

The atopic march and atopic multimorbidity: Many trajectories, many pathways



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The atopic march recognizes the increased occurrence of asthma, allergic rhinitis, or both after atopic dermatitis (AD) onset. Mechanisms for developing atopic comorbidities after AD onset are poorly understood but can involve the impaired cutaneous barrier, which facilitates cutaneous sensitization. The association can also be driven or amplified in susceptible subjects by a systemic T_H2-dominant immune response to cutaneous inflammation. However, these associations might merely involve shared genetic loci and environmental triggers, including microbiome dysregulation, with the temporal sequence reflecting tissue-specific peak time of occurrence of each disease, suggesting more of a clustering of disorders than a march. Prospective longitudinal cohort studies provide an opportunity to explore the relationships between postdermatitis development of atopic disorders and potential predictive phenotypic, genotypic, and environmental factors. Recent investigations implicate disease severity and persistence, age of onset, parental atopic history, filaggrin (*FLG*) mutations, polysensitization, and the nonrural environment among risk factors for development of multiple atopic comorbidities in young children with AD. Early intervention studies to repair the epidermal barrier or alter exposure to the microbiome or allergens might elucidate the relative roles of barrier defects, genetic locus alterations, and environmental exposures in the

risk and sequence of occurrence of T_H2 activation disorders. (J Allergy Clin Immunol 2019;143:46-55.)

Key words: Atopic dermatitis, atopic march, epidermal barrier, asthma, allergic rhinitis, food allergy, endotypes

Atopic dermatitis (AD), which is commonly called eczema,¹ is one of the most common pediatric inflammatory skin disorders, with a prevalence worldwide of approximately 10% to 21%. Based on the 2007 National Survey of Children's Health, the prevalence of AD in US children was 13.0%, with 67% having mild, 26% having moderate, and 7% having severe AD.² The Multicenter Allergy Study birth cohort found that 13.4% had AD by 1 year of age and 21.5% by 2 years of age, attesting to the high prevalence and early onset of AD.³ AD is well recognized to be associated with several other atopic disorders, particularly food allergy (FA), asthma, and allergic rhinitis (AR),⁴ with the co-occurrence of these disorders greater than expected by chance alone, regardless of IgE sensitization.⁵ That each of these atopic disorders has a different peak age of onset has suggested a sequential progression of disease.

One of the difficulties in population-level studies is the formal definition of asthma. Many young children can wheeze with viral respiratory tract infections, in particular rhinovirus and respiratory syncytial virus, but outgrow it by 6 years of age. Therefore the definition of asthma in birth cohorts varies, and some studies use multiple definitions.⁶ Similarly, the diagnosis of AR is challenging because rhinorrhea is a very nonspecific finding and often seen with viral upper respiratory tract infections. However, the seasonal or annual symptoms coupled with positive specific IgE/skin test results can be helpful in diagnosis of AR. Furthermore, repeated measurements in longitudinal studies reduce the risk for misclassification of asthma and AR from erroneous diagnosis.

ASSOCIATION OF AD AND ALLERGEN-SPECIFIC T_H2-DRIVEN DISORDERS: THE ATOPIC MARCH

The earlier mean onset of AD than formally diagnosed asthma and AR has suggested a causal relationship between the occurrence of AD and the development of other comorbidities. The atopic march was originally defined 15 years ago as the natural history of atopic manifestations characterized by a typical sequence of progression of clinical signs of atopic disease, with some signs becoming more prominent while others subside. In general, the clinical signs of AD predate the development of asthma and allergic rhinitis, suggesting that atopic dermatitis is an "entry point" for subsequent allergic disease.⁷ This concept was based on (1) recognition that the risk of asthma and AR was

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Abbreviations used

- AD: Atopic dermatitis
- ALSPAC: Avon Longitudinal Study of Parents and Children
- AR: Allergic rhinitis
- FA: Food allergy
- FLG: Filaggrin
- OR: Odds ratio
- PASTURE: Protection Against Allergy: Study in Rural Environments
- TSLP: Thymic stromal lymphopoietin

increased in children with preceding AD, particularly more severe AD, and (2) a murine model of the atopic march in which epicutaneous sensitization to ovalbumin after tape stripping and development of dermatitis enabled the later development of ovalbumin-induced airway inflammation without the need for airway sensitization.⁸

Since that time, several different definitions of the atopic march have been offered. The strictest definition requires that a patient with AD had asthma subsequently and then AR, with all 3 disorders eventually developing. This was not the originally proposed concept, which simply suggested greater risk of asthma or AR in a child with AD versus a child with normal skin. The more likely order of development was asthma and then AR if both eventually developed based on the recognized age distributions of these atopic disorders. FA was subsequently included as an early component of the march that is strongly linked to AD but can precede or follow AD in occurrence. Indeed, FA often precedes the development of asthma and AR (35% each in one study^{9,10}). Eosinophilic esophagitis (peak age of onset, 3 years) has been suggested to be part of this progression as well, although to a much lesser extent than FA.¹¹

Our current concept of the atopic march is the early occurrence of AD (Fig 1), followed by the increased risk of having 1 or more disorders characterized by allergen-specific type 2 (including T_H2) responses, which might (or might not) include generation of specific IgE and other innate features, such as mucus production and edema. The concept of a march suggests a progression, with AD obligatorily first because its features (eg, barrier defect and inflammation of the skin and/or microbiome alterations¹²) might be required to develop the sensitization for later occurrence of the other disorders. As such, it might be possible to intervene early in the course of AD and prevent the development of allergic comorbidities. Alternatively or in addition, however, there might be an innate predisposition to have more than 1 atopic disorder because of, for example, shared genetic loci or early environmental exposures (eg, exposure to atmospheric irritants/pollutants/allergens or certain microbes, such as through caesarian vs vaginal delivery or skewing of the microbiome toward *Staphylococcus aureus*). The temporal sequence might merely reflect a tissue-specific peak time of occurrence of each disease; this pathway would represent a “cluster” rather than a true progression or march.

POTENTIAL TRAJECTORIES FROM AD TO T_H2-DOMINANT COMORBIDITIES

Longitudinal prospective cohort studies beginning at birth or early during childhood have allowed more refined study of the

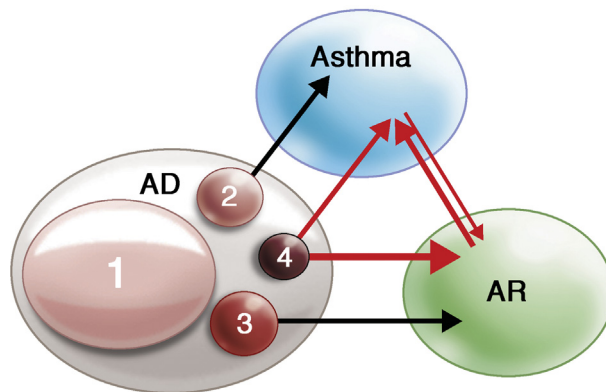


FIG 1. Potential trajectories of disease progression toward asthma and AR in patients with AD initially (the atopic march). Different shades of pink/red/maroon represent different AD endotypes. The majority of patients with AD do not have either of these atopic comorbidities (1). The subsets of patients at highest risk for the atopic march to asthma (2), AR (3), or both (4) tend to have more severe persistent disease, early sensitization, and a family history of atopy. Although it is most common for AD to be the first component of the atopic march, AD can also follow the development of asthma or AR. FA also occurs frequently in children with AD and not infrequently precedes AD.

potential trajectories of children after AD development and suggest that the atopic march, even with its broader definition, does not occur in approximately 50% of children with AD (Table I).^{3,10,13-22} Furthermore, the majority of atopic children do not have early AD, and AD occurrence is not a risk factor for asthma development in adults.^{23,24} These observations emphasize the need to define disease phenotypes (observable characteristics) and endotypes (based on functional or mechanistic biomarkers) that allow prediction of the progression from AD to other atopic disorders and the development of atopic disorders without the occurrence of AD.

One of the difficulties in interpreting epidemiologic data on disease progression in patients with AD is the heterogeneity of data collection among cohorts. Multinational organizations, such as the European consortium of birth cohorts/MeDALL,⁵ have pioneered efforts to harmonize data among cohort studies and use systems biology coupled with both hypothesis-driven and data-driven analyses to understand how pathophysiologic and environmental factors influence the development of atopic diseases and their progression. Despite the focus on cross-sectional analyses of data from multiple cohorts, distinct clusters/endotypes of patients with allergic diseases have been identified that are remarkably similar to those observed with machine learning analyses of longitudinal studies. These observations suggest that, regardless of the methodology, these distinct trajectories of disease progression are likely reproducible and representative of the phenotypes observed in clinical practice. In these studies factors that increase the risk of advancement from AD to other atopic disorders include polysensitization, AD persistence, parental atopy, early age of onset, greater disease severity, and having a filaggrin (*FLG*) mutation (Fig 2).

Data from the larger prospective cohorts (>1000 subjects) are summarized in Table I^{3,10,13-22}; individual studies are not included if part of a meta-analysis. In a 2007 meta-analysis of 13 prospective cohort studies, the pooled odds ratio of having asthma by 6 years of age in children with AD during the first 4 years of life was 2.14 (95% CI, 1.67-2.75) from the 4 birth

TABLE I. Trajectory of development of allergic comorbidities after onset of AD: Prospective longitudinal cohort studies

Cohort/key reference no.	Patient population	Duration of observation	Percentage with AD	AD to asthma	AD to AR	Risk factors identified	Comments and limitations
Canadian Healthy Infant Longitudinal Development (CHILD) study ¹⁴	3495 Canadian infants enrolled from before birth to 5 y 2311 children with 1- and 3-year-old clinical data Test for sensitization to 6 inhalants and 4 foods at 1 y (overall 13.7%)	3 y	11.5% at 1 y and 10.8% at 3 y 4.2% had both sensitization and AD at 1 y	Overall, increased risk of asthma at age 3 y if AD (aRR, 2.23 [95% CI, 1.36-3.67]), sensitization (aRR, 4.37 [95% CI, 2.85-6.69]), or both (aRR, 7.04 [95% CI, 4.13-11.99]) at 1 y No greater risk of asthma if AD without allergic sensitization at 1 y vs non-AD without allergic sensitization (aRR, 0.46; 95% CI, 0.11-1.93)	Overall, increased risk of AR by 3 y if AD (aRR, 4.44; 95% CI, 2.59-7.63) or sensitization (aRR, 4.85 [95% CI, 2.84-8.27]) at 1 y Increased risk if AD and nonsensitized (aRR, 4.53 [95% CI, 2.13-9.63]) and AD with sensitization (aRR, 11.75 [95% CI, 5.73-24.12]) vs non-AD and nonsensitized at 1 y	Sensitization, especially toward development of asthma	<ul style="list-style-type: none"> ● Lack of correlation with severity and potential skewing toward more severe disease ● Highest risk of FA if AD and sensitization (but with FA diagnosis from doctor not based on challenges)
National Child Development Study (NCDS) ^{15,16}	~18,500 babies (>98% of those) babies born in England, Wales, and Scotland; March 3-9, 1958 Collected data on asthma or wheezing	Followed 7, 11, 16, 23, 33, 42, 46, 50, and 55 y ¹⁵	1,053 patients with AD by 23 y, including 35% with onset in year 1 and 54% by 7 y ¹⁶	Prevalence of self-reported asthma after AD 1.0% at 44 y and 2.2% at 33 y Overall 2- to 3-fold increased risk if AD and 1.6-fold at 44 y (based on spirometry, excluding smokers)	Not available	Men with 2-fold risk of asthma vs women if infantile AD	<ul style="list-style-type: none"> ● Potential misclassification because of self-reporting
Avon Longitudinal Study of Parents and Children (ALSPAC) ^{17,18}	Birth cohort of 14,701 children from Avon, United Kingdom Paternoster et al ¹⁷ used children from ALSPAC cohort for latent class analysis of AD subsets with data available from 12 time points for 3480 and from ≥6 time points for 9894 children ¹⁷ Belgrave et al ¹⁸ used 8,665 from cohort for latent class analysis of subsets based on atopic disease; classes shown are this cohort only (see text for combined data) ¹⁸	Birth to 11-16 y ¹⁷ Follow-up at 6, 18, 30, 42, 57, 69, 81, 103, 128, 140, 166, and 198 mo	Prevalence of AD 27% at first year of life, 17.8% at 11 y, and 7% at 16.5 y ¹⁷ Prevalence of classes: early-onset persistent AD (7.3%), early-onset late-resolving AD (7.0%), early-onset early-resolving AD (12.9%), midonset resolving AD (7.0%), late-onset resolving AD (7.9%), unaffected or transient (58.0%) ¹⁷ Within the total group, AD only (15.6%) ¹⁸	All classes associated with asthma at 7 and 13 y; strongest for persistent class: 29% with asthma at 7 y vs 8% of unaffected or transient class; 31% at 13 y vs 7% of unaffected or transient class ¹⁷ Persistent AD and wheeze (2.9%); AD, wheeze, and AR (called atopic march [4.6%]) ¹⁸	Persistent AD with later-onset AR (1.6%) AD, wheeze, and AR (called atopic march [4.6%]) ¹⁸	Children in atopic march class at highest risk of sensitization FLG mutations most strongly associated with persistent group; no association with midonset resolving AD	<ul style="list-style-type: none"> ● Used Bayesian machine learning methods to identify distinct latent classes based on individual profiles of AD, wheeze, and AR¹⁸ ● Analysis does not formally test for causality or temporal relationship with some risk factors.
Prevention and Incidence of Asthma and Mite Allergy (PIAMA) ¹⁷	Birth cohort of 3,963 children from the Netherlands Paternoster et al ¹⁷ used cohort for latent class analysis study Data available from 10 time points for 2,063 and from ≥5 time points for 3,652 children	Age 3 mo to 11 y Follow-up at 0.25, 1, 3, 5, 8, and 11 y	Prevalence of AD 18% in first year and 14% by 11 y Prevalence of classes: early-onset persistent AD (4.9%), early-onset late-resolving AD (3.8%), early-onset early-resolving AD (15.4%), midonset resolving AD (6.5%), late-onset resolving AD (6.5%), unaffected or transient (62.9%)	Persistent and early-onset late-resolving group showed association with asthma at age 7 y; at age 11 y, again the strongest association was with the persistent group	Not available	Strongest associations with asthma at 7, 11, and 13 y with persistent class, but all AD classes showed increased asthma risk No evidence of specific trajectory from AD to asthma	<ul style="list-style-type: none"> ● Used Bayesian machine learning methods to identify distinct latent classes based on individual profiles of AD, wheeze, and rhinitis ● Analysis does not formally test for causality or temporal relationship with some risk factors.

(Continued)

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Cohort/key reference no.	Patient population	Duration of observation	Percentage with AD	AD to asthma	AD to AR	Risk factors identified	Comments and limitations
Protection Against Allergy: Study in Rural Environments (PASTURE) ¹⁹	1,133 (530 farming and 603 nonfarming) women from rural areas in 5 European countries from August 2002 to March 2005	1, 1.5, 2, 3, 4, 5, and 6 y	Point prevalence of AD similar from birth to 6 y (11.4% to 16.9%) Four phenotypes identified with prevalences: 9.2% early transient (n = 96), 6.5% early persistent (n = 67), 4.8% late (n = 50), and 79.5% never/infrequent (n = 825)	8.5% overall 17.5% early persistent AD phenotype; early persistent = onset by 2 y and persistence until 6 y	7.9% overall 21.0% early persistent AD phenotype	Highest risk of asthma in early persistent phenotype Five-fold greater risk of early persistent phenotype if history of allergy in both parents	<ul style="list-style-type: none"> Self-reported data could lead to misclassification. Patients were evaluated by a physician to determine severity at 1 and 6 y of age.
Multicenter Allergy Study (MAS) ^{3,20}	1,123 children from 5 German cities, 1990-ongoing	1, 3, 6, 12, and 18 mos and yearly Up to 7 y reported ³ Further tracking to 13 y ²⁰	Of 1,123 MAS children, 13.4% had AD in first year and 21.5% by 2 y 18.7% with early AD had yearly persistence to 7 y ("persistent")	21.5% cumulative prevalence of AD in first 2 y of life Prevalence of early wheeze greater in children with early AD and scratching vs no AD or AD without scratching (46.3% vs 32.1%, <i>P</i> = .001), link to more severe AD ³ AD preceded wheeze in only 28% of those with both by 2 y. Most with AD had no other allergic condition by 20 y.	AD in first 3 y predicted AR by 20 y (aHR, 1.83; 95% CI, 1.38-2.42) ²⁰	Predictors for poor prognosis if early AD: severity, atopic sensitization, early wheeze, and strong atopic family history ³ Three-fold greater risk of wheeze at 7 y if early AD and concomitant wheeze vs no early AD Three-fold greater risk of concomitant allergies at 20 y if family history of atopy Data do not suggest that AD preferentially precedes wheeze.	<ul style="list-style-type: none"> Study used an allergy risk-enriched sampling strategy and cannot be generalized but represents a high-risk population. Early wheeze based on onset of signs by 3 y
The Odense Adolescent Cohort Study (TOACS) ²¹	15-y follow-up data on 1,206 28- to 30-year-olds who were a subset of 1,501 8th grade students from Odense, Denmark, in July 1995; a subset of these 1,501 were part of a 1996-1997 study as (1) possible AD and hand eczema during last year, (2) present or past inhalant allergy, (3) contact allergy, or (4) control subjects	15 y	Lifetime prevalence of AD among 8th grade schoolchildren: 21.3% 34.1% lifetime prevalence of AD among young adults At 29 y, 50% had persistence of their AD	36.3% (111/306 with AD history) reported "asthma ever"	60.8% (186/306 with AD history) reported "AR ever"	Significant risk factors: hand eczema, AR, and onset before 2 y	<ul style="list-style-type: none"> Most (75%) answered by questionnaire; 39% had clinical examination. There was greater participation in follow-up by those with AD, potentially leading to overestimate of AD prevalence in adults.
Manchester Asthma and Allergy Study (MAAS) ¹⁸	1,136 children recruited prenatally in United Kingdom, 1996-1997 Belgrave et al ¹⁸ used this cohort (and similar ALSPAC birth cohort) to evaluate course of atopy using latent class analysis ¹⁸ Classes shown are this cohort only (see text for combined)	Follow-up at 1, 3, 5, 8, and 11 y	35.6% with AD at 1 y and 23.4% at 11 y Within the total MAAS group, AD only (14.5%) ¹⁸	4.5% with persistent AD and wheeze AD, wheeze, and AR (called atopic march [8.6%])	Persistent AD with later-onset AR in 4.5% AD, wheeze, and AR class (called atopic march) in 8.6%	Combined cohort: sensitization increased risk of all atopic disorders If AD, then asthma, then AR (called atopic march), highest risk of sensitization and persistent AD from infancy to 11 y	<ul style="list-style-type: none"> Diagnosis was based on parental reports but confirmed with medical records in 85% of participants.
Isle of Wight cohort ¹⁰	1,456 enrolled at birth in 1989 on the Isle of Wight, United Kingdom	18-y study with follow-up at 1, 2, 4, 10, and 18 y	AD prevalence 14.2% at 1 or 2 y and 11.9% at 4 y	<i>FLG</i> variant(s) + allergic sensitization is risk factor for asthma between 4 and 10 y of age (31.3% of 16 children without asthma at 4 y vs 4.3% of 532 children with neither risk factor).	<i>FLG</i> variants associated with AR only if allergic sensitization (RR, 1.34; 95% CI, 1.17-1.53), regardless of whether AD (RR, 1.57; 95% CI, 1.23-2.00) or no AD (RR, 1.28; 95% CI, 1.04-1.57).	<i>FLG</i> variants + AD (RR, 3.33-fold; 95% CI, 2.45- to 4.51-fold) and <i>FLG</i> variants + food sensitization (RR, 4.93-fold; 95% CI, 3.61- to 6.71-fold) increased asthma risk in first 18 y Neither AD nor allergic sensitization modified association of <i>FLG</i> variants with AR.	

(Continued)

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Cohort/key reference no.	Patient population	Duration of observation	Percentage with AD	AD to asthma	AD to AR	Risk factors identified	Comments and limitations
Barn/Children Allergic/Allergy Milieu Stockholm Epidemiologic) (BAMSE) ²²	4,089 enrolled at birth in 1994-1996 in Stockholm County	1, 2, 4, 8, and 12 y	Total AD prevalence 15.1% at 1 y, 18.6% at 2 y, 18.7% at 4 y, and 11.6% at 12 y AD only prevalence 13.6% at 1 y, 16.7% at 2 y, 13.8% at 4 y, and 6.7% at 12 y	0.7% of the cohort (5% of those with AD) had both AD and asthma at 1 y, 1.1% (5.9%) at 2 y, 1.1% (5.7%) at 4 y, and 0.7 (6.2%) at 12 y Asthma did not occur in isolation as often as AD or AR. 39.8% with AD had either asthma or AR vs 18.9% without AD	AR increased in association with AD from 0.5% at 2 y to 3.2% at both 4 and 12 y (but AR alone was 4-fold more common). AD, asthma, and AR also increased with 0.6% (3.3% of patients with AD) at 4 y and 1.0% (8.8% of patients with AD) at 12 y.	AR and asthma were more prevalent with severe (22.0%) vs mild (13.8%) AD. Asthma + AR was more prevalent in moderate-to-severe (18.3%) vs mild (9.0%) AD. More persistent AD, asthma, and AR if parental allergy	<ul style="list-style-type: none"> Because of study design, there was greater enrollment of families with allergies in previous children, but loss to follow-up was more frequent among children with allergy-related diseases.
Multiple studies ¹³	Systematic review to assess risk of asthma in children with AD during first 4 y 5,384 total participants from 13 prospective cohorts, including 4 birth cohorts (3,103 subjects)	Follow-up of 6-10 y	AD prevalence ranges from 14.2% to 52.5% of cohort	Pooled OR for risk of asthma after AD onset (vs without AD) in birth cohort studies = 2.14 (95% CI, 1.67-2.75) Prevalence of asthma at 6 y in AD cohort studies was 35.8% (95% CI, 32.2% to 39.9%) for inpatients and 29.5% (95% CI, 28.2% to 32.7%) for combined group of inpatients and outpatients.	Not available	Increased risk of asthma if AD	<ul style="list-style-type: none"> Very mixed cohorts (general population, high-risk infants, birth cohort of mothers with asthma)

aHR, Adjusted hazard ratio; aRR, adjusted risk ratio; RR, risk ratio.

cohorts; the prevalence of asthma at 6 years of age in the 9 other (nonbirth) cohort studies was 29.5% (95% CI, 28.2%-32.7%).¹³

The most recent of these was the Canadian Healthy Infant Longitudinal Development birth cohort study, which found that AD increased the risk of physician/health care professional-diagnosed asthma at 3 years of age only if the AD was accompanied by sensitization to inhalants, foods, or both at 1 year of age.¹⁴ This observation suggests that food sensitization (perhaps through an impaired epidermal barrier) could be a marker of AD severity or an AD endotype (AD plus food sensitization) that is more likely to have additional atopic comorbidities (consistent with the polysensitization data referenced above and that FA/food sensitization itself is associated with severity).²⁵

Data from 2 large prospective longitudinal cohorts was analyzed by using latent class analysis to subclassify AD based on disease course and determine which classes are at highest risk of other atopic diseases. Roduit et al¹⁹ compared babies of farming and nonfarming women in the Protection Against Allergy: Study in Rural Environments (PASTURE) study to divide the cohort into 4 latent classes: (1) never/infrequent, (2) early transient, (3) early persistent; and (4) late. The greatest risk for asthma or AD was in the early persistent AD phenotype.

Paternoster et al¹⁷ combined 2 birth cohorts, the 9894 child Avon Longitudinal Study of Parents and Children (ALSPAC) cohort from the United Kingdom and the 3652 child Prevention and Incidence of Asthma and Mite Allergy cohort from the Netherlands, to track AD outcome and development of asthma in children with AD from birth to 11 to 16 years of age. The best-fit model had 6 classes, including (1) unaffected/transiently

affected, (2) early onset/early resolving (most prevalent AD class), (3) early onset/late resolving, (4) early onset/persistent, (5) late onset/resolving, and (6) midonset/resolving. The more persistent classes (persistent and late resolving) were most strongly associated with *FLG*-null mutations and showed the greatest risk of having coexistent asthma, high IgE levels, and a parental history of atopy. Asthma risk was strongest for the early-onset/persistent class at 7 years (odds ratio [OR], 5.50; 29% vs 8% in normal/transient class) and 13 years (OR, 7.19; 31% vs 7%) and weakest for the early-onset/early-resolving class (OR, 1.56 at 7 years and 1.79 at 13 years).

Belgrave et al¹⁸ combined 11 years of data from the ALSPAC^{17,26} (8665 children) and Manchester Asthma and Allergy Study (1136 children) United Kingdom birth cohorts to determine the temporal trajectory throughout childhood of AD, wheeze, and AR using Bayesian machine learning. These 2 cohorts showed similar cross-sectional patterns, with the prevalence of AR increasing with age and the prevalence of AD and wheeze decreasing with age (see Table I for individual cohort results). The authors disclosed 8 latent classes that were similar between the 2 cohorts and demonstrated great heterogeneity in the course of atopic disease. Among the children in these combined cohorts, 48.8% had a high probability of having AD, wheezing, and/or AR. By 11 years of age, only 3.1% had all 3 atopic march components, the most stringent criterion for the atopic march, with this group primarily having persistent AD. Indeed, 2.7% had persistent AD and wheeze, and another 4.7% had persistent AD and later-onset AR, with only 15.3% having AD alone. Other latent classes included persistent wheeze with later-onset AR, transient wheeze

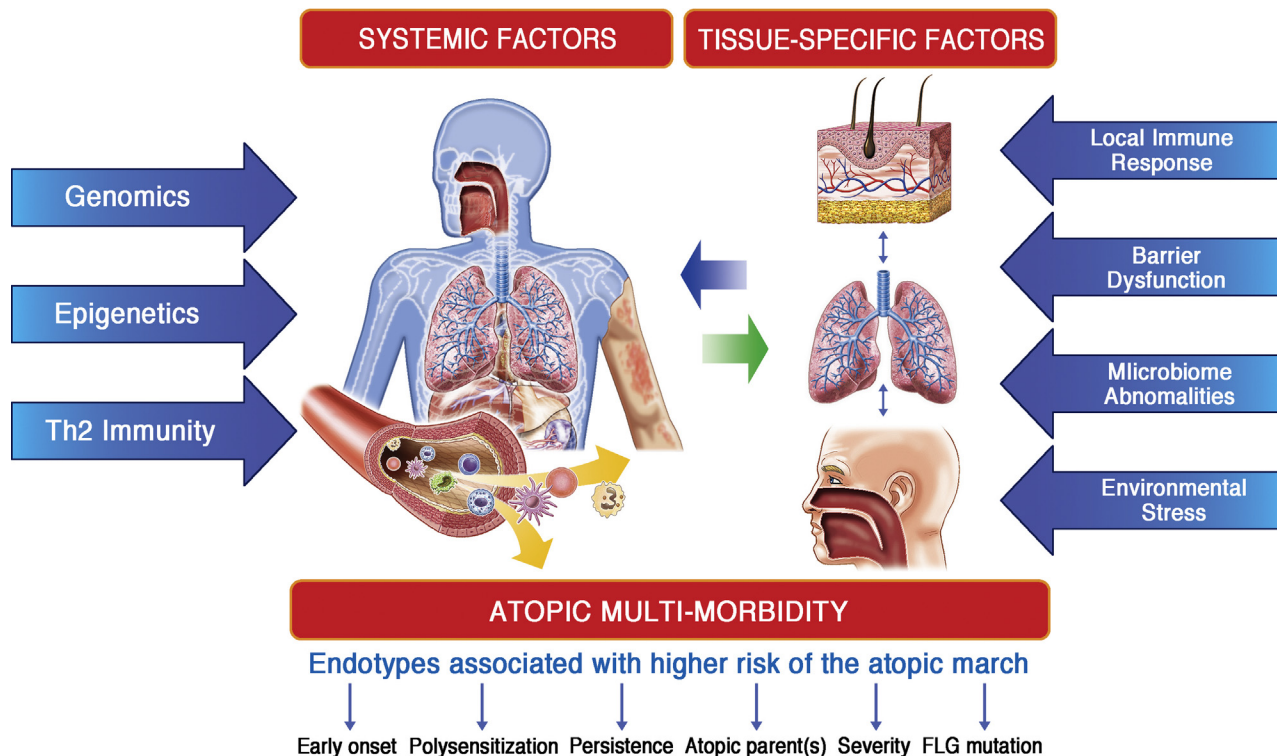


FIG 2. Multifactorial etiology of the atopic march. The atopic march can occur because of sensitization through the early impaired barrier of AD, because of shared genetic and environmental factors that contribute to the development of these atopic disorders as a group, or both. A variety of endotypes are associated with an increased risk of the atopic march.

only, and AR only. It should be noted that latent classes in birth cohorts are models and require further verification in additional cohorts. In the Belgrave et al study,¹⁸ the chronological order of onset of the atopic disorders within each group was not stratified, although it was mentioned that AD tended to precede other forms of atopy in the atopic march group with all 3 disorders but not in the group with persistent AD and wheeze. Sensitization was a significant risk factor for all latent classes with atopy compared with no disease but particularly for those with AD, asthma, and AR.

Latent class analysis was also conducted after removing the cohort with mild severity (“moderate/severe AD”).¹⁸ In this group 52.7% had a low probability of AD, wheeze, and/or rhinitis and a unique class (ie, “transient early AD”) without other features. The atopic march latent class was expected for 7.0%, with a high probability of AD with high persistence. In addition, this group had an increasing probability of asthma with age and a probability of AR in 80% by 11 years, 10.3% with wheeze or wheeze with later-onset rhinitis (40% probability by 5 years), AD or AD with later-onset AR in 10.3%, and AR in 11.6%, particularly between the ages of 5 and 11 years. In another latent class analysis of the Multicenter Allergy Study and PASTURE cohorts, severity was directly associated with asthma risk.²⁷

The data throughout these various studies reinforce the consistent theme in these studies that the early-onset persistent phenotype is the high-risk phenotype for multimorbidity. Furthermore, these studies emphasize the need for additional endotype assessments to determine which subset of young children with AD are at greatest risk and thus candidates for intervention studies to prevent the development of asthma or AR.

MECHANISMS OF ATOPIC MULTIMORBIDITY WITH OR WITHOUT PRIOR AD

Given the number of possible multimorbid disease trajectories reviewed above, several distinct pathways and mechanisms are likely to be involved, some of which are common to all atopic/ T_H2 -dominant disease and others of which are disease specific. It is important to recognize that asthma occurring in the context of atopy (atopic asthma) is itself an asthma endotype most commonly seen for the first time in childhood.²⁸ A full understanding of these mechanisms will require analyses of longitudinal phenotypic data integrated with data on the genome, epigenome, microbiome, and comprehensive exposome to identify the relevant contribution of specific pathways at the trajectory group/endotype or individual level. Identification and characterization (with replication across several cohorts) of AD/atopic endotypes is an emerging field of study and will form the basis for mechanistic dissection of these endotypes, although it will be some time before a full mechanistic understanding is reached.

Although FA was not included in original concepts of the atopic march, the association of FA and AD in early life is the most tightly correlated atopic comorbidity and the best understood at a mechanistic level. The association between AD and FA, especially early-onset or severe AD and FA, has long been recognized. Loss-of-function mutations in *FLG*, which only affect the epidermal barrier, predispose to peanut allergy, even when controlling for the presence of AD and evaluating varying levels of stringency for the definition of peanut allergy.^{29,30} High exposure to environmental peanut allergen in the context of both *FLG*

mutations³¹ and AD has an additive risk for peanut allergy.³² Mouse studies have shown that percutaneous sensitization to food allergen is immunogenic, whereas oral exposure is tolerogenic.⁸ The pivotal Learning Early About Peanut Allergy study advanced these observations and concepts in a clinical trial, which showed a clear reduction in peanut allergy in high-risk infants with AD fed peanut early in life, with approximately 40% of the placebo group of children with AD in these studies having FA at 5 years of age.³³ There has not been consistent evidence that partially or extensively hydrolyzed formulas reduce the risk of AD.³⁴ Taken together, evidence strongly points to a critical role for a disrupted skin barrier,³⁵ with or without the clinically apparent cutaneous inflammation seen in patients with AD, to enable immune exposure to a potential allergen in most cases of early-life FA.

The relationship between AD and respiratory mucosal atopy, including asthma and AR, is less clearly defined, but some strong clues are emerging from genetic studies. Based on a comprehensive genome-wide association study (GWAS), AD, asthma, and AR share many loci (99 potential loci, including many variants in immune response genes),³⁶ suggesting a strongly shared genetic basis. Ferreira et al³⁶ also analyzed the identified loci for differential risk of each risk allele toward each of the individual atopic diseases. As an example, a single nucleotide polymorphism in *FLG* was 1.32-fold more common in patients with only AD when compared with patients with only AR, implying that this single nucleotide polymorphism has a greater tissue-specific risk for AD than other forms of atopy, despite increasing the risk of all 3 diseases: AD, asthma, and AR. These findings might explain the previous finding that *FLG* loss-of-function mutations confer a risk of asthma only in the context of prior AD.^{37,38} Thus early T_H2-dominant skin inflammation might help set the systemic immune context for having T_H2-driven respiratory allergy and might be a prerequisite for these defective barrier genes to confer risk of additional atopic diseases.

Another susceptibility locus on chromosome 11q13.5 is widely reported with AD,³⁹ as well as with other atopic diseases.⁴⁰ Functional variants in *GARP*, a T-cell regulatory gene, are now identified in this locus.⁴¹ Evidence of epistatic effects between barrier genes (*FLG*) and T_H2 genes (*IL4R*) has been demonstrated,¹⁰ and further such interactions remain to be discovered. Tight junctions are also disrupted in patients with AD, asthma, and AR, in part because of T_H2 cytokine effects.⁴²⁻⁴⁶ Epigenetic determinants of atopy are not well understood, but differential methylation of T_H2 lineage-determinant genes, such as *GATA3*, can influence development of both AD and asthma.⁴⁷ Further functional and mechanistic work on these shared loci, the majority of which are located in or close to genes encoding immune pathway proteins, will provide valuable insights into shared immunologic mechanisms in multimorbid atopic subjects.

Key epithelial alarmins, such as IL-33 and thymic stromal lymphopoietin (TSLP), are released by a stressed skin barrier, and although each has a clear T_H2 effect on the respiratory epithelium, compelling evidence of a distal effect of skin-derived alarmins on lung pathology has not yet been demonstrated in human subjects. Assuming a progression from AD, the systemic T_H2-skewed immune context seen in childhood AD might be permissive for viral respiratory tract infections, such as adenoviruses or rhinoviruses, to drive asthma or AR through enhanced respiratory dendritic cell responsiveness or through T_H2 effectors with shared tissue-homing markers (cutaneous lymphocyte antigen, CCR4, and

CCR6) trafficking between skin and mucosal surfaces. The recent identification of “pandendritic” cells suggests a possible shared mechanism across different epithelia.⁴⁸ Polysensitization is common in patients with moderate-to-severe AD and might be a mechanistic link to respiratory allergy, but it is unclear whether polysensitization is an epiphenomenon in the context of sustained T_H2 inflammation or is a primary driver. Nevertheless, a link between aeroallergen sensitization and disease flares of AD and respiratory atopy is well established, indicating a probable link. In a complementary fashion, recognizing that the order of development of diseases is not always “AD first,” it might be posited that the systemic T_H2 inflammation seen in a patient with atopic asthma might make subsequent atopic skin inflammation more likely to develop in genetically susceptible subjects.

TREATMENT TO PREVENT THE DEVELOPMENT OF ATOPIC COMORBIDITIES

Interventions to prevent the atopic march/atopic multimorbidity could theoretically be introduced during pregnancy, shortly after birth, or early after AD onset. The fetus during pregnancy is capable of mounting a T-cell response to antigenic exposure when allergens are presented in amniotic fluid,⁴⁹ and umbilical cord blood mononuclear cells are able to proliferate in response to antigens to express T_H2 cytokines.⁵⁰ However, changes in maternal diet in several studies have not altered the incidence of AD or FA.⁵¹

Early use of probiotics in mothers (or infants) has shown mixed results at 2 years and no effect at 4 years. In a meta-analysis with 17 studies, probiotics given both prenatally and postnatally reduced the occurrence of food hypersensitivity (risk ratio, 0.77; 95% CI, 0.61-0.98), but the variability in the populations and probiotics used makes these data difficult to generalize.⁵² Oral ingestion of food as a means to tolerize appears to be specific to the introduced antigen. Despite the success of early peanut exposure in reducing the incidence of peanut FA by 80%, this intervention has had no effect on the risk of sensitization or allergies to other food or AD resolution.³³ Early exposure to cat/dog has also been shown to prevent sensitization to these allergens,⁵³ but it is unclear whether the effect relates to exposure to the antigen or the animal’s microbiome.

The relationship of FA risk and AD might primarily involve the poor epidermal barrier in patients with AD rather than AD itself. In a cohort of more than 1500 babies of low-risk mothers, 2-day-olds with a transepidermal water loss level in the top quartile had a 7.1-fold increase in development of AD at 1 year of age (vs the bottom quartile), regardless of *FLG* mutation status.⁵⁴ These same neonates with top-quartile transepidermal water loss had an 18.7-fold increased risk (vs bottom quartile) of FA by 2 years of age if they had AD and a 3.5-fold increased risk of FA without AD, showing the importance of epidermal function itself in the development of FA. The early barrier defect of AD in young children involves deficiencies in tight junctions, lipids (especially long-chain ceramides and fatty acids), and some stratum corneum proteins.

Given that the damaged epithelial barrier is thought to allow for allergen penetration and transcutaneous sensitization, 3 studies have examined the application of moisturizers beginning in the neonatal period to prevent AD. Two of these found that application reduced the incidence of AD by 50% at 6 months (124 babies)⁵⁵ and 32% at 32 weeks (118 babies)⁵⁶ compared

with the control group, respectively. The third study tested a ceramide-dominant emollient versus no moisturizer application in 80 babies beginning as neonates and found a trend toward reduced incidence of AD but not significance.⁵⁷ None of these studies demonstrated a reduction in food sensitization, but larger studies are needed and ongoing.

There is growing evidence that alterations in the microbiome can increase the risk of development or exacerbation of AD,^{12,58,59} as well as other atopic disorders.⁶⁰ Early studies suggest that topically applied commensal organisms can improve AD^{61,62} and raise the possibility that early microbiome alteration could both reduce the risk of AD and prevent atopic comorbidities.

Because AD severity is a recognized risk factor in the association with the other T_H2-driven disorders (Fig 2), anti-inflammatory therapy to reduce the severity of AD has been considered as an intervention to prevent the atopic march. Schneider et al⁶³ found no difference in the development of atopic conditions in 1091 at-risk infants with recent-onset AD who were treated early with pimecrolimus cream versus vehicle (with fluticasone cream rescue); however, in comparison with historical norms, the entire cohort had a reduced frequency of asthma and AR in both the active and placebo groups at a mean of 2.8 years after initiation (37% had ≥1 comorbidity, including asthma in 10.7%, AR in 22.4%, and documented FA in 15.9%). As such, this study suggested that general improvement in skin care can decrease the development of other atopic diseases.

A meta-analysis of 6 studies provided evidence that subcutaneous immunotherapy and sublingual immunotherapy could prevent the progression from AR to asthma in high-risk atopic patients (risk ratio, 0.40; 95% CI, 0.30-0.54).⁶⁴ Allergy immunotherapy also reduced the incidence of asthma in 812 children with isolated grass AR (5% vs 10% without).⁶⁵ However, sublingual immunotherapy treatment of 111 high-risk infants with oral house dust mite extract had no effect on house dust mite sensitization or the development of AD, FA, or wheeze.⁶⁶

The recent and emerging availability of T_H2-targeting therapy provides another opportunity for preventing the development of atopic comorbidities because these targets are downstream of several components implicated in the atopic march (eg, IL-33, TSLP, and IL-4/IL-13). The possibility of an early intervention that targets T_H2 immunity is supported by studies showing strong T_H2 skewing in both nonlesional and lesional AD skin^{67,68} and blood⁶⁹ from young children (95% less than 2 years of age) with onset of AD during the previous 6 months. Should targeted therapy against T_H2 molecules (eg, TSLP, tezepelumab; IL-4/IL-13, dupilumab; and IgE, omalizumab) prove safe for young children, early introduction to block the atopic march in high-risk children should be considered, but there is little evidence on which to base decisions about the optimal intervention, its timing based on age or time of disease onset, and its duration of administration.

CONCLUSIONS

Several endotypes that increase the risk of having other T_H2-driven disorders after AD onset have been identified: early AD onset, greater severity, disease persistence, having an *FLG* mutation, polysensitization, and parental atopy. Ultimately, investigations will require better classification of the phenotypes and endotypes of AD to track how these subgroups relate to the

development of other comorbidities after AD. Longitudinal cohort studies are the ideal tool to identify those at greatest risk for progression from AD to another T_H2-mediated disorder and for further investigating the underlying basis for this progression, including whether there is a true march from AD or just a clustering of similar disorders. In contrast to cross-sectional analyses, longitudinal assessment captures repeated measurements and reduces the risk of misclassification because of erroneous diagnosis or self-reporting. These studies will need to establish better definitions of early disease besides AD, which is relatively easy to diagnose. For asthma, this means being able to define the subset of children with early wheezing who would later be designated as having true asthma; indeed, the designation of children with “wheezing” rather than “asthma” in many cohort studies allows for earlier capture.

The confusion between food sensitization, a risk factor for the occurrence of asthma, and true FA is another limitation, particularly when data are collected through questionnaire studies. Even with longitudinal cohort studies, documentation of FA requires a positive food challenge result or history of reactivity after ingestion, making it difficult to capture the true age of onset.

The growing ability in young children to use small amounts of biopsied^{67,68} or noninvasive tape-stripped⁶⁹ skin, swabs for microbiome assessments of the skin and gut, and samples of blood⁷⁰ and saliva/buccal mucosa to identify alterations in gene, protein, and lipid expression patterns, as well as the microbiome, will enable more sophisticated endotyping of early AD. Combined with clinical characteristics and AD course, these personalized biomarker patterns will likely help predict children at risk for AD and its comorbidities, thus allowing early institution of pathogenesis-driven preventive interventions.

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