

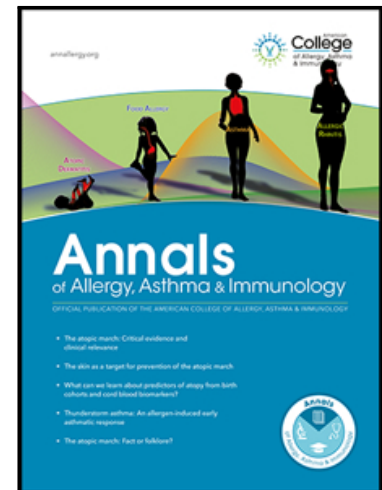
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Abbreviations: AD: Atopic dermatitis; BEEP: Barrier Enhancement for Eczema Prevention;

FLG: Filaggrin

The *atopic march* described progression from AD towards asthma and allergic rhinitis,¹ variably interpreted as initially AD and later wheeze or rhinitis to all three atopic disorders in order of AD, then asthma, then rhinitis. A central role for AD barrier dysfunction was implicated by the development of airway sensitization in tape-stripped murine models sensitized epicutaneously. Data-driven assessments, however, suggest a more complex, multimorbidity relationship among these atopic disorders, reflecting their shared pathomechanisms, environmental triggers, and genetic risk factors.

Trajectories and Risk Factors from Longitudinal Studies

Much refutation of the atopic march concept is based on longitudinal studies, which have yielded trajectories for atopic disorders and identified factors that confer increased risk of having AD and at least one other atopic disorder (for comprehensive review²). In one study, Bayesian machine learning was used to divide outcomes from two pooled longitudinal birth cohort databases into eight latent classes based on onset age of AD, wheeze, and rhinitis (birth-11 years). Although 49% developed atopy and 26% AD (largely mild), only 12% with AD experienced the full atopic march and 40% had either wheeze or rhinitis after AD. AD persistence (active AD on consecutive visits) was most associated with developing wheeze or rhinitis (Figure 1). Atopic polysensitization was another risk factor, especially for AD with wheeze and rhinitis compared to no disease at 8 years. Another longitudinal European birth cohort, comparing infants of farming and nonfarming women, yielded 4 AD latent classes. The early persistent AD phenotype was at greatest risk for developing asthma, allergic rhinitis, and food allergies. Two European longitudinal birth cohorts yielded 6 AD latent classes, with early onset and persistence again

demonstrating strong associations with high IgE levels (sensitization), parental atopy, and asthma. These risk factors provide a framework for counseling families.²

Parental atopy as a risk factor suggests an environmental influence, but also supports genetic predisposition to developing allergic diseases through shared genetic loci. The early onset persistent AD phenotype is most strongly associated with null mutations in *FLG*, encoding profilaggrin, which plays a role in epidermal barrier function, water retention, and acidification. Children with *FLG* variants who develop asthma are likely to have AD first, supporting the occurrence of the atopic march based on endotype and the role of AD-associated barrier dysfunction in allergic sensitization.

Efforts to Prevent the Atopic March

If AD itself predisposes to development of food allergy, asthma, and allergic rhinitis (vs. shared risk factors), then preventing or improving AD could reduce the occurrence of these allergic multimorbid disorders. Regarding barrier repair, initiation of daily emollients during the neonatal period reduced AD incidence in three pilot studies. However, their larger clinical trials found no evidence of prevention. In the Barrier Enhancement for Eczema Prevention (BEEP) randomized controlled trial³, 1394 newborns at high risk for AD applied emollient daily (or not) for one year; at 1 and 2 years there was no difference in occurrence or severity of AD; allergic sensitization to foods trended higher (but without significance) in the emollient group. In the PreventADALL randomized clinical trial of 2,397 newborn infants, no intervention (topical emollient application starting during the newborn period and/or early complementary feeding starting at 3-4 months of age) prevented AD by 12 months of age⁴; the impact of these

interventions on food allergies will be assessed at 3 years. A Japanese study in 549 babies similarly found no difference in occurrence of AD at 1 year with 6 months of treatment with emollient and/or oral administration of synbiotics. Although these data suggest that poor barrier may not drive AD or sensitization, reduced transepidermal water loss as a sign of barrier improvement was not measured and only ~15% (in the BEEP study) had a known *FLG* variant indicative of an inherent barrier defect before AD development.

Trials to prevent the “march” after developing AD have been challenging. In the Study of the Atopic March, 1,091 infants with AD onset within the previous 3 months were randomized to receive pimecrolimus or vehicle with AD flares. At 3 years, the percentages developing asthma (mean 10.7%), allergic rhinitis (22.4%), or food allergy (15.9%) were approximately the same between groups, although lower than historically reported. These data were confounded by the ability of families to rescue after 3 days with an on-label medium-strength steroid (ie, stronger than the pimecrolimus cream)⁵. Oral immunotherapy against house dust mite during the first year of life did not lower the percentage developing AD, wheeze, or food allergy (or even house dust mite sensitization) vs. control high-risk infants². Trials of the injected IL-4 receptor inhibitor, dupilumab, are ongoing in children as young as 6 months; given the shared underlying role of type 2 immunity in AD and other forms of atopy, a carefully-designed registry, tracking prospectively the outcome of treating with dupilumab vs. topicals alone in infants and toddlers with severe AD, but not other allergic disorders, could test the impact of targeting early systemic type 2 immunity in modifying disease course in this high-risk group. Such a study would require large numbers of children and years of serial evaluations.

Conclusions

Pediatric AD is a heterogeneous disorder with numerous factors influencing its course. Not uncommonly, children with AD later develop asthma and/or rhinitis, particularly with greater AD severity. The relative role of antigen exposure through the impaired barrier in AD vs. shared underlying pathogenic factors in the propensity of children with AD to develop other atopic disorders remains controversial. Potential trajectories and risk factors for developing asthma and allergic rhinitis after AD have emerged, primarily from data-driven assessments of longitudinal studies, enabling risk predictions. However, future longitudinal studies with careful environmental assessments, AD phenotyping, documentation of allergic disorders, and comprehensive biomarker assessments will be needed to: i) track subgroups with AD based on phenotypes and endotypes; ii) understand the relationship of trajectories to genetic and environmental factors (including the skin and gut microbiome) and disease control; and ultimately iii) advance individualized management to prevent occurrence of AD and of allergic multimorbidities in children with AD.

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Figure 1. Risk Factors for Other Atopic Disorders in Children with AD.

Risk factors for multimorbidity have been defined based on longitudinal cohort studies. The basis for the association of AD with other atopic disorders (AD as causative vs. AD merely sharing genetic, environmental, and pathogenic factors) remains controversial. Interventions to improve AD or prevent atopy could lower risks.

