

REVIEW ARTICLE

Atopic dermatitis and the atopic march revisited

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Abstract

Atopic dermatitis (AD) has become a significant public health problem because of increasing prevalence, together with increasing evidence that it may progress to other allergic phenotypes. While it is now acknowledged that AD commonly precedes other allergic diseases, a link termed 'the atopic march', debate continues as to whether this represents a causal relationship. An alternative hypothesis is that this association may be related to confounding by familial factors or phenotypes that comanifest, such as early-life wheeze and sensitization. However, there is increasing evidence from longitudinal studies suggesting that the association between AD and other allergies is independent of confounding by comanifest allergic phenotypes. The hypotheses on plausible biological mechanisms for the atopic march focus on defective skin barrier function and overexpression of inflammatory mediators released by the skin affected by AD (including thymic stromal lymphopoietin). Both human and animal studies have provided evidence supporting these potential biological mechanisms. Evidence from prevention trials is now critical to establishing a causal nature of the atopic march. An emerging area of research is investigation into environmental modifiers of the atopic march. Such information will assist in identifying secondary prevention strategies to arrest the atopic march. Despite much research into the aetiology of allergies, little progress has been made in identifying effective strategies to reduce the burden of allergic conditions. In this context, the atopic march remains a promising area of investigation.

Atopic dermatitis (AD) is a chronic inflammatory skin disorder that can impair quality of life, both through its symptoms and through secondary infections (1). Since the latter part of the last century, AD has increased (1, 2) and has become a significant clinical problem due to its prevalence, particularly in infants and young children. Over recent years, the focus on AD as a public health problem has intensified with the recognition that it is associated with an increased risk of developing food allergy, asthma and allergic rhinitis and that these associations may be causal. The term 'atopic march' is often used to describe this progression from AD to other allergic diseases.

The atopic march has been defined as the natural history of atopic manifestations, characterized by a typical sequence of atopic disease in childhood, generally with AD in infancy or early childhood predating the development of other allergic disorders later in childhood. Recent evidence suggests that the atopic march does not always follow this classic

sequence, as, for example, some patients with asthma subsequently develop AD (3). Furthermore, it has been shown that the atopic march can occur at any age (4), not just in childhood. However, multiple longitudinal studies have provided evidence supporting the atopic march between AD and subsequent allergies (4–10) as well as the inter-relationships between subsequent allergic manifestations (11–13). It has been estimated that approximately one-third of patients with AD develop asthma and two-thirds develop allergic rhinitis (14, 15). No data are available on what proportion of patients with AD develop food allergy, although it is acknowledged that AD and food allergy co-associate (16). The common thread linking these allergic disorders is atopy, the predisposition for immunoglobulin E (IgE)-mediated responses to environmental stimuli (17).

While it is generally accepted that the atopic march is a real phenomenon, debate continues around whether the atopic march:

1. represents a causal relationship,
2. occurs due to comanifestation of early-life sensitization and wheeze with early-life eczema,
3. is due to eczema and asthma having shared genetic or environmental risk factors.

The aim of this review is to evaluate the evidence for the paradigm of the atopic march and to clarify the probable nature of these progressions, and implications for clinical care and future research.

Nomenclature and definitions in AD

A clear, consistent definition of AD is critical when evaluating the evidence for the atopic march, but a lack of clarity in the meaning of the term AD has hampered communication among researchers. A position statement published by the European Academy of Allergology and Clinical Immunology (EAACI) (18) suggested a definition of atopy – ‘Atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms of asthma, rhinoconjunctivitis or eczema/dermatitis’. The authors also suggested ‘atopic eczema/dermatitis syndrome’ as an alternative term to describe what was then commonly referred to as ‘atopic eczema/dermatitis’ (18). In 2003, the Nomenclature Review Committee of the World Allergy Organization (WAO) updated the EAACI 2001 position statement (19) and suggested that the term ‘eczema’ should replace the provisional term ‘atopic eczema/dermatitis syndrome’. The update further suggested that ‘eczema’ could be subclassified as ‘atopic eczema’ and ‘nonatopic eczema’ according to the presence or absence of IgE antibodies.

Commonly cited criteria used to define eczema/AD include those of Hanifin and Rajka, the UK Working Party and the European Task Force (20–23). These criteria have generally been developed for identifying eczema in older children and adults. Defining eczema in infants is particularly difficult, as infants suffer from transitory rashes that can resemble eczema and young children often lack the ability to describe the rash as pruritic, thus requiring either subjective interpretation of the child’s behaviour as ‘scratching’. Currently, there are no validated measures for identifying eczema in infancy.

For this review, we have considered the terms ‘atopic dermatitis’ and ‘eczema’ to be synonymous. When evaluating the evidence, we have used the exact terminology (atopic dermatitis or eczema) used by study authors, while reporting as far as possible the exact criteria used by them to define these terms. In keeping with the classification proposed by Johansson et al. (19) and where such extra information was available, we have further divided AD or eczema into disorders associated with or not associated with IgE sensitization.

Is the atopic march causal?

The establishment of a causal relationship requires evidence from prospective studies consistent with the Bradford Hill criteria (24) including an unconfounded temporal relationship, biological plausibility and evidence from randomized

controlled trials that an effective intervention for eczema reduced subsequent allergies (25). We have evaluated evidence on these aspects while discussing alternative views of this association.

Some argue that AD is not causal in the atopic march, but simply the first clinical manifestation of the IgE response with phenotypes such as asthma and allergic rhinitis appearing as the maturing immune system is exposed to risk factors for expression of those diseases. This is supported by the fact that the allergic phenotypes generally appear as the immune system matures in the first decade of life, although eczema can occur within a few weeks of birth. However, the observation that the atopic march can span childhood to middle age (4, 26) counteracts the notion that allergic phenotypes appear simply as a result of maturation of the immune system during childhood.

Another suggested explanation advanced for the associations seen in the atopic march is familial confounding. Childhood allergic disorders and infantile AD are strongly familial and commonly co-aggregate in siblings, perhaps due to shared genetics and environment exposures. However, we have recently shown that the association between infantile eczema and hay fever is unlikely to be completely explained by familial confounding (27).

Longitudinal observational studies and the atopic march

Given the sequential nature of the atopic march, only prospective longitudinal studies can evaluate the evidence in a robust manner, free from recall bias. Longitudinal epidemiological evidence on the atopic march has been emerging over recent decades.

To identify the longitudinal studies that investigated the march from eczema to other allergic diseases, we searched MEDLINE from 1950 to 2013 using the following key words: (((MeSH Heading: exp = (Eczema) OR MeSH Heading = (Dermatitis Atopic)) OR Topic = (“atopic eczema”)) OR Topic = (“atopic march”)) OR Topic = (“allerg* march”) AND MeSH Heading:exp = (Cohort Studies) OR MeSH Heading: exp = (Longitudinal Studies). Figure 1 outlines the full search strategy and its results. The original MEDLINE search returned 1790 manuscripts, which was limited to 1437 by inclusion of only English language journal articles, focusing on human studies and excluding reviews. The titles and abstracts of the 1437 articles were then screened to identify longitudinal studies of either population-based cohorts or high-risk cohorts, which investigated the atopic march from eczema (or atopic dermatitis) to other allergic diseases (asthma, rhinitis or food allergy) and reported measures of associations (odds ratios, relative risks or hazard ratios). These screening criteria identified 41 studies of which the full articles were screened, identifying 17 studies as relevant.

The 17 relevant papers are summarized in Table 1. Fourteen of the included studies are population-based, while three are high-risk cohorts. Substantial methodological differences across the included studies limited the ability to pool study results. The definitions of eczema/atopic dermatitis used

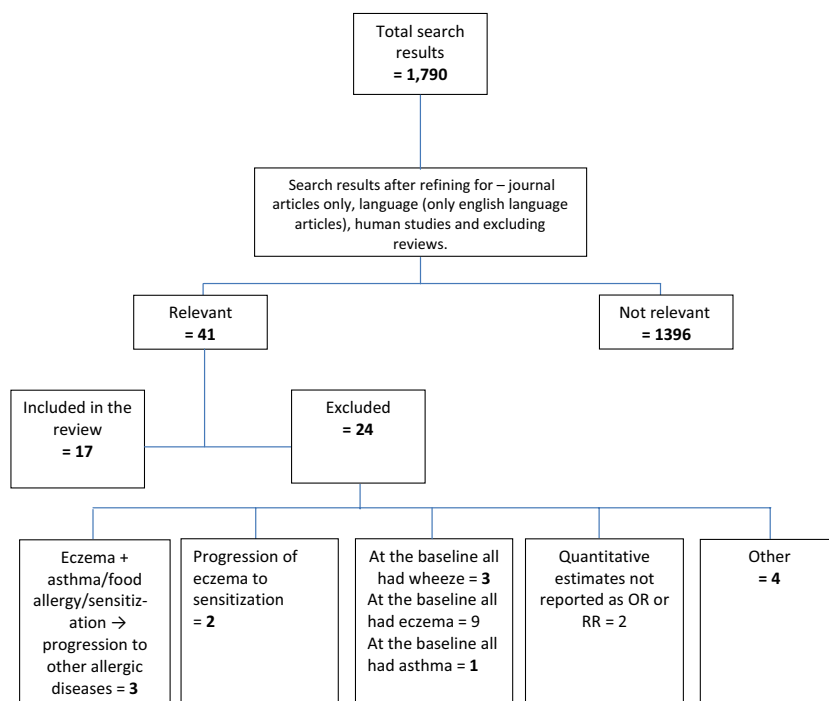


Figure 1 Summary of literature search and manuscript inclusion/exclusion.

across the studies were substantially different, making the comparison of findings difficult. Different confounders were included in adjusted models between studies, and not all studies presented adjusted risk estimates. However, all but one study found at least one statistically significant association between early-onset eczema and subsequent allergic diseases. A number of key papers are discussed in detail below.

As per our search, the first unselected birth cohort study to show an association between early eczema and subsequent asthma was a New Zealand Birth cohort study. It showed that eczema in the first year of life is related to asthma at age 6 years both in girls and boys (28). Since then, multiple birth cohort studies have investigated the march from eczema to other allergic diseases. The Tucson Children's Respiratory Study, of an unselected birth cohort, showed that eczema at the age of 1.5 years was associated with persistent wheezing at age 6 years (OR 2.4; 95% CI 1.3–4.6) (5). Similarly, a whole population-based birth cohort study from the Isle of Wight showed that eczema at age 4 years increased the risk of asthma at age 10 years (OR 2.15; 95% CI 1.24–3.73) (6). While these studies provide evidence supporting the atopic march, the German Multi-Centre Allergy Study (MAS), published almost a decade after the Tucson Children's Respiratory Study, contradicted these findings.

The MAS followed a birth cohort, enriched by children with a family history of allergy, and showed that eczema in the first 2 years of life was associated with an increased risk of current wheeze at age 7 (OR 1.93; 95% CI 1.22–3.06). However, Illi et al. (29) claimed no evidence for an association between eczema and asthma at age 7 years once they adjusted for early wheeze and early-life sensitization (OR

1.46; 95% CI 0.73–2.90). The authors argued that eczema was not an independent risk factor for subsequent asthma and attributed the association to confounding by early wheeze and sensitization comanifested with early-life eczema.

When analysed in the same way as MAS, a study of children with a family history of allergy, Melbourne Atopic Cohort Study (MACS), showed a similar pattern (7): Eczema in the first 2 years of life was associated with an increased risk of asthma at age 6–7 years (OR 2.02; 95% CI 1.33–3.07), but adjustment for early-life wheeze and sensitization made this association not statistically significant (OR 1.45; 95% CI 0.92–2.31). However, further analysis revealed that early-life eczema remained associated with an increased risk of childhood asthma, when adjusted only for early-life wheeze (OR 1.83; 95% CI 1.17–2.85), suggesting that the major cause of 'confounding' was sensitization. The results from this study also showed that, independent of both wheeze and sensitization, AD within the first 2 years of life was associated with an increased risk of childhood asthma in boys (OR 2.45 95% CI, 1.31–4.46), but not girls (7).

It remains highly contentious whether sensitization should be considered a confounder between early-life eczema and risk of other forms of allergic disease. It has been demonstrated that eczema may precede and increase the risk of subsequent sensitization, which in turn increases the risk of asthma, as discussed in the next section. Hence, sensitization that followed eczema is likely to be a step on the biological pathway between eczema and asthma but not a confounder. Adjusting for early-life sensitization without considering the temporal sequence of sensitization and eczema will underestimate the effect of eczema on asthma.

Table 1 A summary of the longitudinal studies of atopic march

Author Year Country	Definition of eczema/AD in study	Crude association of asthma or allergic rhinitis with temporal AD/eczema exposure	Adjusted Outcome measure (95% CI)
Prospective longitudinal studies in population-based cohorts			
Alm et al. (63) 2011 Sweden	Parental affirmative response to 'Has your baby had eczema? (Asked at 12 months of age)'	Allergic rhinitis in the past 1 year at age 4 years Eczema in 1st year – OR 3.76; (2.86–4.93)	aOR 1.97; (1.19–3.26)
Arshad et al. (6) 2005 UK	Parental report of chronic or chronically relapsing itchy dermatitis lasting >6 weeks with characteristic morphology and distribution	Currently diagnosed asthma at 10 years of age (subject with currently diagnosed wheeze and ever-diagnosed asthma) Eczema at 1 year – OR 3.99; (2.61–6.11) Eczema at 2 year – OR 2.60; (1.64–4.13) Eczema at 4 year – OR 3.93; (2.59–5.96)	Reported as NS Reported as NS aOR 3.27; (1.71–6.28)
Bergmann et al. (64) 1998 Germany	Based on four different criteria: (i) Reported diagnosis by family physician; (ii) The examining doctors opinion; (iii) The diagnosis given by the examining doctor; and (iv) A computer algorithm which was used to diagnosis. Obvious AD was diagnosed from a combination of at least three of nine typical signs in at least three of 26 typical anatomical sites	Risk and predictive values of single and combined risk factors for allergic airway disease (asthma or rhinoconjunctivitis at age of 5 years) Atopic dermatitis first 3 months – OR 1.81; (0.96–3.43) Atopic dermatitis first 3 months and at least two atopic family members – OR 4.64; (1.72–12.55)	Not reported
Bohme et al. (65) 2002 Sweden	Parental report of 'Dry skin and itchy rash with typical distribution (face/outer limbs/folds of elbows or behind knees/wrists or fronts of ankles) for (3) 2 weeks; or doctor's diagnosis of eczema'	Atopic dermatitis (AD) up to 2 years of age versus non-AD Wheezing ever Asthma up to 2 years Food allergy; doctor's diagnosis up to 2 years	RP 1.27; (1.14–1.42) RP 1.45; (1.16–1.80) RP 6.14; (4.73–7.97)
Burgess et al. (4) 2008 Australia	Parental affirmative response to either 'Did he/she have infantile (baby) eczema?' or 'Has he/she ever had eczema in the creases (bends) of the elbows, wrists or knees?'	Eczema by age 7 years as a predictor for asthma onset (years) during: Preadolescence (8–12) Adolescence (13–20) Adult life (21–44) From age 8–44 years	HR 1.70; (1.05–2.75) HR 2.14; (1.33–3.46) HR 1.63; (1.28–2.09) Pooled HR 1.73; (1.42–2.12)

Table 1 (Continued)

Author Year Country	Definition of eczema/AD in study	Crude association of asthma or allergic rhinitis with temporal AD/eczema exposure	Adjusted Outcome measure (95% CI)
Horwood et al. (28) 1985 New Zealand	At least one medical attendance for skin rash that was diagnosed as eczema in the first year of life	Asthma (0–6 years) with eczema diagnosis in the first year of life Boys Girls	HR 3.45; $P < 0.001$ HR 5.80; $P < 0.001$
Illi et al. (29) 2004 Germany	Parental report of at least one of 1. AD diagnosis by the family physician 2. Symptoms of AD 3. Visible AD at the time of follow-up.	Atopic dermatitis manifest in the first 2 years of life Current wheeze at age 7 years – OR 1.93; (1.22–3.06)	aOR 1.46; (0.73–2.90)
Martin et al. (26) 2011 Australia	Parental response to either 'Did he/she have infantile (baby) eczema?' or 'Has he/she ever had eczema in the creases (bends) of the elbows, wrists or knees?'	Either infantile eczema or flexural eczema by age 7 years New-onset atopic asthma	aOR, 4.1; (1.9–8.8)
Martinez et al. (5) 1995 USA	Parental report of 'Has a doctor had ever diagnosed the child with eczema'	Eczema present at 1 year of age Transient early wheezing Late-onset wheezing Persistent wheezing	aOR 1.3; (0.7–2.5) aOR 0.7; (0.3–1.6) aOR 2.4; (1.3–4.6)
Ricci et al. (61) 2006 Italy	AD was diagnosed by a physician, 'AD was obtained by completing a rating scale for ten clinical features (erythema, oedema, vesiculation, crusting, excoriation, scaling, lichenification, pigmentation, pruritus, loss of sleep'. Severity of the AD assessed by a scoring system	Asthma onset regarding to severity of AD Moderate AD and onset of asthma – OR 2.588; (1.084–6.175) Severe AD and onset of asthma – OR 4.770; (2.063–11.032)	Not reported
Saunes et al. (8) 2012 Norway	Parental affirmative answer to both questions 'Has your child ever had eczema?' and 'Has your child ever had an itchy rash which was coming and going for at least 6 months?'	Eczema ever reported at age 2 years Current asthma at age 6 years	aOR 1.95; (1.07–3.54)
Stern et al. (32) 2008 USA	Physician diagnosed eczema by 2 years of age	Eczema by 2 years of age Inactive asthma Newly diagnosed asthma at age 22 years Chronic asthma	aOR 3.8; (1.9, 7.8) aOR 1.1; (0.4, 3.3) aOR 2.0; (1.0, 4.1)
von Kobyletzki et al. (9) 2012 Sweden	Parental affirmative response to 'Has your child had an itchy rash at any time in the last 12 months?'	Eczema at baseline at 1–2 years Incidence of asthma during 5 year follow-up – OR 2.85; (1.72–4.71) Incidence of rhinitis during 5 year follow-up – OR 3.14; (2.27–4.36)	aOR 3.07; (1.79–5.27) aOR 2.63 (1.85–3.73)

Table 1 (Continued)

Author Year Country	Definition of eczema/AD in study	Crude association of asthma or allergic rhinitis with temporal AD/eczema exposure	Adjusted Outcome measure (95% CI)
Zeida et al. (66) 2003 Poland	Physician diagnosed eczema	Incidence of asthma History of atopic eczema (Physician diagnosed <1993) – RR 4.66; (1.07–20.20)	Not reported
Prospective longitudinal studies of children with a family history of allergy			
Carlsten et al. (10) 2013 Canada	Clinical diagnosis of AD by allergist based on the presence of a pruritic rash on the face or extensor surface of he arms or legs and flexural lichenification at 2-year and 7-year examinations	Asthma at age 7 years Early-onset nonpersistent AD (AD by age 2 years that was not present at age 7 years) Early-onset persistent AD (AD Present at age 2 and 7 years) Allergic rhinitis at age 7 years Early-onset nonpersistent AD Early-onset persistent AD Eczema during first year of life Asthma between ages 6 and 8 years – OR 2.01; (0.71–5.72) Parental report of eczema in the first 2 years of life as a predictor for current asthma at age 7 years Any eczema – OR 2.02; (1.33–3.07) No eczema Age of eczema onset* Up to 6 months – OR 3.01; (1.82–4.99) 6–12 month – OR 1.32; (0.72–2.43) 12–24 month – OR 1.47; (0.71–3.04)	aOR 2.88; (1.07–7.74) aOR 7.48; (2.53–22.2) aOR 1.75; (0.77–3.94) aOR 3.47; (1.34–8.99)
Klennert et al. (30) 2001 USA	Eczema reported by parents and verified by a physician		Not reported
Lowe et al. (7) 2008 Australia	Parental report of eczema: a doctor diagnosis of eczema or any rash that was treated with topical steroid preparation (excluding rash affecting only the scalp or nappy region)		aOR 1.45; (0.92–2.31) Eczema up to 6 months: In boys: aOR 3.68 (1.67–8.10) In girls: aOR 1.08 (0.46–2.55)

* Compared to infants with no eczema in first 2 years of life.

The interest raised by the 'comanifestation' argument by MAS prompted a systematic review and meta-analysis of the evidence on the atopic march (14). This review included the four population-based cohort studies (5, 6, 29, 30) that achieved an 80% follow-up and confirmed young children with AD are at elevated risk of developing asthma (pooled OR 2.14; 95% CI 1.76–2.75).

Three recently published longitudinal studies have confirmed previous findings that a march from AD to other allergic disorders is evident in both general populations and high-risk children.

The Prevention of Allergy among Children in Trondheim (PACT) Study of an unselected cohort showed that eczema by the age of 2 years was associated with an increased risk of developing asthma at age 6 years (OR 1.80; 95% CI 1.10–2.96) (8). Similarly, the Swedish Dampness in Buildings and Health (DBH) Study found that early childhood eczema was strongly associated with the development of both asthma (OR 3.07; 95% CI 1.79–5.27) and rhinitis (OR 2.63; 95% CI 1.85–3.73) (9). This study also found that those with early-onset eczema, moderate to severe eczema and persistent eczema had the highest odds of developing asthma and rhinitis.

While confirming the atopic march in high-risk children from age 2 to 7 years, Carlsten et al. (10) also showed that only early-onset persistent eczema was associated with all atopy-related phenotypes. Early-onset persistent eczema was associated with paediatric allergist diagnosed asthma (OR 7.48; 95% CI 2.53–22.2), allergic rhinitis (OR 3.47; 95% CI 1.34–8.99) and food allergy (OR 13.4; 95% CI 2.94–61.4). This study was the first to provide clear evidence of an atopic march from AD to food allergy, while there was some prior evidence of challenge-proven cow's milk allergy being one of the earliest steps in the atopic march towards airway inflammation and asthma (31).

Interestingly, although multiple studies have investigated the atopic march during childhood, few have focused on an atopic march from childhood to adulthood. The Tucson

Children's Respiratory Study followed up nearly 600 of their initial participants at age 22 years (32). Eczema before the age of 2 years was not associated with newly diagnosed asthma between ages 2 and 16. In contrast, using data from the Tasmanian Longitudinal Health Study (TAHS), we have shown that both childhood eczema and rhinitis were associated with asthma incidence in adolescence, early adulthood and through to age 44 years (4, 11). The rate ratio for any incident asthma after age 7 years, given eczema by age seven, was 2.0 (95% CI 1.6–2.4). TAHS has also shown that childhood eczema increased the risk of new-onset atopic asthma (OR 4.1 95% CI 1.9–8.8), but not nonatopic asthma. The latter findings suggested that refinement of asthma phenotypes could increase the ability to detect the atopic march (26).

Overall, the weight of evidence favours the hypothesis that AD may lead to asthma and allergic rhinitis, but further investigation of the role of AD in the development of food allergy is needed. While available evidence does not support AD as a *cause* of subsequent allergic disorders, we discuss below some hypotheses that have been explored in the literature as possible biological mechanisms that could explain a causal link.

Potential biological mechanisms in the atopic march

Despite the popularity of the atopic march hypothesis, the mechanisms that might underlie the progression of the atopic march have not yet been elucidated. Mechanisms and biological pathways proposed to date are illustrated in Fig. 2 [reproduced with permission from Burgess et al. (25) and modified to incorporate recent evidence] and discussed below.

One current hypothesis on potential biological mechanisms for the atopic march revolves around defective skin barrier function, a hallmark of AD. This defective skin barrier is thought to allow both epidermal water loss and penetration by high molecular weight structures such as allergens, bacteria and viruses (33).

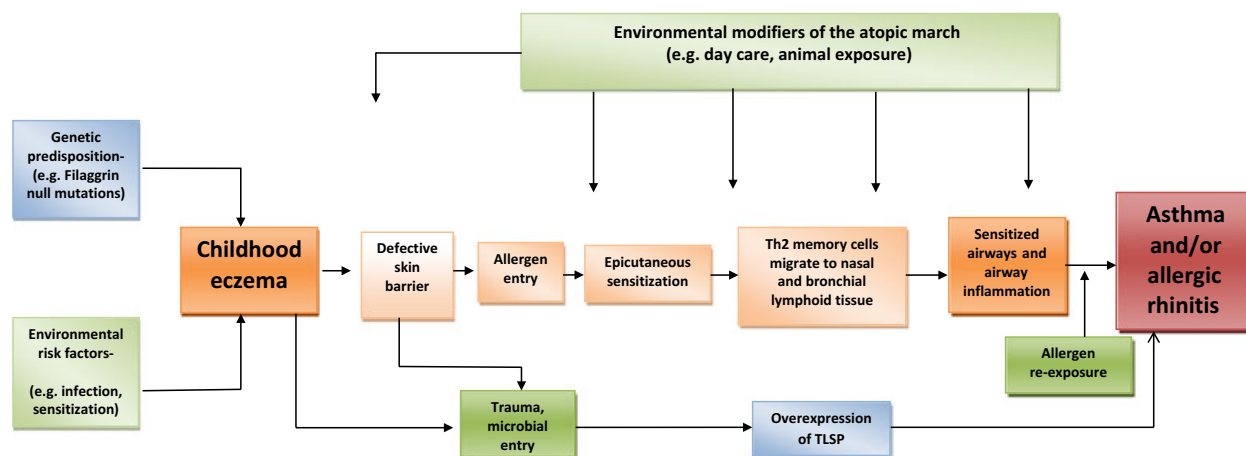


Figure 2 A proposed pathway to explain the atopic march from childhood eczema and the development of asthma and allergic rhinitis [we have reproduced our previously published diagram with permis-

sion from *Journal of Asthma* (25) and modified it to incorporate recent evidence].

One explanation for the increased risk of subsequent allergies with defective skin barrier function in AD is that sensitization to allergens may occur via the defective skin barrier, initiating the atopic march (33). It has been proposed that allergen penetration can lead to transcutaneous sensitization. Some key longitudinal studies have highlighted that IgE sensitization to environmental allergens in eczema is an important factor in progression into asthma. The placebo arm of a randomized controlled trial of children with AD symptoms and a family history of allergy found a significantly higher risk of developing asthma in those sensitized at baseline to egg (RR, 1.4; 95% CI, 1.1–1.7), house dust mite (RR 1.6; 95% CI 1.3–1.9), or grass pollen (RR 1.7; 95% CI, 1.4–2.1) (34). In cohort studies, the presence of early food sensitization in infants with early eczema increased the risk for later asthma (35, 36). These findings suggest that IgE-associated AD is a more precise initial step of the atopic march.

Defects in skin barrier function are also associated with systemic responses such as increased total IgE and airway hyper-reactivity, possibly due to subsequent sensitization. In children, AD seems to be associated with airway inflammation even in the absence of asthma (37). Skin sensitization precedes airway sensitization to the same allergen (38) and is one of the strongest predictors for the development of childhood asthma and allergic rhinitis (39). Together, these findings suggest that interventions to improve barrier function, which is likely to minimize ingress of allergens, could be an important measure to control the onset of the atopic march.

While there has been much interest in the defective skin barrier as the link between AD and subsequent allergies, some studies suggest that keratinocyte-produced thymic stromal lymphopoietin (TSLP) may also link AD and asthma. Chronic skin lesions in AD express TSLP, an interleukin 7-like cytokine released due to trauma, various microbes and inflammation, in turn initiating or exacerbating allergic inflammation (40). Human studies have shown that overexpression of TSLP in skin is associated with both atopic and nonatopic AD (41). Mouse models have shown that a significant elevation of serum TSLP triggers bronchial hyper-responsiveness to inhaled allergens in the absence of epicutaneous allergen sensitization (42). These findings suggest that the link between overexpression of TSLP in the AD skin and other allergic disorders could be independent of the skin barrier defect.

Can we prevent or arrest the atopic march?

If the atopic march is causal, research into preventing its onset as well as arresting it will have significant public health implications. There are two possible points of intervention that may reduce the incidence of asthma and allergic rhinitis: (i) primary prevention, where an intervention is introduced prior to the child developing eczema, which prevents both the onset of AD and the development of subsequent allergies; and (ii) secondary prevention, where an intervention is applied after a child has developed AD but is yet to develop other allergic disorders. The key evidence on each of these interventions is summarized below.

Primary prevention

While there has been a long history of general intervention studies aimed at reducing the incidence of allergic disease, in particular AD, some studies have focused clearly on the atopic march. The main intervention currently under investigation and addressing the atopic march hypothesis is building and maintaining the infant skin barrier function (43). If the increased risk of asthma is in part mediated by the development of transcutaneous allergic sensitization, it may be possible to prevent this progression by maintaining and improving skin barrier function in infants who are not yet sensitized. A number of studies are underway using both standard emollients (44) and ceramide-dominant emollients (45). The safety and feasibility of these interventions are currently being established, and they represent an exciting development in addressing the atopic march hypothesis.

Clinical trials of probiotics and prebiotics are also being considered as interventions for preventing the initiation of the atopic march (46, 47). Probiotics are live beneficial bacterial cultures known to shape the immune system by rebalancing the 'Th2 bias' with which infants are born (47). Prebiotics are supplements or foods containing a nondigestible ingredient that selectively stimulates the favourable growth and/or activity of indigenous probiotic bacteria. Although probiotics and prebiotics have shown promise in treating AD, the evidence is insufficient to make any recommendations (48). It has been speculated that the use of these agents during pregnancy and early life could prevent the initiation of atopic march (46).

Other general interventions tested to date in the primary prevention of allergies fall into the following categories: modification of the infant (formula interventions and promotion of breastfeeding) and maternal diet (avoidance of allergenic foods) and manipulation of the maternal/infant intake of fatty acids. While controversy remains concerning many of these interventions (49) and research continues, in general the results from such interventions have been disappointing (50–53). Recent evidence on timing the introduction of solids (54) and the role of vitamin D in allergic diseases (55, 56) has led to current trials on supplementation with vitamin D during pregnancy and early life, and early introduction of allergenic foods into the infant diet. These interventions are not specific to reducing AD risk and aim to modify infant immune responses, thereby reducing all forms of allergic diseases.

Secondary prevention

If a child develops eczema, it may still be possible to prevent the development of asthma and allergic rhinitis. Relatively few secondary prevention trials have been conducted to date. The Early Treatment of the Atopic Child (ETAC) Study found that 18 months treatment with the antihistamine cetirizine was ineffective in preventing asthma development in children with early AD (34). This was not surprising, as the intervention appeared to have minimal impact on the expression of AD in these children (57). The ETAC Study found that cetirizine delayed or prevented asthma development in a subgroup

of infants with AD sensitized to grass pollen and dust mite. However, the follow-on Early Prevention of Asthma in Atopic Children (EPAAC) Study failed to confirm these findings (58). A 6-year randomized placebo-controlled trial, the Study of Atopic March (SAM), is currently underway. This trial is following 1100 infants with AD being treated with either pimecrolimus cream or placebo. Baseline results have shown increased IgE levels in infants at 3–18 months who are at risk of developing asthma and recommend that therapeutic attempts to prevent asthma should start in infancy (59).

Another aspect of the secondary prevention of atopic march currently of interest is environmental modifiers of the progression from eczema to other allergic diseases (Fig. 2). These investigations were probably triggered by the finding that only a modest proportion of children with eczema will subsequently develop asthma (60, 61). A recently published longitudinal study of children with AD before 3 months and a family history of allergy suggested that exposure to cats (OR 0.16; 95% CI 0.05–0.53) and day care (OR 0.08; 95% CI 0.03–0.19) may reduce the risk of developing asthma (62).

Summary

The evidence to date favours the atopic march hypothesis linking AD as the initial manifestation of atopy with progression to asthma and allergic rhinitis. By contrast, there is a scarcity of robust evidence for a link between AD and food allergy, other than as a co-association. There is as yet no definitive proof that the atopic march is causal, despite there being a clear temporal association and plausible biological mechanisms to explain such an association.

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The findings pertaining to the atopic march are relevant for counselling the parents of children with AD. While their child has an increased risk of developing asthma and allergic rhinitis later in childhood or even adulthood, the average probability of developing asthma is only one in three and allergic rhinitis is two in three. However, these probabilities could be higher among those with severe AD. It is important to establish whether the atopic march is causal, to focus on identifying interventions that can be implemented in either the general population or children with eczema. Evidence from primary and secondary prevention trials is now critical in this context. An emerging area of research into the atopic march is investigation into environmental modifiers. Such information may assist in identifying secondary prevention strategies to arrest the atopic march. Despite substantial research towards identifying the causes of and interventions to prevent allergic diseases, we are yet to identify effective strategies to reduce the burden of these conditions. In this context, the atopic march remains a promising area of investigation.

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Conflicts of interest

The authors declare no conflicts of interest.

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