

REVIEW

Epicutaneous sensitization in the development of food allergy: What is the evidence and how can this be prevented?

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Abstract

There is increasing evidence regarding the importance of allergic sensitization through the skin. In this review, we provide an overview of the atopic march and immune mechanism underlying the sensitization and effector phase of food allergy. We present experimental models and human data that support the concept of epicutaneous sensitization and how this forms one half of the dual-allergen exposure hypothesis. We discuss specific important elements in the skin (*FLG* and other skin barrier gene mutations, Langerhans cells, type 2 innate lymphoid cells, IL-33, TSLP) that have important roles in the development of allergic responses as well as the body of evidence on environmental allergen exposure and how this can sensitize an individual. Given the link between skin barrier impairment, atopic dermatitis, food allergy, allergic asthma, and allergic rhinitis, it is logical that restoring the skin barrier and prevention or treating atopic dermatitis would have beneficial effects on prevention of

Abbreviations: AA, Allergic asthma; AD, Atopic dermatitis; AEs, Adverse events; API, Asthma Predictive Index; AR, Allergic rhinitis; BEEP, Barrier Enhancement for Eczema Prevention; CEQ, Children's Eczema Questionnaire; CER, Ceramides; CLA+, Cutaneous lymphocyte antigen; DC, Dendritic cell; DFI, Dermatitis family impact; EASI, Eczema Area and Severity Index; EOS CER, fatty acid ultra-long-chained ceramides; FA, Food allergy; *FLG*, Filaggrin gene; IDQoL, Infants' Dermatitis Quality of Life; IL, Interleukin; ILC2, Type 2 innate lymphoid cells; IP, Intraperitoneal; LC, Langerhans cells; LN, Lymph node; OFC, Oral food challenge; OVA, Ovalbumin; PA, Peanut allergy; PEBBLES, Prevention of Eczema By a Barrier Lipid Equilibrium Strategy; PGH, Pediatric Global Health; POEM, Patient Oriented Eczema Measure; PreventADALL, Preventing Atopic Dermatitis and ALLergies in Children; PROMIS, Patient Reported Outcome Measurement Information System; RCT, Randomized controlled trial; *S aureus*, Staphylococcus aureus; S, Sphingosine; SC, Stratum corneum; SCORAD, SCORing Atopic Dermatitis; SDI, Shannon Diversity Index; SEB, Staphylococcus enterotoxin B; sIgE, Allergen-specific IgE antibodies; SPT, Skin prick testing; TARC, Thymus and activation-regulated chemokine; TEWL, Transepidermal water loss; Th, T helper cells; TSLP, Thymic stromal lymphopoietin.

Brough and Nadeau are joint first authors and Leung and Lack are joint last authors.

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related allergic diseases, particularly food allergy. We present the experimental and human studies that have evaluated this approach and discuss various factors which may influence the success of these approaches, such as the type of emollient chosen for the intervention, the role of managing skin inflammation, and differences between primary and secondary prevention of atopic dermatitis to achieve the desired outcome.

KEYWORDS

atopic dermatitis, cutaneous sensitization, emollient, filaggrin gene, food allergy

1 | INTRODUCTION

Allergic diseases are the most common chronic diseases in Westernized countries and bear a substantial health and socio-economic burden. Atopic dermatitis (AD) affects approximately 20% to 30% of children.^{1–3} Asthma affects 9%–18%,^{4,5} and allergic rhinitis (AR) affects up to 40% of children.⁶ Food allergy (FA) is an epidemic among children in Westernized countries^{7–9} and significantly impairs quality of life.^{10,11} Between 15 and 40% of children with FA have experienced a severe, life-threatening allergic reaction and 30% report allergies to multiple foods.^{12,13} The rate of confirmed FA is much higher in children with AD.^{14–16} FA is expensive—resulting in \$24.8 billion dollars/year in expenditures to the healthcare system and US families,¹⁷ and in Europe, mean annual household costs were found to be €791 higher among households with a food-allergic child than those without food-allergic children.¹⁸

2 | PATHOGENESIS OF FOOD ALLERGY

The genesis of FA is a complex process, influenced by genes, host immune responses, epithelial function, and environment factors. Increased antibiotic use, nonvaginal births, ultra-sanitary lifestyles, less time spent outdoors, and the resulting “modern” microbial community structures of the gut and the skin, beginning at birth, have been implicated in aberrant immune system maturation, and development of atopy, including FA (Figure 1).¹⁹ For years, it was thought that children became sensitized to food allergens by exposure through the gut (via breastfeeding or early consumption)²⁰; there is now increasing evidence that early life allergen exposure through the skin causes FA (Figure 2),^{21,22} whereas early oral exposure causes tolerance (known as the dual-allergen exposure hypothesis: Figure 3). In the last 5 years, several studies have demonstrated allergen-specific oral tolerance induction to allergenic foods in high-risk children.^{23–27}

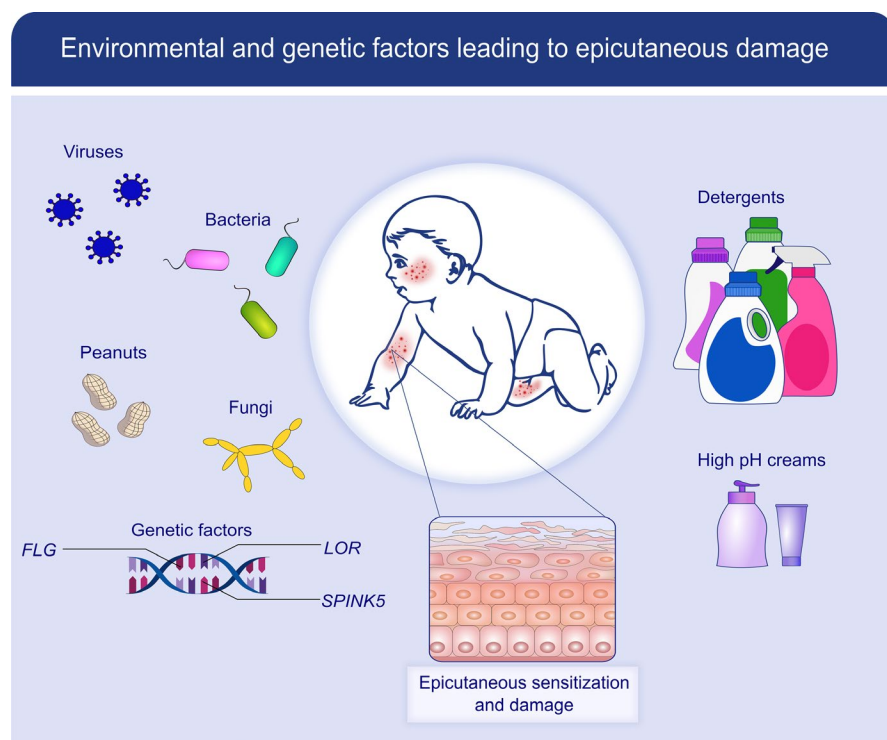


FIGURE 1 Factors leading to skin barrier dysfunction: The skin is constantly exposed to environmental factors, both natural (eg, bacteria, viruses, fungi, food, and aeroallergens) and man-made (eg, detergents, high pH creams and lotions). In those genetically predisposed to allergic disease (eg, filaggrin, SPINK5, and lorincrin gene mutations), these factors lead to skin barrier dysfunction, epicutaneous damage, and allergic sensitization

FIGURE 2 Pathways for skin barrier dysfunction and eczema leading to food allergy: Food allergy is manifested through the skin. (1) the initial step toward food allergy is skin barrier impairment caused by environmental pollutants, detergents, infections, and genetics. (2) Skin barrier impairment leads to skin inflammation and clinical atopic dermatitis. (3) Exposure of allergens through skin that has an impaired barrier (dry) or has clinical atopic dermatitis leads to sensitization and food allergy

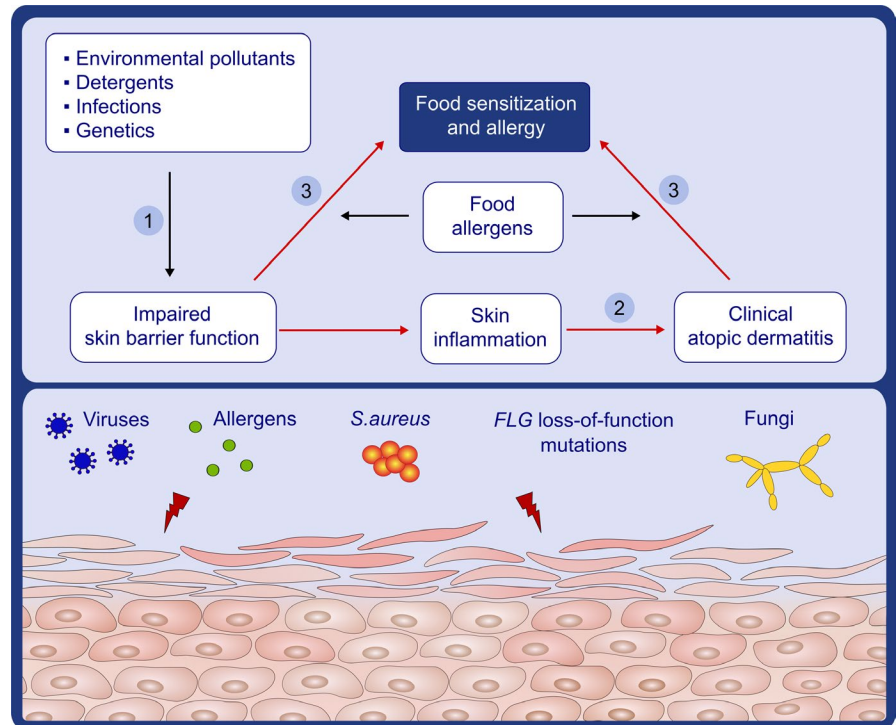
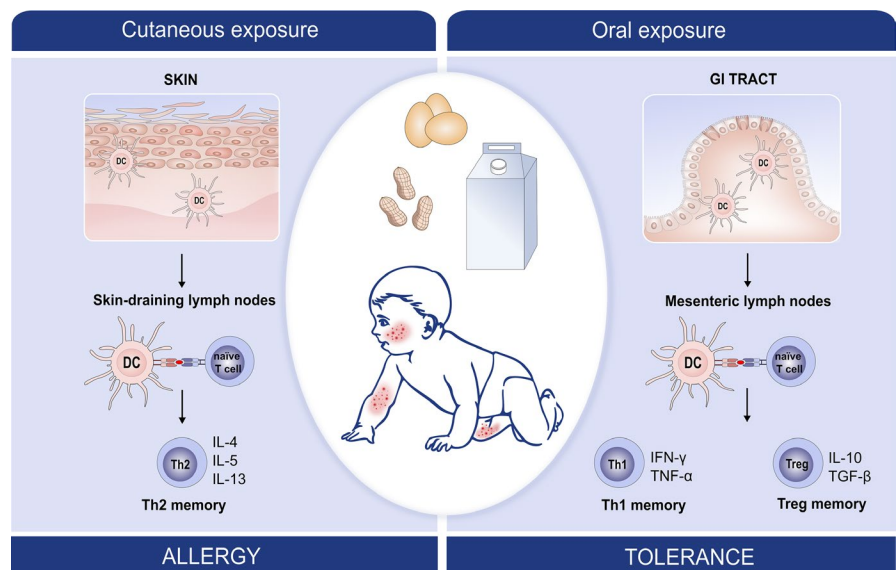


FIGURE 3 Dual-allergen exposure: Increasing evidence suggests that early life allergen exposure through the skin causes T-cell deviation toward a Th2 allergenic type and subsequent food allergy whereas early oral exposure causes T-cell deviation toward tolerogenic Th1 and Treg subtypes (dual-allergen exposure hypothesis)



3 | LIMITATIONS OF ORAL TOLERANCE INDUCTION

The effect of oral tolerance induction appears to be allergen-specific. For example, in the LEAP study, early peanut consumption did not lead to a prevention of tree nut or sesame seed allergy.²⁸ Since FA develops early in life,²⁹ there is a narrow window of opportunity to induce tolerance with oral introduction of multiple foods. In the HealthNuts population-based study, 3.1% of children already had challenge-proven peanut allergy (PA) by 12 months of age, and 9% were egg-allergic.¹ In addition, introduction of multiple allergenic foods into the diet of young infants is challenging. In the EAT study,

the adherence rate for introducing 6 allergenic foods into the diet was only 42%.³⁰ Thus, there is a need for an alternative approach to prevent FA.

There is evidence that diet diversity in infancy reduces food sensitization and allergic asthma (AA), but results for AD and AR are mixed.³¹ A systematic review found that breastfeeding was protective for AA; however, the evidence for AD and AR was weaker with no effect on FA.³² Other methods such as vitamin D supplementation have produced mixed results.^{33,34} There is little evidence for the role of prebiotics, and while meta-analyses and 2 individual studies show some benefit from prebiotics, these studies have issues such as objective evaluation of outcomes, design, and blinding.^{35,36}

4 | ATOPIC MARCH

AD is often associated with the subsequent development of allergic disease, including FA, AA, or AR, as characterized by the concept of the "atopic march."^{37–39} In the ALSPAC study, an oozing, crusting skin rash was an independent risk factor for the development of PA.⁴⁰ Furthermore, early-onset (particularly within the first 3 months), severe AD markedly increases the risk of FA.^{16,41,42} In the HealthNuts study, children with early-onset severe AD had a 50% rate of challenge-proven egg, peanut, or sesame seed allergy by 12 months of age. In the LEAP screening study,⁴³ there was a dose-dependent increase in food sensitizations with increasing SCORing Atopic Dermatitis (SCORAD) levels in children between 4 and 11 months of age. Duration of infantile AD prior to inducing remission with proactive topical steroid treatment has also been shown to increase the risk of FA for each month that passes.⁴⁴ This evidence suggests that shortening the duration of AD, by reducing inflammation, reduces the opportunity for epicutaneous exposure to environmental food allergens thereby preventing sensitization and subsequent FA.

5 | THE IMMUNE RESPONSE BEHIND FOOD ALLERGY

A dysregulated immune system involving a type 2 T helper (Th2) cell-mediated inflammatory response is associated with FA.^{45,46} This involves the formation of specific IgE antibodies against environmental and food allergens, as well as the production of several cytokines, including interleukin (IL)-3, IL-4, IL-5, IL-9, IL-13, IL-25, IL-31, IL-33, and thymic stromal lymphopoietin (TSLP).^{47–50}

The immune response in FA includes two phases.^{51,52} The sensitization phase (Figure 4)⁵³ is initiated when specific resident dendritic cell (DC) subsets capture allergens in the skin (also applicable to airways or gut) and transport the allergens to draining lymph nodes (LNs), where they are processed and presented to naïve CD4 + T cells. Within the LNs, in the presence of IL-4 and endothelial cell-derived type 2 cytokines, the T cells differentiate into allergen-specific CD4 + T cells producing high levels of IL-4 and IL-13. IL-4 and IL-13 favor B-cell isotype class switching to specific IgE and drives the production of IgE memory B cells (Figure 4).⁴⁷ Through facilitated antigen presentation, a very low concentration of allergen can drive complex formation between sIgE, allergen, and low-affinity IgE receptor on antigen-presenting B cells (CD23 + cells)⁵⁴; which then further drives Th2 cell proliferation, leading to further B-cell isotype switching and IgE production.⁵⁵ As the B cells mature, they differentiate into plasma cells and produce large amounts of allergen-specific IgE antibodies (sIgE) which bind to high-affinity FcεRI receptors on the surface of mast cells and basophils.

During this phase, a memory pool of allergen-specific B cells and allergen-specific CD4-positive T helper 2 cells are generated. More recently, a subset of Th2 cells (Th2A cells) have been suggested to play an important role in the allergic immune response.⁵⁶ Group 2 innate lymphoid cells (ILC2), which are found interspersed throughout barrier surfaces in the lung, gut, and skin, are also emerging as key regulators and effectors in type 2 immunity and tissue repair. They are enriched in human skin lesions, and ILC2 isolated from AD lesions, are activated by IL-33. They secrete proallergic cytokines, including IL-5 and IL-13 (Figure 5). IL-5 triggers the recruitment of eosinophils. IL-13 promotes recruitment of inflammatory cells,

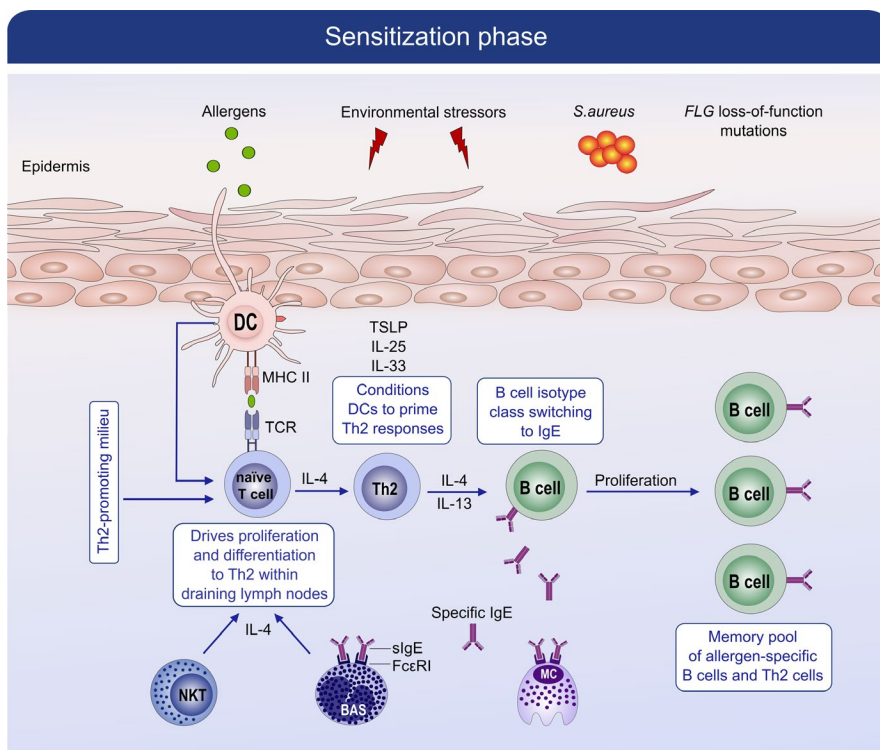
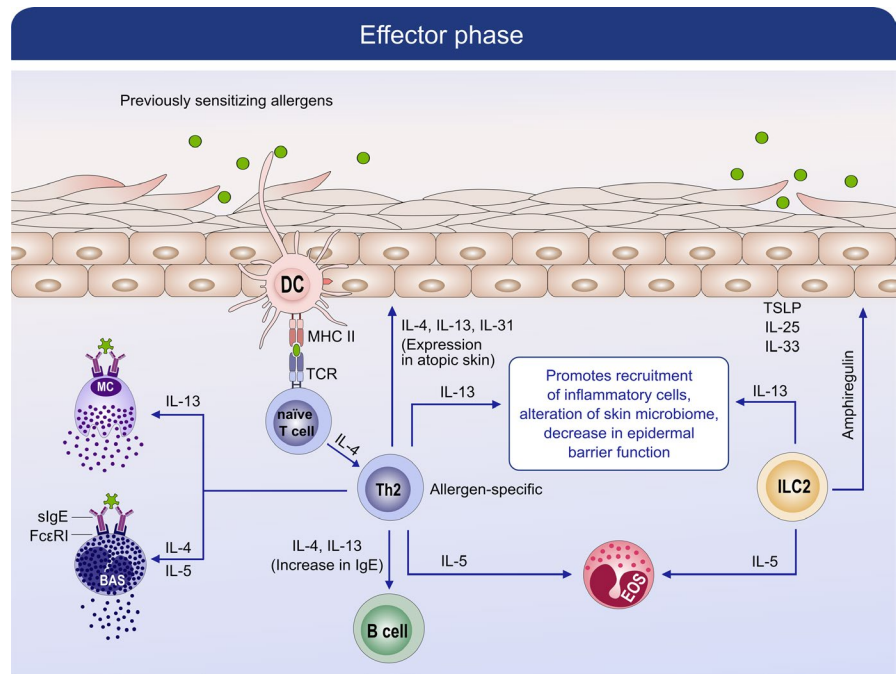


FIGURE 4 Mechanism of sensitization phase in allergic disease. During the allergic sensitization phase, in the setting of an impaired barrier, specific resident dendritic cell (DC) subsets capture allergens in the skin and transport the allergens to draining lymph nodes where they are processed and presented to naïve CD4 + T cells. Within the lymph nodes, the presence of IL-4 and IL-13 favors B-cell isotype switching to specific IgE cells that differentiate into plasma cells and produce large amounts of allergen-specific IgE antibodies (sIgE). The sIgE bind to high-affinity FcεRI receptors on the surface of mast cells and basophils. During the sensitization phase, a memory pool of allergen-specific B cells and allergen-specific CD4-positive T helper 2 cells are generated

FIGURE 5 Mechanism of effector phase in allergic disease. During the effector, which follows the sensitization phase, subsequent encounters with a previously sensitized allergen lead to IgE-cross-linking and activation of basophils and mast cells. Degranulation of mast cells and basophils leads to the release of preformed and de novo mediators which cause the symptoms of the immediate phase reaction as well as the subsequent late-phase reaction by activating memory allergen-specific Th2 cells



alterations in the skin microbiome, and decreases in epidermal skin barrier.^{57–59}

The effector phase (Figure 5) follows the sensitization phase and is triggered when the host subsequently encounters a previously sensitizing allergen and causes cross-linking of FcεRI receptor-bound IgE on sensitized mast cells and basophils leading to the release of preformed and de novo inflammatory mediators. These processes lead to the immediate phase reaction as well as subsequent late-phase allergic reaction through the activation of memory allergen-specific Th2 cells.⁴⁷ As these cytokines accumulate, allergen-specific Th2 cells are activated and produce IL-4, IL-5, and IL-13 among other cytokines. Recent evidence suggests that IL-13 is a key cytokine that drives peripheral inflammation in AD and is overexpressed locally, whereas IL-4 has a more central effect.⁶⁰ The cytokines maintain allergen-specific IgE levels, eosinophilia, mucus production, and recruitment of inflammatory cells to inflamed tissues leading to tissue damage.

6 | COMPONENTS OF IMMUNE SYSTEM LEADING TO EPICUTANEOUS SENSITIZATION

6.1 | Thymic stromal lymphopoietin (TSLP)

An important cytokine believed to play a role in epicutaneous sensitization through an impaired skin barrier is TSLP.⁶¹ TSLP is increased in the stratum corneum (SC) of patients with AD and is positively correlated with AD severity (using SCORAD).⁶² TSLP is highly expressed by the keratinocytes of children with AD⁶³ and by the epithelial cells of asthmatics.⁶⁴ TSLP-deficient mice are protected from developing allergic skin and airway inflammation following

antigen exposure,^{65–67} as well as intestinal food allergy,⁶⁸ which highlights the importance of this cytokine in allergic sensitization. Pro-inflammatory cytokines tumor necrosis factor- α (TNF- α) and IL-1 α , secreted in response to skin stripping,⁶⁹ or scratching, induce TSLP secretion in vivo from human keratinocytes.⁷⁰ TSLP levels increase following topical ovalbumin (OVA) application onto tape-stripped skin.⁷¹ TSLP expression correlates with Langerhans cell (LC) maturation, upregulation of the TSLP receptor on LCs, migration of LCs to skin draining LNs where they promote the differentiation of naïve Th cells to Th2 cells and Th2 proliferation.^{63,66,72} TSLP induces migration of Th2-skewed antigen-presenting cells (APCs) to the mesenteric LNs following tape stripping, providing evidence of a skin to gut migration.⁷³ These findings link TSLP to the early stages of epicutaneous sensitization: increased secretion of TSLP by skin disruption or epicutaneous allergen exposure interaction with LCs to prime T helper cells.

6.2 | Interleukin 33 (IL-33)

IL-33 is another epithelial cytokine that is released in response to defects in skin barrier surfaces characterized by AD.⁷⁴ IL-33 is a member of the IL-1 cytokine family and is expressed in epithelial barrier tissues as well as lymphoid organs and plays an important role in triggering allergic inflammation after exposure to allergens.⁷⁵ IL-33 levels are increased in the skin lesions and serum of individuals with AD^{76,77} and in mouse skin following epicutaneous sensitization with OVA.⁷⁶ IL-33 polarizes skin-derived DCs and innate lymphoid cells to drive type 2 cytokine production following epicutaneous sensitization to peanut extract,⁷⁸ promotes increased secretion of IL-5 and IL-13 by in vitro-polarized Th2 lymphocytes,⁷⁹ and contributes to elevated serum IgE levels and eosinophilia when injected in vivo.⁸⁰

A study exploring the role of IL-33 in epicutaneously sensitized FA found IL-33 to be essential for inducing IgE-dependent anaphylaxis; IL-33-deficient mice and mice treated with soluble IL-33 receptor blocker were protected from oral challenge-induced anaphylaxis.⁸¹ Another study by Galand et al demonstrated increased local and systemic release of IL-33 following mechanical skin injury induced by tape stripping in mice⁸²; IL-33R (ST2) deficiency or ST2 blockade prior to oral challenge significantly reduced the severity of food-induced oral anaphylaxis. The existing evidence suggests that IL-33 plays a key role in epicutaneous sensitization followed by subsequent food-induced anaphylaxis. Neutralization of IL-33 has also been shown as a promising strategy for the treatment for FA and AD.^{83,84}

7 | EXPERIMENTAL MODELS OF EPICUTANEOUS SENSITIZATION

Several animal models have shown that epicutaneous exposure to specific food allergens induces a potent allergic type 2 immune response, associated with IL-4 secretion by T cells from draining LNs and high levels of allergen-specific IgE by B cells.^{85–87} In addition, epicutaneous sensitization to food allergens has been shown to lead to systemic food-allergic reactions, including anaphylaxis, on subsequent oral exposure.⁷¹ Bartnikas et al demonstrated that epicutaneous OVA and/or peanut application onto tape-stripped skin of BALB/c mice led to intestinal mast cell expansion, increased serum IL-4, and food-induced anaphylaxis.⁷¹ Following epicutaneous sensitization, systemic anaphylaxis was induced by a single oral challenge with allergen. Conversely, oral immunization with the cholera toxin (CT) adjuvant failed to induce anaphylaxis on subsequent oral challenge.⁷¹ In other experimental models of IgE-mediated anaphylaxis where mice were sensitized by intraperitoneal (IP) OVA injection with alum adjuvant, anaphylaxis was much harder to elicit on oral challenge, only after multiple oral challenges.^{88,89} This demonstrated that epicutaneous sensitization primes the gut in a more effective manner for subsequent allergic reactions than oral or IP sensitization. When Bartnikas et al performed epicutaneous sensitization in IgE-deficient mice, there was no intestinal expansion of mast cells, no rise in serum IL-4, and no features of anaphylaxis on intragastric challenge, which suggested that the effects arising from epicutaneous sensitization are IgE-dependent.⁷¹ Th2 cytokines IL-4 and IL-13 have also been investigated in experimental food allergy models of epicutaneous sensitization; whereas mice deficient in IL-4 (genetically bred or in the presence of anti IL-4-blocking antibodies) were still able to mount Th2 responses following epicutaneous exposure,^{90,91} IL-13-deficient mice (IL-13^{-/-}) were not.⁹²

In a more recent study by Geha et al,⁹³ mechanical skin injury alone not only promoted cutaneous sensitization to foods, but also expanded and activated intestinal mast cells, thus promoting anaphylaxis in mouse models. Mechanical skin injury causes systemic release of IL-33, which interacts directly with mast cells through the ST2 receptor,⁹⁴ and leads to expansion of both mucosal and submucosal mast

cells in the jejunum.⁹³ Additionally, cutaneous injury led to increased intestinal permeability. The increase in intestinal mast cells as well as permeability that is elicited by mechanical skin injury or scratching may play a significant role in promoting anaphylaxis in patients with FA and AD. In another study by Kawasaki et al⁹⁵ the authors demonstrated that inflammation from skin barrier disruption alone can worsen symptoms of FA even when the exposure to the allergen is removed. BALB/c mice were sensitized epicutaneously by repeated application of OVA through disrupted skin. After the first oral challenge, the skin barrier was further disrupted, and a second oral challenge was performed. Skin barrier disruption amplified the allergic reactions induced by the oral challenge, whereas topical pretreatment with dexamethasone reduced allergic reactions.⁹⁵ These studies highlight the role that a disrupted skin barrier plays in the development of FA and which may also contribute toward the severity of reactions.

Experimental models have carefully evaluated whether the skin barrier needs to be disrupted to achieve epicutaneous sensitization. In most models, mice only developed epicutaneous sensitization with the application of peanut or OVA onto abraded skin.^{85–87,90,96} Conversely, application of peanut or OVA onto intact skin, or bypassing the SC (via subcutaneous skin layer) led to nonallergic responses.⁸⁵ In a recent experimental model, repeated applications of roasted peanut extract onto intact skin induced sensitization to the major peanut allergens Ara h 1 and Ara h 2 and anaphylaxis upon IP peanut rechallenge.⁷⁸ The authors postulated that peanut protein was able to sensitize through the skin without the need for SC disruption or an adjuvant, because peanut protein itself had adjuvant properties. In support of this, they showed that peanut antigen led to bystander sensitization for the milk allergen α -lactalbumin. Having previously shown that application of milk allergen α -lactalbumin onto intact skin did not lead to sensitization or allergy on rechallenge, the authors then showed that concomitant application of peanut protein in addition to milk allergen α -lactalbumin onto intact skin led to anaphylaxis on subsequent oral exposure to milk allergen α -lactalbumin.⁷⁸ In contrast, Walker et al showed that, in filaggrin (FLG)-deficient mice, epicutaneous sensitization to peanut or OVA required costimulation with *Alternaria alternata* or house dust mite extract.⁹⁷

8 | BARRIER DYSFUNCTION AND ITS ROLE IN AD AND FA

The discovery that FLG loss-of-function mutations, which have an important role in formation and integrity of the SC, are highly associated with AD and xerosis (dryness), was a major milestone in understanding AD as a “barrier” disease.^{98,99} Experimental models have shown that filaggrin protein deficiency in the skin leads to facilitated entry of irritants, pathogens, and allergens, thereby eliciting an inflammatory response (Figure 1).^{100,101} Similarly, decreased epithelial nasal barrier function has been shown to facilitate trans-epithelial allergen passage, allergic sensitization, and allergen-induced mast cell degranulation.¹⁰² Thus, barrier impairment may

itself lead to a maladaptive immune system with a predisposition toward atopy.

The local cytokine milieu has also been shown to affect *FLG* expression in the skin.^{115,116} Filaggrin protein expression was assessed in the skin of 69 patients with at least one *FLG* loss-of-function mutation; filaggrin protein was reduced in noninflamed skin and even further in acute AD lesions. Keratinocytes cultured in the presence of IL-4, IL-13, and/or IL-22 had reduced *FLG* expression, whereas those cultured in presence of IFN- γ had increased *FLG* expression.^{117,118} Taken together, these studies show that skin barrier abnormality due to *FLG* loss-of-function mutations can enhance allergen penetration thus favoring Th2 inflammation. On the other hand, Th2 inflammation can impair skin barrier function via a reduction in filaggrin protein expression, leading to a vicious cycle of inflammation and skin barrier disruption.

There has been conflicting research as to whether *FLG* mutations alone increase the risk of FA, in the absence of AD or other factors. Brown et al showed a significant association between *FLG* loss-of-function and challenge-proven IgE-mediated PA, even after adjusting for AD, in cohorts from the UK, the Netherlands, Ireland, and Canada.¹⁰⁵ However, in infants, both the HealthNuts study and the EAT study showed that although *FLG* null mutations increased the odds of food sensitization, it did not significantly increase the odds of FA.^{119,120} Venkataram et al¹²¹ explored the longitudinal relationship between *FLG* mutations and FA; path analysis suggested an association between *FLG* mutations and AD in younger children and the progression to food-allergic sensitization and FA in older children.

Beyond filaggrin, there are multiple other components of the skin barrier that may have a role in AD and FA.¹²² Mutations in the corneodesmosin gene lead to peeling skin disease associated with severe skin barrier defect, pruritus, and FA.¹²³ Peeling skin disease shares clinical features with Netherton syndrome which is caused by *SPINK5* mutations as well as patients with mutations in the transglutaminase 5 gene and desmoglein gene.^{124,125} Importantly, type 2 immune activation is associated with global downregulation of skin barrier genes including filaggrin, loricrin, and involucrin, thereby allowing food allergens to penetrate through the skin.¹²⁶

Environmental factors, such as detergents and microplastics, also have an effect on epithelial barrier function. Anionic surfactants and commercial detergents have been shown to decrease tight junction barrier integrity in human keratinocytes¹²⁷ and human bronchial epithelial cells,¹²⁸ potentially increasing the risk of atopic disease. Surfactants have been shown to disrupt the lamellar architecture in the SC.¹²⁹ In a mouse model, Ochi et al showed that detergent-mediated skin damage promoted IgE/IgG1 responses and Th2 differentiation when epicutaneously sensitized to papain, a protease allergen. They also found that TSLP and IL-33 contributed to epicutaneous papain sensitization and the atopic march upon subsequent airway challenge with the protease allergen.¹³⁰ In humans, application of traditional alkaline soaps increased transepidermal water loss (TEWL) and skin erythema,

which are signs of prolonged damage to the skin barrier.¹³¹ The environmental damage caused by plastics is well documented; however, the role of microplastics, which have become ubiquitous in the environment, on human health is poorly understood. It is in our air, our water, and in the foods we eat. It is within us and has been detected in human lungs and feces. Ingestion of microplastics has been implicated in gut dysbiosis through mechanical disruption and microbiome alterations leading to inflammatory responses.¹³² An in vitro study of peripheral blood mononuclear cells found that high exposure to polypropylene microplastics (~20 μ m and 25–200 μ m) increased histamine levels.¹³³ In an in vitro model of human epithelial colorectal cells, researchers found that exposure to microplastics upregulated transcriptional factors involved in cell inflammation and proliferation. The chronic exposure to low doses of microplastics has the potential to induce epithelial cell injury and alterations to intestinal barrier function.¹³⁴ In a study of human lung epithelial cells, researchers found that exposure to inhaled polystyrene microplastics causes inflammatory and oxidative injury along with the disruption of intercellular junction proteins in the lung, potentially leading to pulmonary barrier dysfunction.¹³⁵

9 | IN VITRO MEASURES OF EPICUTANEOUS SENSITIZATION

In vitro evidence has shown that PA correlates with peanut-specific proliferation in the skin-homing memory T-cell subset, suggesting that sensitization occurs through the skin.^{136,137} The differential peanut-specific Th cell proliferation in peanut-allergic versus peanut-tolerant children was assessed using homing markers on CD4 + Th cells for the skin (cutaneous lymphocyte antigen: CLA+) and gut-associated-lymphoid tissue (integrin α 4 β 7+) as markers for the route of initial sensitization to peanut.¹³⁶ Peanut-specific Th cell proliferative responses were higher in CLA + Th cells in peanut-allergic children than peanut-tolerant children. Cytokine responses from CLA + peanut-specific Th cells in peanut-allergic children showed a trend toward Th2-polarization (IL-13 and IL-4 secretion), whereas responses from α 4 β 7 + peanut-specific Th cells in peanut-tolerant children trended toward Th1 (IFN- γ and TGF- β), suggesting that the origin of peanut sensitization occurs in the skin (Figure 3). Sensitization through the skin may be explained by the route of exposure to food allergens via the environment (dust and surfaces) or through transfer of the food allergen through hand-body contact, which is explored further below.

10 | ENVIRONMENTAL EXPOSURE TO ALLERGENS IN HUMANS

In humans, several observational studies have shown an association between epicutaneous and environmental exposure to peanut

allergens and the development of peanut sensitization^{22,138,139} and challenge-proven PA.^{40,106,139} One of the first studies to highlight the risk of epicutaneous peanut exposure was the ALSPAC birth cohort, where topical creams containing peanut ("Arachis") oil applied onto the skin of children with AD was an independent risk factor for the development of PA (peanut skin prick test (SPT) >8 mm or sIgE > 15k U/L).⁴⁰ Among PA children with AD in the ALSPAC study, 90% had been topically exposed to creams containing *Arachis* oil in the first 6 months of life.⁴⁰ In another study, household peanut consumption was used as an indirect marker of environmental peanut exposure.¹⁰⁶ Peanut-allergic children had a 10-fold higher level of household peanut protein consumption (18.8 g/wk) than high-risk egg-allergic children without PA (1.9 g/wk) ($P < .0001$) and threefold higher level than nonatopic children without PA (6.9 g/wk) ($P < .0001$).¹⁰⁶ Peanut butter consumption was more highly associated with PA than covered forms of peanut foods (eg, chocolate peanuts); the authors postulated that environmental peanut exposure was exerting its impact through the skin, as peanut butter is sticky and therefore more likely to be transferred onto the skin of infants. In support of the dual-allergen exposure hypothesis, infants who had eaten peanut in the first year of life were not affected by environmental peanut exposure. Subsequent studies showed that household peanut consumption is highly correlated with the concentration of peanut in the dust of an infants bedsheet and play area, even if the infant does not eat peanut.¹⁴⁰

Further work analyzing peanut dust concentration in infants with AD, milk, and/or egg allergy showed that, for every unit increase in peanut dust concentration from the living room floor, there was a 1.97-fold increase in peanut sensitization and 2.34-fold increase in PA.²² In a population-based study, children carrying at least one *FLG* loss-of-function mutation were at increased risk of developing PA if they had high environmental peanut exposure in their bed-dust around the time of birth;¹³⁹ for each unit increase in peanut dust concentration during infancy, there was a sixfold increase in school-age peanut sensitization and a 3.3-fold increase in school-aged PA.¹³⁹ In another population-based Swedish study, environmental peanut exposure in high-risk children (based on parental atopy or egg sensitization), increased risk of school-aged peanut sensitization.¹³⁸ Based on this research, one could postulate that reducing environmental exposure to peanut (and potentially other allergenic foods), in high-risk children might reduce the risk of sensitization and allergy; however, this has not been proven. Additionally, peanut levels in areas outside the home are also high (for example in schools)¹⁴¹; thus, an environmental allergen reduction approach may be difficult to implement. In summary, only high-risk children (those with an impaired skin barrier, egg allergy, or predisposition toward atopy) seem to be at risk of peanut sensitization from high environmental peanut exposure, which has important ramifications for future research in this field. Interestingly, associations between impaired skin barrier and allergy may also be pertinent for inhalant allergies; environmental cat exposure

around the time of birth was found to increase the risk of indoor allergen sensitization in children with at least one *FLG* loss-of-function mutations.¹⁴²

11 | THE ROLE OF THE MICROBIOME IN EPICUTANEOUS SENSITIZATION

With growing evidence that food sensitization can occur through the skin, more attention has been paid to dysbiosis of the skin microbiome as a risk factor for AD and FA.¹⁴³ Skin commensals have been found to be essential for resident T cells and they educate keratinocytes to become effective in combating skin pathogens. Conversely, commensals also appear to be required so that the host does not attack normal colonizing flora. Microbial dysbiosis has been observed in infants with AD,^{144,145} particularly with *S aureus* colonization.¹⁴⁶ In a study using minimally invasive skin tape stripping, shotgun metagenomic studies revealed that the skin of AD FA + children was colonized with *S aureus*.¹¹² In contrast, topical transplantation of commensal bacteria from healthy volunteers to patients with AD improved AD severity and reduced topical steroid use; this forms the basis for further work in this area.^{147,148}

Schwartz et al identified a critical role for the microbiome in mice with an impaired skin barrier. The authors reported on their observation of skin inflammation in *FLG*-mutant (*FLG^{fl/fl}*) mice triggered by the interplay between the microbiome; specifically, they reported a shift toward pathogenic staphylococci, IL-1 β , and mast cells.¹⁴⁹ Further experimental models have shown that applying *Staphylococcus enterotoxin B* (SEB) on skin enhances allergic responses to food antigens.^{150–153}

In humans, *S aureus* colonization is significantly associated with AD severity, persistence, and subsequent deterioration of AD.¹⁵⁴ Tsilochristou et al showed the importance of *S aureus* in driving AD severity and specific IgE to cow's milk, hen's egg, and peanut, independent of AD severity in the LEAP study.¹⁵⁴ Additionally, *S aureus* colonization at any time was associated with prevention of acquisition of natural tolerance to hen's egg, and the disruption of oral tolerance induction to peanut.¹⁵⁴ Taken together, these studies highlight the role of *S aureus* dysbiosis in children with AD, on AD severity and risk of AD deterioration, in addition to increasing risk of sensitization to food, enhanced allergic responses, persistence of FA, and inhibition of oral tolerance induction.

12 | PHENOTYPIC MEASURE OF SKIN BARRIER DYSFUNCTION

Functional assessment of the integrity of the epidermis using TEWL has been shown to predict subsequent development of AD regardless of *FLG* mutation status.^{155,156} Raised TEWL has also been

associated with food sensitization (even after adjusting for AD and *FLG* mutation status) in young infants.¹⁵⁷ Increased TEWL may reflect the spectrum of genetic and environmental factors leading to barrier impairment, such as water hardness,^{158,159} frequency of washing, and commercial detergents (known to decrease tight junction barrier integrity in human keratinocytes).^{127,128} These findings are being assessed in randomized controlled trials (RCTs) to prevent AD such as the SOFTER (Softened Water for Eczema Prevention) trial.¹⁶⁰

If the skin barrier is impaired, more water evaporates from the skin enabling allergens, irritants, and bacteria to penetrate the skin.¹⁶¹ Carriage of a *FLG* loss-of-function mutation is associated with increased TEWL at three months, even in the absence of AD,¹⁵⁷ suggesting this already shows a predilection toward skin barrier impairment which could subsequently lead to clinical AD. TEWL at 2 days and 2 months was shown to predict AD at 12 months,¹⁰⁹ and subsequently, the same group showed that raised TEWL predicts FA at 2 years of age.¹¹⁰ In a recently published study, it was shown that TEWL after skin tape stripping separated AD with FA vs AD without FA.¹¹²

13 | IDENTIFYING SKIN BARRIER MARKERS TO PREDICT FOOD ALLERGY

A minimally invasive skin tape-stripping measure of the SC in combination with a comprehensive multi-omics approach was used to determine whether AD with FA (AD FA+) children have skin biomarkers which distinguish them from AD without FA and nonatopic children.¹¹² Despite similar skin disease severity, the SC integrity and *FLG* content were significantly lower in children who were AD FA+ vs. AD FA-. Lipidomics of the SC in the AD FA+ group revealed a relative reduction in esterified ω -hydroxy fatty acid (EO) sphingosine (S) ceramides (CER) which are ultra-long-chained ceramides (EOS CER) required for normal skin barrier function. At the same time, a significant increase in non-hydroxy fatty acid sphingosine ceramide levels was observed in AD FA+ skin samples, resulting in a disproportionate decrease in EOS CER in the skin. Transcriptome studies of the skin tape also revealed the AD FA+ skin samples expressed the highest type 2 immune expression levels.

Interestingly, STS proteomics revealed an immature keratin profile consistent with keratinocyte hyperproliferation in the SC of AD FA+ participants. A network analysis demonstrated that keratin 5, 14, and 16 expression and reduced filaggrin breakdown products (urocanic acid) were strongly correlated with AD FA+, with increased TEWL, and were the most important predictors of AD FA+.¹¹² These data support the importance of skin barrier dysfunction in the pathogenesis of epicutaneous sensitization to environmental foods and may contribute to the persistence or severity of FA by chronically stimulating type 2 immune responses in the skin.

14 | THE ROLE OF EMOLLIENTS TO PREVENT THE DEVELOPMENT OF FOOD ALLERGY

Based on the body of evidence that sensitization occurs through the skin, it would be logical to assume that reducing both severity and duration of AD could potentially reduce the incidence of FA. The summary of the different pilot studies is presented in Table S1. These pilot studies were then followed up by larger RCTs trials; these are presented in Tables 1 (nonlipid emollients), 2 (emollients containing at least one ceramide), and 3 (emollients containing a combination of emollients and topical steroids). A more detailed version of the trials is presented in Table S2. Table S3 lists emollients that have been tested in clinical trials. Pilot studies showed that standard petrolatum-based moisturizers could reduce AD by up to 50%, primarily by enhancing skin hydration.^{107,108} An RCT by Yonezawa et al found statistically lower TEWL, diaper dermatitis, and risk of dry facial or body skin in the interventional group (1-2 applications per day for 12 weeks with a moisturizer containing either paraffin or alcohol/ceramide, $n = 114$) than in the control group ($n = 113$).¹⁶² Conversely, the BEEP (Barrier Enhancement for Eczema Prevention) and PreventADALL (Preventing Atopic Dermatitis and ALLergies in Children) RCTs (Table 1) evaluated whether including petrolatum-based oils in baths or applying petrolatum-based moisturizers from the first few weeks of life (and small "tastes" of allergenic foods in PreventADALL) could prevent AD and FA. Both studies showed no significant reduction in the incidence of AD, and in the BEEP study, there was an increased rate of infections and a trend toward increased food allergy in the intervention group.^{113,114} Similarly, an RCT by Dissanayake et al compared the incidence of AD and FA in the first year of life in infants treated with synbiotics and an emollient (alone or in combination) and controls and found no statistical difference.¹⁶³ The negative findings in these studies were surprising given the pilot study findings, and the authors discussed various reasons as to why this might have occurred including low adherence rate with the intervention (especially PreventADALL), contamination of the control arm (BEEP), and the type of emollient used. The PEBBLES (Prevention of Eczema By a Barrier Lipid Equilibrium Strategy) pilot study (Table 2) used a ceramide-containing trilipid cream (Table S1) for 6 months and demonstrated a reduction in investigator observed AD at 12 months, and food sensitization at 6 and 12 months of age (Figure 6).¹¹¹ Per-protocol analyses showed that in infants who received ≥ 5 days per week of treatment (twice-daily trilipid cream), 0% (0 of 21) of children developed food sensitization compared to 19% (7 of 36) in the control group. Miyaji et al's retrospective cohort study⁴⁴ (Table S1) showed that in infants with moderate-severe AD, proactive topical steroid treatment commenced by 4 months of age versus after 4 months of age was associated with an almost twofold reduction in FA by 24 months (46.3% in the delayed steroid treatment group versus 25.3% in the early steroid treatment group ($P = .01$)). A number of emollient studies

TABLE 1 Randomized trials assessing nonlipid-based emollients for atopic dermatitis

Prevention type	RCT Author and Study Name	Participant Number and Study Arms	Population	Emollient
Primary	Blume-Peytavi, U et al Atopic Dermatitis in Atopy Predisposed Infants (ADAPI) NCT02906475	160 2 arms	0-14 d of age Term newborns 18-to 45-year-old moms Birthweight 2.5 to 4.5 Kg I, II, III, IV Fitzpatrick classification Parent or sibling with physician-diagnosed AD, AR, or AA Must be breastfed and/or on cow's milk-based formula	Milk lotion (no details about brand(s) or ingredients provided)
Primary	Hourihane, JO et al Short-term Topical Application to Prevent Atopic Dermatitis (STOP AD). NCT03871998	242 2 arms	Full-term healthy infant Up to 5 d of age 1st-degree relative with AD, AR, AA, or FA	Commercially available moisturizer (no details about brand(s) or ingredients provided)
Primary	Chalmers, JR et al Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. ¹¹³ ISRCTN21528841	1394 Control group (skin care advice only):701 Intervention group (skin care advice + emollient): 693	Up to 3 wk of age 1st-degree relative with physician-diagnosed AD, FA, AR.	Choice between Doublebase Gel® (Dermal Laboratories Ltd.) & Diprobase Cream® (Merck Sharp & Dohme Ltd.)— paraffin-based without alcohol or lipids
Primary	Skjerven, HO et al Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial ¹¹⁴ NCT02449850	2701 1 of 4 similar sized groups: No intervention Skin care (oil bath and Ceridal face cream) Consecutive introduction (3-4 mo of age) of peanut, milk, wheat, and egg>= 4 d/ wk complementary to breastfeeding Both interventions	Infants General population	Ceridal face cream (alcohol and polyethylene glycol) in skin care group and dual intervention group

Abbreviations: EASI: Eczema Area and Severity Index; IDQoL: Infants' Dermatitis Quality of Life; POEM: Patient Oriented Eczema Measure; RCT: randomized controlled trial.

for prevention of atopic diseases are ongoing (eg, NCT02906475, NCT03871998, NCT03409367, and NCT03667651), and results have not been published (Tables 1 and 2).

Although the experimental and mechanistic studies, to date, build a strong case toward targeting the skin to prevent AD to thereby FA, two large preventative emollient RCTs have been

Duration, Frequency, and Location	Outcome measures	Results
12 mo Applied once daily to entire body and face + Bathing addendum if needed.	Primary: Cumulative AD incidence at 12 mo Secondary: Cumulative AD incidence at 24 mo EASI at 12 and 24 mo IDQoL at 12 and 24 mo TEWL, skin surface pH, and stratum corneum hydration on mid-alveolar forearm at 14 d, 1, 3, 6, 12, and 24 mo.	Study ongoing—no results published to date.
2 mo 2x daily full-body application by intervention group. Standard skin care advice with no moisturizer application in control group.	Primary: Cumulative incidence of AD at 12 mo. Cumulative incidence of IgE-mediated food allergy at 24 mo. Secondary: TEWL and Natural Moisturizing Factor measured at birth, 2, 4, and 8 wk and at 6 and 12 mo. Microbial community and skin biomarker analysis in a subset of study participants, comparison of changes over 1st year between cheek and antecubital fossa and between intervention and control group.	Study ongoing—no results published to date.
12 mo >=1x daily	Primary: Blinded assessment of AD at 24 mo of age using UKWP diagnostic criteria. Secondary: Time to onset of AD. Severity of AD based on EASI & POEM. Confirmed diagnosis of FA at 24 mo to milk, egg, and/or peanut (parental report, allergic sensitization, food challenge—if required). Parental report of clinical diagnosis of any FA between 12 and 24 mo. Safety and cost-effectiveness of prevention strategy. Role of FLG genotyping as possible stratifier of response to emollient intervention.	No statistically significant difference in AD: present at age 2 (within the past year) in 150 (25%) of 612 in control group and in 139 (23%) of 598 in intervention group (adjusted RR 0.95 [95% CI 0.78 to 1.16]; $P = .61$). Subgroup analyses (number of 1st-degree relatives with AD, AA, or AR, FLG genotype, season of birth, water hardness, and probiotic use) also showed no statistically significant differences. Adherence was considered satisfactory in only 51% of intervention group (all of those who did not complete any questionnaires were assumed as not using emollient). Adherence was considered satisfactory at 70% (311 of 442) in those who completed all questionnaires. Adherence in intervention group decreased with each time-point: 466 (88%) of 532 had satisfactory adherence at 3 mo, 427 (82%) of 519 at 6 mo, and 375 (74%) of 506 at 12 mo.
9 mo >= 5 d/wk	Primary: AD assessed first at 12 mo FA to intervention food assessed first at 36 mo Secondary: Recurrent wheeze or AA, allergic sensitization, allergy to other foods, anaphylaxis, and AR	Study closed to recruitment but ongoing for FA assessment. No statistically significant difference in AD: present in 478 (8%) of 596 infants in control group, 64 (11%) of 575 in skin intervention group, 58 (9%) of 642 in food intervention group, and 31 (5%) of 583 in combined intervention group. Risk difference of 3.1% (95% CI -0.3 to 6.5) for skin intervention versus control and 1.0% (-2.1 to 4.1) for food intervention versus control. Reports of Itching, dry skin, and urticaria were similar in all groups.

disappointingly negative (BEEP and PreventADALL); there are several reasons why they might not show a significant effect, as outlined below:

1. The age at which emollients were first applied: If emollients are applied after significant sensitization has progressed, it may difficult to prevent FA. In PEBBLES (Table 2), reduction

TABLE 2 Randomized trials assessing at least one ceramide-containing emollient for atopic dermatitis

Prevention type	RCT Author & Study Name	Participant Number & Study Arms	Population	Emollient	Duration, Frequency, & Location
Primary	Yonezawa K, et al Effects of moisturizing skincare on skin barrier function and the prevention of skin problems in 3-month-old infants: A randomized controlled trial ¹⁶²	227 Control group: 113 Intervention group: 114	1 wk to 3 mo of age	For bathing, Pigeon baby soap [Pigeon, Tokyo, Japan] or Kewpie baby body soap, Cow Brand Soap [Kyoushinsha, Tokyo, Japan]. As moisturizer in intervention group: Pigeon baby milk lotion [Pigeon] or Atopita Milky Lotion© [Tampei Pharmaceutical, Tokyo, Japan].	12 wk Application 1-2x daily with bathing every 2 d in intervention group vs Daily bathing without moisturizer in control group.
Primary	Eric Simpson A Community-based Assessment of Skin Care, Allergies, and Eczema (CASCADE). NCT03409367	1250 2 arms	Up to 2 mo of age Born at > 25 wk of gestation	Choice of over-the-counter lipid-rich emollient (Vaseline/Vanicream/ Cerave healing ointment/ Cerave cream/ Cetaphil cream)	24 mo Once-daily full-body application
Primary	Dissanayake et al Skin care and synbiotics for prevention of AD or FA in newborn infants: A 2 x 2 factorial, randomized, nontreatment controlled trial. ¹⁶³	605 pregnant women recruited - 549 infants enrolled Randomized into 4 treatment arms: Skin care and synbiotics. (n = 137) Synbiotics only (n = 137) Skin care only (n = 138) No intervention (n = 137)	Infants	Locobase® REPAIR cream (Daiichi Sankyo, Japan)	6 mo 2-3x daily
Primary	Lowe A, et al PEBBLES study protocol: RCT to prevent AD, FA and sensitization in infants with a family history of allergic disease using a skin barrier improvement strategy. ¹⁷¹ Phase III ACTRN126170 01 380 381 NCT03667651	760 2 arms (380 in each)	Up to 3 wk of age. 1st-degree relative has a self-reported hx of AA, AD, hay fever/AR or FA.	EpiCeram®	6 mo 6 grams 2x daily

Abbreviations: OFC: oral food challenge; RCT: randomized controlled trial;TARC: thymus and activation-regulated chemokine.

Outcome measures	Results
Primary: TEWL, SCH, skin pH, and sebum secretion at 3 mo of age. Secondary: Incidence of skin problems (eg, diaper dermatitis) at 3 mo of age.	Statically significant lower TEWL (mean $\pm$ SD, 14.69 ± 7.38 vs 17.08 ± 8.26 g/m ² per h, $P = .033$) and higher face SCH (60.38 ± 13.66 vs 53.52 ± 14.55 , $P = .001$) and higher body SCH (58.89 ± 12.96 vs 53.02 ± 10.08 , $P < .001$) in intervention vs. control group. Diaper dermatitis at 1-3 mo of age significantly lower in intervention vs. control group (6.3% vs 15.9%, $P = .022$; RRR = 0.399 [95% confidence interval [CI], 0.174-0.919]). Skin problems at 1-3 mo of age significantly lower in intervention vs. control group (42.1% vs 55.2%, $P = .064$; relative risk ratio, 0.762 [95% CI, 0.569-1.021]). Risk of dry facial skin was reduced with intervention by 48.4% (relative risk ratio, 0.516; 95% CI, 0.333-0.799)). Risk of dry body skin was reduced with intervention by 39.7% (relative risk ratio, 0.603; 95% CI, 0.399-0.911).
Primary: Cumulative incidence of AD at 24 mo of age. Secondary: AD diagnosed by Children's Eczema Questionnaire (CEQ) at 12 and 24 mo. Any prescription topical medication or over-the-counter hydrocortisone usage. Parental report at 3, 6, 9, 12, 15, 18, and 24 mo of provider-diagnosed AD and sleep loss of infant. Parental report of immediate food allergy symptoms or a provider diagnosis of food allergy that was confirmed by prick testing or IgE blood test at 12 and 24 mo. Asthma risk using a modification of the asthma predictive index (API) at 12 and 24 mo. Global Health Status using one question from the PROMIS PGH-7 instrument at 12 and 24 mo. Atopic dermatitis severity as measured by parental report of eczema, age of onset. Time to onset of AD as measured by provider-recorded date of first diagnosis retrieved from review of health record. AD symptom severity as reported by POEM. Atopic dermatitis severity by parent-reported global severity of eczema assessment. IDQoL instrument	Study ongoing—no results published to date.
Primary: Development of AD at 1 y of age Secondary: Prevalence of FA, as reported in the questionnaires at 1 y Sensitization to any food or inhalant allergen at 9 mo of age EASI score at 9 mo of age TARC score at 9 mo of age	Cumulative incidence of AD (itchy skin condition lasting 2 or more mo) at 12 mo of age: 30.9% in group 1, 32.1% in group 2, 38.6% in group 3, and 25.6% in group 4—No statistically significant difference. Incidence of AD AS DEFINED BY UKWPC was 20.4% in group 1, 14.7% in group 2, 21.0% in group 3, and 18.8% in group 4— No statistically significant difference. No statistically significant difference in AD incidence after adjusting for emollient application rate (80% of the parents/guardians in the emollient groups applied emollient at least 2x/d). No statistically significant difference in AD rate when comparing group 1 + 3 (received emollients) to 2 + 4 (no emollients). TARC levels not significantly different between all infants of all groups. TARC levels of infants who developed AD by 9 mo of age also not significantly different between all groups. EASI scores showed mild disease in most babies who developed AD by 9 mo of age (only 5/49 babies with AD had moderate disease). Highest EASI score was 13.6. Median scores did not differ significantly among groups. Prevalence of FA at 1 y of age, sensitization to any food or inhalant allergen at 9 mo of age and allergen-specific IgE showed no difference in AD incidence between groups.
Primary: Presence of AD in first 12 mo of life assessed using UKWP criteria and/or visible AD at time of examination. Secondary: FA, based on skin prick tests, history of reactions and OFC (if wheel ≥ 1 mm) at 12 mo. Adverse events (AEs) to EpiCeram® Skin barrier function as assessed by TEWL at 6 wk and 12 mo. Food sensitization (positive skin prick test) at 12 mo of age.	Study ongoing—no results published to date

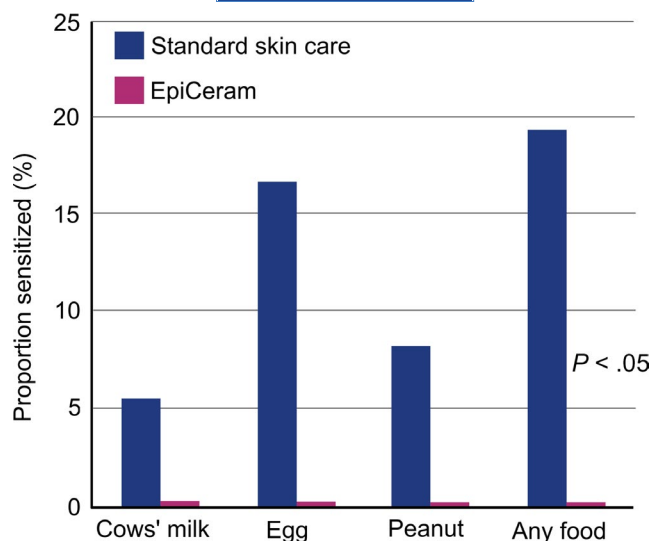


FIGURE 6 Effect of twice-daily EpiCeram® vs standard skin care for the first 6 mo on skin prick test reactivity to food allergens at 12 mo. Results were limited to intervention participants who were treated at least 5 times per week on average. Per-protocol analyses revealed a significant reduction in food sensitization at 12 mo in the treatment group (0%, 0 of 21) compared to the control group (19%, 7 of 36). Reproduced with permission from Lowe AJ, Leung DYM, Tang MLK, Su JC, Allen KJ. *Ann Allergy Asthma Immunol*. 2018 Feb;120(2):145-151

in sensitization was only found in infants where application commenced before 3 weeks. Miyaji et al⁴⁴ (Table S1) showed that delayed proactive topical steroid treatment in AD was a risk factor for FA at 24 months of age.

2. The rate of adherence with the study intervention: The PEBBLES study (Table 2) only showed a reduction in sensitization rates if emollients were applied twice daily for ≥ 5 days a week. In contrast, in the PreventADALL¹¹⁴ and BEEP¹¹³ study, adherence was defined as emollient application once a day, at least 3-4 times a week (less than the 5 days/week in PEBBLES study).
3. Emollient properties: The properties of emollients on skin hydration, skin pH, restoration of the skin barrier, and immune function are all important properties to consider in the choice of emollient for the prevention of FA¹⁶⁴ (Table S3). Emollients can have high pH levels, and high skin pH which can damage skin proteins and lipids, leading to dryness, irritation, itching, and increased TEWL.¹⁶⁵ BEEP and PreventADALL RCTs (Table 1) both used petrolatum-based emollients which have been shown to have lower benefits on TEWL compared to ceramide-containing trilipid creams used in PEBBLES (Table 2).^{166,167}
4. There may be a disconnect between AD and FA development depending on what needs to be reduced (eg, dryness or inflammation or both). This disconnect was shown in other treatments for the prevention of AD that did not result in a reduction of IgE (with probiotics).¹⁶⁸
5. AD is not just a barrier defect, but also an inflammatory process. Targeting inflammation early and aggressively with topical steroids has been shown to be associated with a significant reduction in food sensitization and FA in infants with moderate-to-severe AD.⁴⁴ Thus, treating only the barrier defect in AD may not be enough to protect against the development of FA.
6. The role of environmental food exposure in these studies has not been assessed. It is not known if parents washed their hands prior

TABLE 3 Randomized trials assessing combination of emollients and topical steroids for atopic dermatitis

Prevention type	RCT Author & Study Name	Participant Number & Study Arms	Population	Emollient
Secondary	Yamamoto- Hanada et al Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Early aggressive intervention for infantile AD to prevent development of FA: a multicenter, investigator-blinded, randomized, parallel group controlled trial (PACI Study)-protocol for a RCT ¹⁷⁰ Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis UMIN000028043	650 Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Control group (standard guideline-based treatment): 325 Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Intervention group (early aggressive topical steroids and Heparinoid cream application): 325	7-13 wk old Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Diagnosis of AD (UKWP criteria) with rash development within previous 28 d	Alclometasone dipropionate (Almeta®) to face, Betamethasone Valerate (Rinderon®-V) and Mometasone Furoate (Fulumeta®) to body Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Heparinoid cream (Hirudoid® Soft ointment) as emollient

BOX 1 Major milestone discoveries

- 1911: Oral tolerance induction is first described in an animal model.¹⁰³
- 1994: The first report of epicutaneous sensitization leading to IgE-mediated FA.⁷¹
- 1996: The dual-allergen exposure hypothesis is first proposed.¹⁰⁴
- 2003: The ALSPAC birth cohort shows an association between peanut oil containing creams applied to the skin of children with AD and the development of PA.⁴⁰
- 2006: FLG loss-of-function mutations are confirmed to be major predisposing factor for AD,⁹⁹ thus arguing that AD is a disease resulting from a defective skin barrier.
- 2008: FLG loss of function is shown to be associated with challenge-proven IgE-mediated PA, even after adjusting for AD.¹⁰⁵
- 2009: High household peanut consumption is associated with the development of PA.¹⁰⁶
- 2014-2015: High environmental exposure to peanut (measured in dust) is shown to increase the risk of peanut sensitization and likely allergy in children with mutations in the *FLG* gene or with AD.¹⁰⁶
- 2015: The LEAP randomized controlled trial demonstrates that oral peanut ingestion from 4 to 11 months of age-prevents A in high-risk infants.^{23,24}
- 2013: HealthNuts study shows that by 12 months of age, 3.1% of children have challenge-proven FA and 9% were egg-allergic.¹ There is therefore a narrow window of opportunity to induce tolerance.
- 2014: Japanese,¹⁰⁷ US and UK¹⁰⁸ preventative emollient therapy pilot studies show that early emollient therapy in high-risk children reduces the onset of AD by 33%-50%.
- 2015-2016: TEWL at 2 days is shown to predict not only AD,¹⁰⁹ but also FA at 2 years,¹¹⁰ providing an early marker of disrupted skin barrier predictive of later disease.
- 2017: The PEBBLES pilot study demonstrates a trend toward a reduction in AD and food sensitization in infants treated with trilipid emollient therapy for 6 months.¹¹¹
- 2019: Early (≤ 4 months) versus later (> 4 months) proactive use of topical steroids in infants with AD is associated with a 45% reduction in FA at 2 years (retrospective study).⁴⁴
- 2019: A novel noninvasive technique using skin tape stripping identifies skin barrier dysfunction in AD with FA subjects.¹¹²
- 2020: Two large preventative emollient RCTs using petrolatum-based creams/bath oils show no significant effect on the prevention of AD (BEEP¹¹³ and PreventADALL¹¹⁴) or FA (BEEP).¹¹³

Duration, Frequency, & Location	Outcome measures	Results
28 wk Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Whole body (except scalp) treatment Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Variable application depending on week in study and flares	Primary: Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis OFC-proven IgE-mediated hen's egg allergy at 28 wk of age Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Secondary: Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis OFC test scores at 28 wk Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Total IgE antibody titer and egg white, ovomucoid, milk, soy, wheat, and peanut-specific IgE and IgG4 antibody titers in serum at 28 wk Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis EASI scores at 2, 4, and 8 wk after study entry and at the age of 28 wk Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis POEM scores weekly through study Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Percentage of disease-free days Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Dose of rescue medication (applications) used Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis IDQoL and DFI questionnaires at 2, 4, and 8 wk after study entry and at 28 wk Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Cumulative incidence of IgE-mediated FA assessed by a doctor during study Randomized Trials Assessing Combination of Emollients and Topical Steroids for Atopic Dermatitis Cumulative incidence of wheezing assessed by a doctor during study (parental reports evaluated by doctor)	Study ongoing—no results published to date.

to application of cream and whether increasing the contact of hands onto the skin of the child may have inadvertently increased topical food exposure.

15 | SUMMARY

There is an increasing body of evidence to support the role of a disrupted, inflamed skin barrier being the root cause for the development of food sensitization and allergy.¹⁶⁹ Interest in restoring the skin barrier to prevent AD and FA has gained ground in recent years. Oral tolerance induction has offered a completely new strategy for the prevention of FA; results are compelling for PA²⁴ and moderate for egg allergy.²⁵ If this strategy were to work for other food allergens, it would require the introduction of multiple food allergens very early on in life. Targeting the skin to prevent AD or reduce the duration and severity of AD could prevent the development of FA, by either preventing epicutaneous sensitization or by increasing the window of opportunity to induce oral tolerance by early allergenic food introduction. However, results from two large RCTs using preventative emollient therapy have had initial negative results for the prevention of AD (BEEP¹¹³ and PreventADALL¹¹⁴) and FA (BEEP)¹¹³ and other RCTs are ongoing (CASCADE—A Community-based Assessment of Skin Care, Allergies, and Eczema, and PEBBLES) (Tables 1 and 2). There are also secondary prevention studies (Table 3) using both emollients and proactive topical steroid treatments ongoing or planned (PACI study: Prevention of Allergy via Cutaneous Intervention Study and SEAL-Stopping Atopic Dermatitis and Allergy Study).¹⁷⁰ Regardless as to whether these studies are positive or negative in their findings, they will help inform this important area of research. A summary of the major milestones in this

field are presented in BOX 1 and future research perspectives are presented in BOX 2.

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CONFLICT OF INTEREST

Dr Brough reports personal fees from DBV Technologies and nonfinancial support from ThermoScientific; Dr Nadeau reports grants from National Institute of Allergy and Infectious Diseases (NIAID), Food Allergy Research & Education (FARE), End Allergies Together (EAT), Allergenix, and Ukko Pharma; Grant awardee at NIAID, National Institute of Environmental Health Sciences (NIEHS), National Heart, Lung, and Blood Institute (NHLBI), and the Environmental Protection Agency (EPA); is involved in Clinical trials with Regeneron, Genentech, Alimmune Therapeutics, DBV Technologies, AnaptysBio, Adare Pharmaceuticals, and Stallergenes-Greer; Research Sponsorship by Novartis, Sanofi, Astellas, Nestle; Data and Safety Monitoring Board member at Novartis and NHLBI; Cofounded Before Brands, Alladapt, ForTra, and Iggenix; Chief Intellectual Office at FARE, Director of the World Allergy Organization (WAO) Center of Excellence at Stanford, Personal fees from Regeneron, Astrazeneca, ImmuneWorks, and Cour Pharmaceuticals; Consultant and Advisory Board Member at Ukko, Before Brands, Alladapt, IgGenix, Probio, Vedanta, Centecor, Seed, Novartis, NHLBI, EPA, National Scientific Committee of ITN and NIH Programs; US patents (patent numbers 62/647,389; 62/119,014; 12/610,940, 12/686,121, 10/064,936, 62/767,444; application numbers S10-392); Dr Sindher reports grants from Aimmune, DBV Technologies, and Regeneron; Dr Chan reports nonfinancial support from Novartis and grants from Aimmune; Dr Bahnson reports personal fees from King's College and DBV technologies; Dr Lack reports grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, National Peanut Board (NPB), UK Food Standards Agency (FSA), The Davis Foundation, Scientific Advisory Board member and Stock Options at DBV Technologies, Shareholder at Mighty Mission Me, personal fees/consultancy from Novartis, personal fees/consultancy from Sanofi-Genzyme, personal fees/consultancy from Regeneron, personal fees and consultancy from ALK-Abello; and Drs. Alkotob and Leung have nothing to disclose.

BOX 2 Future research perspectives

- To determine at what age interventions to prevent the development of food sensitization and FA should commence, and the duration of these interventions.
- The degree of adherence to therapies targeting the skin required to achieve a reduction in food sensitization and FA.
- The importance of different emollient properties (skin hydration, skin pH, restoration of the skin barrier, and immune function) for preventing food sensitization and FA.
- The role of topical anti-inflammatory agents as part of the skin care regime to prevent food sensitization and FA.
- The role of reducing environmental food allergen exposure on reduction of sensitization and FA.
- Reduction in *S aureus* colonization in at-risk children on the prevention of FA.

AUTHOR CONTRIBUTIONS

Dr Brough wrote the first draft and incorporated all subsequent changes to document and coordinated final version and submission. Dr Sindher and Dr Alkotob provided assistance with writing, review, references, figures, and tables. Dr Nadeau, Dr Leung, Dr Lack, Dr Chan, and Dr Bahnson provided assistance in writing and reviewing the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supplementary Appendix- Tables

Supplementary Table A

Pilot Author & Study Name	Study Location	Participant Number & Study Arms	Population	Emollient used	Duration, Frequency, & Location	Compliance assessment	Outcome measures	Results	Strengths	Weaknesses/limitations
Stephan Weidinger EARLYEMOLLIENT - Feasibility of Early Emollient Use in Children With Atopic Eczema (EARLYemo) NCT03376243	University of Schleswig-Holstein, Germany	50 All receive structured education on prevention guidelines Only intervention group receive emollient	Up to 2 weeks of age Term newborns 1 st degree relative with AD, AR, or AA	“Lipikar Baume AP+“ emollient	12 months Daily application to entire body including face	Currently publicly available information does not mention how and if compliance to use of the treatments was assessed	1ry: Willingness of parents to get child randomized and to adhere to regimen 2ndry: Cumulative development of AE at age 2 TEWL at age 2 Microbiome diversity at age 2	Not yet published.		Small sample size
McClanahan, D., Wong, A., Kezic, S., Samrao, A., Hajar, T., Hill, E. and Simpson, E. A randomized controlled trial of an emollient with ceramide and filaggrin-associated amino acids for the primary prevention of atopic dermatitis in high-risk infants¹	Oregon Health and Science University, USA	100	Up to 3 weeks of age Moms age 18-45 1 st degree relative with AD, AR, or AA	Cetaphil Restoraderm in intervention group Emollient of choice in control group	12 months Full body application in intervention group Application as needed only on dry skin areas in control group	NA	1ry: Incidence of AD at 12 months 2ndry: Adherence measures Time to disease onset AEs Skin barrier function in a sub-set of subjects	No statistically significant difference in AD diagnosis at 12 months (p= 0.204) and 2 years (p= 0.296) No significant differences in skin barrier or microbiome assessment		Restricting control group to non-full body application Compliance not assessed

NCT01375205										
Simpson et al. Emollient enhancement of the skin barrier from birth offers effective AD prevention²	US (1 center in Oregon) & UK (3 centers)	124 Control group: 60 Intervention group: 64	0-3 weeks of age 1st degree relative with AD, AR, or AA	UK: sunflower seed oil, double-base gel, liquid paraffin 50% in white soft paraffin US: sunflower seed oil, Cetaphil cream, Aquaphor healing ointment	6 months 1x daily Entire body surface with exception of scalp in intervention group	Visit or telephone call at week 6, 12, 18, & 24 No specification of method used by parents to document/recall adherence	1ry: Assessing feasibility of interventional approach for upcoming larger trial Relevant 2ndry: Age of onset of AD Cumulative incidence of AD at 6 months Incidence of emollient-related AEs	Intervention group preferred cream/gel formulation (67.2%) over oil (23.4%) & ointment (9.4%) 85% of parents in intervention used emollients >= 5 days/week Daily emollient use significantly reduced cumulative incidence of AD at 6 months (43% in control group vs 22% in emollient group); relative risk reduction of 50%	Early intervention Attempted to control for other factors by providing both intervention & control groups with skin care guidelines Blinded assessor performed skin exams & AD diagnosis	Did not include infants with 1st degree relative with FA Parents not blinded as to emollients used Unable to assess for time of onset of AD due to low occurrence Objective AD assessment criteria not specified Used several types of emollients without stratifying them It is not known if parents washed their hands prior to application of cream and whether increasing the contact of hands onto the skin of the child may have inadvertently increased topical food exposure through a lipid mediator (the emollient)-also applies to other studies
Lowe et al. A phase I study of daily treatment with a Ceramide-	RWH + Department s of Allergy Immunology and Dermatology	10 Phase I, Open-label, non-controlled	0-4 weeks of age 1st degree	Epiceram®	6 weeks 3x daily application	Daily diary card by parents documenting application & any AEs	1ry: Participant compliance & frequency of AEs 2ndry:	80% applied study cream on 80% or more of days No related AEs reported	Provision of useful information about recruitment strategies for	No control group Small sample size (10 participants) Wide variation in

dominant triple lipid mixture Commencing in neonates³ ACTRN1260900 0727246	y at RCH, Melbourne, Australia		relative with hx of AD, AR, AA, or FA				Presence of AD, assessed using UKWP criteria Parent reported doctor-diagnosed AD Measures of TEWL, surface pH, & SC hydration		future phase II trial Looked into skin biophysical profile	amount of cream applied in total (34 - 277 grams) Wide variation in average amount of cream that was used per application (3.6 - 7.2 grams) Short duration of study
Horimukai et al. Application of moisturizer to neonates prevents development of AD⁴	Japan at a single center (NCCHD)	118 Control group: 59 Intervention group: 59	Newborns Parent or sibling with AD	Emulsion-type moisturizer (sodium dodecyl sulfate, sodium lauryl sulfate, alcohol)	6 months >= 1x daily to whole body surface Petroleum jelly prescribed to both groups (request by IRB)	Daily diary by parents documenting skin condition, areas of application, amount of moisturizer	1ry: Incidence of AD at week 32 of life assessed based on modified Hanifin and Rajka criteria (at week 4, 12, 24, & 32 of life) 2ndry: Allergic sensitization based on serum levels of egg-white sIgE TEWL, SC hydration, & pH, & skin colonization by <i>S. Aureus</i> Onset of allergic diseases, such as FA & asthma	AD lower by 32% in neonates who received emulsion-based moisturizer by week 3 Risk of AD significantly lower in intervention group (hazard ratio, 0.48; 95% CI, 0.27-0.86) Daily application of emulsion-type moisturizer during first weeks of life increased SC hydration at week 12 Infants with skin lesions had > 3x risk for allergic sensitization No statistically significant effect on allergic sensitization based on egg-white sIgE No statistically significant difference in detection of <i>S.aureus</i> in cheek samples or <i>FLG</i> mutations	Same blinded dermatologist assessed patients Looked into other allergic disease onset Looked into skin biophysical profile & <i>S.aureus</i> colonization Looked into <i>FLG</i> mutations & <i>S. aureus</i> colonization	If an infant with skin rash or AD skin did not show any sign of pruritus, dermatologist made a diagnosis of skin rash only When given a diagnosis of AD, infants were immediately removed from study No information about amount of petroleum jelly used by intervention group
Lowe et al. Phase II: RCT of a barrier lipid	RWH + Department of Allergy Immunology and	77 Control group: 38	<= 3 weeks of age	Epiceram®	6 months 6 grams 2x daily	Did not mention how & if compliance was assessed	1ry: Presence of AD assessed using UKWP criteria at 6 weeks & 6 months	Adherence to intervention was high (76% applied cream for ≥5 days per week)	Larger group than phase 1 & presence of control group	Study was underpowered for both AD and FA There were problems

replacement strategy for the prevention of AD and allergic sensitization: the PEBBLES pilot study ⁵	Dermatology at RCH, Melbourne, Australia	Intervention group: 38	Parent with AA, AD, hay fever/AR, or FA		Full skin surface		TEWL assessed on forearm & forehead at 6 weeks & 6 months 2ndry: AD (diagnosed by medical practitioner) that was not verified by study investigators during treatment period & in 6 months after AD severity as measured SCORAD at 6 weeks, 6 & 12 months of age SPT reactivity to six common food (cows' milk, peanut & hens' egg) and aeroallergens (house dust mite, rye grass & cat dander): wheal $\geq$ 3mm than negative saline control at 6 & 12 months post randomization Biomechanical properties of skin (pH, hydration, oiliness) at 1.5, 6, & 12 months post randomization	No significant effect of routine barrier lipid replacement in early life on AD or sensitization outcomes Trend towards reduced risks of AD (non-significant) & food sensitization in intervention group at 6 & 12 months of age Per protocol analyses (only including infants who received $\geq$ 5 days/week of study treatment) revealed a significant reduction in food sensitization at 12 months in treatment group (0%, 0 of 21 vs. 19%, seven of 36, P=0.04). No differences between groups in biophysical properties of skin	Longer follow-up (up to 12 months of age) Specified exact amount to be used by parents Looked at reactivity to aeroallergens via SPT Looked at skin biophysical profile	with adherence to therapy Food challenges were not performed to confirm FA
Chamlin et al. Ceramide-dominant barrier repair lipids alleviate childhood AD: Changes in barrier function provide a sensitive indicator of disease activity ⁶	Pediatric Dermatology Clinics at the Mt Zion Medical Center, UCSF	24 Open-label, non-controlled	Children (mean age 6.4 years; range, 1.5-12 years) Stubborn-to-recalcitrant AD	Triceram Continued use of their regimen of topical tacrolimus &/or steroids	21 weeks 2x daily Involved & uninvolved skin sites decreased to once daily after 12 weeks	Did not mention how & if compliance to use of the treatments was assessed	Efficacy of newly developed, ceramide-dominant, physiologic lipid-based emollient, when substituted for currently used moisturizers	Combined SCORAD values for all participants declined rapidly, became significant by 3 weeks, with still further improvement at weeks 12 & 20 or 21 Improvement in SCORAD values correlated significantly with changes in TEWL, particularly in involved skin TEWL values declined in parallel with SCORAD values during treatment & when SCORAD values plateaued in the later	Demonstrated that TEWL could provide an objective measure of AD severity & TEWL measurements may provide a more sensitive indicator of treatment-related fluctuations in disease activity Demonstrated	Small sample size (n=24) Did not assess ceramides for stand-alone therapy Decreased application frequency at 12 weeks of 21-week treatment period Looked at tape strips from 5 patients only

								weeks of therapy, TEWL levels reflected further changes in barrier status SC hydration increased progressively in involved skin but only significant at 20-21 weeks & improvement correlated with SCORAD only at involved sites SC integrity as measured by increased # of strippings needed to penetrate permeability barrier showed improvement (significant at 6 weeks). Improvement initially correlated with SCORAD but integrity scores declined between 12-21 weeks with decreased frequency of emollient application Pretreatment tape strips: ultrastructural features typical of SC in AD; after switch to Triceram: intercellular domains replete with normal numbers of lamellar bilayers	that TriCeram can help restore skin integrity	
Sugarman et al. Efficacy of a lipid-based barrier repair formulation in moderate-to-severe pediatric AD⁷	Multicenter, USA	121 Control group: 59 Intervention group: 62	6 months-18 years Moderate-to-severe ad Not on systemic therapy	Epiceram® compared to Fluticasone (Cutivate) cream	28 days 2x daily treatment of lesions dime-sized application of Epiceram® for intervention group	Did not mention how & if compliance to use of the treatments was assessed	Reduction in disease severity, assessed as SCORAD scores Improvement in pruritus Improvements in sleep habits	Fluticasone-treated group showed significantly greater improvement in SCORAD & IGA scores at 14 days (57.6 % change vs. 36.6 % change for Epiceram® group), but not significant at 28 days IGA, sleep habit scores, subjective pruritus, patient/family self-	Investigator-blinded Explained significantly lower SCORAD in Fluticasone arm at 14 days as potentially due to:	Short duration of treatment did not allow for possible latent effects of EpiCeram® Subjects not blinded as some had recently used Fluticasone cream Four participants from intervention group

			(except antihistamine or antibiotic)		Or Fluticasone propionate 0.05 %; (but hydrocortisone 2.5 % to face + body folds) for control group Cetaphil lotion to non-lesional areas 2x daily for all participants			assessment showed significant improvement at 14 & 28 days in both groups but no statistically significant difference (except for IGA at 14 days)	- vaso-constrictive properties of topical steroids which reduces erythema (a SCORAD component) -decrease in inflammation is quicker (initial response to topical steroids) vs. time for barrier restoration (response to EpiCeram®) Showed that EpiCeram® has potential to be used as stand-alone therapy or with Fluticasone as needed (for flares) in moderate to severe AD	were treated with rescue topical fluticasone initially due to worsening of AD Initial SCORAD was 10 % higher for EpiCeram® group (did not achieve statistical significance but may have contributed to results found at 28 days) Majority of participants were females (62.7 %) & African American (55.9 %) No placebo group: this is in-line with ethical research as these were patients with moderate to severe AD Lack of use of topical steroids (in EpiCeram® arm) to target inflammation –AD is not just a barrier defect, but also an inflammatory process, driven, at least initially by Th2, thus makes a significant contribution toward food sensitization and allergy. Treating a barrier defect in AD may therefore not be enough in protecting against the development of FA
Miyaji et al. Earlier	Tokyo, Japan	177 infants with AD	Retrospective cohort	Topical steroids Alclometas	Early treatment group initiated treatment with	No specification of method used	Incidence of IgE-mediated FA during 22-24 months of age	25.3% of participants in early treatment group and 46.3% of participants in	First to demonstrate that early	Some characteristics, associated with more severe AD, showed

aggressive treatment to shorten the duration of AD in infants resulted in fewer food allergies at 2 years of age ⁸		Early treatment group: 89 Delayed treatment group: 88	study using data obtained from EMR of infants (≤12 months of age) with AD	one dipropionate (Almeta®) to face Betamethasone Valerate (Rinderon®-V) and Mometasone Furoate (Fulumeta®) to body Heparinoid cream (Hirudoid® Soft ointment) as emollient (Refer to Yamamoto-Hanada et al in Table 3).	topical steroids within 4 months of onset of AD. Delayed treatment group initiated topical steroids more than 4 months after onset of AD.	by parents to document/recall adherence		delayed treatment group developed FA with a significant difference between the two groups (p=0.01). Logistic regression analysis showed time period until start of aggressive treatment of AD was a risk factor for FA during 22-24 months of age (OR, 3.8, 95%CI, 1.5, 9.6, p=0.004).	aggressive topical corticosteroid treatment to shorten the duration of AD in infants was significantly associated with a decrease in later development of FA	statistically significant differences between the two groups during the first visit.
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Table A. Pilot Studies Assessing Emollients or proactive topical steroids for Atopic Dermatitis

AD: Atopic Dermatitis; AR: Allergic Rhinitis; AEs: Adverse Events; EMR: Electronic Medical Record; FA: Food Allergy; RWH: Royal Women's Hospital; RCH: Royal Children's Hospital; Hx: history; UKWP: United Kingdom Working Party; TEWL: trans-epidermal water loss; NCCHD: National Center for Child Health and Development; sIgE: specific Immunoglobulin E; *FLG*: Filaggrin; SC: Stratum corneum; SCORAD: SCORing Atopic Dermatitis; SPT: skin prick testing; UCSF: University of California, San Francisco; IGA: Investigator's global assessment

Supplementary Table B

Prevention type	RCT Author & Study Name	Study Location	Participant Number & Study Arms	Population	Emollient used	Frequency, location, & Duration	Compliance assessment	Outcome measures	Results	Strengths	Weaknesses/limitations
1ry	Yonezawa K, et al. Effects of moisturizing skincare on skin barrier function and the prevention of skin problems in 3-month-old infants: A randomized controlled trial⁹	Japan	227 Control group: 113 Intervention group: 114	1 week to 3 months of age	For bathing, Pigeon Baby Soap [Pigeon, Tokyo, Japan] or Kewpie Baby Body Soap, Cow Brand Soap [Kyoshinsha, Tokyo, Japan] As moisturizer in intervention group: Pigeon Baby Milk Lotion [Pigeon] or Atopita Milky Lotion® [Tampei Pharmaceutical, Tokyo, Japan]	12 weeks Application 1-2x daily with bathing every 2 days in intervention group Vs Daily bathing without moisturizer in control group	Currently publicly available information does not mention how and if compliance to use of the treatments was assessed	1ry: TEWL, SCH, skin pH and sebum secretion at 3 months of age 2ndry: Incidence of skin problems (e.g. Diaper dermatitis) at 3 months of age	Statically significant lower TEWL (mean ± SD, 14.69 ± 7.38 vs 17.08 ± 8.26 g/m ² per h, P = 0.033) and higher face SCH (60.38 ± 13.66 vs 53.52 ± 14.55, P = 0.001) and higher body SCH (58.89 ± 12.96 vs 53.02 ± 10.08, P < 0.001) in intervention vs. control group Diaper dermatitis at 1-3 months of age significantly lower in intervention vs. control group (6.3% vs 15.9%, P = 0.022; RRR= 0.399 [95% confidence interval [CI], 0.174–0.919]). Skin problems at 1-3 months of age significantly lower in intervention vs. control group (42.1% vs 55.2%, P = 0.064; relative risk ratio, 0.762 [95% CI, 0.569–1.021]). Risk of dry facial skin was reduced with intervention by 48.4% (relative risk ratio, 0.516; 95% CI, 0.333–0.799) Risk of dry body skin was reduced with intervention by 39.7% (relative risk ratio, 0.603; 95% CI, 0.399–0.911)	Looked at skin pathology (not only eczema) including diaper area	Short duration of intervention Different bathing frequency in control vs intervention group

1ry	Eric Simpson A Community-based Assessment of Skin Care, Allergies, and Eczema (CASCAD E) NCT03409367	Multi site, USA	1250 2 arms	Up to 2 months of age Born at > 25 weeks of gestation	Choice of over the counter lipid-rich emollient (Vaseline® /Vanicream®/ Cerave® Healing Ointment/ Cerave® cream/ Cetaphil® cream)	24 months Once daily full body application	Currently publicly available information does not mention how and if compliance to use of the treatments was assessed	1ry: Cumulative incidence of AD at 24 months of age 2ndry: AD diagnosed by CEQ at 12 and 24 months Any prescription topical medication or over-the-counter hydrocortisone usage Parental report at 3, 6, 9, 12, 15, 18 and 24 months of provider-diagnosed AD and sleep loss of infant Parental report of immediate food allergy symptoms or a provider diagnosis of food allergy that was confirmed by prick testing or IgE blood test at 12 and 24 months Asthma risk using a modification of the API at 12 and 24 months Global Health Status using one question from the PROMIS PGH-7 instrument at 12 and 24 months AD severity as	Study ongoing- no results published to date.	Allowed inclusion of infants without family history of atopy Email and text message reminders of instructions Outcome assessors are blinded	Allowing enrollment as late as 2 months of age Did not specify Vaseline® and Vanicream® products used (we assumed Vaseline® Healing Jelly Original and Vanicream™ Moisturizing Cream for Baby were used)
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								measured by parental report of eczema, age of onset Time to onset of AD as measured by provider-recorded date of first diagnosis retrieved from review of health record AD symptom severity as reported by POEM Atopic dermatitis severity by Parent-reported global severity of eczema assessment IDQoL instrument			
1ry	Blume-Peytavi Atopic Dermatitis in Atopy Predisposed Infants (ADAPI) NCT02906475	Charite University, Berlin, Germany	160 2 arms	0-14 days of age Term newborns 18-45 year old moms Birthweight 2.5 to 4.5 Kg I, II, III, IV Fitzpatrick classif	Milk Lotion (no details about brand(s) or ingredients provided)	12 months Applied once daily to entire body and face + Bathing addendum if needed	Currently publicly available information does not mention how and if compliance to use of the treatments was assessed	1ry: Cumulative AD incidence at 12 months 2ndry: Cumulative AD incidence at 24 months EASI at 12 and 24 months IDQoL at 12 and 24 months TEWL, skin surface pH, and Stratum Corneum Hydration on mid-alveolar forearm at 14 days, 1, 3, 6, 12, and 24	Study ongoing- no results published to date.	Looking at milk lotion- not done by other studies	Did not standardize bathing routine for the 2 arms Food Allergy outcomes not assessed Bathing addendum not defined by currently available info Did not specify ingredients/brand of milk lotion

				ication n Parent or sibling with physician diagnosed AD, AR, or AA Must be breast fed and/or on cow-milk based formula				months			
1ry	Jonathan Hourihane Short-term Topical Application to Prevent Atopic Dermatitis (STOP AD) NCT03871998	Cork University Maternity Hospital, Ireland	242 2 arms	Full term healthy infant Up to 5 days of age 1 st degree relative with AD, AR, AA, or food	Commercially available moisturizer (no details about brand(s) or ingredients provided)	2 months 2x daily full-body application by intervention group Standard skin care advice with no moisturizer application in control group	Currently publicly available information does not mention how and if compliance to use of the treatments was assessed	1ry: Cumulative incidence of AD at 12 months Cumulative incidence of IgE-mediated food allergy at 24 months 2ndry: TEWL and Natural Moisturizing Factor measured at birth, 2, 4 and 8 weeks and at 6 and 12 months Microbial community and skin biomarker analysis in a subset	Study ongoing- no results published to date.	Looked into incidence of food allergies at 24 months of age	Type or name of moisturizer used in intervention group has not been specified Control group not allowed to use moisturizer Did not specify ingredients/brand of moisturizer

				allergy				of study participants, comparison of changes over 1 st year between check and antecubital fossa and between intervention and control group			
1ry	Lowe A, Su J, Tang M, et al. PEBBLES study protocol: RCT to prevent AD, FA and sensitization in infants with a family history of allergic disease using a skin barrier improvement strategy¹⁰ Phase III ACTRN12617001380381 NCT03667651	The Royal Women's Hospital (RWH) and Departments of Allergy Immunology and Dermatology at the Royal Children's Hospital, Melbourne, Australia	760 2 arms (380 in each)	Up to 3 weeks of age 1st degree relative has a self-reported hx of AA, AD, hay fever/AR or FA	EpiCeram®	6 months 6 grams 2x daily	Online diary completed by parents on a weekly basis documenting AEs, frequency of EpiCeram® application, use of other creams Study team weighs remaining cream at all follow-up visits	1ry: Presence of AD in first 12 months of life assessed using UKWP criteria and/or visible AD at time of examination 2ndry: FA, based on skin prick tests, hx of reactions & OFC (if wheel ≥ 1 mm) at 12 months AEs to EpiCeram® Skin barrier function as assessed by TEWL at 6 weeks & 12 months Food sensitization (positive skin prick test) at 12 months of age	Study ongoing- no results published to date.	Large sample size n=760 OFC to confirm FA 1st study to test if routine prophylactic use of a ceramide-dominant emollient prevents development of AD beyond active treatment period & prevents development of FA & allergic sensitization EpiCeram® not available on market in Australia which will help prevent use by control group	Single blind (outcome assessor blinded); coordinator & parents not blinded Parents of children in the control group will not be told to withhold skin care from their infant for ethical but information on use will be collected

1ry	Chalmers, J.R., Haines, R.H., Mitchell, E.J. et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial ¹¹ ISRCTN21528841	Multi center, UK	1394 Control group (skin care advice only): 701 Intervention group (skin care advice + emollient): 693	Up to 3 weeks of age 1 st degree relative with physician-diagnosed AD, AA, AR	Choice between: Doublebas e Gel® (Dermal Laboratories Ltd.) & Diprobase Cream® (Merck Sharp & Dohme Ltd.)- paraffin based without alcohol or lipids	12 months ≥1x daily	Online questionnaires at 3, 6, 12, 18, 36, 48 & 60 months	1ry: Blinded assessment of AD at 24 months of age using UKWP diagnostic criteria 2ndry: Time to onset of AD Severity of AD based on EASI & POEM Confirmed diagnosis of FA at 24 months to milk, egg, and/or peanut (parental report, allergic sensitization, food challenge- if required) Parental report of clinical diagnosis of any FA between 12 and 24 months Safety & cost-effectiveness of prevention strategy Role of <i>FLG</i> genotyping as possible stratifier of response to emollient intervention	Study closed to recruitment but ongoing No statistically significant difference in AD: present at age 2 (within the past year) in 150 (25%) of 612 in control group and in 139 (23%) of 598 in intervention group (adjusted RR 0.95 [95% CI 0.78 to 1.16]; p=0.61) Subgroup analyses (number of 1st-degree relatives with AD, AA, or AR, <i>FLG</i> genotype, season of birth, water hardness, and probiotic use) also showed no statistically significant differences Adherence was considered satisfactory in only 51% of intervention group (all of those who did not complete any questionnaires were assumed as not using emollient) Adherence was considered satisfactory at 70% (311 of 442) in those who completed all questionnaires Adherence in intervention group decreased with each time-point: 466 (88%) of 532 had satisfactory adherence at 3 months, 427 (82%) of 519 at 6 months, and 375 (74%) of 506 at 12 months	Long-term follow up with annual online questionnaires after 24 th month visit (up to 60 months) AD that develops will be treated per practice guidelines regardless of group & patient will continue in study Assessment of time-to-onset of AD Assessor-blind	Intervention group patients can switch between the two emollients during the trial Adherence was defined as satisfactory in intervention group if emollients were applied just 3–4x/week to most of the body (at least 2x to face and neck, arms and legs, or trunk) Adherence was captured with a questionnaire at 3, 6, and 12 months – not recorded on a daily basis Contamination of control arm: 18% (82 of 457) of control group reported emollient application to most of body at least 3x/week at 3 months, 17% (62 of 372) at 6 months, and 15% (49 of 324) at 12 months (this excluded children with a parental report of doctor-diagnosed AD who were likely to be using emollients as treatment) Petrolatum-based emollients have been shown to have lower benefits on TEWL and ceramide creams No mechanistic studies
1ry	Skjerven	Nor	2701	Infant	Ceridal	9 months	Currentl	1ry:		AD	Petrolatum-based

	HO et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial.¹² NCT02449850	way (2149) & Sweden (552) multicentre	1 of 4 similar sized groups: - No intervention - Skin care (oil-bath & Ceridal face cream) - Consecutive introduction (3-4 months of age) of peanut, milk, wheat, & egg ≥ 4 days/week complementary to breastfeeding - Both interventions	General population	face cream (alcohol & polyethylene glycol) in skin care group and dual intervention group	≥ 5 days/week	publicly available information does not mention how and if compliance to use of the treatments was assessed	AD assessed first at 12 months FA to intervention food assessed first at 36 months 2ndry: Recurrent wheeze or AA, allergic sensitization, allergy to other foods, anaphylaxis, & AR	No statistically significant difference in AD: present in 478 (8%) of 596 infants in control group, 64 (11%) of 575 in skin intervention group, 58 (9%) of 642 in food intervention group, and 31 (5%) of 583 in combined intervention group. risk difference of 3.1% (95% CI -0.3 to 6.5) for skin intervention versus control and 1.0% (-2.1 to 4.1) for food intervention versus control Reports of Itching, dry skin, and urticaria were similar in all groups	assessment by a blinded assessor FA confirmed by OFCs when appropriate	emollients been shown to have lower benefits on TEWL and ceramide creams Effects of application of emollients onto normal skin (i.e. a primary prevention study) on the immune system, microbiome and barrier properties not looked at Adherence was low but analysis was done per-protocol: only 497 (43%) of 1158 used bath oils at least 4x/week, only 514 (44 %) used facial cream at least 4x/week, and only 316 (27%) were fully adherent to use of both emollients
1ry	Dissanayake et al. Skin care and synbiotics for prevention	Tokyo, Japan	605 pregnant women recruited - 549 infants enrolled	Infants	Locobase® REPAIR cream (Daiichi Sankyo, Japan)	6 months 2-3x daily	Diary was maintained to record the number of times	1ry: Development of AD at 1 year of age 2ry: Prevalence of FA, as	Cumulative incidence of AD (itchy skin condition lasting 2 or more months) at 12 months of age: 30.9% in group 1, 32.1% in group 2, 38.6% in group 3, and 25.6% in group 4 – No statistically significant difference	Large cohort of infants followed for at least 1 year with continued follow-up.	Method of emollient application may have differed. Caregivers advised to apply emollient to cheeks and the peri-oral region but application of emollient on other areas of the

	n of AD or FA in newborn infants: A 2 x 2 factorial, randomized, non-treatment controlled trial ¹³		Randomized into 4 treatment arms: Skin care and synbiotics. (n=137) Synbiotics only (n=137) Skin care only (n=138) No intervention (n=137)				and the amount of emollient applied each month	reported in the questionnaires at 1 year Sensitization to any food or inhalant allergen at 9 months of age EASI score at 9 months of age TARC score at 9 months of age	Incidence of AD as defined by UKWPC was 20.4% in group 1, 14.7% in group 2, 21.0% in group 3, and 18.8% in group 4– No statistically significant difference No statistically significant difference in AD incidence after adjusting for emollient application rate (80% of the parents/guardians in the emollient groups applied emollient at least 2x/day) No statistically significant difference in AD rate when comparing group 1+3 (received emollients) to 2+4 (no emollients) TARC levels not significantly different between all infants of all groups TARC levels of infants who developed AD by 9 months of age also not significantly different between all groups EASI scores showed mild disease in most babies who developed AD by 9 months of age (only 5/49 babies with AD had moderate disease) Highest EASI score was 13.6. Median scores did not differ significantly among groups		body was not prohibited – which may have led to a biased outcome as the total area of application may have varied between infants. Application of moisturizers was not prohibited in the no-intervention group due to ethical reasons – which may have masked the effect of the moisturizer used as an intervention
2ndry	Yamamoto Hanada et al. Early	Multi center, Japan	650 Control group (standar	7-13 weeks old Diagn	Alclometasone Dipropionate (Almeta®)	28 weeks Whole body (except	Emollient & TCS application includin	1ry: OFC-proven IgE-mediated hen's egg allergy at 28 weeks	Study ongoing- no results published to date.	Assessors blinded	If emollients are applied after sensitization has commenced, it may difficult to prevent FA or induce oral tolerance

	aggressive intervention for infantile AD to prevent development of FA: a multicenter, investigator-blinded, randomized, parallel group controlled trial (PACI Study)-protocol for a RCT¹⁴ UMIN000028043		d guideline-based treatment): 325 Intervention group (early aggressive topical steroids & Heparinoid cream application): 325	osis of AD (UKW P criteria) with rash development within previous 28 days	to face, Betamethasone Valerate (Rinderon®-V) and Mometasone Furoate (Fulumeta®) to body Heparinoid cream (Hirudoid® Soft ointment) as emollient	scalp) treatment Variable application depending on week in study & flares	g rescue assessed at 2, 4, 8, & 28 weeks (method of documentation/ collection not specified)	of age 2ndry: OFC test scores at 28 weeks Total IgE antibody titer & Egg white, ovomucoid, milk, soy, wheat, & peanut-specific IgE & IgG4 antibody titers in serum at 28 weeks EASI scores at 2, 4, & 8 weeks after study entry & at the age of 28 weeks POEM scores weekly through study Percentage of disease-free days Dose of rescue medication (applications) used IDQoL and DFI questionnaires at 2, 4, & 8 weeks after study entry & at 28 weeks Cumulative incidence of IgE-mediated FA assessed by a doctor during study Cumulative incidence of wheezing assessed by a doctor during study (parental reports evaluated by doctor)			
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Table B. Randomized Trials Assessing Emollients or proactive topical steroids for Atopic Dermatitis
 OFC: oral food challenge; POEM: Patient Oriented Eczema Measure; EASI: Eczema Area and Severity Index; TARC: Thymus and activation-regulated chemokine; IDQoL: Infants' Dermatitis Quality of Life; DFI: Dermatitis Family Impact, RCT: Randomized controlled trial

Supplementary Table C

Type	Brand	Class	Ingredients	Uses	Trial using drug
Natural Unsaturated Fats	Sunflower seed oil by William Hodgson and Co.	Oil	High in vitamin E. Varying ratios of linoleic acid (polyunsaturated fat) and oleic acid (monounsaturated fat). ¹⁵	Food, fuel, cosmetics, and emollients.	Simpson et al. ²
Paraffin based	Double-base Gel by Dermal Laboratories ¹⁶	White opaque gel ¹⁶	Isopropyl myristate 15% w/w, liquid paraffin 15% w/w, glycerol, carbomer, sorbitan laurate, trolamine, phenoxyethanol, and purified water. ¹⁶	Dry or chapped skin conditions such as AD, psoriasis or ichthyosis. ¹⁶	Simpson et al. ²
	Liquid paraffin 50% in white soft paraffin – generic ²	Ointment	Liquid paraffin 50% in white soft paraffin.	Relief of dry skin conditions ¹⁷	Simpson et al. ²
	Diprobase Cream by Bayer	Cream	No pharmacologically active components ¹⁸ , liquid paraffin + white soft paraffin + water, cetomacrogol + cetostearyl alcohol as emulsifying agents, chlorocresol as antimicrobial preservative, phosphoric acid, sodium dihydrogenphosphate and sodium hydroxide. ¹⁹	Skin protection before taking a bath and hydration of skin after showering; suitable for everyday use – as often as required ¹⁹	Chalmers et al. ²⁰
	Cetaphil Moisturizing Cream by Galderma	Cream	Water, Glycerin, Petrolatum, Dicaprylyl Ether, Dimethicone, Glyceryl Stearate, Cetyl Alcohol, Prunus Amygdalus Dulcis (Sweet Almond) Oil, PEG-30 Stearate, Tocopheryl Acetate, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Dimethiconol, Benzyl Alcohol, Phenoxyethanol, Glyceryl Acrylate/Acrylic Acid Copolymer, Propylene Glycol, Disodium EDTA, Sodium Hydroxide. ²¹	Moisturizer for sensitive dry skin ²¹	Simpson et al. ² , Sugarman et al. ⁷ , Eric Simpson - CASCADE
	Aquaphor healing ointment by Beiersdorf	Ointment	Active ingredient: Petrolatum (41%) – Skin protectant. Inactive ingredients: Mineral Oil, Ceresin, Lanolin Alcohol, Panthenol, Glycerin, Bisabolol. ²²	Multi-purpose ointment for extremely dry skin including lips	Simpson et al. ²

	Atopita Milky Lotion© by Tampei Pharmaceutical ²³	Lotion	Water, zinc oxide, mineral oil, petrolatum, behenyl alcohol, diglycerin, hydrogenated palm oil, pentylene glycol, olefin oligomer, sorbitol, behenes-20, isononyl isononanoate, dimethicone, batyl stearate, polyglyceryl-2 stearate, lanolin Cholesteryl fatty acid, mugwort leaf extract, glycyrrhizic acid 2K, allantoin, BG, glyceryl stearate (SE), phenoxyethanol, xanthan gum, sodium metaphosphate ²³	Moisturization and UV-protection for infant's dry skin ²³	Yonezawa K, et al. ⁹
	Vaseline® Healing Jelly Original by Vaseline ²⁴	Jelly	White petrolatum (100% pure – triple purified) ²⁴	Restore dry and damaged skin and protect minor cuts ²⁴	Eric Simpson – A Community-based Assessment of Skin Care, Allergies, and Eczema (CASCADE)
Alcohol Based	Shiseido “2e emulsion” by Shiseido ⁴	Lotion	Glycerin, xylitol, butylene glycol, behenyl alcohol, batyl alcohol, hydrogenated polydecene, dimethicone, squalane, pentaerythrityl tetraethylhexanoate, Simmondsia chinensis (JOJOBA) seed oil, PEG-60 glyceryl isostearate, PEG-5 glyceryl isostearate, carbomer, potassium hydroxide, sodium metaphosphate, phenoxyethanol, tocopherol, and water.	Moisturizer	Horimukai et al. ⁴
Alcohol +Paraffin based	Ceridal face cream by Steifel, GSK sold in Asia and North West Europe ²⁵	Cream gel ²⁶	Olea Europaea Oil, Glycerol, Pentylene, glycol, viscoleo oil, Hydroxyethyl Cellulose, Xanthan Gum ²⁶	Dry skin moisturizer	Carlsen et al. ²⁷ , Eric Simpson -CASCADE
	Vanicaream™ Moisturizing Cream for Baby ²⁸	Cream ²⁸	Purified water, petrolatum, sorbitol, cetearyl alcohol, propylene glycol, cetearth-20, simethicone, glyceryl stearate, PEG-30 stearate, sorbic acid, BHT ²⁸	Moisturizer to help irritated and dry skin; full body application; suitable for children of all ages. ²⁸	Eric Simpson- CASCADE

	Lipikar Balm AP+ Moisturizer For Dry Skin by Laroche-Posay ²⁹	Cream ²⁹	Aqua, butyrospermum parkii butter / shea butter, glycerin, dimethicone, niacinamide, paraffinum liquidum / mineral oil, cetearyl alcohol, brassica campestris oleifera oil / rapeseed seed oil, ammonium, poly-acryldimethyltauramide / ammonium poly-acryloyldimethyl taurate, peg-100 stearate, glyceryl stearate, peg-20 methyl glucose sesquisteate, cera microcristallina / microcrystalline wax, paraffin, sorbitan tristearate, dimethiconol, mannose, disodium edta, capryloyl glycine, vitreoscilla ferment, xanthan gum, pentaerythrityl tetra-di-t-butyl hydroxyhydrocinnamate, sodium benzoate	Dry skin moisturizer suitable for as young as 2 weeks of age ²⁹	Stephan Weidinger - EARLYEMOLLIENT - Feasibility of Early Emollient Use in Children With Atopic Eczema (EARLYemo)
Heparinoid +Alcohol based	Hirudoid soft ointment by Medinova	Heparinoid cream or gel	Heparinoid 0.3% w/w as active ingredient, anhydrous eucerine, emulsifying cetostearyl alcohol type A, glycerol, isopropyl alcohol, methyl parahydroxybenzoate(E218), myristyl alcohol, potassium hydroxide, propyl parahydroxybenzoate (E216), purified water, stearic acid and thymol. ³⁰	Local anti-coagulant preparation relieves pain and inflammation in addition to promoting healing ³⁰	Yamamoto-Hanada et al. ^{8, 14}
Ceramide based	EpiCeram® developed by Ceragenix ³¹ (acquired by Primus pharmaceuticals ³²)	Emulsion in tube or airless pump form	Ceramide (Hydroxypropyl Bispalmitamide MEA), conjugated linoleic acid (CLA), and cholesterol in patented 3:1:1 ratio, the ratio with the best efficacy to restore skin barrier function mimicking skin's natural lipid composition, Purified Water, MultiSal™ Neolipids*, Glyceryl Stearate, Squalane, Glycerin, PEG-100 Stearate, Petrolatum, Dimethicone, Phenoxyethanol, Citric Acid, Palmitic Acid, Xanthan Gum, Potassium Hydroxide, Disodium EDTA, Sorbic Acid, Capric Acid. *Proprietary microencapsulation system for gradual delivery of key ingredients including Ceramide, CLA, Cholesterol and Palmitic Acid (Formulated with E.Cerifera (Candelilla) wax, corn syrup solids, and modified food starch). Steroid-free, fragrance-free, paraben-free and propylene glycol-free. ³³	Prescription-only emulsion for affected skin in patients with AD; to be covered with a dressing of choice for broken skin. ³⁴ Only emollient, which has shown a benefit in reduction of food sensitization, ¹⁰ has low pH (~5), similar to physiological pH of skin, and contains free fatty acids that activate Peroxisome Proliferator-Activated Receptors (PPARs), ³⁵ which is reduced in AD.	Lowe et al. ^{5, 10} Sugarman et al. ⁷

	Triceram (previous name for EpiCeram® when it was over the counter ^{31, 36} by Ceragenix	Emulsion	Same as EpiCeram®; no changes in chemical structure (see above).	Same as EpiCeram® (see above)	Chamlin et al. ⁶
Paraffin +Ceramide based	Locobase REPAIR Cream by Daiichi Sankyo	Cream	Petrolatum, water, paraffin, mineral oil, glycerin, sorbitan oleate, carnauba wax, cholesterol, ceramide 3, oleic acid, palmitic acid, (acrylic acid / alkyl acrylate (C10-30)) copolymer, tromethamine. ³⁷	Dry skin moisturizer	Dissanayake et al. ¹³
	CeraVe Healing Ointment ³⁸	Ointment	Petrolatum, Paraffinum Liquidum / Mineral Oil / Huile Minerale, Paraffin, Ozokerite, Dimethicone, Aqua / Water / Eau, Ceramide Np, Ceramide Ap, Ceramide Eop, Carbomer, Sodium Lauroyl Lactylate, Proline, Cholesterol, Phenoxyethanol, Tocopheryl Acetate, Tocopherol, Hydrolyzed Hyaluronic Acid, Panthenol, Pantolactone, Phytosphingosine, Xanthan Gum, Ethylhexylglycerin ³⁸	Dry skin moisturizer ³⁸	Eric Simpson- CASCADE
Alcohol+ Ceramide based	Pigeon Baby Milk Lotion® by Pigeon ³⁹	Lotion	Water, Glycerin, Propanediol, Sodium Hyaluronate, Sodium Citrate, Citric Acid, PPG-4-Ceteth-20, Cholesteryl Isostearate, Dipotassium Glycyrrhizate, Dipropylene Glycol, Ceramide 2, Phenoxyethanol, Sodium Benzoate, Ethylhexylglycerin ³⁹	Mildly acidic dry-skin moisturizer ³⁹	Yonezawa K, et al. ⁹
	Cetaphil Restoraderm Eczema Soothing Moisturizer	Lotion	Colloidal Oatmeal 1% (active ingredient), Allantoin, Arginine, Behenyl AlcoholButyrospermum Parkii (Shea) Butter, Caprylic/Capric, Triglyceride, Caprylyl Glycol, Ceramide NP, Ceteareth-20, Cetearyl Alcohol, Cetyl Alcohol, Citric Acid, Cyclopentasiloxane, Dimethiconol, Disodium EDTA, Disodium Ethylene, Dicocamide PEG-15, Disulfate, Glycerin, Glyceryl Stearate, Glyceryl Stearate Citrate, Helianthus Annuus, (Sunflower) Seed Oil, Niacinamide, Panthenol, Pentylene Glycol, Sodium Hyaluronate, Sodium PCA, Sodium Polyacrylate, Sorbitol, Tocopheryl Acetate, Water ⁴⁰	Dry skin moisturizer, "colloidal oatmeal, ceramide and patented Filaggrin technology™ ⁴⁰	Mcclanahan et al ¹

Paraffin+ Alcohol + Ceramide based	CeraVe Moisturizing Cream ³⁸	Cream	Aqua / Water / Eau, Glycerin, Cetearyl Alcohol, Caprylic/Capric Triglyceride, Cetyl Alcohol, Ceteareth-20, Petrolatum, Potassium Phosphate, Ceramide Np, Ceramide Ap, Ceramide Eop, Carbomer, Dimethicone, Behentrimonium Methosulfate, Sodium Lauroyl Lactylate, Sodium Hyaluronate, Cholesterol, Phenoxyethanol, Disodium Edta, Dipotassium Phosphate, Tocopherol, Phytosphingosine, Xanthan Gum, Ethylhexylglycerin ³⁸	Patented delivery system for dry and very dry skin ³⁸	Eric Simpson- CASCADE
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Table C: Emollients that have been tested in clinical trials for Atopic Dermatitis

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