Early intervention and prevention of allergic diseases

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Abstract
Food allergy (FA) is now one of the most common chronic diseases of childhood often lasting throughout life and leading to significant worldwide healthcare burden. The precise mechanisms responsible for the development of this inflammatory condition are largely unknown; however, a multifactorial aetiology involving both environmental and genetic contributions is well accepted. A precise understanding of the
1 | INTRODUCTION

Atopic conditions, including atopic dermatitis (AD), food and environmental allergies and asthma, have become an important public health concern worldwide. This review will focus primarily on early interventions to prevent food allergy (FA). Recent studies reinforce the strong connection between early severe AD and the development of FA. Paediatric FA has become an epidemic in many countries, with increasing rates in the past few decades, although substantial variations from 1% to 10% exist by country. To date, some of the highest rates have been observed in high-income countries such as the United Kingdom, United States, and Australia, where population-based surveys and analyses of healthcare utilization data suggest the burden of disease has substantially increased. While there is consensus that prevalence has increased in many parts of the world, the magnitude is difficult to ascertain due to numerous factors, including a lack of systematic population-based surveillance efforts incorporating repeated, validated prevalence assessments, and high-quality estimates lacking from many countries. Figure 1 visualizes the most recently available population-based estimates of paediatric FA prevalence.

It is also difficult to estimate FA prevalence globally or compare rates by country because of the limited international coordination of disease surveillance efforts, leading to heterogeneity in study design, FA case definitions, and study populations. Even in studies with similar populations, direct comparisons of prevalence rates are challenging as there are variations in social, cultural, and economic factors. Despite the literature gaps, extensive research into paediatric FA epidemiology provides insight into possible FA aetiology and promising disease prevention avenues. For example, an epidemiologic finding of disparate rates of infant peanut allergy among genetically similar populations in the UK and Israel led to insights regarding the protective role of early life exposure to major food allergens. These insights have now been tested in randomized controlled trials (RCTs) and translated into clinical practice guidelines that advocate the early introduction of allergenic solids for the prevention of food allergy.

The multifactorial aetiology of FA is well-recognized, with environmental and genetic factors contributing to FA development. However, strategies to manage FA remain limited in most cases to strict allergen avoidance and managing allergic reactions, including education and training patients/caregivers to administer epinephrine during suspected anaphylaxis, which can adversely impact patient/caregiver quality of life. Food allergen immunotherapy appears to offer transient protection but is allergen-specific, time-intensive, and side effects limit tolerability. Even when gold standard treatments exist, prevention remains the ultimate goal since it can circumvent early morbidity from disease and ameliorate treatment burden.

AD often heralds the atopic march and frequently precedes the development of FA, allergic asthma and allergic rhinitis. Whether AD is the primary insult, or the earliest manifestation of other underlying factors is not yet fully established. However, AD is a significant risk factor for FA and may play a key role in FA prevention. Numerous studies suggest a causal role of cutaneous sensitization in FA’s development where both the skin barrier and immunology are thought to be key players.

The true global prevalence for AD is also unclear, with previous studies indicating paediatric AD prevalence varying by country. Between 1999 and 2004 the International Study of Asthma and Allergies in Childhood incorporated a standardized school-based sampling methodology and symptom questionnaire to estimate current AD prevalence among 6–7-year-olds in 60 countries and estimates for 13–14-year-olds in 96 countries. Subsequent studies have independently verified this increase in prevalence of AD across several countries. These landmark findings are visualized in Figures 2 and 3. However, they are nearly 20 years old, and no comparable effort to systematically assess longitudinal changes in the global prevalence of AD has since been undertaken.

Early life nutrition is another staple of FA prevention. It has been studied to varying degrees, including the impact of oral tolerance...
induction, breast and formula feeding, Vitamin D, dietary diversity, and the role of prebiotics, probiotics and symbiotics. The interaction of the skin and diet come together in the interplay between oral tolerance induction and epicutaneous allergen exposure. This forms the basis of the dual allergen exposure hypothesis, which proposes that epicutaneous food allergen exposure in early life is associated with the development of FA, whilst early life oral exposure is protective.22-24

![Prevalence of paediatric food allergy](image)

Finally, microbial factors may impact FA prevention with the mode of delivery at birth, pet exposure and bacterial (S. aureus) colonization. The roles of viruses and fungi are still unknown. This review will explore AD, the infant diet, microbial factors, and the complex interplay of all factors in FA development, focusing primarily on early intervention to prevent FA. We conclude our review with a discussion of future and ongoing research including key topics that must be addressed.

2 | CUTANEOUS FACTORS AND ENVIRONMENTAL EXPOSURES IN THE DEVELOPMENT OF FA

Early AD is implicated in the subsequent development of allergic diseases, including FA, asthma, allergic rhinitis and is termed the ‘atopic march’. In the ‘outside-in’ hypothesis, skin barrier defect allows penetration of allergens and microbes leading to atopic sensitization whereas, in the ‘inside-out’ paradigm, a polarized immune response leads to a defective skin barrier (Figure 4). A summary of changes identified in AD compared to healthy skin in the microbiota, skin barrier, and inflammatory cytokines are outlined in Table 1.

Experimental models and clinical observations in humans support the concept of epicutaneous food allergen sensitization. The epidermis plays a key role in maintaining the skin barrier against allergens, irritants and microbes potentially penetrating the skin and eliciting the host immune response. These events are facilitated by skin barrier dysfunction in AD, promoting the penetration of food allergens from topical application or the environment. Lack et al. first reported that peanut allergy was associated with the topical application of skin creams containing peanut protein. Subsequently, Fox et al. reported increased FA in households that ate peanuts. In addition, Brough et al. found a dose-dependent increase in peanut sensitization and allergy in infants exposed to higher peanut protein levels in household dust, particularly in patients with skin barrier impairment, as assessed by either filaggrin (FLG) null mutations, leading to low FLG expression in the skin, or children with AD or egg allergy. These observations supported a role for the ‘outside-in’ process of food sensitization where exposure to environmental peanut in an individual with skin barrier dysfunction leads to enhanced FA.

The ‘inside-out’ process implicates the immune response in making the skin barrier more susceptible to skin epithelial dysfunction, development of AD, and allergen entry. The current understanding of AD’s pathogenesis is centred on the robust activation of Type
2 (IL-4, IL-13, IL-31) and Type 22 (IL-22) cytokine axes in both skin and serum. Model systems showed that type 2 cytokine activation inhibits keratinocyte terminal differentiation products (ie filaggrin and loricrin), tight junctions (ie claudins), and lipid products. Recent findings show that Th2 cytokines decrease antimicrobial peptides, causing AD skin to be more prone to colonization of infectious organisms, such as \( S. \) aureus. Thus, IL-4 and IL-13 play a hallmark role in the Th2 immune response in AD, contributing to both immune activation and skin barrier dysfunction. IL-31, another Th2 cytokine, has been shown to interact synergistically with IL-4, driving pruritus and contributing to the inflammatory and barrier defects of AD. The Th22 axis also plays a role in suppressing the epidermal barrier and the lichenification and increase of S100 calcium-binding protein A (S100As) in chronic AD lesions. Additional pro-inflammatory axes, including Th17, are preferentially upregulated in certain AD populations, such as Asians and children, revealing the heterogeneous nature of AD across its subtypes.

20% 15% 10% 5% Data unavailable


correlations with disease severity scores and the functional barrier measure trans-epidermal-water-loss (TEWL).

Allergic disease development is associated with a Th2 cell-mediated inflammatory response described above. Allergic disease is preceded by the formation of specific IgE (sIgE) antibodies against environmental and food allergens, also known as the sensitization phase. In epicutaneous sensitization, specific resident dendritic cell (DC) subsets residing in the skin sample antigens and present to naïve CD4\(^+\) T cells in draining lymph nodes. This promotes differentiation into allergen-specific CD4\(^+\) T cells favouring B cell isotype class switching to sIgE cells further driving the production of IgE memory B cells. Through the maturation and production of plasma cells, large amounts of sIgE antibodies are produced. The sensitization phase drives the production of a large memory pool of allergen-specific B cells and Th2 cells.

The sensitization phase is followed by the effector phase, which is triggered by subsequent exposure to previously sensitized allergens. This causes cross-linking of sIgE bound to receptor FceRI on sensitized mast cells and basophils. Activation of these cells leads to the release of inflammatory mediators triggering an allergic reaction. The immune mechanisms linking the skin and gut have their origins in skin injury-induced release of IL-33 from keratinocytes,
leading to intestinal mast cell hyperplasia and food-induced anaphylaxis in mice.\textsuperscript{83} IL-33 blocking antibodies have also been shown to prevent peanut allergy induced anaphylaxis.\textsuperscript{84}

Interestingly, skin sampling in patients with peanut allergy but not AD reveals low filaggrin levels but increased long-chained lipid species, which may protect the skin from dryness and AD.\textsuperscript{85} Other risk factors have been associated with peanut allergy, including filaggrin mutations, severe infantile AD, environmental irritant exposures such as detergents and \textit{S. aureus} colonization on the skin.\textsuperscript{86-88}

Skin dysbiosis, often observed among individuals with AD, is often characterized by reduced microbial diversity and the presence of one or few dominant microbes. The loss of commensal microbes is likely due to several factors including host genetics, local immune response, environmental factors such as pH, temperature, humidity, hygiene practice and exposure to antibiotics. It is estimated that 30\% to 100\% of individuals with AD are colonized by \textit{S. aureus}, a dominant pathogen implicated in this disease (Figure 5A).\textsuperscript{89} \textit{S. aureus} affects the development of both innate and adaptive immune responses. It can lead to uncontrolled inflammation by inducing lymphocyte and macrophage activation. The increased presence of \textit{S. aureus} in the dermis directly correlates with a Th2 response evidenced by increased expression of IL-4, IL-13, IL-31 and TSLP (Thymic Stromal Lymphopoietin).\textsuperscript{30} These Th2 cytokines in turn suppress the production of antimicrobial peptides (AMPs) by the skin that inhibits \textit{S. aureus} proliferation.\textsuperscript{31} Therefore, it is not surprising that colonization by \textit{S. aureus} is associated with increased AD severity and treatment thereof has been shown to decrease disease severity.\textsuperscript{70,91}

\textit{Malassezia} spp., previously known as \textit{Pityrosporum}, is a genus of lipophilic yeast. Its role in AD’s pathogenesis was initially speculated when some AD patients responded to topical and systemic antifungal therapies.\textsuperscript{82-86} A large population study showed more than 40\% of children with seborrheic dermatitis during early childhood will develop AD later on, suggesting early sensitization of seborrheic skin may result in the onset of AD.\textsuperscript{97} Most of the \textit{Malassezia} species lack fatty acid synthases genes, therefore relying on exogenous fatty acid sources that are abundant at certain cutaneous sites such as the head, neck and skin folds (Figure 5B).\textsuperscript{98} Although the pathogenesis of \textit{Malassezia} spp in AD is not entirely clear, yeast is known to trigger a multitude of immune responses. It is estimated that 80\% of adults with AD have detectable \textit{Malassezia} IgE antibodies.\textsuperscript{99-101} \textit{Malassezia} spp. in the epidermis and dermis, can be recognized by keratinocytes and Langerhans cells as well as dermal DCs. These antigen presenting cells in turn activate downstream immunologic cascades that lead to the release of pro-inflammatory cytokines such as TNF-alpha, IL6, IL-8, IL-10, and IL-12p70. Induced expression of TLR2 and TLR4 on human keratinocytes and DCs upon exposure to \textit{Malassezia} spp. have been observed, suggesting direct activation of innate immune response.\textsuperscript{102,103} In addition, the NLRP3 inflammasome in skin DCs can also be activated by \textit{Malassezia} spp with subsequent release of Th2 cytokines (eg IL-1beta, IL-4, 5, 13) likely directly contributing to AD pathogenesis.\textsuperscript{104,105}

There is growing interest in understanding the specific roles of different bacteria in skin well-being. Many cosmetic products using a variety of formulations and diverse bacterial strains have been developed and filed for patents. However, there is a significant lack of scientific evidence to support the claims from these products.\textsuperscript{106} Clinical manipulation of the skin microbiome as therapy for a variety of skin diseases is actively being explored. Several clinical trials have been conducted using targeted microbiome transplant via topical probiotic cream in the treatment of AD.\textsuperscript{107} These proof of concept studies have enrolled very limited numbers of subjects, and there is insufficient evidence currently reported. Nonetheless, there have been no safety concerns reported. Larger scale, randomized, controlled trials are underway.

Lamellar bilayer structural integrity is highly organized in normal skin, seen under electron microscopy, but very abnormal in those with AD and peanut allergy. The epidermis in AD with peanut allergy is associated with high TEWL, high type 2 immune activation, \textit{S. aureus} colonization, reduced filaggrin breakdown products, and a reduced proportion of long-chained lipid products. These observations suggest that a defective skin barrier in patients with AD and peanut allergy may predispose affected individuals to epicutaneous allergen sensitization.
The availability of minimally invasive skin tape sampling techniques may play an important role in identifying infants with early epidermal barrier dysfunction who may benefit from timely initiation of novel therapies for skin barrier dysfunction, non-lesional immune activation, and microbial dysbiosis. Using this technique epidermal profiling of lipids, proteins, and transcriptome identifies differences in the epidermis between patients with peanut allergy and AD versus AD alone.36,85

Barrier protection is the cornerstone of AD management. Skin hydration and prevention of TEWL are keys in maintaining skin barrier homeostasis. Animal studies also suggest that changes in hydration and corneocyte adhesion within stratum corneum affect the development and maturation of the epidermis.108 Although there has been considerable controversy about whether early application of skin emollients can prevent AD and FA,20 these studies have often not targeted high-risk infants with pre-existing skin barrier dysfunction. Moreover, the ingredients of emollients have not been optimized for infant skin barrier repair. The use of topical steroids to prevent AD flares and control subclinical inflammation is being evaluated as a potential strategy to prevent FA in AD.20 Other novel pathogenesis-based topical and systemic therapies targeting inflammation of the skin have also been investigated for their roles in preventing FA.109

<table>
<thead>
<tr>
<th>TABLE 1 A summary of changes identified in atopic dermatitis compared to healthy skin in the microbiota, skin barrier, and inflammatory cytokines</th>
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<tbody>
<tr>
<td><strong>Element or characteristic</strong></td>
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<tr>
<td>Skin microbiome</td>
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<tr>
<td>Microbial diversity</td>
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<tr>
<td><em>S. aureus</em> colonization (including MRSA)</td>
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<tr>
<td><em>S. aureus</em> virulence factors</td>
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<tr>
<td>Commensal bacteria</td>
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<tr>
<td>Malassezia spp.</td>
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<tr>
<td>Skin Barrier</td>
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<tr>
<td>Filagrin gene expression and breakdown products including natural moisturizing factor</td>
</tr>
<tr>
<td>Skin pH</td>
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<tr>
<td>Transepidermal water loss (TEWL)</td>
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<tr>
<td>Tight junction expression and function</td>
</tr>
<tr>
<td>Organization of the lipid bilayer and fatty acid chain length</td>
</tr>
<tr>
<td>Inflammatory cytokines</td>
</tr>
<tr>
<td>IL-4, -13, and other Th2 cytokines</td>
</tr>
<tr>
<td>Thymic Stromal Lymphopoietin (TSLP)</td>
</tr>
<tr>
<td>IL-31</td>
</tr>
<tr>
<td>IL-33 &amp; ILC2s</td>
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Petrolatum, a non-physiologic mineral lipid, is often considered a gold standard ointment-based emollient that can prevent TEWL effectively for 4–6 h. Therefore, to maintain optimal skin hydration, ointment-based emollients should be applied 3 to 4 times daily to provide complete protection. However, ointment-based emollients can also exacerbate AD; therefore, alternatives must be considered.
Lipids including ceramide, fatty acids and cholesterol are mixed in appropriate ratio within stratum corneum to maintain its integrity. Atopic skin is known to be deficient in lipids especially ceramide and hygroscopic amino acids that are the result of filagrin breakdown products. Newer generations of emollients containing these lipids have been developed in recent years. A recent study demonstrated a trilipid cream was more effective than a paraffin-based emollient in reducing TEWL and sIgE levels. However, efficacy in AD or FA prevention is yet to be proven in a randomized clinical trial. While treating AD patients with a barrier-based approach, a liver X receptor agonist upregulated terminal differentiation and lipid products in the skin of patients with AD, consistent with its mechanism of action; however, it was not associated with clinical benefit or suppression of immune products (Th17/Th22/IL6). This suggests that although barrier-based approaches may be valuable for disease prevention, the immune abnormalities perpetuate the AD disease phenotypes and should be targeted to resolve active AD.

The discovery of cytokine dysregulation in non-lesional skin from AD patients suggest the role of systemic therapy especially for individuals with severe disease. The increased understanding of AD’s immune pathogenesis led to the development of immune-based treatments targeting Th2 cytokines. Downregulation of immune markers in the skin of patients treated with such agents highly correlated with reductions in disease severity scores, demonstrating clinical improvement. Furthermore, the Th2-targeting anti-IL-4R mAb dupilumab was shown to induce significant changes in the microbiome of skin lesions, again supporting the key role of the Th2 cytokines in inducing the disease pathogenesis.

3 | DIETARY FACTORS

The obvious dietary factor relevant to the establishment of oral tolerance (and susceptibility to FA) is food allergens. Oral tolerance is the active maintenance of both mucosal and systemic non-responsiveness to ingested food allergens. The induction of tolerance to dietary antigen is a multistep process; dietary vitamin A plays a critical role in its regulation. CD103+ dendritic cells (DC) in the gut associated lymphoid tissue (GALT) express elevated levels of retinal dehydrogenase (RALDH) enzymes which enhance their ability to metabolize dietary vitamin A. Antigen-loaded CD103+ DC migrate to the mesenteric lymph node (MLN) from the intestinal lamina propria (LP). Retinoic acid (RA) produced by these DC and by stromal cells in the MLN induce the expression of the gut homing receptors CCR9 and α4β7 favouring TGF-b dependent conversion of Foxp3+ regulatory T cells (Tregs). Committed Tregs then home back to LP, expanding under the influence of IL-10 produced by CX3CRI+ macrophages. Some Tregs exit the mucosa via the lymph or bloodstream to promote systemic tolerance. Elegant studies in germ-free mice on an antigen-free diet showed that, in the small intestine, Foxp3+ Tregs are induced by exposure to dietary antigen.

In the large intestine, however, Foxp3+ Tregs are induced by a subset of the mucosa-associated bacteria which comprise the intestinal microbiota.

The increasing prevalence of FA parallels increases in other non-communicable diseases and can be explained, in part, by alterations in the composition and function of the commensal microbiome. 21st century lifestyle practices including increased antibiotic use, low fibre/high fat diets, reduced exposure to infectious diseases, Caesarean birth and formula feeding have collectively depleting populations of bacteria beneficial to health. In addition to dietary antigen induced Foxp3+ Tregs, a bacteria-induced barrier protective response is required to prevent allergic sensitization to food. Clostridia-induced IL-22 production by type 3 innate lymphoid cells (ILC3) is necessary and sufficient to reduce intestinal epithelial permeability to dietary allergen. IL-22 protects the intestinal epithelial barrier by regulating epithelial proliferation and the production of mucus and antimicrobial peptides. The mechanisms by which intestinal bacteria, particularly those in the Clostridia class, regulate mucosal immunity and allergic disease are increasingly understood. Prominent among these is their ability to ferment short-chain fatty acids (SCFAs) from dietary fibre. SCFAs have potent immunomodulatory effects correlated with host health including induction of colonic Tregs and improvement of allergy symptoms in a mouse model. Butyrate, in particular, is an important energy source for colonic epithelial cells. Butyrate drives oxygen consumption by colonocytes through beta-oxidation, which maintains a locally hypoxic niche for butyrate-producing obligate anaerobes. Early dysbiosis characterized by an impaired capacity to produce butyrate may be a common feature of allergic diseases. Tryptophan metabolites, from both dietary and bacterial sources, also play a central role in regulating tolerance in the gut. Catabolism of tryptophan to indole derivatives produces ligands which bind to the aryl hydrocarbon receptor on innate lymphoid cells (ILC3) and stimulate the production of IL-22 to regulate epithelial barrier permeability. Finally commensal bacteria can metabolize bile acids to produce bioactive mediators which regulate T-cell differentiation in the intestinal lamina propria (Figure 6).

The data suggest that compositional and proportional differences in the gut microbiome are linked to the generation of diverse favourable neurotransmitters and neuromodulators, which are associated with the degree of AD symptoms. They can also affect skin barrier dysfunction and immune system dysregulation, which are the key pathophysiology in the development of AD. The gut microbiome can modulate the gut-skin axis through direct and indirect pathways. Tryptophan produced by the gut microbiome causes an itching sensation in the skin, whereas Lactobacillus and Bifidobacterium species can produce γ-aminobutyric acid (GABA), which inhibits skin itch. Escherichia and Enterococcus species can produce serotonin, which is involved in skin pigmentation. Moreover, cortisol, usually released under stress conditions, can change gut epithelium permeability and barrier function by altering...
the composition of the gut microbiome. This also alters the levels of circulating neuroendocrine molecules, such as tryptamine, trimethylamine, and serotonin, and thereby modifies the skin barrier and skin inflammation.

The dual allergen exposure hypothesis is supported by evidence from mouse models that food allergen exposure was necessary for the development of tolerance, as well as observational studies in humans linking allergen avoidance in the first few years of life with the development of FA. Specifically, a cross-sectional study showed that early in life peanut consumption in Israel was associated with a lower prevalence of peanut allergy than a population with a similar ancestry in the UK, where peanut was typically avoided in the first few years of life. Whereas avoidance of food allergens in an infant’s diet was standard advice in many countries, advice has changed, and oral tolerance induction is being used as a strategy to prevent peanut and other FA by introducing food allergens early into the diet of young infants. The LEAP study showed that early introduction could reduce the rate of peanut allergy by 86% in non-sensitized children and the LEAP-On study confirmed that this protection against peanut allergy remained one year after complete subsequent avoidance of dietary peanut from 5 to 6 years of age. The impact of early peanut introduction in LEAP was peanut specific and did not protect against other FA. The EAT study (a lower risk, exclusively breastfed population) showed similar results for peanut in a per protocol analysis. It also showed that consuming cooked egg in infancy was associated with a reduction in egg allergy. Since, subsequent studies and a meta-analysis have confirmed the efficacy of this approach, and a recent Japanese study has shown that early introduction of cow’s milk in early infancy protects against the development of milk allergy. Introducing multiple foods early and continuing to eat them regularly proved challenging for most families in the EAT study. The study identified several factors associated with reduced adherence to this strategy: increasing maternal age, feeding difficulties in the neonate, and non-Caucasian ethnicity. This could help identify families who might benefit from further support to encourage early weaning.

Many other dietary factors have been studied for their association with FA and/or AD. Observational studies have been summarized in a number of systematic reviews focusing on the maternal and infant diet or the maternal diet during pregnancy alone. Collectively over a hundred papers from observational studies have been identified reporting dietary patterns, diet diversity, fruit and vegetable intake, fat and fatty acid intake, vitamin and mineral intake, and a wide range of other dietary exposures, including alcohol, tea or coffee intake. Summarizing these studies using meta-analysis is limited as study exposures and outcome definitions are highly heterogeneous. A comprehensive review by the UK Food Standards Agency focusing on maternal and infant dietary intake concluded that there is no consistent evidence for associations between dietary exposures and allergy outcomes based on observational studies. Other systematic reviews have, however, attempted to summarize findings from these studies.

3.1 Breastfeeding

A recent systematic review from EAACI indicated that breast feeding may not reduce the risk of FA or cow’s milk allergy. This echoes the recommendations of both the American Academy of Pediatrics (AAP), the AAAAI/ACAAI/CSACI 2020 consensus statement and the EAACI FA prevention guidelines, indicating that no conclusions can be made about the role of breastfeeding in preventing or delaying the development of any food allergies. In terms of AD the AAP guidance concluded that exclusive breastfeeding for 3 to 4 months decreases the development of eczema in the first 2 years of life. The systematic review by Garcia-Larsen et al. indicated that breast feeding of any duration does not seem to have a protective effect on FA but that there is some weak evidence that breast feeding may prevent the development of AD in the infant. Breast feeding is, however, recommended for all mothers due to the numerous benefits for both mother and infant.

3.2 Dietary patterns and food groups

Dietary patterns, such as the Mediterranean diet, have not been associated with reduced AD or FA in offspring. During pregnancy, no studies report on maternal dietary patterns in lactation and AD or FA outcomes in the infant. However, two systematic reviews tentatively conclude that fruit, vegetable, and yoghurt intake in pregnancy may prevent onset of AD and that margarine and vegetable oil may increase the risk of AD. Studies of the associations between intake of particular foods and infant FA are lacking. Diet patterns in infancy have not been associated with infant AD. One study indicates that a diet pattern of predominantly home-cooked food may prevent FA.

3.3 Diet diversity

Diet diversity is the number of different foods, food groups or food allergens eaten over time, such as the first year of life. Recently there has been considerable interest in the effect of infant diet diversity in preventing allergic diseases. A task force report from the European Academy of Allergy and Clinical Immunology (EAACI) suggested that increased diet diversity in infancy may reduce the risk of developing allergic diseases such as asthma, AD, allergic rhinitis or FA in later childhood. Two observational studies have shown increased diet diversity in the first year of life to be associated with reduced FA by six and ten years. Using data from Europe and the UK, these observational studies suggest that early oral intake of a variety of foods and food allergens, once the infant is developmentally ready, may reduce the incidence of FA in the first 10 years of life. Studies focusing on diet diversity in infancy and AD in childhood are however less clear. The LISA study found that increased diet diversity within the first 6 months of life (but not 4 months of life) reduced the risk of doctor diagnosed AD up to 2 years of age as
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<th>Topic</th>
<th>Year (reference)</th>
<th>Study or publication title</th>
<th>Author(s)</th>
<th>Key findings and contributions to allergy</th>
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<td>Ancient Maternal Dietary Avoidance</td>
<td>2735–2598 BC</td>
<td>Interdictions Concerning Foods</td>
<td>Chinese emperors Shen Nong and Huang Di</td>
<td>Advised pregnant women to avoid shrimp, chicken, meat, and other agents incriminated in skin lesions</td>
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<tr>
<td>Defining a Disease and a Medical Specialty</td>
<td>1906</td>
<td>Allergy</td>
<td>von Pirquet C</td>
<td>'For this general concept of a changed reactivity I propose the term Allergy. 'Allos' implies deviation from the original state, from the behaviour of the normal individual, as it is used in the words Allorhythmia, Alloptropism'</td>
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<tr>
<td>Oral Tolerance Induction</td>
<td>1908</td>
<td>A case of egg poisoning</td>
<td>Schofield AT</td>
<td>First modern oral desensitization for food allergy</td>
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<td>Diagnosing Food Allergy and Inducing Oral Tolerance</td>
<td>1912</td>
<td>A case of allergy to common foods</td>
<td>Schloss OM</td>
<td>The early development of food extracts for scratch testing; identification of ovomucoid as the major egg allergen and its use for oral desensitization</td>
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<td>The Concept of Immunoglobulin E</td>
<td>1921</td>
<td>The Prausnitz-Küstner Test</td>
<td>Prausnitz O &amp; Küstner H</td>
<td>Demonstrated passive sensitization of the skin in health subjects by transferring serum from a sensitized individual using the PK test</td>
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<td>Diagnosing Food Allergy</td>
<td>1950</td>
<td>Allergy for corn and its derivatives: experiments with a masked ingestion test for its diagnosis</td>
<td>Loveless MH</td>
<td>Amid widely varying reports of the incidence of corn allergy, recognized that positive tests and patient histories often do not match a 'blindfold test', and appealed for standardized FA testing</td>
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<tr>
<td>The Discovery of IgE</td>
<td>1966–8</td>
<td>Immunoglobulin E, a new class of human immunoglobulin</td>
<td>K &amp; T Ishizaka; Johansson SGO &amp; Bennich H</td>
<td>The search for reagin concludes with the nearly simultaneous identification of IgE, the critical component of an immediate hypersensitivity reaction</td>
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<tr>
<td>Diagnosing Food Allergy</td>
<td>1970</td>
<td>Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children; Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure</td>
<td>May CD, Bock SA, et al.</td>
<td>The gold standard of diagnosis, the double-blind, placebo-controlled oral food challenge was described and became more accessible to the practicing allergist; defined a SPT &lt;3 mm as negative</td>
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<tr>
<td>Mechanisms of Sensitization</td>
<td>1996</td>
<td>The dual exposure hypothesis</td>
<td>Lack G &amp; Golding J</td>
<td>'Avoidance measures would serve only to reduce exposure to peanuts to low levels, and this could paradoxically increase allergic sensitization to peanuts: low dose exposure to allergens favours production of IgE and as little as 1 µg of inhaled allergen a year may be sufficient to induce allergic sensitization via the airways'</td>
</tr>
<tr>
<td>Notable limitations</td>
<td>Study population</td>
<td>Study type</td>
<td>Level of evidence215</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------</td>
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<td></td>
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<tr>
<td>Ancient Chinese History, lacking detailed methods</td>
<td>Ancient Chinese</td>
<td>The first known official guideline recommending food avoidance to prevent disease, via Emperor’s decree</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Opinion</td>
<td>n/a</td>
<td>Clinical observations</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>London clinic patient</td>
<td>Case report</td>
<td>Level 5</td>
<td></td>
</tr>
<tr>
<td>Single case</td>
<td>New York clinic patient</td>
<td>Case report</td>
<td>Level 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prausnitz (tolerated fish) &amp; Küstner (allergic to fish)</td>
<td>Mechanistic</td>
<td>Level 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Survey of American Academy of Allergy members, case series from US allergy clinics</td>
<td>Case series and cohort</td>
<td>Level 4</td>
<td></td>
</tr>
<tr>
<td>The IgE receptor, discovered a few years later, confirmed the effector functions of IgE</td>
<td>Myeloma cell lines</td>
<td>Mechanistic</td>
<td>Level 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>US asthma centre</td>
<td>Cohort</td>
<td>Level 4</td>
<td></td>
</tr>
<tr>
<td>Opinion, observed less peanut allergy in some cultures outside Britain that also frequently consumed peanut</td>
<td>n/a</td>
<td></td>
<td>Level 5</td>
<td></td>
</tr>
</tbody>
</table>

(Continues)
In 1982, Dr. May reflected on the history of food allergy and commented: The probability of encountering these obstacles in the future decades, due to increasing prevalence, improved epidemiologic studies and increased awareness of food allergy given the risk for severe reactions including fatal anaphylaxis, the study of food allergy is contributing to the understanding of the mechanisms of sensitization and the origins of atopy. In 1982, Dr. May reflected on the history of food allergy and commented: The probability of encountering these obstacles in the future decades, due to increasing prevalence, improved epidemiologic studies and increased awareness of food allergy given the risk for severe reactions including fatal anaphylaxis, the study of food allergy is contributing to the understanding of the mechanisms of sensitization and the origins of atopy.

Note: At the time of publication of most of these milestones, the existence of food allergy was questioned by many in the medical community, including most allergists. Despite how remarkable and significant these achievements were for the field of allergy and immunology, it was not until the end of the 20th century that food allergy as a field began to overcome the reputation of being scientifically weak. Over the past three or four decades, due to increasing prevalence, improved epidemiologic studies and increased awareness of food allergy given the risk for severe reactions including fatal anaphylaxis, the study of food allergy is contributing to the understanding of the mechanisms of sensitization and the origins of atopy.

### TABLE 2 (Continued)

<table>
<thead>
<tr>
<th>Topic</th>
<th>Year (reference)</th>
<th>Study or publication title</th>
<th>Author(s)</th>
<th>Key findings and contributions to allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosing Food Allergy</td>
<td>1997227 &amp; 2001228</td>
<td>Food-specific IgE values predict OFC outcomes</td>
<td>Sampson HA &amp; Ho DG; Sampson HA</td>
<td>Proposes and validates predictive values or cut-offs, guiding the decision to perform an OFC</td>
</tr>
</tbody>
</table>

Note: At the time of publication of most of these milestones, the existence of food allergy was questioned by many in the medical community, including most allergists. Despite how remarkable and significant these achievements were for the field of allergy and immunology, it was not until the end of the 20th century that food allergy as a field began to overcome the reputation of being scientifically weak. Over the past three or four decades, due to increasing prevalence, improved epidemiologic studies and increased awareness of food allergy given the risk for severe reactions including fatal anaphylaxis, the study of food allergy is contributing to the understanding of the mechanisms of sensitization and the origins of atopy.

### TABLE 3 Major milestones in studying the prevention of atopy

<table>
<thead>
<tr>
<th>Area of focus</th>
<th>Year (reference)</th>
<th>Study name or publication title</th>
<th>Author</th>
<th>Key findings or recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous Sensitization</td>
<td>1994232</td>
<td>Increased airways responsiveness in mice depends on local challenge with antigen</td>
<td>Saloga J, et al.</td>
<td>First evidence to support that sensitization could occur through skin contact</td>
</tr>
<tr>
<td>The Role of Filaggrin in AD</td>
<td>2006112</td>
<td>Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis</td>
<td>Palmer CNA, et al.</td>
<td>AD was more common in homozygous or compound heterozygous for FLG null alleles, and nearly absent in those without</td>
</tr>
<tr>
<td>The Role of Filaggrin in FA</td>
<td>201186</td>
<td>Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy</td>
<td>Brown SJ, et al.</td>
<td>FLG loss-of-function mutations significantly increase the risk of peanut allergy, suggesting a role for epithelial barrier dysfunction</td>
</tr>
<tr>
<td>Skin Barrier Dysfunction and Transcutaneous Sensitization in FA</td>
<td>201447</td>
<td>Peanut allergy: Effect of environmental peanut exposure in children with filaggrin loss-of-function mutations</td>
<td>Brough HA, et al.</td>
<td>Exposure to peanut protein in household dust demonstrated a dose-response relationship with measures of peanut sensitization and allergy at 8 and 11 years in children with FLG mutations, when controlling for other factors; no effect of exposure was seen in children with WT-FLG</td>
</tr>
<tr>
<td>Preventative Emollient Therapy for AD</td>
<td>2014234</td>
<td>Application of moisturizer to neonates prevents development of atopic dermatitis</td>
<td>Horimukai K, et al.</td>
<td>Daily application of an emulsion-based moisturizer starting at 1 week of life prevented AD in 1/3 of infants at 8 months</td>
</tr>
<tr>
<td>Oral Tolerance Induction</td>
<td>2015235</td>
<td>Learning Early About Peanut (LEAP) &amp; follow-on study (LEAP-On)</td>
<td>du Toit, et al.</td>
<td>Early introduction and regular consumption of peanut in infants at high risk for FA prevents peanut allergy, and likely induces durable, and long-lasting tolerance</td>
</tr>
</tbody>
</table>
### Table 3: Major milestones in studying the prevention of atopy

<table>
<thead>
<tr>
<th>Topic</th>
<th>Year (reference)</th>
<th>Study or publication title</th>
<th>Author(s)</th>
<th>Key findings or recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Tolerance Induction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preventative Emollient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin Barrier Dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cutaneous Sensitization</strong></td>
<td>2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>The Role of Filaggrin in FA</strong></td>
<td>2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>The Role of Filaggrin in AD</strong></td>
<td>2006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Increased airways responsiveness</strong></td>
<td>2016</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Application of moisturizer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Common loss-of-function variants</strong></td>
<td>2014</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2 (Continued)

<table>
<thead>
<tr>
<th>Notable limitations</th>
<th>Study population</th>
<th>Study type</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly atopic population, at high risk for FA</td>
<td>US tertiary care, academic allergy clinic</td>
<td>Cohort</td>
<td>Level 4</td>
</tr>
<tr>
<td>Murine skin differs from human skin</td>
<td>Murine model</td>
<td>Mechanistic</td>
<td>Level 5</td>
</tr>
<tr>
<td>Only 2 mutations had been identified and analysed, both common in those of European ancestry, but rare in other ethnicities</td>
<td>UK, general population</td>
<td>Population-based, longitudinal birth cohort</td>
<td>Level 2</td>
</tr>
<tr>
<td>Different definitions of AD and criteria for diagnosing peanut allergy were used in the different populations; difficult to distinguish the role of AD from FLG status, and other variables affecting the development of peanut allergy; the effect varied in different populations despite all being predominantly white and of European ancestry</td>
<td>9 Irish families with ichthyosis vulgaris and/or AD; 2 cohorts of Scottish children with and without asthma; Danish children from the COPSAC study</td>
<td>Multiple cohorts</td>
<td>Level 2</td>
</tr>
<tr>
<td>Peanut allergy not challenge-proven in all subjects; overall small number of subjects with peanut allergy, FLG gene status, and exposure history; excluded non-Caucasians as the 6 FLG mutations studied were only defined in Caucasians</td>
<td>UK, high-risk infants (family history of atopy)</td>
<td>Observational study within randomized controlled study</td>
<td>Level 3</td>
</tr>
<tr>
<td>Control group could use petroleum jelly if desired, which may be beneficial for SB, limiting the impact of the intervention</td>
<td>Japan, high risk</td>
<td>RCT</td>
<td>Level 2</td>
</tr>
<tr>
<td>Excluded infants with peanut SPT &gt; 4 mm at entry</td>
<td>UK, high-risk cohort</td>
<td>Randomized, open-label, controlled trial</td>
<td>Level 2</td>
</tr>
</tbody>
</table>
well as early skin or allergic symptoms. This was confirmed by 3 more studies. In contrast, three studies found an increased risk of increased diet diversity on AD outcomes in childhood. Of interest, an increase in microbial diversity was found at week 52 of peanut OIT; the authors postulated this could be a result of the immunomodulatory effect on the host immune system in successful desensitization or as a direct cause from peanut flour on the gut microbiota.

<table>
<thead>
<tr>
<th>Area of focus</th>
<th>Year (reference)</th>
<th>Study name or publication title</th>
<th>Author(s)</th>
<th>Key findings or recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventative Trilipid Emollient Therapy for AD and FA</td>
<td>2018&lt;sup&gt;236&lt;/sup&gt;</td>
<td>A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: The PEBBLE5 Pilot Study</td>
<td>Lowe AJ, et al.</td>
<td>Twice daily application of emollient rich in ceramides to infants in the first 3 weeks of life through 6 m demonstrated a trend towards less AD and food sensitization at 12 month; infants who had emollient applier BID for at least 5/7 day per week did have a significant reduction in food sensitization</td>
</tr>
<tr>
<td>Assessing Skin Barrier Dysfunction</td>
<td>2019&lt;sup&gt;85&lt;/sup&gt;</td>
<td>The non-lesional skin surface distinguishes atopic dermatitis with food allergy as a unique endotype</td>
<td>Leung DYM, et al.</td>
<td>Using a noninvasive, well-tolerated skin tape stripping method, identifies unique immature skin barrier characteristics in the stratum corneum that distinguish between children with AD and FA (AD + FA + ) from those with AD but without FA (AD + FA −)</td>
</tr>
<tr>
<td>Proactive Early AD Treatment and the Prevention of FA</td>
<td>2020&lt;sup&gt;237&lt;/sup&gt;</td>
<td>Prevention of Allergy via Cutaneous Intervention (PACI) pilot</td>
<td>Miyaji Y, et al.</td>
<td>Earlier aggressive treatment of AD shortened its duration in infants, and resulted in fewer food allergies at 2 years of life</td>
</tr>
<tr>
<td>Preventative Petrolatum Emollient Therapy for AD and FA</td>
<td>2020&lt;sup&gt;238&lt;/sup&gt;</td>
<td>Barrier Enhancement for Eczema Prevention (BEEP)</td>
<td>Chalmers JR, et al.</td>
<td>No evidence for prevention of AD at 2 years with daily emollient use, but possible slight increase in infection risk, and nonsignificant increase in FA (largely to egg) in the intervention group</td>
</tr>
<tr>
<td>Oral Tolerance Induction</td>
<td>2020&lt;sup&gt;160&lt;/sup&gt;</td>
<td>Preventing food allergy in infancy and childhood systematic review</td>
<td>de Silva D, et al.</td>
<td>Early introduction of cooked egg (not raw or pasteurized egg) likely helps prevent egg allergy; avoiding supplementation with cow’s milk-based formula in the first week of life may slightly reduce milk allergy; nearly every other dietary intervention reviewed has little to no effect</td>
</tr>
<tr>
<td>Preventative Petrolatum Emollient Therapy for AD and FA</td>
<td>2020&lt;sup&gt;239&lt;/sup&gt;</td>
<td>Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL)</td>
<td>Skjerven HO, et al.</td>
<td>Found no decrease in AD or FA at 12 m with skin emollient use, early complementary feeding or both</td>
</tr>
<tr>
<td>Link between Emollient use and Food Allergy</td>
<td>2021&lt;sup&gt;213&lt;/sup&gt;</td>
<td>Association of frequent moisturizer use in early infancy with the development of food allergy</td>
<td>Perkin M, et al.</td>
<td>Observed an increased risk of food allergy with the application of moisturizer more frequent than once daily</td>
</tr>
</tbody>
</table>

### 3.4 Vitamins and minerals

Vitamin D insufficiency and deficiency have been associated with IgE sensitization and FA in some studies but not others. There is little evidence from interventional studies of vitamin D supplementation for primary allergy prevention as reviewed by Yepes-Nunez, et al. The lack of clear evidence from observational studies
<table>
<thead>
<tr>
<th>Notable limitations</th>
<th>Population studied</th>
<th>Type of study</th>
<th>Level of evidence&lt;sup&gt;215&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food sensitization only assessed at 1 year, not later in life and not challenge-proven; Small (n = 80), pilot study</td>
<td>Australia, high-risk infants (parental history of atopy)</td>
<td>Pilot randomized, parallel, single-blind, controlled trial</td>
<td>Level 3</td>
</tr>
<tr>
<td>Results require validation in larger, diverse populations with challenge-proven allergy to a variety of foods, not just peanut</td>
<td>62 US children classified as AD + FA +, AD + FA− or controls</td>
<td>Blinded, prospective mechanistic study</td>
<td>Level 3</td>
</tr>
<tr>
<td>Smaller, retrospective pilot study; cohorts had significant differences in baseline characteristics</td>
<td>Japan</td>
<td>Retrospective cohort</td>
<td>Level 4</td>
</tr>
<tr>
<td>Choice of emollient; limited FA assessment; median time to initiation of skin care at 11 days of life</td>
<td>UK, high risk</td>
<td>Pragmatic, parallel group RCT</td>
<td>Level 2</td>
</tr>
<tr>
<td>Many are small studies with low certainty of evidence, findings need to be validated in large, heterogeneous populations</td>
<td>n/a</td>
<td>Systematic review with meta-analysis</td>
<td>Level 2</td>
</tr>
<tr>
<td>Skin intervention started at 2 weeks of life using a bath oil and cream; early food introduction began with peanut butter at 3 m; overall poor adherence in the intervention groups; low statistical power to assess FA (results for FA at 3 years forthcoming)</td>
<td>Scandinavian standard risk birth cohort</td>
<td>Prospective interventional, cluster-randomized controlled trial</td>
<td>Level 2</td>
</tr>
<tr>
<td>All but 1 case of FA developed in children with at least 1 atopic parent; AD only assessed at 3 m enrolment visit; the cohort frequently used oils for baby massage, which may prevent formation of an intact skin barrier; unable to control for some potential confounding factors</td>
<td>UK, exclusively breastfed standard risk cohort enrolled in the EAT study and randomized to standard vs early introduction of 6 foods with poor protocol adherence</td>
<td>Retrospective analysis of questionnaire data</td>
<td>Level 3/4</td>
</tr>
</tbody>
</table>

about the role of vitamin D in FA risk is in part related to the multiple factors influencing vitamin D levels that need to be accounted for when designing studies. These factors include sun exposure, country and latitude of residence, migratory status, skin colour, ethnicity, age, diet, vitamin D supplementation (timing, formulation and dose), genetic polymorphisms affecting metabolism, epigenetic changes contributing to vitamin D levels, vitamin D binding protein, interaction with disease-associated genetic polymorphisms (eg ORMDL3),...
definition of vitamin D insufficiency/deficiency, and time-points to assess levels (longitudinal versus cross-sectional).169

One systematic review indicated that intake of beta-carotene, vitamin E, zinc, calcium, magnesium, and copper during pregnancy might be protective of offspring AD.168 This review also summarized a small number of papers indicating that copper and vitamin C intake during pregnancy may reduce the risk of offspring FA. In contrast, vitamin D intake was associated with an increased risk of offspring FA. The amount of vitamins and minerals taken in these studies did not align with healthy eating guidance, and the results should be interpreted with caution.168

3.5 | Antioxidants

Oxidative stress has recently been explored in the development of AD and FA. Oxidative stress results from an imbalance in reactive oxygen species (ROS) and antioxidant defence, which may lead to release of pro-inflammatory cytokines, alter enzymatic function and thereby impaired skin barrier function.194 In OVA-sensitized mice, oral supplementation of capsaicin reduced oxidative stress and IL-33 but did not reduce IgE production.195 Intake of nuts has also been shown to reduce oxidative stress inflammation.196 There are currently no guidance regarding the use of antioxidant supplementation in FA prevention.17,160,167,169

3.6 | Fatty acid consumption

The role of omega 3 fatty acids in the prevention of FA and AD needs further clarification. Omega-3 fatty acids clearly have immunoregulatory effects, with a particular role in tolerogenic immune responses; however, studies show contradicting results, most likely due to timing of intervention, lack of standardized formats (food or supplement, source of supplement), standardized doses, and lack of measuring serum fatty acid levels at study entry.172,197 As an example of this confusion, the EAACI guidelines17 state that no recommendation can be made for or against the prevention of food allergies. The BSACI guidelines198 suggest that omega-3 fatty acids may help reduce the risk of AD in early life and the ASCIA guidelines199 recommend 3 portions of fatty fish per week in infants.

3.7 | Role of fibre, prebiotics, probiotics and synbiotics in allergy prevention

Gut microbiota structure and function is an important consideration in the development of FA and AD. The composition and metabolic activity of the gut microbiota has significant effects on mucosal immune responses, which make the gut an interesting target for immune modulation. Microbial metabolites, particularly butyrate, may protect against the development of allergic disorders via their effect on T-regulatory cells.200,201 Diet plays an important role in shaping the gut microbial metacommunity.

Diet diversity172,202 and increased fibre intake203,204 increase gut microbiome diversity and butyrate production. Prebiotics provided as dietary fibre or human milk oligosaccharides, probiotics and synbiotics have been shown to affect gut microbiome structure and function. The role of fibre intake, pre, pro and synbiotics in the prevention of AD and food allergies are currently unclear. The authors are unaware of any clinical trials assessing the role of fibre intake on the prevention of food allergies or AD. A recent meta-analysis of 14 prevention studies showed a pooled relative risk reduction in AD in those treated with probiotics versus placebo; however, on subgroup analyses it was only mixed strains of probiotics that had a significant effect. Probiotics administered solely to infants did not prevent the development of AD, but effects were significant when probiotics were administered to both pregnant mothers and their infants or solely to pregnant mothers. The authors cautioned about interpreting the significance of results due to heterogeneity among the studies and lack of standardized measurements.205

The World Allergy Organization (WAO) recommends probiotics during pregnancy, lactation and/or infancy for the prevention of AD but acknowledges the low level evidence that this recommendation is based on.206 The WAO guideline panel also acknowledged that the available evidence on prebiotic supplementation to reduce the development of AD and FA is currently uncertain. The guidelines did however recommend that probiotics could be added to the diet of non-exclusively breastfed infants, both at high and at low risk for developing allergy. This is a conditional recommendation with very low certainty of evidence.207

The most recent FA prevention guidelines did however not make any recommendations for the use of pre, pro or synbiotics on the prevention of AD or FA. The European Academy of Allergy and Clinical Immunology (EAACI) FA prevention guidelines concluded that no recommendation can be made for or against the use of prebiotics, probiotics or synbiotics in pregnancy, when breastfeeding or in infancy.17 The joint FA prevention consensus statement from the American Academy of Asthma, Allergy and Immunology (AAAAI), American College of Allergy and Clinical Immunology (ACAAI) and the Canadian Society of Allergy and Clinical Immunology (CSACI) concluded that no recommendation can be made regarding the use of pre and probiotics in allergy prevention.14 This echoes a similar statement from the Australian Society of Clinical Immunology and Allergy (ASCIA).208 The guidelines were supported by a systematic review indicating that probiotic supplementation throughout pregnancy, lactation and/or infancy may prevent AD but the evidence for FA prevention is lacking. Garcia-Larsen et al.159 indicated that maternal supplementation, with Lactobacillus rhamnosus may reduce risk of AD and sensitization to milk but not clinical FA outcomes. This systematic review did not find an overall preventative effect of probiotics or allergy prevention. Despite wide-spread interest, synbiotics have not been studied in allergy prevention.
Results from RCTs have been summarized in several guideline papers and systematic reviews, with or without meta-analysis, to guide families. Results from these meta-analyses largely support current recommendations from the American Academy of Pediatrics (AAP), \(^{169}\) EAACI, \(^{17}\) and the consensus statement from the 3 North American allergy societies. \(^{16}\)

### 4 | CONCLUSIONS

The 2000 AAP policy \(^{209}\) recommended avoidance of allergenic foods for breastfeeding mothers and delayed introducing allergenic foods to infants to prevent FA was based on expert opinion informed by a limited number of low quality studies. \(^{210}\) These guidelines influenced infant feeding practices for almost 20 years, \(^{211}\) while FA continued to increase, rather than decrease. These guidelines were reversed in 2008, but not replaced with comprehensive guidelines, only limited recommendations. \(^{210}\) With publication of data from higher-quality studies, recent guidelines offer a comprehensive approach to maternal/infant diet. \(^{16,17,212}\) The foundation for these studies and ongoing efforts to study the prevention of atopy was laid throughout the 1900s by pioneers in the field (Tables 2 and 3).

It is critical to not only have consistent diagnostic criteria for the conditions being studied, but also to have comparable outcomes that are patient-relevant when possible. This will allow for valid and complete comparisons across studies in diverse populations, including high and general risk populations, regionally and globally. Reliable estimates of the global burden of atopic disease and improved epidemiologic data for these conditions is crucial to gain support for and acceptance of prevention guidelines.

Interventions to prevent AD and FA targeted at the first few months of life are not early enough for some babies. There are likely factors already in place within the first few weeks of life, or earlier, particularly in at-risk infants who may start the march towards atopy and a Th2 milieu in the womb. The proposed increased risk for FA with more than daily application of moisturizer in the EAT wards atopy and a Th2 milieu in the womb. The proposed increased risk for FA with more than daily application of moisturizer in the EAT study cohort highlights the need for earlier assessments and interventions among diverse and representative populations employing consistent disease definitions using easily applied and clinically relevant assessments. \(^{213}\) This finding further cautions against drawing potentially premature conclusions when important confounders cannot be adequately accounted for. These most recent findings add to the conflicting evidence about the potential to prevent AD to reduce the risk of FA. \(^{214}\) Further, this supports the need for intervention trials designed from the outset to study FA using a broadly accepted definition as the primary outcome, beginning in the first weeks of life, with intentionally developed treatment groups and carefully planned assessments in hopes of Stopping Eczema and Allergy (SEAL, NCT03742414). The SEAL Study will also attempt to answer ongoing research questions identified in this review, summarized in Box 1.

It is unlikely that there is a single way to stop the atopic march once underway or a master switch that could render all the external factors discussed in this review ineffective at inducing a Th2 response. It remains important to investigate these potential targets for prevention (Figure 7) and continue to search for others. Given the remarkably conflicting results within and between studies on the microbiome and a wide variety of dietary factors, it seems that well-informed guidelines in these areas are farther off in the future, and may require extensive public health campaigns to slowly change behaviours if successful approaches can be identified.

It is of course still necessary to provide recommendations before definitive evidence that is applicable to diverse populations is available. In the interim, recent updates from North America\(^{15}\) and Europe\(^{17}\) are more unified with those from Australasia. \(^{212}\) There will certainly be disagreement with some aspect of any guideline, but these do represent a responsible approach towards prevention of atopic conditions, based on the presently limited evidence base. Well-designed trials must continue in the face of unprecedented challenges faced today by study subjects, clinical researchers, and scientists so that the field can move closer to an understanding of

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**BOX 1  Topics for future research**

- Definitions of disease that are easy to apply, widely accepted and clinically relevant
- Accurate estimates of the global epidemiologic burden of atopy
- Incorporate patient-relevant outcomes for FA and AD into trial designs
- Earlier timing of interventions to address skin barrier dysfunction (SBD)
- Randomized trials focusing on maternal and early life nutrition with robust measurements of food, macro and micronutrient intake and clearly defined study outcomes
- Current efforts should be broadened to more fully understand the mechanisms underlying initiation, maintenance, loss, and redevelopment of tolerance
- Fully characterize the molecular mechanisms underlying the phenotypes of SBD that place some, but not all patients with AD at a significantly increased risk for atopy, particularly FA
- Distinguish other SBD phenotypes, as seen in seborrheic dermatitis and psoriasis from those in AD identifying potential targets to maintain tolerance later in life
- Identify targeted treatment approaches to heal the SBD associated specifically predisposing to atopy
- Ongoing evaluation of environmental exposures including irritants, pollution, pollen, bacteria, viruses and fungi
- Begin to better understand the complex interaction of the commensal microbiome of the gut and skin with potentially pathogenic bacteria and fungi
- Focus the study of environmental and microbial factors on identifying modifiable risks for manageable public health interventions benefiting the majority of the global population
the complex mechanisms driving allergic sensitization early in life. Effective strategies for the prevention of atopic conditions, particularly AD and FA will almost certainly be the result.

ACKNOWLEDGEMENTS
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CONFLICTS OF INTEREST
Dr. Brough reports receiving research grants from the National Institutes of Health (NIH) (U01 # AI147462), Aimmune and DBV Technologies and speaker fees from DBV Technologies and Sanofi outside of the submitted work. Dr. Lanser reports grants and personal fees from Aimmune Therapeutics, grants and personal fees from DBV Technologies, grants and personal fees from Genentech, personal fees from Allergenis, personal fees from Hycor, personal fees from GSK, grants from US NIH/NIAID-sponsored Consortium on Food Allergy Research, grants from Regeneron, outside the submitted work. Dr. Sayantani Sindher reports grants from NIH, grants from Regeneron, grants and other from DBV Technologies, grants from AIMMUNE, grants from Novartis, grants from CoFAR, grants and personal fees from FARE, other from Astra Zeneca, outside the submitted work. Dr. Chan report grant funding from National Institutes of Health (NIH) (U01 # AI147462) and Aimmune for the ARC005 study. Dr. Santos reports grants and personal fees from Medical Research Council (G0902018, MR/M008517/1 and MR/T032081/1); grants from Food Allergy Research and Education (FARE), Asthma UK and the

FIGURE 7 Diagram of possible causal associations between genetics, skin exposures, diet leading to eczema and/or food allergy. The interplay between genetics, diet, and skin/microbiome exposure are connected by arrows showing the direction of causality hypothesized to ultimately influence food allergy. The relevant causal factors of the dual allergen exposure hypothesis are outlined by the blue rectangle. This hypothesis postulates that allergen exposure through the skin leads to the development of food allergy. The degree of a broken skin barrier involved with eczema is thought to interact with allergen exposure to increase the probability of allergy development with increasing barrier disfunction. While early introduction of food and diet diversity has been proven to prevent food allergy (dark green), other factors such as breastfeeding, commensal bacteria metabolizing bile acids, tryptophan from dietary/commensal bacterial sources, dietary fibre, vitamins, pre, pro and synbiotics have weaker evidence base for this (light green). Reducing eczema severity has yet to be consistently shown as a preventative causal mechanism. Nevertheless, eczema severity exists as one of the strongest predictors of food allergy, and therapies to heal a broken skin barrier remain as a leading mechanism to mediate the prevention of food allergy.
NIHR through the Biomedical Research Centre (BRC) award to Guy’s and St Thomas’ NHS Foundation Trust, during the conduct of the study; grants from Immune Tolerance Network/National Institute of Allergy and Infectious Diseases (NIAID, NIH); personal fees from Thermo Scientific, Nutricia, Informed, Novartis, Allergy Therapeutics, Buhlmann, as well as research support from Buhlmann and Thermo Fisher Scientific through a collaboration agreement with King’s College London. Henry Bahnson reports personal fees from King’s College, London, UK, during the conduct of the study; personal fees from DBV technologies, outside the submitted work. Guttmann-Yassky reports research funds (grants paid to the institution) from: Abbvie, Almirall, Amgen, AnaptysBio, Asana Biosciences, AstraZeneca, Boehringer-Ingelheim, Cara Therapeutics, Eli Lilly, Galderma, Glenmark/Ichnos Sciences, Innovadmeer, Janssen, KAO, Kiniksa, Kyowa Kirin, Leo Pharma, Novan, Pfizer, Railexar, Regeneron Pharmaceuticals, UCB Consultancy fee from: Abbvie, Almirall, Amgen, Arena, Asana Biosciences, AstraZeneca, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cara Therapeutics, Connect Pharma, Eli Lilly, EMD Serono, Evidera, Galderma, Ichnos Sciences, Incyte, Janssen Biotech, Kyowa Kirin, Leo Pharma, Pandion Therapeutics, Pfizer, RAPT Therapeutics, Regeneron Pharmaceuticals, Inc., Sanofi, SATO Pharmaceutical, Siolta Therapeutics, Target PharmaSolutions, UCB, Ventyx Biosciences. Dr. Gupta reports receiving research support from the National Institutes of Health (NIH) (R21 ID # AI135705, R01 ID # AI130348, U01 ID # AI138907), Food Allergy Research Education (FARE), Rho Inc, Melchiorre Family Foundation, Sunshine Charitable Foundation, Waldor Foundation, UnitedHealth Group, Thermo Fisher Scientific, Genentech, and the National Confectioners Association (NCA); serves as a medical consultant/advisor for Aimmune Therapeutics, Before Brands, AllerGenis LLC, Kaléo Inc, Novartis, Genentech, DBV Technologies, and Food Allergy Research and Education (FARE); is employed by Ann & Robert H. Lurie Children’s Hospital of Chicago; and is professor of paediatrics and medicine at Northwestern University Feinberg School of Medicine. Dr. Lack reports grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), other from Food Allergy & Research Education (FARE), other from MRC & Asthma UK Centre, other from UK Dept of Health through NIHR, other from National Peanut Board (NPB), grants from UK Food Standards Agency (FSA), other from The Davis Foundation, during the conduct of the study; personal fees and other from DBV Technologies, other from Mighty Mission Me, personal fees from Novartis, personal fees from Sanofi-Genzyme, personal fees from Regeneron, personal fees from ALK-Abello, personal fees from Lurie Children’s Hospital; outside the submitted work. Dr. Lack has the following patents: Special Oral Formula for Decreasing Food Allergy Risk and Treatment for Food Allergy, Granulocyte-based methods for detecting and monitoring immune system disorders, Methods and Assays for Detecting and Quantifying Pure Subpopulations of White Blood Cells in Immune System Disorders, and Microfluidic Device and Diagnostic Methods for Allergy Testing Based on Detection of Basophil Activation. Dr. Nagler reports grants from National Institutes of Health (NIAID) and is the President and co-founder of ClostraBio, Inc. Dr. Teng and Dr. Sampath report no conflicts of interest.

**AUTHOR CONTRIBUTION**

Dr. Brough coordinated the group, amalgamated sections, reviewer responses and references. Dr. Chan and Dr. Ruchi wrote the introduction and arranged Figures therein. Dr. Brough, Dr. Sindher, Dr. Teng, Dr. Leung and Dr. Guttmann-Yassky wrote the cutaneous and environmental exposure section and created figures for this section. Dr. Venter, Dr Santos, Dr. Lack and Dr. Nagler wrote the dietary factors section and Dr Nagler created the figure for this section. Dr Lanser, Dr. Bahnson, Dr. Sampath and Dr. Nadeau wrote the conclusion section, and box of future research perspectives. Dr. Bahnson created the causal diagram. Dr. Lanser created the Tables. Dr. Ciaccio wrote the abstract. Dr. Brough, Dr Lanser and Dr. Nagler proof-read the final document, figures and checked references. All authors reviewed the manuscript.

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