

Halting the March: Primary Prevention of Atopic Dermatitis and Food Allergies



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Date of Original Release: March 1, 2020. Credit may be obtained for these courses until February 28, 2021.

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Fatima Bawany, BA, Lisa A. Beck, MD, and Kirsi M. Järvinen, MD, PhD (authors); Robert S. Zeiger, MD, PhD (editor)

Learning objectives:

1. To understand why atopic dermatitis (AD) may predispose individuals to developing food allergies.
2. To synthesize recent evidence regarding various primary prevention methods.
3. To learn about the current practice guidelines on strategies for primary prevention of atopic diseases.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: F. Bawany is an investigator for an investigator-initiated, Pfizer-funded, atopic dermatitis trial. L. A. Beck is supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number U19AI117673; is a consultant for Abbvie, Allakos, Arena Pharma, Astra-Zeneca, Connect Biopharma, LEO Pharma, Lilly, Novan, Novartis, Pfizer, Regeneron, Sanofi, UCB, and Vimalan; is or has been an investigator on Abbvie, LEO Pharma, Pfizer, and Regeneron atopic dermatitis trials; and owns stock in Pfizer and Medtronic. K. M. Järvinen is supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number U01AI131344 and National Center for Advancing Translational Sciences under Award Number R21002516; is a consultant for Merck and DBV Technologies; and is an investigator on Aimmune food allergy trial. R. S. Zeiger declares no relevant conflicts of interest.

Atopic dermatitis (AD) is one of the most common inflammatory skin conditions, affecting 15% to 30% of children and 2% to 10% of adults. Population-based studies suggest that having AD is associated with subsequent development of other atopic diseases, in what is known as the “atopic march.” We will provide an overview of studies that investigate primary

prevention strategies for the first 2 diseases in the march, namely, AD and food allergies (FA). These strategies include emollients, breastfeeding, microbial exposures, probiotics, vitamin D and UV light, water hardness, and immunotherapy. Some studies, including randomized controlled trials on emollients and microbial supplementation, have found

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No funding was received for this work.

Conflicts of interest: F. Bawany is an investigator for an investigator-initiated, Pfizer-funded, atopic dermatitis trial. L. A. Beck is supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number U19AI117673; is a consultant for Abbvie, Allakos, Arena Pharma, Astra-Zeneca, Connect Biopharma, LEO Pharma, Lilly, Novan, Novartis, Pfizer, Regeneron, Sanofi, UCB, and Vimalan; is or has been an investigator on Abbvie, LEO Pharma, Pfizer, and Regeneron atopic dermatitis trials; and owns stock in

Pfizer and Medtronic. K. M. Järvinen is supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number U01AI131344 and National Center for Advancing Translational Sciences under Award Number R21TR002516; is a consultant for Merck and DBV Technologies; and is an investigator on Aimmune food allergy trial.

Received for publication September 26, 2019; revised December 4, 2019; accepted for publication December 5, 2019.

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2213-2198

© 2019 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaip.2019.12.005>

Abbreviations used

AAP-	American Academy of Pediatrics
AD-	Atopic dermatitis
AIT-	Allergen immunotherapy
aOR-	Adjusted odds ratio
AR-	Allergic rhinitis
AS-	Asthma
CI-	Confidence interval
EAACI-	European Academy of Allergy and Clinical Immunology
FA-	Food allergy
HMO-	Human milk oligosaccharide
OR-	Odds ratio
PEBBLES-	Prevention of Atopic Dermatitis by a Barrier Lipid Equilibrium Strategy
PreventADALL-	Preventing Atopic Dermatitis and Allergies in Children
RCT-	Randomized controlled trial
RR-	Relative risk
SCORAD-	SCORing Atopic Dermatitis
SPT-	Skin prick test
TEWL-	Transepidermal water loss
WAO-	World Allergy Organization

encouraging results; however, the evidence remains limited and contradictory. With regard to breastfeeding, microbial and lifestyle exposures, vitamin D and UV light, water hardness, and immunotherapy, the lack of randomized controlled trials makes it difficult to draw definitive conclusions. Current American Academy of Pediatrics guidelines support the idea that breastfeeding for 3 to 4 months can decrease AD incidence in children less than 2 years old. Recommendations regarding a direct relationship between breastfeeding on FA, however, cannot be made because of insufficient data. Regarding microbial supplementation, most guidelines do not recommend probiotics or prebiotics for the purpose of preventing allergic diseases because of limited evidence. Before definitive conclusions can be made regarding these interventions, more well-designed, longitudinal, and randomized controlled trials, particularly in at-risk populations, are required. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:860-75)

Key words: Atopic dermatitis; Eczema; Atopic march; Food allergy; Primary prevention

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin conditions. In the United States, it affects approximately 15% to 30% of children and 2% to 10% of adults.¹ AD typically begins in early childhood, with up to 60% of cases presenting within the first year of life, and 85% within the first 5 years.^{1,2} It is characterized by eczematous, pruritic lesions that can persist into adulthood.²

Currently, treatment options for children with moderate or severe AD are inadequate. According to the 2010 Global Burden of Disease survey, among common skin conditions, AD is associated with the highest number of disability-adjusted life-years and years lived with disease.³ The cost of managing AD in the United States ranges from approximately 400 million to 4 billion dollars (inflated from 2008 dollars).⁴ For families, out-of-

pocket costs can consume up to 10% of household income.⁵ Patients with AD also often suffer from social stigma and psychiatric comorbidities. In a recent survey, 51.3% of adults with AD reported that their disease limited their lifestyles, and 39.1% avoided social interactions because of it.⁶ In addition, patients with AD have higher rates of sleep disturbances, depression, anxiety, conduct disorder, and attention deficit hyperactivity disorder.⁷⁻⁹ In summary, AD poses a significant financial, social, and psychological burden for patients and their families.

In addition to its cutaneous manifestations, AD predisposes individuals to other atopic diseases, a phenomenon known as the atopic march.^{2,10} The atopic march has been defined as a “natural history of atopic manifestations” including AD, food allergy (FA), asthma (AS), allergic rhinitis (AR), and eosinophilic esophagitis.^{7,11} However, it is still unclear whether the atopic march represents a temporal or causal relationship, partly due to the fact that most studies are cross-sectional rather than longitudinal.¹² Furthermore, it is unclear whether the sequence of atopic conditions can be predicted, and which of these are, in fact, linked.

AD is often thought to be the first disease in the atopic march.¹¹ This has prompted trials on primary prevention (eg, interventions introduced *before* an individual develops AD, in order to prevent AD or other atopic conditions) and secondary prevention (eg, interventions introduced *after* AD develops to limit the severity of AD or other atopic conditions). Other studies have reviewed tertiary prevention strategies, which relieve symptoms associated with AD or other atopic conditions. Trials on secondary prevention have investigated methods including topical steroids, emollients, calcineurin inhibitors, probiotics/prebiotics, and environmental modifications.^{2,11,13} Tertiary prevention methods include anti-inflammatory therapies, phototherapy, emollients, trigger avoidance, and in severe cases, immunosuppression.¹⁴ In this article, we will review primary prevention of AD. Because FA is often among the first atopic diseases to manifest, and the order in which AD and FA develop is not always clear, we will also review primary prevention of FA. We will focus on studies that have been conducted in the past 5 years, but will also include seminal studies before this time period, as well as key review articles.

METHODS

Data sources

All 3 authors independently searched databases including PubMed and Cochrane Reviews through July 2019 to identify reviews, experimental studies, and society guidelines on primary prevention of allergic diseases. Additional references were located using references cited by these studies. Information regarding studies currently in progress was gathered using presentations from recent scientific meetings and correspondences with investigators.

Inclusion and exclusion criteria

We included in this review studies that met the following criteria: (1) subjects were children not previously diagnosed with allergic disease, (2) the intervention focused on preventing AD, FA, or food sensitization, and (3) the intervention was evaluated in at least 3 publications. Studies in any language were included, as long as an English translation was available. For topics with a comprehensive number of papers, we used the analyses of review articles and meta-analyses if published within the last 5 years. Seminal papers older than 5 years were also included.

Studies were generally excluded if they (1) focused on secondary or tertiary prevention (ie, subjects already diagnosed with an allergic disease or sensitization before intervention), (2) did not study AD, FA, or food sensitization, (3) only studied adults, (4) studied an intervention for which there are less than 3 publications, and (5) were published more than 5 years ago. Of note, some studies that met 1 or more of the exclusion criteria have been included to provide additional context for a topic.

Data extraction

Data extracted included first author, year of publication, country, study type, subject age and allergic risk (high-risk or low-risk), intervention administered and its duration, and outcomes.

ATOPIC DERMATITIS AND FOOD ALLERGIES

Approximately one-third of patients with AD have symptomatic FA, which is significantly higher than the estimated rate of FA in the general population of 10.8%.^{15,16} This finding has spurred investigations into the relationship between AD and FA. The current evidence, however, is limited. Many studies on this topic report IgE sensitization rather than challenge-proven FA, the gold standard for diagnosis,¹⁷ and many report neither. Sensitization is universally associated with IgE-mediated FA, and higher levels of sensitization increase the probability of having clinical FA. However, sensitization is not synonymous with FA and is far more common than clinical FA.^{17,18} This makes interpretation of these results challenging, as food sensitization can overestimate the prevalence of FA. Nevertheless, tests for IgE sensitization are still used, as they are safer and easier to perform than oral food challenges. For this reason, we have included studies that define FA only by food sensitization.

One of the first studies to demonstrate a potential march from AD to FA was a cohort study of 373 high-risk infants (ie, with 1 first-degree relative with AS or 2 first-degree relatives with other IgE-mediated diseases, including AD and FA).¹⁹ Investigators found a strong association between early-onset persistent eczema (ie, eczema that first developed before 2 years of age and was still present at 7 years of age) and the development of food allergen sensitization by 7 years of age (odds ratio [OR]: 13.4, 95% confidence interval [CI]: 2.94-61.4). Subsequent studies have supported these findings.^{10,20} A systematic review of 66 studies determined that patients with AD had higher levels of food sensitization compared with healthy controls (OR: 6.18, 95% CI: 2.94-12.98).¹⁰ This was especially true for severe AD.²¹ At 3 months of age, subjects with SCORing AD (SCORAD) >20 had significantly higher rates of sensitization (adjusted odds ratio [aOR]: 25.60, 95% CI: 9.03-72.57) than those with SCORAD <20, considered mild AD (aOR: 3.91, 95% CI: 1.70-9.00).

Many patients with AD are sensitized to food allergens even before they ingest foods orally, raising questions regarding how food sensitization occurs.⁷ Studies of umbilical cord blood IgE levels in patients with clinical FA or food sensitization suggest that sensitization primarily occurs postnatally.^{22,23} Current literature points to skin barrier dysfunction as a possible mechanism.¹¹ Patients with AD have a defective skin barrier due to genetic and acquired defects in stratum corneum and tight junction proteins, lipid abnormalities, mechanical insults from scratching, *Staphylococcus aureus* virulence factors, and environmental exposures such as harsh soaps or detergents. Individually and collectively, these factors lead to increased transepidermal water loss (TEWL), greater allergen penetration, epithelial

alarmin production, immune activation, and ultimately, IgE sensitization.

This pathophysiological model has been supported by recent observational and experimental studies. Children with AD and FA (diagnosed by either positive skin prick test [SPT] or documented FA) were found to have more stratum corneum abnormalities and skin barrier dysfunction (higher TEWL) compared with both healthy controls and patients with AD without FA.²⁴ In infants with AD, a history of peanut exposure through dust on living room floors was associated with an increased risk of peanut sensitization (OR: 1.97, 95% CI: 1.26-3.09) and peanut allergy (OR: 2.34, 95% CI: 1.31-4.18).²⁵ This association was absent in subjects without AD, suggesting that the presence of AD identifies a subset of children with skin that is more permissive to allergen entry and sensitization.

In fact, skin barrier dysfunction has been independently associated with food sensitization even in patients without AD.²¹ In a study of 1293 infants from the Babies After Scope: Evaluating the Longitudinal Impact Using Neurological and Nutritional Endpoints birth cohort, infants with upper-quartile TEWL at 2 days of age had significantly higher rates of FA (positive SPT or oral food challenge) at 2 years of age, regardless of whether they had AD (OR: 4.1, 95% CI: 1.5-4.8).²⁶ Higher rates of food sensitization and FA have also been reported in children with mutations in genes affecting skin barrier proteins, including *filaggrin* and *SPINK5*.²⁷⁻²⁹

Studies using murine models have further elucidated the mechanisms linking skin sensitization to FA. Topical peanut exposure was able to initiate IgE sensitization, Th2 cytokine production, and anaphylaxis, even in mice with healthy skin.³⁰ IgE sensitization was increased when Treg cells were down-regulated, indicating that Treg cells may have a protective role.³¹ Finally, skin injury resulted in expansion and activation of intestinal mast cells and increased gut permeability, leading to food sensitization and an allergic response on oral exposure to foods.³² Based on these studies, it appears that exposure to an allergen through a perturbed and alarmin-producing epithelium promotes an IgE response and changes in T-helper cell and cytokine profiles that predispose an individual to FA. Although the pathophysiological links between AD and FA continue to be investigated, there is sufficient evidence to support the notion that patients with AD are at increased risk of other atopic conditions, which may be in part due to the permissiveness of their skin to allergen sensitization. Therefore, designing primary prevention studies in this population would be of great interest.

PRIMARY PREVENTION STRATEGIES

Emollients

Given the importance of skin barrier dysfunction in AD and FA, several studies have explored skin barrier enhancement as a means of primary prevention. The skin has 2 barrier structures, the stratum corneum and tight junctions.^{33,34} Patients with AD have stratum corneum abnormalities due to alterations in lipid composition and organization, defects in structural proteins, and trauma from scratching.³⁵ AD is also associated with reduced expression of several tight junction proteins, including claudin-1, -4, and -23, which compromises tight junction integrity.³³ As a result, the dendritic processes of Langerhans cells can penetrate tight junctions and sample foreign antigens, initiating an immune response.^{33,34} Furthermore, sensory nerve endings

extend to the skin surface and are likely responsible for the reduced itch threshold.³⁶ The combination of these defects may enable the influx of allergens and irritants.

The skin barrier is especially compromised during infancy. Much like patients with AD, infants have higher levels of TEWL and reduced ceramides than healthy adults, indicating that some degree of skin barrier dysfunction is observed in all infants.^{37,38} They may therefore be particularly susceptible to developing allergen sensitization and AD. As a result, therapies that fortify the skin barrier during infancy may, in theory, prevent the development of AD and FA.

To date, only a handful of trials have been conducted on the use of emollients to prevent AD, many of which have not yet been published. Two studies found that daily emollient therapy in high-risk neonates, that is, infants with first-degree relatives with atopic disease, resulted in a relative risk reduction in AD incidence of 0.50.^{39,40} In one of these studies,³⁹ control group subjects were instructed to avoid all moisturizers; in the other, they were permitted to use petroleum jelly as necessary.⁴⁰ In addition to reducing AD incidence, emollient use also led to higher levels of stratum corneum hydration^{40,41} and lower levels of TEWL.⁴¹ Only one of these studies analyzed effects on FA and found no significant change in IgE levels with emollient use.⁴⁰ However, subjects with AD (OR: 2.86, 95% CI: 2.2-6.73, $P = .043$) or skin lesions (OR: 3.73, 95% CI: 1.49-9.36) had higher rates of IgE sensitization, irrespective of emollient use, supporting the idea that skin barrier dysfunction predisposes subjects to food sensitization.

Several trials studying emollients for primary prevention of allergic diseases are currently underway. The Prevention of AD by a Barrier Lipid Equilibrium Strategy (PEBBLES) study is the first randomized controlled trial (RCT) to analyze results beyond the treatment period.⁴² Its pilot study involved 80 high-risk neonates (ie, with family history of allergic disease) who received either twice-daily EpiCeram, a ceramide-based emollient (intervention), or no skincare advice (control). At 12 months, 6 months after treatment, the relative risk for AD was 0.60 with emollient use, but this was not statistically significant. TEWL was also not significantly different between the 2 groups. Food allergen sensitization, however, was significantly reduced with emollient use (0% vs 19%). Notably, 39% of the control group used emollients an average of 3 or more days per week. Investigators are currently conducting a larger trial (N = 760) to further evaluate effects on food allergen sensitization.

Two larger studies have cast doubt on the efficacy of emollients in AD prevention. The Preventing AD and Allergies in Children (PreventADALL) study included 2396 infants from the general population in Norway (Skjerven—presented at 2019 European Academy of Allergy and Clinical Immunology [EAACI] Congress). The intervention group applied mineral oil and Ceridal, a ceramide-based emollient, beginning at 2 weeks of age, and consecutively introduced common allergenic foods (peanut, milk, wheat, and egg) beginning at 3 months of age. The control group received no intervention, but it is unclear whether they were specifically instructed to avoid emollients.⁴³ At 12 months, emollient use had not reduced AD incidence. On the contrary, it slightly increased the risk of AD by 3.1% (95% CI: -0.3% to 6.5%) and reduced the time to presentation (hazard ratio: 1.63, 95% CI: 1.12-2.37). Investigators found some evidence that emollients may reduce challenge-proven FA,

a relationship that will be further investigated with their 36-month readout.

The second study, the Barrier Enhancement for Eczema Prevention trial, included 1395 high-risk infants (ie, with a first-degree relative with AD, AS, or AR) (Boyle—presented at 2019 EAACI Congress). The intervention group applied Doublebase gel or Diprobace cream for 1 year, whereas the control group received only general skincare advice.⁴⁴ At 2 years old, investigators found no significant differences in AD incidence (relative risk [RR]: 0.95, 95% CI: 0.78-1.15, $P = .61$), severity, or time to presentation. In addition, FA (ie, food sensitization, physician-diagnosed allergy, or parent-reported allergy) was slightly increased in the intervention group, although this was not statistically significant. This study may have been underpowered, as only 74% of subjects in the intervention group were compliant at 12 months, and 15% to 18% of controls were using a moisturizing product.

Earlier studies suggested that emollients were a safe and simple method of preventing AD. Theoretically, emollients may reduce skin permeability, improve hydration, and repair a defective stratum corneum.⁴⁵ However, recent studies have cast doubts on their efficacy in preventing AD and suggest that they may be more efficacious in preventing FA. Although emollients may be more cost-effective than other therapies for allergic diseases, they can present a high out-of-pocket expense for families, as most insurers refuse to cover them.⁴⁶ Furthermore, compliance with daily regimens may be an issue, although the studies conducted thus far have, for the most part, had high compliance rates.

Much remains to be elucidated regarding “best practices” for emollient use. It is unclear whether emollients prevent AD and FA, or simply delay their development or severity. Furthermore, little effort has been made to evaluate the relative importance of different ingredients in emollients. The aforementioned studies used a variety of emollients—oil or lipid based^{41,43} (Skjerven 2019 EAACI Congress), gels or creams⁴⁴ (Boyle 2019 EAACI Congress), and emulsion type.⁴⁰ One study allowed subjects to choose 1 of 5 emollients, which included oils, ointments, gels, and creams.³⁹ The PEBBLES and PreventADALL studies used ceramide-containing emollients, with the rationale that patients with AD often have reduced ceramides levels⁴² (Skjerven 2019 EAACI Congress). The wide variation in emollients employed may have contributed to the variation in results. Studies in murine models have shown that creams with an acidic pH, such as ceramide formulas, are more effective in preventing AD-like lesions than those with a neutral pH.⁴⁷ Notably, in many of these studies, a substantial number of subjects in the control group applied emollients, which may have influenced the results. One of the only studies in which control subjects were explicitly directed to avoid emollients showed a significant reduction in AD incidence with emollient use.³⁹ Lastly, the duration and frequency of the optimal treatment regimen remain unclear, and studies have varied in the dosing schedules they have used. Many questions remain regarding emollient use for primary prevention of AD and FA. More studies, particularly longitudinal studies with large sample sizes, are needed to investigate this further.

Breastfeeding

A large number of studies have explored whether breastfeeding can prevent atopic disease. There are several mechanisms by which breastfeeding could, in theory, prevent AD and FA. These include reduced exposure to allergenic dietary proteins, such as

cow's milk protein in infant formula; prevention of infections that may initiate or exacerbate atopic disease; or development of the infant immune system using immunomodulatory factors, as we recently reviewed.⁴⁸ Breastfeeding also provides one of the first and primary means of impacting infant microbiome development, which may affect the development of FA and AD.⁴⁹

The question of the protective effects of human milk feeding can be addressed from several aspects, including the following: (1) how the duration of *exclusive* breastfeeding protects against AD and FA; (2) how the duration of *any* breastfeeding impacts the development of these atopic diseases; (3) whether *never* versus *ever* breastfeeding impacts the development of allergies; and (4) whether the *intensity* of breastfeeding or bottlefeeding impacts atopic disease. Studies can also be divided into those assessing infants at high risk for atopic diseases and those studying infants from the general population. The literature on this topic is expansive, and for this reason, we will refer to the analyses conducted by recent reviews, meta-analyses, and systematic reviews on AD and FA.

Regarding the duration of exclusive breastfeeding, the recent American Academy of Pediatrics (AAP) infant feeding guidelines⁵⁰ summarize the results of the most recent meta-analysis on the topic.⁵¹ This meta-analysis includes studies that compared exclusive breastfeeding for 3 to 4 months versus 6 months or longer,^{52,53} including a cluster RCT with a 6.5-year follow-up.⁵⁴ The authors concluded that there was no difference in AD, AS, or other atopic outcomes with exclusive breastfeeding for 3 to 4 months versus 6 months or longer. Notably, the analysis on FA was based on only 1 study, in which exclusive breastfeeding was associated with lower risk of parent-reported allergy, but not challenge-confirmed allergy.⁵²

In another recent meta-analysis and systematic review,⁵⁵ studies were grouped into those reporting incidence of eczema before and after the age of 2 years. This analysis included 6 cohort studies that showed that *exclusive* breastfeeding for at least 3 to 4 months reduced the cumulative incidence of eczema in the first 2 years of life (OR: 0.74, 95% CI: 0.57-0.97), 2 of which showed particularly protective effects.^{56,57} No differences in eczema incidence were found between more and less breastfeeding (15 cohort studies, 1 cross-sectional study). Breastfeeding was not associated with reduced eczema incidence after 2 years.^{58,59} This suggested that the protective effects of breastfeeding may be limited to infantile eczema. This review noted that the evidence on breastfeeding and atopic diseases is largely of low quality. With regard to AD, many studies were based on parental questionnaires, which may have led to recall bias. The evidence on FA was highly heterogeneous, and most diagnoses were made by parental report, leading investigators to conclude that there was no association between breastfeeding and FA prevention.

A more recent systematic review similarly concluded that the limited evidence does not suggest an association between the duration of breastfeeding and AD, or never versus ever being breastfed and AD.⁶⁰ The vast majority of associations were not significant, and the studies conducted had low generalizability, impact, and internal validity. There was also insufficient evidence to draw conclusions regarding breastfeeding and FA. Only 3 articles studied the association between breastfeeding duration and FA, and 5 analyzed the relationship between never versus ever breastfeeding and FA. These studies had limited methodological rigor and examined heterogeneous outcomes.

To date, the only cluster RCT on this topic is the Promotion of Breastfeeding Intervention Trial (included in the most recent review discussed above). This study included 17,046 mother-infant dyads from the general population of Belarus. The experimental group was encouraged to exclusively breastfeed in accordance with the World Health Organization guidelines. This intervention was successful; at 6 months, 12 times more women in the intervention group were exclusively breastfeeding compared with the control group. At 12 months, this intervention reduced the risk of AD by 46%.⁶¹ However, this effect was diminished at the 6.5-year follow-up.⁵⁴ In fact, exclusive breastfeeding was associated with increased positive SPTs. At the 16-year follow-up, the intervention group had reduced rates of flexural dermatitis (OR: 0.46, 95% CI: 0.25-0.86) on examination, but no differences in eczema based on questionnaire responses.⁶² Although these data suggest that exclusive breastfeeding may reduce AD risk, there were several important factors that may have impacted the results. In the intervention group, less than half of the women were exclusively breastfeeding at 6 months. In addition, in the control group, 60% of women were breastfeeding to some degree at 3 months. Investigators noted that the initial data on eczema were not audited, and subsequent data may have been subject to recall bias or under-reported if eczema had not been diagnosed by a physician.

With regard to FA, we noted in a recent review on immunomodulatory factors in breast milk and FA that it is difficult to draw conclusions about the impact of breastfeeding on FA for a number of reasons.⁴⁸ Theoretically, human milk provides immunomodulatory factors, including IgA, specific antibodies, and cytokines associated with protection against atopic diseases.^{48,63,64} Breast milk also transfers beneficial microorganisms and human milk oligosaccharides (HMOs), which facilitate the growth of intestinal microbes, alter immune responses in the infant, and are associated with protection against FA.⁶⁵⁻⁶⁷ However, the studies on this topic have varied widely in their methodologies (definitions of breastfeeding, risk of the populations assessed, and definition and diagnosis of FA, whether family report or physician diagnosed), and no true RCTs have been conducted. Second, current environmental exposures and allergy prevalence are drastically different than when many earlier studies were conducted. As such, there may be many confounding factors influencing the results, including duration of breastfeeding, overall hygiene in the country of study, and family history of allergic diseases. Furthermore, given the diversity in composition of breast milk between individuals, intrinsic immune factors differ greatly, making it difficult to draw unifying conclusions about the effect of breastfeeding in general.

In 2019, the AAP published updated guidelines on breastfeeding for the prevention of allergic diseases.⁵⁰ It currently supports the idea that breastfeeding for 3 to 4 months can decrease AD incidence in children less than 2 years old. However, breastfeeding for longer time periods does not confer additional benefits. The AAP also concluded that there is currently no evidence for delaying the introduction of allergenic foods beyond 4 to 6 months or restricting diet during pregnancy or lactation to prevent allergies. Lastly, the current data regarding a direct relationship of breastfeeding on FA are insufficient to make recommendations.

Although there is a lack of conclusive evidence that breastfeeding prevents atopic diseases, it confers numerous other health benefits for infants and mothers and is highly recommended. In

infants, it can reduce rates of diabetes and obesity, prevent infections, and improve intelligence.⁶⁵

Microbial and lifestyle exposures

In 1989, Strachan⁶⁸ noted in an epidemiologic study of 17,414 British children that family size and number of older children in a household were inversely associated with the prevalence of hay fever or AD. This was one of the observations that gave rise to the hygiene hypothesis, which implies that infection in early childhood, mediated in part by contact with many siblings, protected against atopic diseases, whereas reduced family size and higher standards of cleanliness contributed to atopic disease.

Since the Strachan study,⁶⁸ numerous studies have attempted to test the hygiene hypothesis. A review of 64 studies⁶⁹ on environmental exposures and AD found that increasing family size and exposure to household endotoxins (an indicator of microbial exposure)⁷⁰⁻⁷² and pets⁷³ were associated with reduced AD incidence. A more recent review found that not all microbial exposures may be protective. Some, such as varicella zoster virus^{74,75} and earlier entry into daycare, were associated with reduced risk of AD.⁷⁶ Others, including respiratory syncytial virus and *S. aureus*,⁷⁷ were associated with increased AD risk. Furthermore, in one study, foreign-born children had significantly lower odds of allergic diseases compared with those born in the United States.⁷⁸ However, as they remained in the United States, their risk of developing allergic disorders increased, indicating that the protective effects of microbial exposures may be temporary.

Many studies have studied the protective effects of farming lifestyles in particular on atopic diseases,^{79,80} including those of the Amish and Old Order Mennonites.⁸¹⁻⁸³ Children who grow up on traditional farms are exposed to high endotoxin levels and have reduced rates of AS and allergic disease. In addition, living on farms is associated with greater microbial diversity in household dust, which has been in turn associated with lower rates of AS.⁸⁴ In earlier studies, the individual factors that appeared to be associated with this "farm-life effect" included consumption of unpasteurized farm milk⁷⁹ and exposure to hay,⁸⁵ farm animals, and stables.^{79,86,87} More recent studies have confirmed significant reductions in the risk for atopic disease with childhood exposure to farm animals,^{88,89} grain,⁸⁸ and unpasteurized milk.⁸⁹⁻⁹¹ This protective effect is thought to be mediated through upregulation of Treg cells⁹² or inhibition of Th2 responses due to lower levels of activation markers and increased levels of inhibitory receptors.⁹³ Notably, when these exposures were removed, rates of atopy increased, as seen with Polish villagers who removed many animals from their farms after joining the European Union.⁹⁴ Together, these observations have given rise to the biodiversity hypothesis, which suggests that the microbial diversity in natural environments reduces the risk for allergic diseases.^{95,96}

The temporal window for the immunomodulatory effects of a farming lifestyle extends back to the prenatal period. Maternal microbial exposures during pregnancy appear to have a strong impact on atopic sensitization and allergic disease in offspring.^{79,86,87,97} Prenatal exposures to farm animals,^{79,86,97,98} manure,⁹⁹ stables,⁸⁶ and unboiled farm milk⁹⁸ have specifically been associated with reduced risk. At a mechanistic level, maternal exposure to farm life was associated with increased levels of TLR7 and TLR8,⁹¹ TNF- α and IFN- γ ,¹⁰⁰ and Treg

cells in neonatal cord blood.¹⁰¹ It was also associated with increased expression of innate immunity receptors (TLR2, TLR4, CD14) in blood samples from school-aged children and reduced allergic sensitization.⁸⁶

Most of the data on farming lifestyles have shown protective effects on respiratory diseases and inhalant allergen sensitization. The data on AD and FA are more limited and mixed. Some studies have found significantly reduced risk of AD with childhood or prenatal farming exposures,^{87,97,99} whereas others have not.^{79,80,102,103} One of the largest studies on the topic, the Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community Advanced Survey (GABRIEL Advanced Survey), showed reduced risks of AD with prenatal exposure to manure and cow shed (aOR: 0.80, 95% CI: 0.69-0.93), but the association was weaker than that seen with other allergic diseases.⁹⁹ Another large cross-sectional study, the Prevention of Allergy Risk factors for Sensitization In children related to Farming and Anthroposophic Lifestyle (PARSIFAL) study, found reduced risk for AD of borderline statistical significance.⁸⁰ The evidence on FA has been inconsistent, and very few studies have been conducted on the topic.¹⁰⁴ Three studies that included data on childhood farm exposure and food sensitization suggested a protective effect from certain allergens.¹⁰⁵⁻¹⁰⁷ However, these results were not statistically significant. One study has reported a significantly lower prevalence of FA in farming communities compared with the general population.¹⁰⁸

The literature on this topic is extensive and still not entirely conclusive. Because of the variety of exposures on farms, it is challenging to determine which factors reduce disease risk. Farm animals, stables, and unpasteurized farm milk have been associated with protection in several studies, referenced above. However, exposures vary significantly between farm types and countries, making it difficult to draw a unifying conclusion on farming lifestyles as a whole. One study on Amish and Hutterite farming communities found that although the 2 communities had similar genetic ancestries and lifestyles, they differed in their farming practices and the prevalence of AS.⁸² The Amish, with traditional single-family farms, had significantly lower rates of AS compared with the Hutterites, who had communal farms, which may have reduced individual exposures to the farming environment. Notably, many studies conducted on farming lifestyles did not specify what types of farms were investigated, which may have significantly impacted their results. In fact, even communities with similar farm types may differ in other exposures that can impact the development of allergic diseases. A study conducted on Amish and Old Order Mennonite communities found significantly lower rates of allergic diseases in the Amish, although both communities have traditional, one-family farms with slight differences in farming practices.¹⁰⁸

Furthermore, very few longitudinal studies have been conducted on this topic, which makes it challenging to determine if the effects of farming lifestyle on atopic disease in childhood persist into adulthood. Several studies on endotoxin exposure in childhood found that the protective effects on AD were no longer present by as early as 1 year of life.^{70,72} Another cross-sectional study suggested that prenatal farming exposure was protective against AS, hay fever, and eczema, but continued exposure was required to maintain optimal protection.⁸⁷ On the other hand, a recent study found that adults who had been brought up on farms had reduced rates of sensitization, despite

having moved to an urban environment.¹⁰⁹ Another challenge is that many studies conducted thus far have relied on questionnaires, which introduce bias. One study, for example, found that although 46.7% of subjects reported allergic symptoms, only 25% had been diagnosed with allergies.¹¹⁰ It is well known that rates of self-reported FA are up to 4 times higher than challenge-confirmed allergy.¹¹¹

In summary, with regard to the protective effects of farming lifestyle on AD and FA, further studies must be conducted before a definitive conclusion can be made, given the contradictory and incomplete evidence. Questions remain on whether there is a “critical window” when exposures can reduce risk of atopic disease. Very few studies have explored whether a protective effect can be seen with farming exposures in late childhood or adulthood. Lastly, although evidence suggests that farming lifestyles can reduce atopic diseases, the prospect of implementing farming exposures as such presents logistical challenges that make it less practical than other preventive methods. However, perhaps protective aspects of farming lifestyles, such as consuming fresh fruits, vegetables, and roots, and exposing children to the natural environment, as proposed in the Nature Step program in Finland, may prove beneficial in protection against atopic diseases.⁹⁵

Probiotics, prebiotics, and synbiotics

Since the 1990s, studies in humans and mice have found that individuals with allergic disease have reduced microbial diversity, with variations in the relative proportions of certain microbial species.¹¹² This has generated interest on whether manipulating the microbiota through probiotics, prebiotics, or synbiotics can prevent atopic diseases. Probiotics are live microorganisms administered for the purpose of conferring health benefits.¹¹³ Prebiotics are compounds that can be used by host microorganisms to confer health benefits.¹¹⁴ Synbiotics are combinations of prebiotics and probiotics.

The literature on the use of probiotics to prevent AD is extensive and varied. There are several reviews and meta-analyses on this topic, with the most recent one being Li et al, in 2019.¹¹⁵ In an analysis of 28 studies from 2006 to 2018, investigators found that probiotic supplementation was protective against AD (OR: 0.69, 95% CI: 0.58-0.82, $P < .0001$). However, only prenatal and postnatal supplementation led to a significant reduction in AD.¹¹⁶⁻¹¹⁹ Studies used various microbial species, including *Lactobacillus* (N = 15 studies), *Bifidobacterium* (N = 16), and *Propionibacterium* (N = 3). Protective effects were only seen with microbial mixtures or with single-species interventions of *Lactobacillus rhamnosus* or *Lactobacillus paracasei*.

Although this review suggested that probiotics reduce the incidence of AD, their utility is still not well understood. Several studies that initially reported reductions in AD incidence found that this effect was no longer present during follow-up years later.^{120,121} This may suggest that probiotics delayed AD onset rather than preventing it entirely. Furthermore, although the efficacy of probiotics is likely species dependent, it may be host dependent as well. For example, one study found that subjects who developed AD despite probiotic use had higher levels of *Bifidobacterium dentium* in their intrinsic microbiota, suggesting that the host microbiota may alter efficacy.¹²² Another study found that 13 years after treatment, subjects who had been delivered by Cesarean section and received probiotics continued to have reduced AD incidence compared with controls (18.9% vs

37.5%), whereas those who had been delivered vaginally did not.¹²¹ This suggested that probiotics may have remedied deficiencies in the intrinsic microbiota of children delivered via Cesarean section.¹²³ The above-mentioned systematic review also reported that probiotic efficacy varied based on geographical location, suggesting that environmental exposures can alter response.¹¹⁵

Several studies have been conducted since the above-mentioned review that have further confirmed or refuted its findings. One study found that prenatal-only supplementation with *L. rhamnosus* HN001 did not reduce AD incidence at 12 months, although prior studies had shown that prenatal and postnatal supplementation of the same species reduced AD incidence.^{117,124-127} Another study investigated *L. rhamnosus* and *Bifidobacterium animalis* supplementation in late infancy, which resulted in reduced AD incidence.¹²⁸ This contradicts earlier findings in which postnatal supplementation was shown to be ineffective,^{115,129,130} including a study that also used strains of *Lactobacillus* and *Bifidobacterium*.¹³¹

Although probiotic use has shown promise in preventing AD, the evidence on FA is inconclusive. The majority of studies have shown no significant changes in food allergen sensitization, regardless of intervention timing or species used.^{121,127,128,130,132-134} Others found inconsistent or temporary reductions in sensitization, which were only present at certain time points during follow-up.^{125,126,135} One study in Cesarean-delivered infants found that probiotic supplementation more than halved the risk of food sensitization (OR: 0.33, 95% CI: 0.12-0.85).¹³⁶ However, a second study on a similar number of Cesarean-delivered infants found no differences in food sensitization.¹²¹ Because of the heterogeneity of these results and the lack of studies investigating challenge-proven FA, it is difficult to draw conclusions regarding the effects of probiotics on FA.

Although probiotics may confer health benefits to an individual, they can also rarely cause adverse events.¹³⁷ Several case reports have demonstrated systemic infections or metabolic or immune dysfunction resulting from probiotic use.¹³⁸ The Agency for Healthcare Research and Quality has noted that the risks associated with probiotics have not been well documented, making it difficult to draw conclusions regarding their safety.¹³⁹

In addition, the mechanism of action of probiotics remains unclear and may be multifactorial. Probiotics may change the composition of the intestinal microbiota or the functionality of existing bacteria.¹¹⁵ They may also modulate immune responses in the body, including the production and expression of IgA and toll-like receptors.^{49,115} They have also been shown to inhibit Th2, Th17, and Th22 responses, and increase anti-inflammatory cytokines such as IL-10 and TGF- β , as well as Th1, Th22, and Treg activity.¹⁴⁰⁻¹⁴² Notably, the mechanisms of action may differ depending on the probiotic species used and host characteristics.¹⁴³

The evidence on prebiotics is more limited. Prebiotics include nondigestible oligosaccharides that mimic HMOs found in breast milk.^{144,145} HMOs may protect against infectious diseases and FA, generating interest on whether prebiotics can protect against allergic disease.¹⁴⁶

One of the first studies on this topic included 206 high-risk infants (with a parental history of allergic disease).¹⁴⁷ At 6 months, investigators found significantly lower rates of AD with prebiotic supplementation (9.8%, 95% CI: 5.4-17.1) compared

with controls (23.1%, 95% CI: 16.0-32.0). These effects persisted at 2 and 5 years of follow-up.^{148,149} Subsequent studies, however, were less promising. Two studies on high-risk infants (ie, with parental or sibling history of allergic disease) found no statistically significant differences in eczema incidence or severity with prebiotic supplementation.^{150,151} Two studies on infants from the general population¹⁵² or those with no family history of atopic disease¹⁵³ found protective effects on AD. In one of these studies, however, this effect was no longer present at 5 years, leading investigators to conclude that prebiotics may be more effective in higher-risk infants.¹⁵⁴

With regard to FA, only one study has investigated the effects of prebiotics.¹⁵² Infants who received prebiotics had significantly lower rates of allergic reactions to cow's milk protein (3.23% vs 15.09%) and FA symptoms than controls. Prebiotics also reduced cow's milk IgG in a second study, although other food allergen IgE levels remained unchanged.¹⁵¹

Recent reviews have determined that the evidence on prebiotics and allergic diseases is highly heterogeneous and has risks of bias.^{144,145} One review determined that prebiotics may reduce risks of FA (RR: 0.28, 95% CI: 0.08-1.00) and eczema (RR: 0.57, 95% CI: 0.30-1.08), but noted that the evidence was of low certainty.¹⁴⁴

There are only 2 RCTs on the use of synbiotics to prevent AD or FA. The first of these reported that synbiotics reduced the rate of eczema (OR: 0.74, 95% CI: 0.55-0.98) and IgE-associated allergic diseases (OR: 0.71, 95% CI: 0.51-1.00), including challenge-proven FA.¹¹⁶ The second did not study FA, but found reduced eczema risk with synbiotic supplementation (OR: 0.12, 95% CI: 0.02-1.04).¹⁵⁵ A meta-analysis of these studies concluded, however, that these results were not significant, which is, in part, reflected by the wide CI.¹⁵⁶

Much remains to be elucidated regarding the use of microbial supplementation in preventing allergic diseases. With regard to probiotics, further studies are required on IgE sensitization and FA, given the lack of conclusive evidence on this topic. In addition, studies have not identified the optimal timing or duration of intervention. The Probiotics in Pregnancy study, which is currently underway, will explore the effects of probiotic supplementation starting at 14 to 16 weeks of gestation, rather than during the third trimester like the majority of earlier studies.¹⁵⁷ For prebiotics, there are currently no studies on the preventative effects of supplementation in breastfeeding or pregnant women, or exclusively breastfed infants.¹⁴⁴ Future studies should address key confounders, including mode of delivery, underlying allergic risk, and environmental exposures, and include mechanistic readouts. Furthermore, studies may want to consider cutaneous administration of probiotics, as this may be a relevant route of administration that has not yet been explored.

Currently, most guidelines, including those published by the AAP and the EAACI, do not recommend probiotic or prebiotic supplementation for the purpose of preventing allergic diseases due to lack of definitive evidence.^{158,159} The World Allergy Organization (WAO) is one of the few organizations that recommends probiotics for high-risk infants, given the possibility of preventing AD, although it does not recommend a certain probiotic and notes that the evidence is of "low quality."¹⁶⁰ The WAO also conditionally recommends prebiotic supplementation in infants who are not exclusively breastfed, although it notes

that this evidence is of very low certainty and quality and should not change breastfeeding practices.¹⁴⁴

Vitamin D and UV light

Several studies have found an association between vitamin D and allergic diseases. The majority of vitamin D is obtained through UVB exposure in sunlight.¹⁶¹ The prevalence of allergic diseases is higher in areas where there is reduced sun exposure, such as the Northern United States.^{162,163} In addition, individuals born in the fall or winter, when there is low UVB exposure, have higher rates of FA, food-induced anaphylaxis, and AD.^{164,165} The question from these epidemiological observations is: what is the critical window to ensure vitamin D sufficiency (eg, sunlight exposure), and is the relationship causal or simply strongly linked to another factor that affects the development of allergic diseases?

Some investigators have argued that these associations are causal. Vitamin D plays an important role in epithelial barrier, wound repair, development of tolerance, and innate immune functions.¹⁶⁶⁻¹⁶⁸ It has been shown to promote skin barrier formation and epithelial cell migration.^{169,170} It also modulates immune responses. Immune and epithelial cells express the vitamin D receptor, and signaling increases the production of antimicrobial peptides.¹⁷¹ Furthermore, vitamin D promotes anti-inflammatory cytokine expression, leading to inhibition of Th2 responses, dendritic cell activity, IgE secretion, and TLR production, and upregulation of Treg activity.^{168,172,173} Prenatal vitamin D supplementation has also been associated with increased levels of proinflammatory cytokines (especially IL-17A) in umbilical cord blood, and increased expression of TLR2 and TLR9, which, collectively, may reduce the risk for allergic diseases such as AS and infections later in life.¹⁷⁴

The vast majority of recent studies on vitamin D and allergic disease are observational and investigate its effects on AS. Several studies, however, have found that low vitamin D levels are associated with more severe AD and food sensitization.¹⁷⁵⁻¹⁷⁸ Similarly, high levels of cord blood or maternal vitamin D have been associated with reduced AD risk.^{177,179} In an Australian study, infants with low vitamin D levels (<50 nmol/L at 1 year of age) had an 11-fold higher risk of challenge-confirmed peanut allergy and 4-fold higher risk of egg allergy at 1 year.¹⁸⁰ However, this same study found that these effects may be influenced by factors such as an individual's race and ethnicity. A smaller case-control study in Australia, on the other hand, did not find an association between vitamin D insufficiency at birth or 6 months of age and challenge-proven FA at 1 year of age.¹⁸¹

Although several observational studies have noted a correlation between vitamin D levels and allergic disease, most of these studies had small sample sizes. Importantly, a number of studies have failed to find an association between vitamin D levels or exposure and allergic diseases. There are many potential confounders, including lifestyle factors, environmental exposures, skin pigmentation genetic risks, and the fact that we measure the inactive form of vitamin D (1-hydroxyvitamin D) and not the active form (1,25-dihydroxyvitamin D). The lack of RCTs and longitudinal studies makes it challenging to draw conclusions about causality and persistence of protective effects. Only 1 RCT has been conducted on vitamin D and childhood wheeze, eczema, FA, lung function, and markers of airway

inflammation.¹⁸² In 3 years of follow-up, this study found that prenatal supplementation of vitamin D did not have a protective effect on any of the readouts.

Overall, a recent review concluded that the evidence for vitamin D preventing allergic disease is of “very low” certainty according to the Grading of Recommendation, Assessment, Development, and Evaluation methodology.¹⁸³ The WAO has also concluded that there is “no support” for vitamin D reducing allergic disease in children, and the existing evidence is of “very low” certainty.¹⁸⁴ Although vitamin D may be used for other indications, it does not seem to have a protective effect on allergic diseases.

Water hardness

In the late 1990s, a large ecological study of 4141 primary school children in the UK found that water hardness was associated with the increased 1-year prevalence (aOR: 1.54, 95% CI: 1.19-1.99) and lifetime prevalence (aOR: 1.28, 95% CI: 1.04-1.58) of eczema.¹⁸⁵ Subsequent studies in Japan,¹⁸⁶ Spain,¹⁸⁷ Denmark,¹⁸⁸ and Belgium¹⁸⁹ found similar associations.

Hard water contains high levels of minerals such as calcium and magnesium carbonates, including calcite, gypsum, and dolomite.¹⁹⁰ These minerals can interact with soaps and form surfactants, insoluble precipitates that bind to the skin and cause epithelial barrier disruption.¹⁹¹ Calcium, in particular, may impact the epithelial barrier in many ways. The epidermis has a calcium gradient, which is thought to facilitate protein synthesis, epidermal differentiation, cell adhesion, and lamellar body secretion.¹⁹² In subjects with underlying barrier dysfunction, such as those with mutations in the *filaggrin* gene, increasing levels of calcium in water have been associated with greater TEWL.¹⁹³

Several experimental studies have been conducted to investigate the effects of hard water on the skin. One study found that washing subjects' skin with water of increasing hardness was associated with greater deposition of surfactants, TEWL, and indicators of protein denaturation and lipid disordering.¹⁹⁰ When water was softened, surfactant production was reduced. Washing with hard water also led to significantly drier and more erythematous skin.^{190,194} Similarly, in mouse models of AD, application of metallic soaps and water led to increased levels of IgE and proinflammatory cytokines, including IL-4, IL-5, IL-13, TSLP, and TGF- β .¹⁹⁵ Subsequent washes with soft water improved pruritus, dryness, and TEWL, and reduced IgE and Th2 cytokines.

The 2 RCTs on this topic focused on water softeners as eczema therapy. Neither demonstrated improvement in eczema with the addition of water softeners.^{191,196} One trial, the Softened Water Eczema Trial, sponsored by the United Kingdom National Institute for Health Research Technology Assessment, found that although objective measures of eczema did not improve, small but significant improvements were seen in patient-reported outcomes.¹⁹⁶

Currently, no RCTs have been conducted on water softeners for primary prevention of AD or FAs. One group is in the process of organizing a primary prevention study.¹⁹³ Although observational and noncontrolled experimental studies have suggested an association between water hardness and AD, confounding variables, reporting biases, and reverse causation may be impacting these results. Furthermore, these associations may be age dependent; although water hardness was associated with

AD risk in children of primary school age, no such correlation was observed in older children, suggesting that other variables may need to be taken into account.^{185,187} Given the lack of RCT evidence on the topic, definitive conclusions cannot currently be made regarding the use of water softeners in primary prevention of allergic diseases.

Immunotherapy

In recent years, interest has grown regarding the use of allergen immunotherapy (AIT) as a means of primary prevention. Immunotherapy involves administration of an allergen, usually over several years, to induce an immune response that promotes tolerance.¹⁹⁷ For years, AIT has been used as a treatment option for many allergic diseases (AS, AR, and FA),¹⁹⁸⁻²⁰⁰ particularly when they are insufficiently controlled with standard therapies. It can reduce allergic symptoms and the need for medications and is heralded as the “only treatment that can change the course of allergic disease.”^{197,201,202} Immunotherapy also shows promise as a secondary prevention strategy, but there is no clear evidence that it is useful for the management of AD.²⁰³ Recent evidence suggests that AIT in AR may be protective against AS (RR: 0.40, 95% CI: 0.30-0.54).²⁰⁴ This has led the EAACI to recommend 3 years of AIT in children and adolescents with “suboptimally controlled” AR to prevent AS in the short term.²⁰¹

With regard to AIT and primary prevention, only 2 RCTs have been conducted, and only one of these studied AD and FA. This trial involved high-risk infants (ie, with at least 2 first-degree relatives with atopic disease) who received oral house dust mite AIT twice daily for 1 year.²⁰⁵ This led to significant reductions in sensitization to any common allergen, including food allergens (16.0% absolute risk reduction, 95% CI: 1.7%-30.4%). No significant differences were noted in eczema or FA, however. In a follow-up study 18 months after treatment, the trend of reduced sensitization was maintained, but was no longer statistically significant.²⁰⁶ This study was underpowered, which may have significantly impacted results. Furthermore, the intervention was administered for only 1 year beginning in infancy, which is shorter and earlier than when AIT is typically administered in clinical practice.

Although immunotherapy has had dramatic benefits on the treatment of allergic diseases, its efficacy in primary prevention has not been demonstrated. Furthermore, AIT requires regular treatments and frequent clinic visits, which may be costly and reduce adherence.²⁰¹ It has also been associated with high rates of local adverse reactions, and less commonly, systemic reactions.^{197,207} Lastly, a report from the WAO asserted that no overarching conclusions can be made about AIT, as each product varies in its allergen targets, patient population, optimal dosage, duration, and form of administration.²⁰⁸ Given these challenges and the lack of evidence, the EAACI has concluded that in healthy individuals, AIT cannot currently be recommended for prevention of allergic disease or new sensitizations.²⁰¹

CONCLUSIONS

AD, FA, AR, and AS are common atopic diseases that frequently appear as dyads or triads, with AD and FA typically developing early in life, and AR and AS manifesting later in some patients. The temporal and individual progression from AD, FA, AS, and AR is commonly referred to as the “atopic march.”^{11,209-211} Although epidemiological studies have observed this progression in some patients, this is not proof of causality.^{7,209-216}

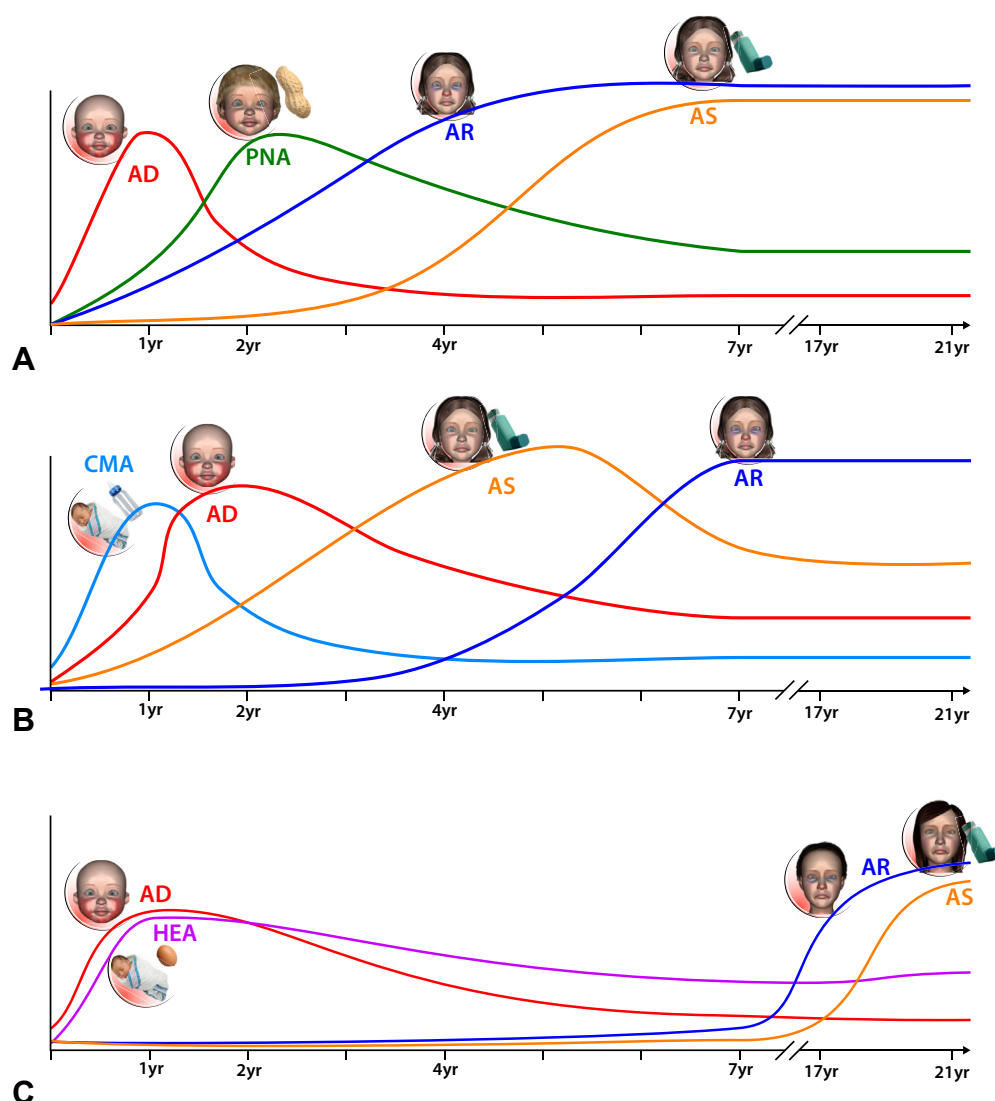


FIGURE 1. Hypothetical examples of different atopic march patterns based on the severity and age of onset of atopic dermatitis (AD) or food allergy (FA), based on the specific FA. **A**, AD precedes peanut allergy (PNA), which evolves to allergic rhinitis (AR) followed by asthma (AS) in early childhood. While AD resolved in most, PNA does not. **B**, Cow's milk allergy (CMA) precedes AD, and while CMA outgrows, AD does not resolve in all after early childhood. AS develops in early and AR in later childhood. **C**, AD and hen's egg allergy (HEA) initiate the march (with similarly early age of onset) and resolve in most by late childhood, but AS and AR do not develop until early adulthood.

Furthermore, the determinants that drive this progression and the frequency with which this progression occurs are still poorly understood. Therefore, studies with targeted interventions during critical developmental windows are needed to clarify whether pathophysiological features of an early atopic condition such as AD or FA are critical determinants of the development or greater severity of other atopic conditions.^{11,209,210,212-215}

How many atopic patients' disease path follows something resembling an "atopic march" has been hotly debated.^{11,12,217} A recent longitudinal study that used Bayesian machine learning found 8 groups of children with similar patterns of eczema, wheeze, and rhinitis.²¹⁸ In some groups, wheezing was the more common early life condition, rather than AD. In fact, only 3.1% of children progressed through the classic atopic march, as defined by progression from AD to wheezing, followed by rhinitis. Notably,

patterns such as persistent eczema and wheeze, or persistent eczema with later-onset rhinitis were not considered consistent with the atopic march, although some could argue differently. There are numerous weaknesses of this study, namely, that the 2 birth cohort studies used (Manchester Asthma & Allergy Study [MAAS] and Avon Longitudinal Study of Parents & Children [ALSPAC]) had no data on food sensitization/allergy, which as we have highlighted in this review is one of first manifestations of an allergic individual. In addition, children with data from as little as 2 time points were included; the diagnoses of wheeze, rhinitis, and eczema were based on parental accounts; and there were no data available for children <1 or >11 years of age. Collectively, we feel that the complete natural history of common atopic diseases was not captured in this article. Nevertheless, this has spurred debate on how commonly the atopic march is observed.^{11,218}

To address this important question, we need to establish a consensus on the definition of the atopic march. It should be noted that there may be different atopic march patterns based on the severity and age of onset of AD or FA, or based on the specific FA (Figure 1). For example, one might first develop either AD $\pm$ FA followed by either resolution of one or both of these conditions and development of a subsequent additional atopic disorder, or persistence of AD $\pm$ FA in addition to the development of a third or fourth atopic condition. Whether entry into the atopic march is always through the presentation of AD or FA is also not clear. Many publications rely on soft diagnoses obtained through history of symptoms or parent report, rather than diagnosis by well-trained physicians using established diagnostic criteria. This is especially important, as we are realizing that accurately phenotyping allergic diseases is not a trivial endeavor. We know that the severity of AD is a key factor in predicting subjects who will progress down the atopic march.¹⁷ Therefore, studies must incorporate validated disease severity assessments in their analyses. Many studies on the atopic march have failed to even address the presence or absence of FA or characterize the type and number of food allergens sensitized to; even fewer studies have documented robust and accurate measures of the clinical FA.

Based on our current understanding of the importance of a leaky skin barrier in the early development of food and aeroallergen sensitization, targeting barrier repair to prevent the development of AD, FA, and ultimately the full atopic march is conceptually appealing. However, clinical trials have been quite contradictory. It remains to be seen whether the efficacy of emollients can be improved by identifying the ideal characteristics of the emollient, timing of the intervention, frequency of applications, and potential confounders (eg, racial/ethnic differences, nutrition, environmental factors such as pollutants, temperature, humidity, sun exposure, etc.). Interestingly, although the use of emollients to prevent AD remains controversial, it now appears that emollients may reduce food sensitization or FA. RCTs are also underway to evaluate whether water softeners may improve barrier function, but the benefits of this intervention are still uncertain.

Regarding breastfeeding, the evidence is limited. A recent systematic review concluded that the evidence does not suggest an association between the duration of breastfeeding and AD, or “never” versus “ever” being breastfed and AD.⁵⁵ There are a few small RCTs that demonstrate a protective effect of breastfeeding only for infantile eczema. Currently, the AAP (2019) has determined that there is evidence that exclusive breastfeeding for 3 to 4 months decreases cumulative incidence of AD in the first 2 years of life.⁵⁰ The evidence regarding prevention of FA is limited, and most studies are underpowered to answer this question. However, it should be noted that because human milk composition varies between mothers, so may its protective factors, which is not captured in most epidemiologic studies.⁶³

Farming lifestyle has shown protection against AD and perhaps FA in a limited set of studies; however, the specific factors responsible for the protection are still unknown and therefore interventions based on these findings have not been pursued. Regarding probiotic supplementation, the evidence is conflicting. A recent review and meta-analysis found that probiotic supplementation was protective against AD, but only studies using *both* prenatal and postnatal supplementation showed a significant reduction in AD.¹¹⁵ Currently, most

guidelines do not recommend probiotic or prebiotic supplementation for the purpose of preventing allergic diseases due to conflicting and low-quality evidence and lack of clarity on which supplements are both safe and effective.^{158,159} This field is plagued by the variation in probiotics and prebiotics used, and it is possible that the most effective approach has yet to be identified. The data on vitamin D supplementation are likewise conflicting, and current guidelines do not support the use of vitamin D administration for prevention of allergic diseases in pregnant woman or young children.¹⁶⁰

Finally, AIT cannot be recommended for prevention of allergen sensitization or allergic diseases.²⁰¹ It is tempting to speculate whether prevention of FA by early introduction of specific foods could serve as a means to halt the atopic march. Data from the Learning Early About Peanut (LEAP) show that whereas early introduction serves as a powerful tool to prevent peanut allergy, there was no effect on other atopic manifestations, including AS, eczema, rhinoconjunctivitis, and other food or aeroallergen sensitization.²¹⁹ This would argue that prevention of a specific FA, such as peanut allergy, serves no purpose in prevention of the atopic march. However, egg or cow's milk allergy may have a stronger link with the development of other atopic diseases, and therefore it would be interesting to see whether early introduction of those foods would benefit the march.

In addition to new trials aiming at prevention of AD and FA, understanding the “march patterns” and how to predict them appears to be a critical step in order to develop well-designed interventional trials aimed at halting or minimizing the extent or severity of the atopic march.

Acknowledgment

The authors would like to acknowledge Dr Eric Simpson, Professor of Dermatology at Oregon Health & Science University, for helpful discussions, particularly on the use of emollients as a primary prevention strategy.

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