

Epidemiology of Atopic Dermatitis and Atopic March in Children

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KEYWORDS

• Atopic dermatitis • Atopic march • Epidemiology

Epidemiology (derived from the Greek terms *epi* meaning upon, among; *demos* meaning people, district; and *logos* meaning study, word, discourse) is the study of what is upon people.¹ In medicine, it refers to diseases that are affecting people and the study of factors affecting an illness. There are several ways to examine the epidemiology of a disease. Studies can include the prevalence (total number of active cases) or the incidence (risk of new cases) of a disease. By examining these 2 factors, the natural history of a disease can be studied. This review focuses on the prevalence and natural history of atopic dermatitis (AD).

PREVALENCE OF AD

Prevalence has been examined in different ways with each having its own benefits and faults. The most accurate way is an expert physician diagnosis of all patients in a community. However, this is labor intensive and not practical on a larger scale. Another approach is to pick a random population and have an expert physician confirm the diagnosis and estimate population prevalence based on a small subset of patients. This approach has the inherent problem of scaling the conclusion based on a small population. A third approach is to use the *International Classification of Diseases, Ninth Revision* (ICD-9) codes to estimate the prevalence based on medical records. However, ICD-9 codes are neither universally used nor always coded correctly. The fourth approach is to base prevalence on standardized questionnaires given to physicians or families to determine diagnosis. The questionnaires are validated based on physician history and physical examination. This method has been used for most worldwide prevalence data.^{2,3} The International Study of Asthma and Allergies in Childhood (ISAAC) is a worldwide epidemiologic research program established in 1991 using this technique. It has been used in 3 different phases and in more

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than 100 countries. The most recent completed phase was done in 245 collaborating centers in 99 countries with a total of 1,187,496 children participating. The prevalence was determined in 2 age groups (6–7 and 13–14 years). In the 13- to 14-year age group, 233 centers from 97 countries participated, and in the 6- to 7-year age group, there were 144 collaborating centers participating from 61 countries. For AD or flexural eczema, 3 questions were asked to the families in their native language. Children were classified as having had flexural eczema in the past 12 months if their parents answered yes to 2 of the 3 following questions: “Has your child ever had an itchy rash which was coming and going for at least 6 months?” “Has your child had this itchy rash at any time in the last 12 months?” and “Has this itchy rash at any time affected any of the following places: folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?”⁴ A high correlation between answering yes to 2 questions and the diagnosis of flexural eczema has been found.^{2,5,6}

Studies by ISAAC have found 60-fold variation in prevalence of flexural eczema, ranging from 0.3% to 20.5%.^{2,5} Examination of prevalence across the world reveals some interesting findings (Fig. 1).^{2,3} The prevalence of eczema is higher in wealthy nations, and there are pockets of high prevalence in countries with lower incomes, suggesting multiple causes for the existence of eczema.

The ISAAC study also found an increase in AD in both the age groups (6–7 and 13–14 years) albeit in only a 7-year period because phase III was a repeat of phase I.⁶ There was a significant increase in the prevalence of AD, ranging from 0.07% to 1.09% in 48 countries with decrease in 8 countries and little change in 12 countries in the 6- to 7-year age group and increase in 47 countries, decrease in 32 countries, and little change in 26 countries in the 13- to 14-year age group (Fig. 2). Overall, the increase in prevalence occurred primarily in previous areas of low prevalence, whereas the areas with previous high levels showed leveling off.^{6,7} These results raise the question whether the increase is caused by increased recognition or other changes in

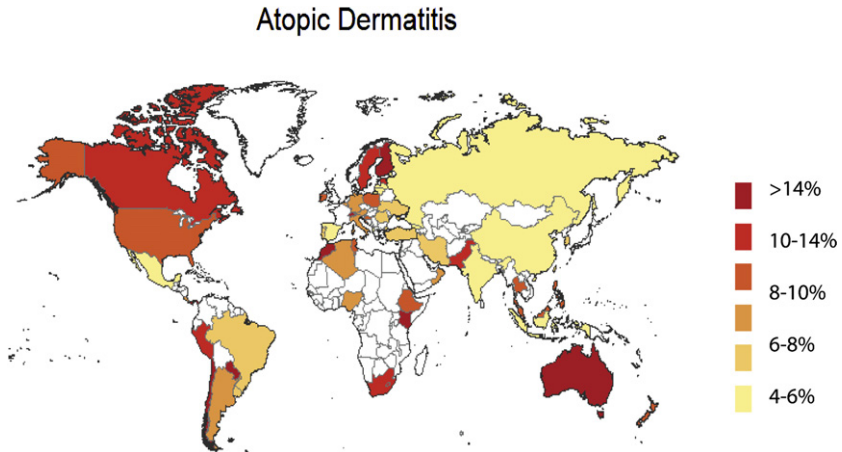


Fig. 1. Prevalence of AD in the world based on ISAAC Phase 1–3 studies in children aged 13 to 14 years. (Data from Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–43.)

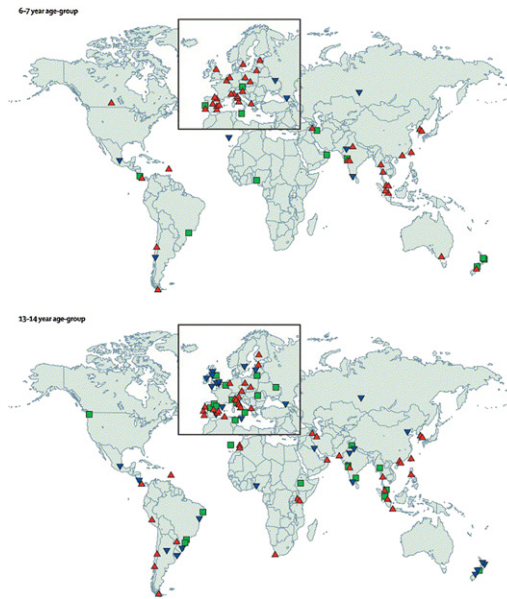


Fig. 2. World map showing direction of change in the prevalence of eczema for 6- to 7-year and 13- to 14-year age groups. Each symbol represents a center. ▽, prevalence reduced by 1 SE per year; □, little change; △, prevalence increased by 1 SE per year. (From Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:740; with permission.)

environment, because the period of 7 years is too short for major genetic or ecological changes.

In a population-based study from the United States, the prevalence of eczema among children aged 5 to 9 years was estimated at 17.2% in Oregon schoolchildren, which is consistent with ISAAC data.⁸ Estimates were based on questionnaires that were validated by physical examination of select children. Based on strict criteria of a physician diagnosis, the prevalence was found to be 6.8%. A similar nationwide survey was done in 60,000 households in the United States. The survey had a 70% response rate representing 116,000 individuals, with eczema in 1 of the 4 areas in the body in 17% of the individuals and defined eczema in 10.7%.⁹ These results are similar to that of the studies by ISAAC, indicating the prevalence to be between 10% and 20% in the United States depending on the diagnostic criteria.

IS AD ATOPIC?

There is a debate whether AD is truly linked to atopy. The most recent ISAAC study suggests a possible answer for differences observed in previous results. Studies have shown either no link or a link or possible link between atopy and atopic AD.

In the ISAAC phase II study, 32,205 schoolchildren aged 8 to 12 years from 20 countries were examined for flexural eczema and also had skin prick testing done to both species of dust mite (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), cat hair, *Alternaria tenuis*, mixed tree and grass pollens, and allergens of local

relevance.⁴ Among 17 affluent countries (with a gross national per capital income >\$9200), 13 had statistically significant odds ratios (ORs) for a positive association between flexural eczema and atopy with a combined OR of 2.69. In the nonaffluent countries, only 2 of 13 countries (Estonia and India) had a borderline positive association, and combined countries had an OR of 1.17. The OR for the association of atopy with flexural eczema plotted against income was highly significant ($P = .006$). Another way to answer this question is to observe the fraction of atopic patients with flexural eczema, which was 27.9% and 1.2% for affluent- and nonaffluent-country centers, respectively. This fraction suggests multiple types of flexural eczema (an allergic type in affluent countries and nonatopic type in nonaffluent countries) that are consistent with the data of finding pockets of high prevalence in affluent and nonaffluent countries.

NATURAL HISTORY OF AD

An important aspect of the natural history of AD is the number and percentage of patients who will outgrow their disease. Ricci and colleagues¹⁰ studied 205 children, who were followed up from 6 to 36 months to 22 to 27 years of age by a standardized questionnaire. Overall, 60% reported that their eczema resolved, with the patients with severe AD reporting a longer time to resolution (6 years of age for severe and 5.5 years of age for mild AD). Patients with egg allergy and AD tended to take longer to outgrow their AD.

The Multicenter Allergy Study (MAS) followed up a birth cohort of 1314 children in Germany.¹¹ The study classified the outcome in 3 age categories into 3 groups (intermittent, resolution, and persistent). It was found that 13.4% of the studied population had AD by 1 year of age and 21.5% of patients had AD by 2 years of age. At 7 years of age, 43% were in complete remission, 38% had an intermittent pattern, and 19% had persistent symptoms, with more than half of the patients with AD showing some signs of the disease past 7 years of age. Risk factors for persistent AD were initial severity (OR 5.86) and atopic sensitization (OR 2.76), with severity being the strongest risk factor identified.¹¹

In the ALSPAC (Avon Longitudinal Study of Parents and Children) study, 1509 randomly selected children were followed up from birth to 5 years of age.¹² Among them, 495 (33%) had early-onset AD before 18 months of age, 273 (18%) had onset after 18 months of age, and 429 (49%) were not affected. Only 2% had eczema at every study visit (1, 6, 18, 30, and 42 months). The study classified 40% of children as intermittent (symptoms of some of the clinical visits) early-onset AD and 22% as intermittent late-onset AD, with 35% affected at 4 years of age. The risk factor identified in this study for persistent AD was elevated serum IgE levels at 12 months of age. Similar to the MAS, there was a higher rate of AD in this population than reported in the ISAAC study, suggesting a higher rate if physician diagnosis is used rather than questionnaires. Also, the rate of resolution was similar, indicating that 30% to 40% of children still had AD in early school-age years.

ATOPIC MARCH

Patients with AD may develop a typical sequence of food allergy, rhinitis, and asthma, which develop at certain ages; some may persist for several years, whereas others may resolve with increasing age.¹³ This progression of atopic manifestations from AD to allergic rhinitis to asthma is known as the atopic march (**Fig. 3**), which has been supported by several cross-sectional and longitudinal studies (**Table 1**).^{10,14,15,17–22,24} In a review, van der Hulst and colleagues²¹ examined

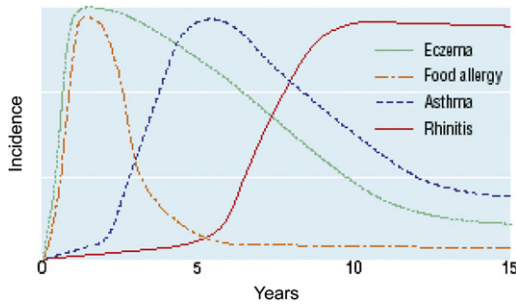


Fig. 3. Progression of the atopic march. (From Barnetson RS, Rogers M. Childhood atopic eczema. *BMJ* 2002;324:1376; with permission.)

13 cohort studies, 4 birth studies, and 9 cohort studies on children with eczema from 1950 to 2006 for this link. The investigators found an OR of 2.14 for developing asthma after eczema compared with children without eczema. In this analysis, approximately 30% of children with eczema developed asthma.

In a close examination at some of the pivotal trials, the Tucson Children's Respiratory Study found that 18% of children with wheezing at 6 years of age had eczema before 2 years of age.¹⁴ The cohort has now reached 22 years of age, and childhood asthma is associated with eczema, whereas adult-onset asthma is not.²³ Also, the increased risk of developing asthma in a patient with eczema may be true only for the subgroup with specific IgE to aeroallergens, because 2 studies found a significantly stronger association with asthma for atopic eczema compared with nonatopic eczema.^{18,20} This large study also supports a particular phenotype of allergic eczema that progresses into an allergic phenotype of asthma.

In addition, the Tucson Children's Respiratory Study has developed an asthma predictive index, which includes physician-diagnosed AD and allergic sensitization as part of the criteria for risk factors of asthma.²⁴ The asthma predictive index has a modest positive predictive value of 47.5% at 6 years of age and an excellent negative predictive value of 91.6%. Further evidence for the linkage of atopy, AD, and asthma showed that children with atopy have decreased lung function at 3 years of age.²⁵

The MAS also found a relationship between atopy, eczema, and wheezing similar to the previous 2 studies.¹⁵ Illi and colleagues¹⁶ suggested that eczema and early wheezing were a separate phenotype and not part of the atopic march. The investigators found that early eczema without early wheezing was not associated with increased wheezing at 7 years of age. However, the risk for developing asthma was higher in children with early eczema and atopic sensitization (OR 6.68) than the association of early eczema with wheezing (OR 2.84).²⁶ These studies suggest that atopy along with eczema is a major risk factor for progression in the atopic march as shown in the Tucson Study.

In addition, severity of eczema is another risk factor because Gustafsson and colleagues¹⁷ found that more than 50% of young children with severe AD ultimately developed asthma and approximately 75% developed allergic rhinitis. Similarly, Ricci and colleagues¹⁰ followed up 252 children with AD and found that 33% of those with mild AD developed asthma when compared with 25% with moderate AD and 59% with severe AD. The OR for developing asthma adjusted to mild being 1 was 2.59 for moderate AD and 4.77 for severe AD.

Table 1

Studies examining eczema and development of asthma

Study	Patient Population	Major Findings
Martinez et al, 1995 ¹⁴	Birth cohort of 826 children in Tucson, Arizona, upto 6 y of age	• OR 2.4 risk factor for eczema for developing persistent wheezing compared with noneczema • 18% of persistent wheezers had asthma compared with 7.7% of nonwheezers
Kulig et al, 1999 ¹⁵ and Illi et al, 2001 ¹⁶	1314 newborn infants in 5 German cities; followed up at 7 y	• By age 5 y, 69% who had developed AD by 3 mo of age were sensitized against aeroallergens; rate of aeroallergen sensitization increased to 77% in all high-risk children • By age 5 y, 50% of children with AD had allergic airway disease or asthma
Gustafsson et al, 2000 ¹⁷	94 children with AD, aged 4–35 mo at recruitment, followed up to age 7 y	• AD resolved in 35.1% of children • 43% developed asthma and 45% developed allergic rhinitis • Risk of developing asthma was higher in children with a family history of eczema
Novembre et al, 2001 ¹⁸	77 children with AD, aged 2–11 y	• 59% of early atopy/eczema developed asthma compared with 25% of late atopy/eczema and 0% of nonatopic eczema
Ohshima et al, 2002 ¹⁹	169 Japanese infants with AD followed up for 4 y	• 35% had developed asthma by the end of the study
Wuthrich and Schmid-Grendelmeier, 2002 ²⁰	22 children with AD, 2–4 y to 10–12 y	• 60% of the children with atopic eczema developed asthma compared with 14% of children with nonatopic eczema

Ricci et al, 2006 ¹⁰	252 children with AD, aged 6–36 mo, followed up until remission or stabilization of AD	• AD disappeared in 60.5% of cases • Average age for recovery was 6 y for severe, 5.8 y for moderate, and 5.5 y for mild form of AD • Asthma developed in 34.1% of cases and rhinoconjunctivitis in 57.6% • Severity of AD is predicable for the onset of asthma
Porsbjerg et al, 2006 ⁴⁸	291-patient cohort, followed up from 7–17 y to 19–29 y of age	• Eczema predicted the development of asthma (OR 3.2)
van der Hulst et al, 2007 ²¹	3103 patients from 4 birth cohort studies and 2278 patients from 9 eczema cohort studies	• Risk of developing asthma was elevated in young children with AD in the birth cohort studies (OR 2.14; 95% CI, 1.67–2.75) • Prevalence of asthma at age 6 y in eczema cohort studies was 35.8% among inpatients and 29.5% in a group of both inpatients and outpatients • About 1 of 3 children with eczema experienced asthma in later childhood
Kapoor et al, 2008 ²²	2270 children with physician-confirmed AD, aged 2–17 y, living in the United States	• 33.3% had symptoms of only asthma or allergic rhinitis • 38% had symptoms of asthma and allergic rhinitis • Nearly 66% of children reported an additional form of AD by age 3 y (ie, atopic triad)
Stern et al, 2008 ²³	849 birth cohort, followed up to 22 y of age	• Eczema by 2 y of age had OR of 3.8 for chronic asthma compared with 2.0 for inactive asthma

Abbreviation: CI, confidence interval.

MODELS FOR ATOPIC MARCH

Environmental and genetic evidence suggest that a defect in epithelial barrier integrity may contribute to the onset of AD and progression of the atopic march.²⁷ The integrity of the barrier, which controls the transcutaneous movement of water and prevents entry of external irritants, microbes, and allergens, is assessed by measuring transepidermal water loss. Impairment of the epithelial barrier function has been shown via an increase in transepidermal water loss in both lesioned skin and clinically unaffected skin in AD.²⁸ Epidermal skin barrier's integrity and function may be impaired by a range of irritants and allergens, which may lead to cytokine production, inflammation, and the development of eczematous lesions.

The likelihood that epidermal barrier dysfunction can initiate systemic sensitization and increase the risk of asthma and other allergic diseases is supported by experimental data, with the progression from allergic rhinitis to asthma or from AD to asthma in mouse models.^{29–31} In these murine models, T cells have been shown to be critical because sensitization does not occur in the absence of $T\alpha\beta$ cells but does occur without B cells, IL-4, IL-5, and interferon gamma.^{32–34} In addition, a key role for thymic stromal lymphopoietin (TSLP) has been hypothesized. TSLP is highly expressed in the skin of sensitized mice, and its deletion prevents the atopic march from occurring.³⁵ Furthermore, the importance of expression of TSLP in the skin is underscored because the expression of TSLP in the peripheral blood does not lead to development of the asthma phenotype, while the induction of TSLP with topical application of a vitamin D analogue leads to a murine model of the atopic march and asthma.³⁶ IL-17 also has an important role in these murine models, because it is necessary for the induction of airway hyperresponsiveness.³⁷

GENETIC SUPPORT FOR ATOPIC MARCH

Epithelial barrier defects derived from loss-of-function mutations in the filaggrin gene have been identified as a strong predisposing factor for AD as well as for other inflammatory conditions, such as ichthyosis vulgaris.^{38,39} The filaggrin gene encodes profilaggrin, a highly phosphorylated protein found in the keratohyalin granules in the granular layer of the outer epidermis. Mutations of the filaggrin genes can lead to impaired keratinization and defects in the epidermal barrier and thus probable increase to allergen sensitization.^{40,41}

Smith and colleagues⁴¹ were the first to show that loss-of-function mutations, R501X and 2282del4, in the filaggrin gene were responsible for ichthyosis vulgaris in 15 families, which is the most common inherited disorder of keratinization. Based on the results, it was estimated that these mutations were present in 9% of the European population.³⁸ Subsequent studies and a comprehensive meta-analysis have confirmed both the filaggrin polymorphisms as major risk factors for AD.^{42–45} Although research shows a significant association of the 2 filaggrin mutations with asthma and allergic rhinitis, there is no apparent association between filaggrin and asthma without the coexistence of AD.³⁸ In a subgroup of German children participating in the ISAAC study, filaggrin variants increased the risk more than 3-fold for AD and more than 2-fold for allergic rhinitis independent of AD.⁴⁴ Of course, ascertaining the precise contribution of filaggrin mutations to the overall prevalence of these atopic diseases is confounded by temporal and disease severity factors in conjunction with putative environmental effects. The theory is that filaggrin leads to a leaky skin layer allowing penetration of allergen leading to sensitization. This sensitization is seen as positive skin test (atopy), and leaky skin barrier leads to AD. The subsequent sensitization through T cells and TSLP leads to development of asthma. This model is supported

by circumstantial evidence (association of AD and atopy and the development of asthma) in the MAS, Ricci and colleagues',¹⁰ and Tucson studies.^{11,46} Also, the genetic evidence of the association between filaggrin, asthma, and atopy is supported by this model.⁴⁷

SUMMARY

AD is one of the most common pediatric skin disorders with a prevalence of 20% in several studies.⁸ The actual incidence is hard to estimate because most studies have examined point prevalence. AD like many other atopic diseases has increased in occurrence in the last couple of decades. However, the increase seems to be stabilizing in developed countries, with most of the current increase in areas with low prevalence in the past.⁶ There is a difference in the relationship between atopy and eczema in countries with higher and lower incomes. The wealthier countries show a strong relationship between flexural eczema and atopy, which was not seen in the poorer countries based on family income and skin testing.⁷ This finding along with differences in prevalence suggests different flexural eczema or AD phenotypes.

The natural history of AD has also been clarified over the last several years. Although previously AD was thought to resolve, recent longitudinal studies indicate that about 50% of patients with AD have intermittent symptoms until 7 years of age. Also, most patients with AD have symptoms early in life (<24 months of age). The natural history of AD is also associated with the development of other atopic diseases. Almost every study that examined this feature has found similar salient points. About 30% of the patients may develop asthma, whereas nearly 66% develop allergic sensitization and symptoms of allergic rhinitis.¹¹ The studies have also consistently found about a 2-fold increase in OR for development of asthma, which increases with AD severity.¹⁷

The discovery of the filaggrin gene and the relationships between filaggrin mutations and AD and murine models and the development of asthma from AD have suggested a potential model of pathogenesis. A proposed model is that the filaggrin mutations in susceptible patients (or other variation in the epidermal differentiation layer of the skin) lead to increased barrier disruption,⁴¹ transepidermal water loss, and increased penetration of allergens and/or microorganisms (due to decreased synthesis of antimicrobial peptides).⁴⁸ These allergens along with microorganisms cause a T_H2 sensitization that is dependent on TSLP.^{32,33,35} The T cells or antigen-presenting cells move to lymph nodes causing a systemic sensitization and the development of asthma. Additional studies are needed to confirm this model in humans.

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