Role of atopic dermatitis management in the prevention of food allergy

Elizabeth Huiwen Tham[1], Kiwako Yamamoto-Hanada[2], Agnes Sze Yin Leung[3], and Yukihiro Ohya[2]

[1]National University of Singapore Yong Loo Lin School of Medicine
[2]Kokuritsu Kenkyu Kaihatsu Hojin Kokuritsu Seiiku Iryo Kenkyu Center Byoin Allergy Center
[3]The Chinese University of Hong Kong Department of Paediatrics

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Abstract

Food allergy is postulated to originate from cutaneous sensitization through a disrupted skin barrier, particularly in atopic dermatitis (AD). Strategies for food allergy prevention currently centre around early allergic food introduction, but there is now increasing evidence for the role of early skin barrier restoration in the form of prophylactic emollient therapy and early aggressive, proactive treatment of established AD for food allergy prevention. Research gaps that remain to be addressed include the type of emollient or anti-inflammatory medication which confers the greatest efficacy in preventive or proactive skin treatment respectively, the duration of therapy, and the window of opportunity for these interventions.

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Running title: Skin management for food allergy prevention

Elizabeth Huiwen Tham,[1,2,3] Kiwako Yamamoto-Hanada,[4,5] Agnes Sze Yin Leung,[6,7] Yukihiro Ohya[4,5]

[1]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore (NUS), Singapore

[2]Khoo Teck Puat-National University Children's Medical Institute, National University Health System (NUHS), Singapore

[3]Human Potential Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[4]Allergy Center, National Center for Child Health and Development, Japan

[5]Medical Support Center for Japan Environment and Children's Study (JECS), Natonal Center for Child Health and Development, Japan

[6]Department of Paediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong Special Administrative Region (HKSAR)

[7]Hong Kong Hub of Paediatric Excellence, The Chinese University of Hong Kong, HKSAR

Corresponding Author

Elizabeth Huiwen Tham

Division of Allergy, Immunology & Rheumatology, Department of Paediatrics

Khoo Teck Puat - National University Children's Medical Institute

National University Health System, Singapore

1E Kent Ridge Road, NUHS Tower Block Level 12, Singapore 119228

DID: (65) 6772 4420 | Fax: (65) 6779 7486

Email: elizabeth_tham@nus.edu.sg

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Abstract

Food allergy is postulated to originate from cutaneous sensitization through a disrupted skin barrier, particularly in atopic dermatitis (AD). Strategies for food allergy prevention currently centre around early allergic food introduction, but there is now increasing evidence for the role of early skin barrier restoration in the form of prophylactic emollient therapy and early aggressive, proactive treatment of established AD for food allergy prevention. Research gaps that remain to be addressed include the type of emollient or anti-inflammatory medication which confers the greatest efficacy in preventive or proactive skin treatment respectively, the duration of therapy, and the window of opportunity for these interventions.

Keywords

Atopic dermatitis, eczema, food allergy, treatment, skin barrier, prevention

Introduction

Early onset atopic dermatitis (AD) has been strongly linked with food allergy.[1] The dual-allergen exposure hypothesis postulates that food allergy pathogenesis arises from a disrupted skin barrier in early life which promotes allergen penetrance, cutaneous sensitization and downstream Th2 cytokine dysregulation and production of antigen-specific IgEs, manifesting in clinical allergy upon oral challenge.[2] Conversely, oral exposure to food allergens before this pathway has been established promotes tolerance. Early introduction of allergenic foods, either single foods like egg or peanut, [3, 4] or multiple foods[5] to infants at high-risk of food allergy have been shown to reduce the risk of food allergy development.

Other strategies for food allergy prevention have centered mainly around primary prevention of AD, and thus prevention of food allergy as a secondary effect. However, recent studies have suggested that in the presence of established AD, secondary prevention of food sensitization or even food allergy might be achieved through aggressive treatment of AD in early infancy.[6, 7] This would potentially restore the disrupted skin barrier before the development of cutaneous sensitization. This review thus aims to summarize emerging strategies in skin management for food allergy prevention.

Evidence for epicutaneous sensitization in FA pathogenesis

In support of the dual allergen exposure hypothesis, epicutaneous exposure to food allergens induces a potent pro-allergic Th2 immune response, leading to systemic food-allergic reactions, including anaphylaxis, on

subsequent oral exposure in mice.[8]Murine models have consistently shown that epicutaneous sensitization through an impaired skin barrier primes the gut for subsequent allergic reactions more effectively than oral or intraperitoneal sensitization.[8-10] IL-33 is released by mechanical skin injury and interacts with ST2 receptors on mast cells, resulting in expansion of intestinal mast cells, increased intestinal permeability, and anaphylaxis following oral exposure in mice.[11, 12]Furthermore, skin barrier disruption worsened symptoms of food allergy (FA) even after allergen exposure was removed, whereas topical steroid treatment could reduce allergic reactions in mice.[13]One of the mechanisms for epicutaneous sensitization is thought to occur through enhanced cutaneous antigen capture by activated Langerhans cells which penetrate tight junctions to a greater extent in AD lesional skin compared to healthy skin.[14]

Epidemiological studies have found a link between exposure to environmental food allergens through the skin, and the development of food sensitization and allergy. The Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort was the first to report that 90% of peanut-allergic children with AD had been exposed to peanut creams containing *Arachis* oil in the first six months of life.[15] In children with peanut allergies, a dose-response relationship was observed between environmental peanut exposure and peanut allergy development.[16] In children with FLG mutations, greater quantities of household peanut protein exposures significantly raised the risk of peanut sensitization.[17]

Cutaneous sensitization can also occur through high-dose, high frequency skin exposures even with an intact skin barrier. Fukutomi et al. reported that among Japanese women, contact exposure to hydrolysed wheat protein in facial soaps was significantly associated with an increased risk of wheat allergy.[18] Boussault et al. noted that children with AD exhibited greater oat sensitization compared to unexposed children, which could be attributed to repeated application of oat-based cosmetics on their inflamed skin.[19]Preliminary evidence also suggests that clinically significant coconut allergy is more common in topical coconut emollient users.[20]

The use of multi-omic analyses have further enhanced our understanding of epicutaneous sensitization of food allergens. Earlier studies have shown that microbial dysbiosis, characterized by an overgrowth of*Staphylococcus aureus* , is associated with skin barrier dysfunction as it degrades epidermal structural proteins and metabolizes lipids.[21, 22] A temporal association was also evident, in which the increased *S. aureus* abundance was found to precede the onset of AD in birth cohort studies.[23-25]Furthermore, in a study that utilized minimally invasive skin tape stripping (STS), children with AD and FA were found to have increased transepidermal water loss (TEWL) that was associated with higher levels of *S. aureus* abundance, lower filaggrin breakdown fatty acid content and enhanced type 2 immune responses in their non-lesional skin, as compared to those without FA and nonatopic controls.[26] Other evidence has also shown that*S. aureus* colonization in humans prevented natural tolerance to cow's milk, hen's egg, and peanut, and disrupted oral tolerance induction to peanut.[27] There is likely a complex multidirectional interplay among these various factors on the risk of AD and FA, which also depends on the genetic and environmental factors impacting a given individual. Overall, a growing body of evidence supports the hypothesis that the development of food sensitization and allergy is primarily caused by an inflamed skin barrier with perturbed skin microbiome.

Skin barrier therapy for AD and FA prevention

Consequently, skin care interventions in early life have been explored as a strategy for AD and FA prevention, through reduction of transepidermal water loss (TEWL) and skin barrier repair before onset of disease. In 2014, two separate randomized controlled trials (RCTs) from USA/UK and Japan were published simultaneously, demonstrating that the application of moisturizers in high-risk infants with a family history of AD in the first 2 months of life reduced AD risk by age 6 and 9 months.[28, 29] Horimukai et al[28]found no significant differences in egg sensitization at 32 weeks, but Simpson et al[29] did not assess food sensitization or FA outcomes. In 2020, two large randomised controlled trials conducted in Norway / Sweden (Preventing Atopic Dermatitis and ALLergies in childhood - PreventADALL study) and the United Kingdom (Barrier Enhancement for Eczema Prevention – BEEP study) also failed to demonstrate any effect of skin emollient applications on AD development in normal-risk (PreventADALL) or high-risk (BEEP) infants.(Table 1)[30, 31] PreventADALL further found that there was also no benefit of this intervention against food sensitization or FA by age 36 months.[32] The BEEP study, however, showed a trend towards increased FA in children who

received the skin intervention, although this was statistically non-significant.[31] The Prevention of Eczema By a Barrier Lipid Equilibrium Strategy (PEBBLES) pilot study in 80 infants used a ceramide-dominant triple lipid moisturizer in high-risk infants from the first 3 weeks of life for 6 months, and reported a trend towards reduced incidence of AD and food sensitization at age 12 months.[33] Longitudinal follow up is still ongoing to assess the impact of this intervention on food allergy outcomes.[34] The Short-term Topical Application to Prevent Atopic Dermatitis (STOP AD) trial found that daily application of an emollient containing ceramides, fatty acid and oats for the first 8 weeks of life reduced the incidence of atopic dermatitis at age 6 and 12 months in high-risk infants, compared to standard skin care.[35] There were, however, no significant differences in food sensitization rates between both groups, but its impact on food allergy could not be assessed due to small numbers.

A Cochrane meta-analysis by Kelleher et al found that all types of early skin interventions, inclusive of bath oils, bathing practices as well as emollients, anytime in the first year of life were not protective against AD development, and could potentially increase the risk of skin infections.[36] Another meta-analysis examined the effect of only emollients in the first 6 weeks of life on AD development at any age and found that this intervention was potentially efficacious in high-risk populations but not in normal-risk infants; might delay rather than completely prevent AD onset; and was of benefit if applied continuously rather than with an interval between treatment cessation and AD outcome assessment.[37] Both meta-analyses found a similar trend towards increased food sensitization, albeit powered only by the BEEP study at that time.

Combined interventions

Dissanayake et al explored the utility of a combined intervention approach in a 2x2 factorial trial where one group received a combination of synbiotics and a ceramide-based emollient from birth to 6 months, a second group received synbiotics only, a third group emollient alone and a last group with no intervention (Table 1).[38]However, they found no differences in food sensitization or FA prevalence by age 1 year between any of the groups. PreventADALL also had four study arms: skin intervention alone; early allergenic food introduction alone; combined skin and food intervention; and no intervention. FA prevalence was only reduced in the arm receiving early allergenic food introduction as compared to no intervention, akin to the LEAP study,[3] but no difference compared to the skin intervention group.

Types of skin intervention

One of the possible reasons for the variable findings in the above clinical trials is the type of skin intervention used. Most commercially available moisturizers are either oil-based (emollients), water-based (humectants) or occlusives and each have different effects on the skin barrier, TEWL, skin pH and stratum corneum hydration status. A head-to-head study comparing different types of emollients in adults with AD found that both glycerol-only and urea-glycerol combination emollients were able to improve TEWL and natural moisturizing factor (NMF) levels, and protected against skin irritation caused by sodium lauryl sulphate (SLS) exposure.[39] However, paraffin-based emollients had no effect on the skin barrier and even reduced NMF levels in the skin. Paraffin- or petrolatum- based emollients were, however, one of the most common types of emollients used in the moisturizer trials.[30-32, 40] The Effective Prevention of Atopic dermatitis by applying Fams baby (PAF) study found that a commercial emollient (Fams baby) applied once daily in high-risk infants from birth to age 32 weeks reduced both AD and food allergy risk compared to twice daily application and also in comparison to another commercial emollient (2e). (Table 1) [41] Both emollients contained a combination of various ingredients, thus while it is difficult to identify the active ingredient which may exert a greater effect in allergy prevention, these findings suggest a role for further research into this area.

Earlier murine studies demonstrated that the optimal concentration of lipid mixtures that was able to accelerate skin barrier recovery was a combination of cholesterol, ceramides, essential and non-essential free fatty acids in a 3:1:1:1 ratio, with cholesterol as the dominant lipid.[42] A test cream containing this tri-lipid combination was shown in a subsequent clinical trial to be able to improve skin integrity and hydration, reduce TEWL and SLS-induced irritation to a greater extent than a basic emollient.[43] Newer generation

moisturizers now incorporate a 3:1:1 ratio of cholesterol, ceramides, and free fatty acids to maintain a skin composition and pH which is most similar to the human skin's natural composition.

A small pilot study compared the effects of 12 weeks of total body application of daily tri-lipid cream (EpiCeram, provided by Primus Pharmaceuticals) vs a paraffin/petrolatum-based cream (Aveeno) in infants between 4 and 9 months with and without dry skin/AD.[44] They found that infants using the tri-lipid cream had lower total IgE, higher total IgG4, lower peanut-specific IgG4/IgE ratios, as well as lower levels of pro-inflammatory IL-4+ expressing CD4+ T cells and higher levels of IL-10+ expressing and LAP+ -expressing CD4+ T cells than infants using the paraffin/petrolatum-based cream. This suggests that the tri-lipid emollient was superior to the paraffin/petrolatum-based cream in reducing Th-2 proinflammatory responses and promoting tolerogenic T cell pathways. The ongoing PEBBLES study also used a similar tri-lipid, ceramide dominant emollient as its primary intervention.[33] Its promising pilot findings of reduced AD and food sensitization in the treatment arm suggests that tri-lipid emollients may also be superior to basic paraffin/petrolatum-based moisturizers in AD and FA prevention.

Bathing frequency and type of bath oils could also impact the skin barrier. The Enquiring About Tolerance (EAT) study enrolled normal-risk infants at birth to examine the effect of early allergenic food introduction on food allergy outcomes.[45] A post-hoc analysis in this study found that increased bathing frequency was associated with increased TEWL, even after excluding infants with existing AD in a sensitivity analysis. Bath oils and emollients were also used more frequently in infants who had raised TEWL levels, suggesting the possibility that early bathing practices with skin interventions causing skin barrier disruption could account for increased rates of food sensitization or food allergy. However, a subsequent publication did not find significant associations between bathing frequency and food allergy overall in this cohort.[46] In this follow-up study, however, increased use of moisturizer at 3 months of age was associated with increased food sensitization and food allergy, assessed at 1 and 3 years of age, even in those with no visible eczema at baseline.[46] Each additional moisturization per week was associated with an 18% increase in the odds of developing food allergy in infants without visible eczema; and 20% in infants with eczema. Parental reports suggested that the most common type of moisturizers used in EAT was olive oil. There was, however, insufficient power to analyze the type of moisturizer formulation against FA risk in this study. It could thus be postulated that topical moisturizer applications could either increase skin exposure to food allergens on the hands of caregivers; facilitate passage of food allergens across the skin barrier or may have a direct deleterious effect on the skin barrier which allows passage of the food allergen through to the dermis.

Eczema treatment for food allergy prevention

In established eczema, early intervention to prevent food sensitization or clinical food allergy, the next stage in the pathogenesis of the atopic march, is paramount. Several studies have examined various modes of eczema treatment approaches for food allergy prevention. A systematic review found that targeting only barrier repair through skin care did not prevent food allergy.[47] Schneider et al.[48] reported that pimecrolimus 1% cream applied in a reactive treatment (i.e., application only on visible eczema lesions) did not prevent food allergy in infants with atopic dermatitis. Weak anti-inflammatory medications used in the reactive treatment for clinical lesions alone might thus be insufficient to prevent food allergy development. It was thus hypothesized that sufficient anti-inflammatory treatment for both clinical and subclinical skin lesions may be required, through a proactive approach.

Proactive treatment is a long-term maintenance approach using anti-inflammatory agents for active and previously active flare-prone skin to treat chronic subclinical skin inflammation and prevent flares-up.[49, 50] Proactive treatment that follows initial induction of remission has been used for long-term control of persistent atopic dermatitis.[51, 52] Fukuie et al conducted a randomized open-label trial comparing proactive topical corticosteroid therapy (twice weekly application to all previous flare areas after complete resolution of a flare) to reactive therapy (topical corticosteroids only during a flare) in children aged 3 months to 7 years with moderate to severe AD.[53] The proactive group experienced significant reductions in AD severity, quality of life scores and serum TARC levels compared to the reactive group. Another observational study found that infants aged 1-4 months who received active eczema treatment with topical glucocorticoids for 10 days

followed first by maintenance therapy with pimecrolimus 1% cream twice daily for 3 months, and continued on pimecrolimus twice daily three times a week until age 1 year had a lower risk of food allergen sensitization compared with infants who received only reactive treatment with topical steroids during eczema flares. [54] A retrospective study by Miyaji at al.[6] also suggested that early enhanced proactive topical steroid therapy on both clinical and subclinical skin lesions of infants with atopic dermatitis might prevent the onset of food allergy. Yamamoto-Hanada et al.[55, 56] subsequently conducted a randomized controlled trial, the Prevention of Allergy via Cutaneous Intervention (PACI) Study, to examine the efficacy of early aggressive, proactive treatment of infant eczema for prevention of hen's egg allergy. They found that early enhanced proactive treatment of both visible and non-visible eczema lesions in infants with a low potency topical steroid cream from birth resulted in a 25% reduction in hen's egg allergy onset at the age of 28 weeks when compared with reactive therapy - conventional treatment targeting only visible eczema lesions. The PACI study thus demonstrated proof of principle that enhanced proactive treatment targeting both clinical and subclinical lesions of early-onset eczema could reduce food allergy risk, confirming the importance of adequate treatment of eczema for food allergy prevention. However, there was a trend towards reduced body weight and height in the enhanced treatment group compared to the conventional group, suggesting that further refinement of this approach is likely required. For example, the potency and duration of topical steroid applications may require tailoring according to the severity of skin inflammation. Non-steroid topical ointments such as topical PDE4 inhibitors and topical JAK inhibitors may also be safer alternatives but have yet to be studied in this context.

The Stopping Eczema and Allergy (SEAL) study [NCT03742414] is an ongoing randomized, controlled, parallel design, open-label phase 2 clinical trial which is recruiting infants from who have already developed atopic dermatitis (AD or eczema) by 12 weeks of age. The study aims to compare the efficacy of proactive treatment with a tri-lipid skin barrier cream (Epiceram) versus a moisturizer, plus proactive use of a topical corticosteroid: fluticasone propionate cream 0.05%, against reactive AD therapy as standard care, in reducing the occurrence and severity of AD in early infancy and for prevention of FA. The primary outcome is challenge-proven food allergy at age 3 years, and secondary outcomes include changes in baseline AD severity (Scoring Atopic Dermatitis (SCORAD)) at ages 1, 2 and 3 years. The results of this study will shed further insights into the utility of early aggressive AD therapy for FA prevention.

Existing measures for food allergy prevention, such as early introduction of allergenic foods, may be less efficacious in infants with uncontrolled eczema. In the Prevention of Egg Allergy with Tiny Amount Intake (PETIT) study, Natsume et al. showed that infants with poorly controlled eczema developed hen's egg allergy despite early introduction of hen's egg.[57] In the Learning Early About Peanut allergy (LEAP) study, the protective effect of early peanut introduction was lower in infants with severe eczema (67% reduction) compared with children with mild (85% reduction) and moderate (87% reduction) eczema.[58] This suggests that in infants with moderate to severe eczema, it is essential for a combination of skin (adequate eczema control) and oral (early allergenic food introduction) interventions to be implemented in tandem for the greatest protective effect against food allergy development prevention, in line with the dual-allergen exposure hypothesis.[59, 60]

Conclusions

The existing literature suggests that selected skin interventions, such as tri-lipid emollient use from birth in high-risk infants and proactive treatment of AD in early life might reduce the risk of AD and FA. There remains, however, several gaps that could be addressed in future studies. The window of opportunity in early infancy for skin treatment for AD and FA prevention appears to be narrow, as AD onset is typically in the first 2 months of life. Future research could focus on answering specific gaps which include the type of emollient or anti-inflammatory medication to be used as prophylactic or proactive AD therapy respectively; duration of skin treatment; frequency of applications; specific body sites, lesional vs non-lesional skin and total body surface area to be treated; how to identify high-risk infants at birth; and the utility of combination therapies or non-steroid-based immunomodulators for pro-active AD treatment. Deeper endophenotyping to identify biomarkers for high-risk infants who would benefit from these interventions would further enhance

the efficacy of targeted interventions.

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Impact statement

There is now increasing evidence for the role of early skin barrier restoration in the form of prophylactic emollient therapy in high-risk infants and early aggressive, proactive treatment of established atopic dermatitis for food allergy prevention

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Table 1: Early Skin interventions for prevention of food sensitisation and food allergy

Study, year, country, (study name), population type	**Number per arm**	**Intervention type & duration of intervention**	**Food sensitization measure used**	**Food sensitisation outcomes**	**Food allergy (FA) outcome measure used**	**Food allergy (FA) outcomes**
Horimukai et al 2014, Japan[28] Study period: Nov 2010 - Nov 2013 High risk infants	n = 118 Intervention = 59 control = 59	Emulsion-type moisturizer (2e [Douhet] emulsion) Within 7 days of birth to 32 weeks or until eczema onset	sIgE to egg white and ovomucoid at 32 weeks	**Egg white:** Intervention = 42%, control = 45% **Ovomucoid:** Intervention = 19%, control = 6.8%	NA	NA
Dissanayake et al 2019, Japan[38] Study period: Oct 2012 to Mar 2014 Normal risk infants	n = 275 Intervention = 138 control = 120	Ceramide-based emollient 2-3x/day on cheeks, peri-oral area or any other parts of the body Birth to 6 months	sIgE to egg white, milk and ovomucoid at 9 months	**Egg or milk:** Intervention = 60.5%, Control = 46.1%	Parent questionnaire at 1 year	**Egg or milk:** Intervention = 11% control = 13%
Lowe et al, 2017, Australia (PEBBLES pilot)[33] Study period: May 2013 - July 2014 High risk infants	n = 80 Intervention = 41 Control = 39	Ceramide-dominant tri-lipid moisturizer (Epiceram) 2x/day for at least 3 days per week Within first 3 weeks of life to 6 months	SPT to egg, milk, peanut at 6months and 12months	Egg, milk or peanut (6mth) Intervention = 12.8% control = 22.9% Egg, milk or peanut (12mth) Intervention = 8.8% control = 19.4% Egg (6mth) Intervention = 10.3% control = 17.1% Egg (12mth): Intervention = 5.9% control = 16.7%	NA	NA

Study, year, country, (study name), population type	**Number per arm**	**Intervention type & duration of intervention**	**Food sensitization measure used**	**Food sensitisation outcomes**	**Food allergy (FA) outcome measure used**	**Food allergy (FA) outcomes**
Chalmers et al 2020, United Kingdom (BEEP)[31] Study period: Nov 2014 - Nov 2016 High-risk infants	n = 1394 Intervention = 693 Control = 701	Petrolatum-based emollients applied at least 3-4 times per week to most of the child's body (at least two of face and neck, arms and legs, or trunk) Birth to 1 year	SPT to milk, egg and peanut at 2 years	**Egg, milk, or peanut:** Intervention = 12%, control = 9% **Egg:** Intervention = 9%, control = 7%	Oral food challenge to milk, egg and peanut at 2 years	**Egg, milk or peanut:** Intervention = 7%, control = 5% **Egg:** Intervention = 6%, control = 4%
Bradshaw et al, United Kingdom (BEEP 5 year follow up)[40] Study period: Nov 2017 – Nov 2021 High-risk infants	n = 976 Intervention = 467 Control = 509 (completed qnn at 5 yr)	Petrolatum-based emollients applied at least 3-4 times per week to most of the child's body (at least two of face and neck, arms and legs, or trunk) Birth to 1 year	NA	NA	Parental report of clinical diagnosis of FA at 3, 4, 5 years	**Intervention:** 3 years = 9% 4 years = 6% 5 years = 4% Ever FA = 15% **Control:** 3 years = 5% 4 years = 3% 5 years = 3% Ever FA = 14%
Skjerven et al 2022, Norway / Sweden (PreventADALL 3 year follow up)[32] Study period: April 2015 – April 2017 Normal risk infants	n = 2397 (total) Skin intervention = 575 Food intervention = 642, Combined (skin + food) = 583 Controls = 596	Skin intervention: Application of paraffin-based cream and emulsified oil baths to face for at least 3-5 days per week for at least 16 weeks of the full 25 weeks Before 4 weeks of age, for 25 weeks	Skin prick test	**Skin intervention group:** Any food = 2.2% Peanut 2.0% Milk 0.1% Wheat 0.3% Egg 0.6% **No skin intervention group:** Any food = 2.4% Peanut 1.6% Milk 0.1% Wheat 0.2% Egg 0.8%	Parental interview +/- skin prick test	**Skin intervention group:** Any food = 2.1% Peanut 1.6% Milk 0.1% Wheat 0% Egg 0.5% **No skin intervention group:** Any food = 1.6% Peanut 1.1% Milk 0.2% Wheat 0% Egg 0.5%

Study, year, country, (study name), population type	**Number per arm**	**Intervention type & duration of intervention**	**Food sensitization measure used**	**Food sensitisation outcomes**	**Food allergy (FA) outcome measure used**	**Food allergy (FA) outcomes**
Chaoimh et al 2022 United Kingdom (STOP-AD)[35] Study period: Apr 2019 – Nov 2020 High risk infants	n= 321 Intervention = 161 Control = 160	Ceramides, oat, fatty acid containing moisturizer twice daily to whole body excluding scalp for first 8 weeks Birth to 2 months	Skin prick test	Intervention = 3.3% Control = 3.6%	NA	NA
Inuzuka et al 2023 Japan (PAF)[41] Study period: August 2020 – September 2021 High-risk infants	n= 60 Intervention A = 20 Intervention B = 20 Active control = 20	Intervention A: Emulsion-type moisturizer (Fam's baby) twice daily Intervention B: Emulsion-type moisturizer (Fam's baby) once daily Active control: Emulsion-type moisturizer (2e [Douhet] emulsion) Within 7 days of birth to 32 weeks or until eczema onset	sIgE to egg white, ovomucoid, milk, wheat, soy, peanut.	**All intervention groups**+ egg white (median) =0.0 UA/ml, ovomu-coid(median) =0.0 UA/ml, milk(median) =0.0 UA/ml, wheat (median) =0.0 UA/ml, soy(median) =0.0 UA/ml, peanut. (median)=0.0 UA/ml	Parental interview	**Any food allergy**+ Intervention A= 0% Intervention B= 5% Active control C= 0%

Study, year, country, (study name), population type	**Number per arm**	**Intervention type & duration of intervention**	**Food sensitization measure used**	**Food sensitisation outcomes**	**Food allergy (FA) outcome measure used**	**Food allergy (FA) outcomes**
Yamamoto-Hanada et al 2023, Japan[55] Study period: Jul 2017 – Feb 2021 (PACI) Infants with early-onset eczema at 7-13 weeks of age	n = 640 Intervention = 318 Control = 322	Enhanced early skin treatment (modified proactive treatment) or conventional reactive treatment using topical corticosteroids From 7-13 weeks til 28 weeks of age	sIgE to egg white, ovomucoid, milk, wheat, soy, peanut. Ara h 2 at 28 weeks of age	**Egg white:** Intervention = 44.9%, control =52.9% **Ovomucoid:** Intervention = 7.6%, control =10.1% **Milk:** Intervention = 14.6 Control = 14.2% **Wheat:** Intervention = 6.1% Control = 4.7% **Soy:** Intervention = 3.5% Control = 2.2% **Peanut:** Intervention = 1.0% Control = 2.5% **Ara h 2:** Intervention = 0.0% Control = 0.0%	Oral food challenge for egg allergy Food allergy diagnosis during intervention (doctor's interview)	**Egg allergy** Intervention = 31.4% Control = 41.9% **Food allergy diagnosis during intervention** Intervention = 1.57% Control = 1.55%

+ Unpublished data provided by the authors of the PAF study