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Invited Review Article

Prevention of food allergy – skin barrier interventions

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ABSTRACT

The relationship between infant skin health and food allergy pathogenesis is the focus of intense research activity, on the basis that interventions to improve infant skin health may potentially lead to the prevention of food allergy. Current evidence does not provide conclusive findings on the mechanisms of food allergy development but does support the possibility that food allergy develops through transcutaneous sensitisation to allergenic peptides. In this article, we review the evidence for this model of food allergy development, assess strategies currently being tested for prevention of food allergy through cutaneous interventions, and identify key knowledge gaps which might be explored in future work.

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Introduction

Allergic diseases are among the most common chronic health conditions affecting young people in many regions of the world.¹ Food allergy specifically affects between 4 and 8% of children.^{2,3} It is not just a disease of childhood, with IgE mediated food allergy reported by up to 10% of adults.⁴ The risk factors and determinants of food allergy pathogenesis are not yet clear but may include altered microbial exposures, nutritional factors such as vitamin D status, or other features of urbanisation and specific exposures related to small family size.⁵

Atopic dermatitis (AD) is typically the first allergic disease to manifest in early childhood, affecting up to 30% of young children in some regions. AD is strongly associated with risk of allergic sensitisation to both inhaled and food allergens.⁶ In young infants with early onset AD (<3 months) who require prescription topical steroids, IgE mediated food allergy confirmed by oral food challenge occurs in up to 50%.⁷

Recent studies have identified the first interventions with proven efficacy for primary prevention of allergic diseases, with early ingestion of allergenic foods now shown to reduce risk of food sensitisation and allergy.^{8,9} An important limitation of early allergenic food introduction as a strategy to prevent food allergy is that it works in an allergen-specific manner, with no evidence to date of

bystander tolerance induction effects. This means that multiple food introductions are necessary to prevent all food allergy. Studies where more than one allergen have been introduced at a time have been less effective, highlighting that multiple, regular allergenic food introduction in young infants is relatively burdensome, limiting its potential for food allergy prevention.⁹

A second area of current interest in primary prevention, with potential to prevent allergy to more than one food, or more than one allergic disease concomitantly, is prevention of transcutaneous sensitisation during infancy. This may be achieved in a number of ways – by reducing cutaneous allergen exposure, preventing activation of the cutaneous immune system or limiting interaction between allergens on the skin and the local immune system through promotion of skin barrier function. Some approaches would aim to limit sensitisation to food allergens alone, others could potentially impact on both food and inhalant sensitisation and overall skin health and thereby prevent eczema, food allergy, allergic rhinoconjunctivitis and/or asthma.

In this review we will focus specifically on food allergy and examine the evidence that the skin is an important site for allergic sensitisation in early life. We will also explore how transcutaneous sensitisation to food allergens might potentially be prevented, summarising approaches currently being field tested and others which might be investigated in the future.

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Evidence for the skin being an important site for allergic sensitisation to foods in early life

Animal studies

The relationship between a disrupted skin barrier and food allergy is demonstrated in murine studies. Mice who were exposed to food antigens peanut and ovalbumin across a stratum corneum which was disrupted by tape stripping, mimicking atopic dermatitis, demonstrated a potent systemic immune response to the antigen.¹⁰ In a further study examining the differences between first exposure route, mice that were primarily exposed to peanut via a transcutaneous route had increased levels of peanut allergy than those who had initial oral exposure. The mice with initial oral exposure actually became tolerant to peanut, whereas mice with initial skin exposure never became tolerant to peanut, and in fact demonstrated symptoms suggestive of anaphylaxis at oral dose.¹¹ Most of the evidence for transcutaneous sensitisation has focused on peanut antigen, however this work has been replicated in mice using β -lactoglobulin, a major cow's milk antigen.¹²

Genetic studies

The major genetic risk factors for AD are genetic variants which lead to increased skin permeability and reduced skin barrier function.¹³ The gene encoding for Filaggrin (FLG) is the most studied gene in this area. FLG is a filament binding protein in the stratum corneum. FLG mutation carriers are known to have an increased risk of AD and a significant increase in the risk of peanut allergy, suggesting that a defect in the skin barrier is associated with the increase risk of development of peanut allergy.^{14,15} FLG mutations are also associated with asthma and allergic rhinitis, and with allergic sensitisation.¹⁶ Other genetic risk factors for food allergy are often genetic variants associated with skin barrier dysfunction too. A defect in SPINK-5 gene mutation, causes Netherton syndrome, a severe autosomal recessive skin disorder associated increased IgE levels and hair shaft abnormalities.¹⁷ Variants

of this mutation have recently been associated with increased risk of food allergy, in children who do not express other phenotypic features of Netherton syndrome.¹⁸ Interestingly, the association between FLG mutation status and food allergy is also independent of the presence of AD.¹⁹ This suggests that disruption of skin integrity may be an important first step in the pathogenesis of food allergy and may not depend on the presence of clinically manifest inflammation in the skin. The lack of direct heritability and the lack of complete concordance in twin studies demonstrates that allergic diseases are multifactorial and not dependent solely on genetic factors.²⁰ However, gene–environment interactions are likely to be important in food allergy pathogenesis since there are clear genetic risk factors which appear to interact with environmental exposure to lead to food allergy. Figure 1 is a simplified schema to suggest how allergic sensitisation to foods may work in the context of impaired skin barrier function.

In vitro studies

Evidence for cutaneous exposure to food antigens leading to food hypersensitivity is also seen in *in vitro* studies. CLA (Cutaneous Lymphocyte antigen) is a surface homing receptor on T lymphocytes which originates from dermal venules. It is used as a surrogate marker for initial transcutaneous exposure to an antigen. The T cell proliferative response to peanut in peanut allergic children is predominantly CLA dominant, suggesting that peanut sensitisation is likely to have occurred via the cutaneous route. Children who were peanut tolerant, on the other hand, had a mixed CLA/ $\alpha 4\beta 7$ T cell response, i.e. T cells expressing a gastrointestinal homing marker. This suggested peanut tolerant children had experienced primary peanut exposure via the gastrointestinal tract.²¹

Observational human studies

AD has long been closely associated with food allergy. The rates of confirmed IgE mediated food allergy in patients with AD range from 30% to over 50%, depending on the population surveyed.^{22,23}

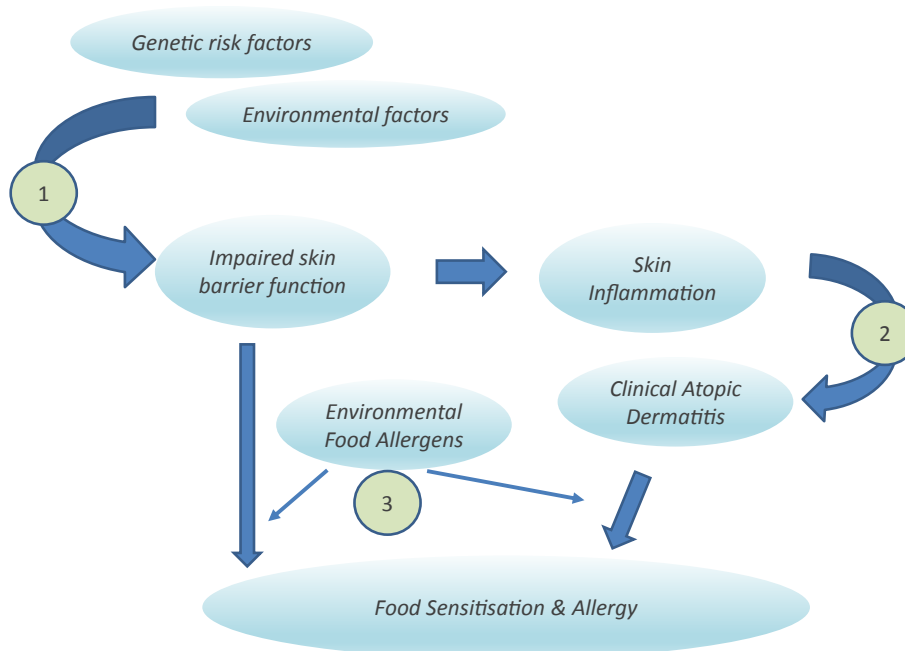


Fig. 1. Potential mechanism explaining the relationship between infant skin health, AD and FA. 1, Protecting the skin barrier; 2, Decreasing skin inflammation; 3, Reducing environmental allergen.

Most children with AD have mild AD. However, as shown in the study discussed above, children with moderate to severe AD have an increased prevalence of food allergy.⁷ Participant data from the EAT study showed that children with AD were significantly more likely that those without AD to be sensitised to food allergens, with severity of AD being an independent risk factor for food allergen sensitisation.²⁴ More direct evidence for a relationship between skin barrier and food allergy is seen in the Avon Longitudinal Study of Parents and Children cohort, where both skin inflammation, and the direct application of antigen to infant skin, in the form of peanut containing skin oils, were associated with food allergy.²⁵ Transcutaneous sensitisation is also supported by observations that peanut protein levels in the household environment, which relate to household consumption,²⁶ are associated with risk of peanut allergy when there is a genetically defective skin barrier, or in the presence of clinical atopic AD.^{27,28}

What is the mechanism underlying the relationship between the skin and food allergy?

So there is clear evidence from both genetic, epidemiological and murine studies, that defective infant skin function is associated with food sensitisation and food allergy, and there is some evidence for an association between skin inflammation in the form of AD, and increased risk for food allergy. It is however unclear whether these relationships are due to i. an underlying skin barrier defect being a key determinant of food allergy risk, ii. skin inflammation secondary to defective skin barrier as the key determinant of food allergy or iii. a non-causal association – with shared genetic risk factors manifesting in different organ systems concurrently. We will examine each potential explanation individually, as each one has different implications for interventions to prevent food sensitisation and allergy.

i. Skin barrier effect

There is significant support for the hypothesis that skin barrier dysfunction, rather than skin inflammation *per se* explains the relationship between markers of skin health in infancy and allergic sensitisation disease. The early skin barrier undergoes changes at birth, with the adaption to the non-aquatic extra-uterine environment. Neonatal skin has a thinner stratum corneum, less natural moisturising factor and lipids than adult skin.²⁹ Despite this, trans-epidermal water, as a non-invasive measurement of skin barrier function, is initially lower at birth, and increases over the first two months of life whereby it plateaus by 6 months.³⁰ Healthy adult trans-epidermal water loss (TEWL) is dependent on the body area measured, however when compared to the forearm, where infant measurements are routinely taken, adult TEWL levels are significantly lower than in infants at any time.³¹ This suggests that infants have an impaired barrier function compared to adults, and that skin barrier changes the most in the first two months of life.

It is well established that there is increased transepidermal loss in both affected and clear looking skin in those with AD, first described in the 1980s.³² However changes were also seen in skin barrier function before the development of AD or food allergy in a group of UK children enrolled in a food allergy prevention study.³³ Taken together, these data suggest that skin barrier function is related to atopic dermatitis and likely food allergy risk. The data also suggest that use of TEWL as a marker for the skin's ability to retain water appears to be a reasonable surrogate for skin barrier function which prevents antigens, including potentially sensitising food antigens, from crossing the stratum corneum and encountering antigen presenting cells.

ii. Shared genetic risk factors manifesting in different organ systems

FLG and other epidermal barrier proteins are highly expressed in the skin. However, they are also expressed in the upper part of the oesophagus and mouth.³⁴ So, it is not yet certain that transcutaneous sensitisation explains the relationship between FLG mutations, AD and food sensitisation or allergy. It is possible that separate processes account for the relationship between FLG mutations and AD (in the skin), and between FLG mutations and other allergic diseases (in the oropharynx or oesophagus). Similarly although increased household peanut is associated with increased peanut allergy, and such an association is greatest for those with AD or FLG mutations this association does not directly prove transcutaneous sensitisation to peanut.²⁶ Sensitisation to household peanut may not occur through direct topical exposure, but rather through inhalation or ingestion of environmental peanut. In mice when cholera toxin, which disrupts the gastrointestinal mucosa, is administered alongside a known allergen it will induce sensitisation to allergens even when given orally.³⁵ So perhaps the skin barrier is not the only barrier involved in sensitisation to food allergens. The finding that both FLG and SPINK-5 genetic associations with food allergy are of similar strength, whether or not AD is present, supports the possibility of independent processes for AD and food allergy development.¹⁹

iii. Skin inflammation that accompanies AD

As discussed above, there is for a strong association between skin inflammation, in the form of clinically apparent AD, and food sensitisation and allergy.⁷ The dose–response relationship between AD severity in infancy and risk of food allergy suggests the possibility of a causal relationship between AD severity and the pathogenesis of food allergy. Possibilities are that skin inflammation, the functional impairments which predispose to it, or the treatments that are applied to manage it, may predispose infants to food sensitisation. There is some evidence that proactively treating those with AD with topical corticosteroids, will lower the IgE and even food specific IgE, although the correlation with symptoms is unclear.³⁶ It is seen in murine studies, that increased transcutaneous inflammation increases the symptoms of food allergic reactions.³⁷

With these three possibilities in mind, the concept of preventing allergy by preventing transcutaneous sensitisation to food antigens is being actively explored by several groups internationally. Table 1 summarises most of the ongoing and planned studies which aim to prevent food allergy as a primary or secondary outcome, by inhibiting the assumed process of transcutaneous sensitisation.

How might transcutaneous sensitisation to foods be prevented?

The findings discussed above are largely observational in nature, and definitive proof that measures to prevent transcutaneous sensitisation to foods can effectively prevent food allergy can only come from prospective intervention trials. In this section we will explore how food sensitisation and allergy might be prevented by inhibiting the pathway of transcutaneous sensitisation, referring where necessary to the ongoing or published studies cited in Table 1.

i. Protecting the skin barrier – primary prevention of AD and food sensitisation

Emollient therapy is a mainstay in the treatment of AD as it reduces the severity of AD and increases time between AD flares.³⁸

Table 1

Summary of published and ongoing skin barrier intervention trials.

Authors or Principle Investigator	Trial Name	Country	Intervention (I)/Control (C)	Duration of intervention	No. of Participants Randomised	Main outcome(s)	Authors' conclusion if published	Weblink to published article or trial registry number
Primary prevention trials								
Blume-Peytavi (commenced 2016)	Atopic Dermatitis in Atopy Predisposed Infants (ADAPI)	Germany	I: Milk lotion is applied once daily to infant's entire body including the face. If bathing, addendum is used in addition to water. C: No predetermined or standardised skin care regiment is prescribed.	12 months	160	Cumulative incidence of AD at 12 weeks.	Not Applicable	NCT02906475
Carlsen (commenced 2014)	Preventing Atopic Dermatitis and ALLergies in Children-the PreventADALL study.	Norway	I: Group 1 - skin care (oil-bath at least 5 days per week from 0.5 to 9 months of age); Group 2 - consecutive introduction, between 3 and 4 months of age, of peanut, milk, wheat, and egg at least 4 days per week complementary to breastfeeding; Group 3 - both interventions. C: No intervention	9 months	2701	AD and food allergy to intervention foods.	Not Applicable	NCT02449850
Dissanayake <i>et al.</i> (2019)	Skin Care and Synbiotics for Prevention of Atopic Dermatitis or Food Allergy in Newborn Infants: A 2 × 2 Factorial, Randomised, Non-Treatment Controlled Trial	Japan	I: Group 1 - Received a combination of synbiotics and skincare Group 2 - Received synbiotics only Group 3 - Received skincare only C: No intervention	6 months	549	Identify the efficacy of emollients and synbiotics in preventing atopic dermatitis and food allergy in infants in the first year of life.	A total of 459 infants qualified for the outcome assessment at 1 year old. Neither the emollient or synbiotics showed any effect on reducing the development of atopic dermatitis and food allergy at 1 year old.	https://www.karger.com/Article/FullText/501636
Flohr (commenced 2018)	Softened Water for Eczema Prevention Pilot Trial (SOFTER)	UK	I: Domestic ion-exchange water softener installed prior to birth. C: No intervention	6 months	80	Determine the visibility and/or the severity of eczema.	Not Applicable	NCT03270566
Lowe <i>et al.</i> (2018)	A randomised trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitisation: the PEBBLES pilot study	Australia	I: Twice daily application of emollient (approx. 6 g on full body) C: Standard infant skin management.	6 months	80	The incidence of eczema up to 6 months of life and skin barrier function. The presence of allergic sensitisation.	A trend towards a reduced incidence of atopic dermatitis and food sensitisation at 6 months and 1 years old.	https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.15747
Lowe (commenced 2018)	The PEBBLES Study - Testing a Strategy for Preventing Eczema and Food Allergy in High Risk Infants (PEBBLES)	Australia	I: EpiCeram, 6 g per application two times per day treatment. C: Standard Skin Care Advice	12 months	760	The presence of atopic dermatitis in the first 12 months. Food Allergy diagnosis at 12 months.	Not Applicable	NCT03667651
McClanahan (2019)	Comparing Cetaphil Restoraderm System Versus Standard Skin Care in Infants	US	I: full body application of Cetaphil® Restoraderm® moisturiser daily. Cleanser only as needed during bathing. C: Emollient of their choice on an as needed basis.	12 months	100	Cumulative incidence of AD at 12 months.	A non-significant trend towards decrease in AD at 12 months 13.2% vs. 25.0% (P = 0.204).	https://onlinelibrary.wiley.com/doi/full/10.1111/jdv.15786
O'B Hourihane (commenced 2019)	Short-term Topical Application to Prevent Atopic Dermatitis (STOP AD)	Ireland	I: Apply a commercially available moisturiser to protect the skin barrier for the first 2 months of life. Twice daily, whole-body application.	2 months	242	Cumulative atopic dermatitis incidence at 12 months and cumulative incidence of	Not Applicable	NCT03871998

Ohya <i>et al.</i> (2014)	Application of moisturiser to neonates prevents development of atopic dermatitis	Japan	C: Standard skincare advice. No moisturiser in the first 2 months. I: Daily application of emollient. C: No intervention.	32 weeks	118	IgE mediated food allergy at 2 years. Cumulative incidence of atopic dermatitis and eczema. The presence of allergic sensitisation.	Daily moisturising during the first 32 weeks of life reduces the risk of atopic dermatitis/eczema in infants. Allergic sensitisation during this time period is associated with the presence of eczema but not with moisturising.	https://www.jacionline.org/article/S0091-6749(14)01160-9/abstract
Simpson <i>et al.</i> (2014)	Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention	US and UK	I: Parents were offered a choice of 3 emollients and asked to apply full-body emollient therapy and given an infant skin care advice booklet. C: Parents were asked to use no emollients and given an infant skin care advice booklet.	6 months	124	The main clinical outcome was the cumulative incidence of atopic dermatitis at 6 months.	Daily emollient therapy from birth to 6 months reduced the cumulative incidence of atopic dermatitis. Demonstrates a feasible, safe and effective approach for atopic dermatitis prevention. Larger trials are needed to confirm this.	https://reader.elsevier.com/reader/sd/pii/S009167491401118X?token=3A9094D7CEB3664C7B96605601BBA3FD4E25720D48F5F177A71B31D7D77E7D6EE251587807B06A05DF54374E7D0D8841
Simpson (<i>commenced 2018</i>)	A Community-based Assessment of Skin Care, Allergies, and Eczema (CASCADE)	US	I: Once daily full body lipid rich emollient. C: Educational material about skin care.	24 months	1250	The cumulative incidence of AD at 24 months of age as recorded in health records.	Not Applicable	NCT03409367
Weidinger (<i>commenced 2017</i>)	A Pilot Study to Determine the Feasibility of Early Emollient Use in Children With High Risk for Atopic Eczema - EARLYemollient	Germany	I: Daily application of emollient to infant's entire body including the face for the first year. Parents also receive structured education, general advice on best skin care practice for infants. C: Parents received structured education comprising of general advice on best practice skin care for their baby.	12 months	50	Cumulative incidence of atopic eczema within 2 years of randomisation and age of onset of atopic eczema.	Not Applicable	NCT03376243
Williams (<i>commenced 2017</i>)	The Barrier Enhancement for Eczema Prevention (BEEP)	UK	I: Parents given best practice infant skin care advice plus advice on how to apply emollient at least once a day for a year to their child's skin. C: Parents given best practice infant skin care advice only.	12 months	Max. of 1400 participants will be recruited.	Identify, confirm and diagnose eczema and allergy at 12 and 24 months of age.	Not Applicable	ISRCTN21528841
Yonezawa <i>et al.</i> (2018)	Effects of moisturising skincare on skin barrier function and the prevention of skin problems in 3-month-old infants: A randomised controlled trial	Japan	I: Routine bathing every 2 days and the use of a moisturiser once or twice a day. C: Common skincare regime used in Japan: Routine bathing daily and no moisturiser.	12 weeks	227	The incidence of skin problems and skin barrier function in infants at 3 months old.	The intervention group had significantly lower rates of diaper dermatitis between birth and 1 month old and tended to have lower rates of body skin problems between 1 and 3 months. Moisturising improved skin barrier function and prevented diaper dermatitis.	https://www.ncbi.nlm.nih.gov/pubmed/28983938

(continued on next page)

Table 1 (continued)

Authors or Principle Investigator	Trial Name	Country	Intervention (I)/Control (C)	Duration of intervention	No. of Participants Randomised	Main outcome(s)	Authors' conclusion if published	Weblink to published article or trial registry number
Secondary prevention trials								
Nadeau (to commence 2020)	SEAL (Stopping Atopic Dermatitis and Allergy) Study: Prevent the allergic march by enhancing the skin barrier	US and UK	I: Active Intervention arm Children with AD before 10 weeks of age. Sequential skin care with the twice-daily use of a tri-lipid skin barrier cream (SBC). Clinically apparent eczema is managed with a short course of topical steroids (fluticasone propionate cream to the body and/or hydrocortisone to the face) C: Standard of care	36 months	750	Cumulative number of challenge-proven food allergy (egg, cow's milk, peanut, sesame, fish, wheat, and 9 tree nuts) and atopic dermatitis assessment.	Not Applicable	NCT03742414
Ohya (commenced 2017)	Early Aggressive Intervention for Infantile Atopic Dermatitis to Prevent Development of Food Allergy: a Multicenter, Investigator-Blinded, Randomised, Parallel Group Controlled Trial (PACI Study)	Japan	I: Aggressive treatment group: Early aggressive treatment with topical anti-inflammatory drug (proactive method). C: Standard treatment group: Standard treatment based on the Guidelines for the Management of Atopic Dermatitis (2016) (reactive method).	6 months	650	Presence of oral food challenge-proven IgE-mediated hen's egg allergy at the age of 28 weeks.	Not Applicable	UMIN000028043

In general, emollients may improve skin barrier function and thereby reduce skin water loss; improve skin hydration directly; or aim to achieve both aims simultaneously. However, emollients are a heterogeneous group and have many different properties dependent on their ingredients and formulation and the way these change after application to skin. Not all products improve skin barrier function, some may even impair skin barrier function by damaging the stratum corneum or removing skin lipids.³⁹ A recent Japanese study assessing the impact on skin barrier of two different types of moisturisers in infants, showed both moisturisers applied daily, improved stratum corneum hydration, but neither affected TEWL.⁴⁰

Primary prevention trials have shown mixed findings for the topical application of emollients in early infancy. The BEEP pilot study and the study by Horimonaki *et al.* showed a significant decrease in AD at the end of the intervention period, of daily emollient therapy.^{41,42} The latter study showed no effect on allergic sensitisation to common food allergens. The PEBBLES pilot study and the study by McClanahan *et al.* each found non-significantly decreased AD prevalence in the intervention group, and in PEBBLES non-significantly decreased food sensitisation.^{43,44} A recent factorial trial evaluating both synbiotics and skin care interventions showed no changes in AD prevalence between the control and intervention groups and no change in food sensitisation rates either.⁴⁵ Food sensitisation was assessed in approximately half the trials,^{42,44,45} with no clear reduction. Food allergy is less prevalent than AD, and whether no change in food allergen sensitisation in these studies is due to limited power, or an absence of effect, will hopefully be clarified soon through the findings of the larger BEEP and PreventADALL studies which each evaluate food allergy as a secondary outcome.^{46,47}

The studies included all have somewhat different trial designs, along with different interventions. To combine these results together, and to assess whether emollients work at all for AD or food allergy, or just in certain subgroups, it is important to examine the data more systematically. Individual participant data meta-analysis is the gold standard of meta-analysis and makes optimum use of data gleaned during trials. An IPD meta-analysis of all skin barrier intervention studies for primary prevention of AD and food allergy is well under way through Cochrane via the SCiPAD collaboration (Skin Care interventions for the Prevention of Allergy Disease).⁴⁸ Potential trial outcomes and their interpretation is summarised in Table 2.

While most intervention trials are examining ways to actively promote barrier function between the skin and potential external environmental antigens that may lead to sensitisation or damage to the skin structure, another approach would be to reduce exposure to harmful substances such as soaps, sodium laureth sulphate, shampoos, hard water or specific irritants. The SOFTER study (Softened Water for Eczema Prevention) is one such approach – SOFTER is a feasibility study, focusing on reducing infant skin exposure to hard water, and the subsequent effect on eczema development.⁴⁹

ii. Avoiding environmental food allergens – primary prevention of food sensitisation

Peanut levels in the environment are correlated positively with self-reported intake of these allergens.²⁶ In children with AD or FLG mutations the level of peanut allergen is associated with peanut sensitisation and allergy.²⁸ A Spanish study showed a significant association between household nut consumption (peanut, almond or walnut) and allergic sensitisation to the same nuts, with interactions with AD and egg sensitisation.⁵⁰ Importantly for each of these three nuts, in houses that reported no ingestion of these nuts, no infant was sensitised to that nut. This therefore supports an

Table 2

Implications of potential findings from ongoing barrier promotion trials.

Overall effect	Atopic dermatitis	Food allergy	Implications for understanding disease pathogenesis
At least one of AD or FA increased	No effect or increased	No effect or increased	Application of skin barrier treatments can promote cutaneous sensitisation, inflammation and disease
No effect	No effect	No effect	Current skin barrier treatments are unable to impact on skin barrier function and/or stratum corneum hydration sufficiently to change disease risk
At least one of AD or FA decreased	No effect or decreased	No effect or decreased	Increased skin barrier function and/or stratum corneum hydration can prevent the development of sensitisation and disease

association between household consumption of nuts and child nut sensitisation.

Previously environmental reduction of allergen has been completed successfully for inhaled allergen, albeit without a positive impact on disease incidence.⁵¹ The avoidance of environmental food allergens for preventing food sensitisation and allergy in infants has been tested in multiple trials, usually as part of a multifaceted intervention trial for preventing allergic diseases.⁵² In infants themselves, however it is clear from recent studies that, rather than avoidance, the early oral introduction of allergenic foods, can decrease the incidence of food allergy through oral immune tolerance.⁵³ However, an approach which has not yet been robustly investigated and may be effective alone or in combination with oral tolerance for preventing food allergy, is whole household avoidance of common allergenic foods. How long this needs to be for is unknown, either through the first year of an infant's life, or at least until they are successfully eating the allergen. To date, we are not aware of any randomised controlled trials exploring this possibility.

iii. Reducing inflammation - secondary prevention of food allergy

Reducing inflammation caused by AD may prevent food sensitisation and allergy. As discussed above, there is evidence that early onset skin inflammation (AD) and severe skin inflammation (AD) are most strongly associated with food sensitisation and disease than later onset or less severe inflammation. The concept that proactive treatment of established AD may lead to improved outcomes for patients is widely discussed.⁵⁴ The innovative first-in-class labelled the "PACI" from Japan, is currently testing whether "early, aggressive" use of topical anti-inflammatory treatments in infants with early onset AD might lead to reduced food sensitisation or allergy.⁵⁵ At a population level a targeted intervention may be more feasible than interventions which require all infants or households to change their behaviour. However the acceptability of this would need to be tested as many parents are concerned about steroid application in their children.⁵⁶

Conclusions

Several lines of evidence suggest that the transcutaneous sensitisation plays an important role in the onset of food allergy in children. Specifically, the first year of life appears to be a period where impaired skin barrier function and/or skin inflammation may lead to sensitisation and disease, especially in the context of high environmental exposure to relevant antigen(s). Definitive proof that skin barrier dysfunction during infancy causes food allergy can only be provided by clinical trials which aim to promote skin barrier function. Many such trials are now underway and a metaanalysis of all results is expected in 2020. The possibility of whole household avoidance of specific food allergens or proactive

anti-inflammatory management of AD in infancy, will also need to be explored if we are to fully understand whether preventing transcutaneous sensitisation can reduce the population burden of food allergy.

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Conflict of interest

The authors have no conflict of interest to declare.

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