skin barrier impairment in the development of AD and allergic sensitization [26, 27].

## Impaired Skin Barrier Function

An intact epidermal barrier is a prerequisite for the skin to function as a physical and chemical barrier. Genetically determined alterations of the epidermis or lipid composition contribute to skin barrier dysfunction leading to inflammation. Moreover, the defective epidermal barrier allows easier and enhanced environmental allergen penetration through the skin, facilitating the interaction of the allergens with the local antigen-presenting cells and immune effector cells. This may lead to systemic IgE sensitization and transition from the non-atopic state to the atopic state of the disease (fig. 3). This is called the 'outside-in hypothesis', explaining the association between AD and an increased risk of developing food allergy, asthma and allergic rhinitis (atopic march). Allergic sensitization would be mainly a secondary phenomenon in AD and an important trigger of disease flares and driver of disease chronicity. Patients carrying variations for filaggrin and other genes and suf-





**Fig. 2.** World maps showing changes in the prevalence of AD symptoms for 13- to 14-year-olds (**a**) and 6- to 7-year-olds (**b**) in consecutive prevalence surveys conducted 5–10 years apart (between ISAAC Phases One and Three). SE = Standard error of the change. Reproduced from Williams et al. [15] with permission from Elsevier.

fering from an early onset and rather severe form of AD have the highest risk to develop allergic diseases and specifically asthma.

The skin barrier defect in AD also predisposes to colonization or infection by pathogenic microbes (e.g. *S. aureus*) whose exogenous proteases can also further damage the skin barrier.

Causes of this abnormal skin barrier are complex and driven by a combination of genetic and immunological factors (see above) but also environmental factors (fig. 3).

Typically, addition of environmental interactions such as washing with soap and detergents can further impair the barrier function.

### Environmental Factors and Microbial Exposure

Significant variations in the prevalence between and within countries (e.g. urban-rural gradient of disease) suggest environmental factors in addition to genetic factors as the main drivers of change in disease burden. En-

sensitization to allergens, leading to the IgE-associated form of AD. Scratching, bacterial infections or other environmental factors such as soap act as aggravating factors due to their damaging effect on the skin barrier.

Factor	Associated effect
Climate	
Low outdoor temperature	Increased risk
UV light exposure	Protective
Urban vs. rural setting	Increased risk
Diet	
Fresh fruits	Protective
Fish (during pregnancy)	Protective
Fast-food	Increased risk
Breastfeeding	Protective
Delayed weaning	Increased risk
Obesity	Increased risk
Pollution/tobacco smoke	Increased risk

Also, studies have suggested that microbial exposure could influence the development of AD (table 2) [28]. The 'revised' hygiene hypothesis states that the decrease in early childhood exposure to prototypical infections (e.g. hepatitis and tuberculosis) and, by extension, in any microbial exposure [29] has increased the susceptibility to allergic disease. For AD, this hypothesis has been supported by some observations such as that the youngest among siblings has the lowest risk of AD or that AD risk is decreased in infants attending day care during their first year of life. The influence of a farm environment (and exposure to a variety of microfloras) has also been extensively studied within cohorts [30–35]. The results showed that rather than living on a farm, it is the consumption of unpasteurized farm milk during the first 2 years of life and the direct contact of pregnant mothers with farm animals which appeared to be protective [32, 35].

Studies on pets also proposed dog exposure as a protective factor [36], while for cat exposure, the situation is less clear with much more heterogeneous results [37].

The risk of developing AD is increased in infants who have been exposed to a cat during their first year of life only if they carry filaggrin mutations. This example underlines the complex interplay between genetics and the environment.

Antibiotics (rather than the infection itself which is treated with the antibiotics) seemed to be linked to an increased risk of AD [38, 39]. The explanation may be linked to the microbiota changes related to antibiotic use, knowing that the microbiota influences the immune response. There is actually evidence showing that the early gut microbiota of children who develop AD later in life is different from that of children who do not develop AD, both in terms of composition [40–43] and diversity [44]. More recently, the skin microbiota has been suggested to be involved in the homeostasis of the immune system of the skin and may also have an impact on AD [45].

### Prevention of AD

Taking into account the burden on health-care resources, the impact on the quality of life of patients and their caregivers, together with increasing evidence that AD may progress to other allergic phenotypes, there is a clear need to improve disease prevention [46]. The still growing understanding of the pathoetiology and of environmental risk factors for AD contributes to this goal [47].

Due to the childhood prevalence of the disease, prevention is focused on the perinatal period. It is recognized that prevention should start as soon as possible (even possibly in utero), targeting the skin barrier, immune/allergy and environmental aspects.

#### Infant Feeding

Breastfeeding is a protective factor even though little evidence shows that exclusive breastfeeding beyond 3 months of age is protective [48]. While food avoidance was proposed earlier, the results of recent observational studies have shown that delaying the introduction of solids is a risk factor for AD [49–53], and today, methods favoring tolerance induction are used. For infants who cannot be breastfed, infant formulas have been developed. Specifically, partially hydrolyzed or extensively hydrolyzed formulas are proposed to fit infants at risk of allergy and infants already having symptoms of cow's milk allergy. Intervention studies have shown that prolonged feeding with a partially hydrolyzed whey formula, compared to a cow's milk formula, may result in an around 45% reduction in infantile AD in at-risk infants [54, 55]. The German Infant Nutritional Intervention

**Table 2.** Individual factors linked to microbial exposure (nonexhaustive list)

Factor	Effect on risk of AD
Day care	Day care attendance in the first 2 years of life is protective.
Farm environment and animals	Consumption of unpasteurized farm milk during the first 2 years of life is protective. Pre- and postnatal exposure to farm animals is protective.
Pets	Dog exposure in early life is protective.
Endotoxin exposure	High endotoxin exposure levels and/or exposure during the first year of life are risk factors.
Antibiotics	Postnatal antibiotic exposure is a risk factor.
Gut microbiome	Diversity and composition (Lactobacilli and Bifidobacteria) of the gut flora are protective factors.

(GINI) study even reported a significant risk reduction in AD up to 10 years of age for infants who received a whey-based partially hydrolyzed formula and those who received an extensively hydrolyzed casein formula [56–58]. One of the plausible mechanisms behind this observation is that a low exposure to protein or peptides (such as hydrolyzed proteins) could educate the immune system to develop tolerance.

#### Modulating the Gut Flora

Pre- and probiotics have also been used during the prenatal and/or postnatal period in an attempt to modify the gut microbiota towards more diversity and a 'healthier' composition. Different probiotics (mainly Lactobacilli and Bifidobacteria), used individually or in combination and administered at different periods (prenatally and/or postnatally), have been used in clinical trials. A recent meta-analysis associated the consumption of probiotics during pregnancy and early life with a relative risk reduction for AD of 21% [59]. Encouraging results have also been obtained with prebiotics (substrates inducing growth and activity of probiotics). A Cochrane review and a meta-analysis recently showed that using prebiotics in the postnatal period could reduce AD by 30% at 2 years of age [60]. However, due to heterogeneity in studies, further research is still needed before pre- and/or probiotics can be routinely recommended as an effective means to prevent AD [61].

### *Dietary Supplementation*

Dietary supplementation (vitamins, zinc, selenium, oils, etc.) has also been tested prenatally or postnatally [62]. Due to its immune-modulatory effect, vitamin D has been studied in the AD prevention context; however, results are still conflicting. Numerous studies also suggested that a high consumption of fish during pregnancy decreased the risk of developing AD in the infant [63]. Similar results were obtained when fish was consumed during late infancy [64, 65].

## ***The skin barrier may constitute a target of primary prevention of progression of eczema into allergic airway diseases.***

### *Preventing a Skin Barrier Breakdown*

Due to its major role in AD initiation, protecting the skin barrier should be a powerful measure for prevention, especially in children who carry skin barrier gene mutations and show early signs of skin barrier impairment. Moreover, the skin barrier may constitute a target of primary prevention of progression of eczema into allergic airway diseases. Encouraging results have been obtained with the application of emollients, combined with soap

avoidance, and a large-scale randomized clinical trial is underway (Barrier Enhancement for Eczema Prevention study; <http://www.beepstudy.org>).

### **Conclusion**

AD is a multifactorial, chronic inflammatory and heterogeneous skin disorder resulting from interactions between genetic, immune and environmental factors. It is common in most countries, although the prevalence varies greatly throughout the world. Recent data revealed that AD is a disease of developed as well as developing countries, and in poorer countries, AD will be competing for meager resources. AD has become a significant public health problem because of its presence in most countries and its increasing prevalence, together with increasing evidence that it may progress to other allergic phenotypes. The last few years have seen important improvement in the understanding of the interactions between the skin barrier, genetic and immunological factors. A better understanding of the key environmental risk factors that could be influenced, changed or modified is important for a better prevention of the disease.

### **Disclosure Statement**

The author declares no conflicts of interest.

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