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Skin care interventions in infants for preventing eczema and food allergy (Review)

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[Intervention Review]

Skin care interventions in infants for preventing eczema and food allergy

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ABSTRACT

Background

Eczema and food allergy are common health conditions that usually begin in early childhood and often occur together in the same people. They can be associated with an impaired skin barrier in early infancy. It is unclear whether trying to prevent or reverse an impaired skin barrier soon after birth is effective in preventing eczema or food allergy.

Objectives

Primary objective

To assess effects of skin care interventions, such as emollients, for primary prevention of eczema and food allergy in infants

Secondary objective

To identify features of study populations such as age, hereditary risk, and adherence to interventions that are associated with the greatest treatment benefit or harm for both eczema and food allergy.

Search methods

We searched the following databases up to July 2020: Cochrane Skin Specialised Register, CENTRAL, MEDLINE, and Embase. We searched two trials registers and checked reference lists of included studies and relevant systematic reviews for further references to relevant randomised controlled trials (RCTs). We contacted field experts to identify planned trials and to seek information about unpublished or incomplete trials.

Selection criteria

RCTs of skin care interventions that could potentially enhance skin barrier function, reduce dryness, or reduce subclinical inflammation in healthy term (> 37 weeks) infants (0 to 12 months) without pre-existing diagnosis of eczema, food allergy, or other skin condition were included. Comparison was standard care in the locality or no treatment. Types of skin care interventions included moisturisers/emollients; bathing products; advice regarding reducing soap exposure and bathing frequency; and use of water softeners. No minimum follow-up was required.

Data collection and analysis

This is a prospective individual participant data (IPD) meta-analysis. We used standard Cochrane methodological procedures, and primary analyses used the IPD dataset. Primary outcomes were cumulative incidence of eczema and cumulative incidence of immunoglobulin (Ig)E-mediated food allergy by one to three years, both measured by the closest available time point to two years. Secondary outcomes included adverse events during the intervention period; eczema severity (clinician-assessed); parent report of eczema severity; time to onset of eczema; parent report of immediate food allergy; and allergic sensitisation to food or inhalant allergen.

Main results

This review identified 33 RCTs, comprising 25,827 participants. A total of 17 studies, randomising 5823 participants, reported information on one or more outcomes specified in this review. Eleven studies randomising 5217 participants, with 10 of these studies providing IPD, were included in one or more meta-analysis (range 2 to 9 studies per individual meta-analysis).

Most studies were conducted at children's hospitals. All interventions were compared against no skin care intervention or local standard care. Of the 17 studies that reported our outcomes, 13 assessed emollients. Twenty-five studies, including all those contributing data to meta-analyses, randomised newborns up to age three weeks to receive a skin care intervention or standard infant skin care. Eight of the 11 studies contributing to meta-analyses recruited infants at high risk of developing eczema or food allergy, although definition of high risk varied between studies. Durations of intervention and follow-up ranged from 24 hours to two years.

We assessed most of this review's evidence as low certainty or had some concerns of risk of bias. A rating of some concerns was most often due to lack of blinding of outcome assessors or significant missing data, which could have impacted outcome measurement but was judged unlikely to have done so. Evidence for the primary food allergy outcome was rated as high risk of bias due to inclusion of only one trial where findings varied when different assumptions were made about missing data.

Skin care interventions during infancy probably do not change risk of eczema by one to two years of age (risk ratio (RR) 1.03, 95% confidence interval (CI) 0.81 to 1.31; moderate-certainty evidence; 3075 participants, 7 trials) nor time to onset of eczema (hazard ratio 0.86, 95% CI 0.65 to 1.14; moderate-certainty evidence; 3349 participants, 9 trials). It is unclear whether skin care interventions during infancy change risk of IgE-mediated food allergy by one to two years of age (RR 2.53, 95% CI 0.99 to 6.47; 996 participants, 1 trial) or allergic sensitisation to a food allergen at age one to two years (RR 0.86, 95% CI 0.28 to 2.69; 1055 participants, 2 trials) due to very low-certainty evidence for these outcomes. Skin care interventions during infancy may slightly increase risk of parent report of immediate reaction to a common food allergen at two years (RR 1.27, 95% CI 1.00 to 1.61; low-certainty evidence; 1171 participants, 1 trial). However, this was only seen for cow's milk, and may be unreliable due to significant over-reporting of cow's milk allergy in infants. Skin care interventions during infancy probably increase risk of skin infection over the intervention period (RR 1.34, 95% CI 1.02 to 1.77; moderate-certainty evidence; 2728 participants, 6 trials) and may increase risk of infant slippage over the intervention period (RR 1.42, 95% CI 0.67 to 2.99; low-certainty evidence; 2538 participants, 4 trials) or stinging/allergic reactions to moisturisers (RR 2.24, 95% 0.67 to 7.43; low-certainty evidence; 343 participants, 4 trials), although confidence intervals for slippages and stinging/allergic reactions are wide and include the possibility of no effect or reduced risk.

Preplanned subgroup analyses show that effects of interventions were not influenced by age, duration of intervention, hereditary risk, *FLG* mutation, or classification of intervention type for risk of developing eczema. We could not evaluate these effects on risk of food allergy. Evidence was insufficient to show whether adherence to interventions influenced the relationship between skin care interventions and risk of developing eczema or food allergy.

Authors' conclusions

Skin care interventions such as emollients during the first year of life in healthy infants are probably not effective for preventing eczema, and probably increase risk of skin infection. Effects of skin care interventions on risk of food allergy are uncertain.

Further work is needed to understand whether different approaches to infant skin care might promote or prevent eczema and to evaluate effects on food allergy based on robust outcome assessments.

PLAIN LANGUAGE SUMMARY

Skin care interventions for preventing eczema and food allergy

Does moisturising baby skin prevent eczema or food allergies?

Key messages

Skin care treatments in babies, such as using moisturisers on the skin during the first year of life, probably do not stop them from developing eczema, and probably increase the chance of skin infection.

We are uncertain how skin care treatments might affect the chances of developing a food allergy. We need evidence from well-conducted studies to determine effects of skin care on food allergies in babies.

What are allergies?

An immune response is how the body recognises and defends itself against substances that appear harmful. An allergy is a reaction of the body's immune system to a particular food or substance (an allergen) that is usually harmless. Different allergies affect different parts of the body, and their effects can be mild or serious.

Food allergies and eczema

Eczema is a common skin allergy that causes dry, itchy, cracked skin. Eczema is common in children, often developing before their first birthday. It is sometimes a long-lasting condition, but it may improve or clear as a child gets older.

Allergies to food can cause itching in the mouth, a raised itchy red rash, swelling of the face, stomach symptoms or difficulty breathing. They usually happen within 2 hours after a food is eaten.

People with food allergies often have other allergic conditions, such as asthma, hay fever, and eczema.

Why we did this Cochrane Review

We wanted to learn how skin care affects the risk of a baby developing eczema or food allergies. Skin care treatments included:

• putting moisturisers on a baby's skin;

• bathing babies with water containing moisturisers or moisturising oils;

• advising parents to use less soap, or to bathe their child less often; and

• using water softeners.

We also wanted to know if these skin care treatments cause any unwanted effects.

What did we do?

We searched for studies of different types of skin care for healthy babies (aged up to one year) with no previous food allergy, eczema, or other skin condition.

Search date: we included evidence published up to July 2020.

We were interested in studies that reported:

• how many children developed eczema, or food allergy, by age one to three years;

• how severe the eczema was (assessed by a researcher and by parents);

• how long it took for eczema to develop;

• parents' reports of immediate (under two hours) reactions to a food allergen;

• how many children developed sensitivity to a particular food allergen; and

• any unwanted effects.

We assessed the strengths and weaknesses of each study to determine how reliable the results might be. We then combined the results of all relevant studies and looked at overall effects.

What we found

We found 33 studies involving 25,827 babies. These studies took place in Europe, Australia, Japan, and the USA, most often at children's hospitals. Skin care was compared against no skin care or care as usual (standard care). Treatment and follow-up times ranged from 24 hours to two years. Many studies (13) tested the use of moisturisers; others mainly tested the use of bathing and cleansing products and how often they were used.

We combined the results of 11 studies; eight included babies thought to have high risk of developing eczema or a food allergy.

What are the main results of our review?

Compared to no skin care or standard care, moisturisers:

• probably do not change the risk of developing eczema by the age of one to two years (evidence from 7 studies in 3075 babies) nor the time needed for eczema to develop (9 studies; 3349 babies);

• may slightly increase the number of immediate reactions to a common food allergen at two years, as reported by parents (1 study; 1171 babies);

• probably cause more skin infections (6 studies; 2728 babies);

• may increase unwanted effects, such as a stinging feeling or an allergic reaction to moisturisers (4 studies; 343 babies); and

• may increase the chance of babies slipping (4 studies; 2538 babies).

We are uncertain whether skin care treatments affect the chance of developing a food allergy as assessed by a researcher (1 study; 996 babies) or sensitivity to food allergens (2 studies; 1055 babies) at age one to two years.

Confidence in our results

We are moderately confident in our results for developing eczema and the time needed to develop eczema. These results might change if more evidence becomes available. We are less confident about our results for food allergy or sensitivity, which are based on small numbers of studies with widely varied results. These results are likely to change when more evidence is available. Our confidence in our findings for skin infections is moderate but is low for stinging or allergic reactions and slipping.

Summary of findings 1. Skin care intervention compared to standard skin care or no skin care intervention for the prevention of eczema and food allergy

Patient or population: infants age 12 months or younger

Setting: prevention

Intervention: skin care intervention

Comparison: standard skin care or no skin care intervention

		Assumed risk	Corresponding risk			
Outcome	**Standard care**	**Skin care intervention**	**Relative effect (95% CI)**	**No. participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Eczema diagnosis by 1 to 2 years	150 per 1000	155 per 1000 (122 to 197)	RR 1.03 (0.81 to 1.31)	3075 (7)	MODERATE[a]	In sensitivity analysis that included studies that measured eczema using Hanifin and Rajka, or UK Working Party methods only, total N = 2919(6), the pooled treatment effect for eczema by 1 to 2 years was RR 1.02, 95% CI 0.78 to 1.34. In a separate sensitivity analysis including studies rated as low risk of bias only, total N = 1739(3), the pooled treatment effect for eczema by 1 to 2 years was RR 0.97, 95% CI 0.81 to 1.17
IgE-mediated food allergy (oral food challenge) by 1 to 2 years	50 per 1000	127 per 1000 (50 to 335)	RR 2.53 (0.99 to 6.47)	996 (1)	VERY LOW[b]	In a sensitivity analysis that examined IgE-mediated food allergy as measured by oral food challenge or based upon a panel assessment of clinical history and/or allergic sensitisation by 1 to 2 years, total N = 1115 (1), was RR = 1.46, 95% CI 0.91 to 2.34. For parent report of a doctor diagnosis of food allergy at 1 to 2 years, total N = 1614 (3), and the pooled treatment effect was RR 1.02, 95% CI 0.80 to 1.31. No low risk of bias sensitivity analysis was possible

Slippages (over the intervention period)	20 per 1000	29 per 1000 (14 to 87)	RR 1.42 (0.67 to 2.99)	2538 (4)	LOW[c]	-
Skin infection (over the intervention period)	50 per 1000	67 per 1000 (51 to 89)	RR 1.34 (1.02 to 1.77)	2728 (6)	MODERATE[d]	-
Stinging/allergic reactions to moisturisers (over the intervention period)	40 per 1000	90 per 1000 (27 to 298)	RR 2.24 (0.67 to 7.43)	343 (4)	LOW[c]	-
Time to onset of eczema	24 months	27.9 months (21.1 to 36.9 months)	HR 0.86 (0.65 to 1.14)	3349 (9)	MODERATE[e]	-
Parent report of immediate reaction to common food allergen (at 2 years)	160 per 1000	204 per 1000 (160 to 258)	RR 1.27 (1.00 to 1.61)	1171 (1)	LOW[f]	-
Allergic sensitisation to a food allergen (at 1 to 2 years)	90 per 1000	78 per 1000 (26 to 242)	RR 0.86 (0.28 to 2.69)	1055 (2)	VERY LOW[g]	-

[a]Downgraded one level for heterogeneity driven by one trial contributing 21.8% of the weight of the analysis, for which the review authors were unable to identify a plausible explanation.

[b]Downgraded one level for overall high risk of bias due to missing data (29%), and two levels for imprecision due to small numbers of events from a single study, with wide confidence intervals, which include both a harmful effect and no effect.

[c]Downgraded by two levels for imprecision due to small numbers of events, with wide confidence intervals, which include both a harmful effect and a beneficial effect.

[d]Downgraded by one level for imprecision due to wide confidence intervals, which include both a harmful effect and no effect.

[e]Downgraded one level for heterogeneity driven by more than one trial, for which review authors were unable to identify a plausible explanation.
[f]Downgraded two levels for imprecision due to small numbers of events from a single study, with wide confidence intervals, which include both a harmful effect and no effect.
[g]Downgraded one level for heterogeneity, for which the review authors were unable to identify a plausible explanation, and two levels for imprecision due to wide confidence intervals, which include both a harmful and a beneficial effect.

BACKGROUND

Please see Table 1 for explanations of specific terms used in this review.

Description of the condition

Allergic diseases such as eczema and food allergy are some of the most common long-term health conditions in children and young people (Bai 2017; Van Cleave 2010). There is no definitive cure for allergic disease, although treatments can be used to alleviate symptoms. The burden of allergic disease on the individual, the family, and society is significant (Gupta 2004; Pawankar 2014). The prevalence of allergic disease appears to have increased; traditionally, higher prevalence was seen in high-income countries, but prevalence of allergic disease is now increasing in urban cities of low- and middle-income countries (Deckers 2012; Prescott 2013).

Eczema is a chronic inflammatory skin disorder, diagnosed clinically based on a collection of symptoms, primarily including itch. Its aetiology is complex and involves interaction between genes, environment, the immune system, and impairment of the skin barrier (Leung 2004). Eczema with immunoglobulin (Ig)E sensitisation, either by IgE antibody or by skin prick test, is classified as atopic eczema (Johansson 2003). This review is focused on prevention of eczema and food allergy in infants and children and does not address adult-onset eczema, which has different associations from childhood atopic eczema (Abuabara 2019). Likewise this review does not address adult-onset food allergy, which accounts for a small proportion of food allergy among adults, resulting in loss of tolerance to a food that the adult previously tolerated (Ramesh 2017).

Atopic eczema (atopic dermatitis) is most often associated with other atopic diseases and typically presents in younger children; it may be the first step along the so called 'allergic march' (Leung 2004). Eczema often occurs in families with atopic diseases such as asthma, allergic rhinitis/hay fever (and food allergy), and atopic eczema. These diseases share a common pathogenesis and are frequently present together in the same individual and family. The word 'atopy' refers to the genetic tendency to produce IgE antibodies in response to small quantities of common environmental proteins such as pollen, house dust mites, and food allergens (Stone 2002; Thomsen 2015). Around 30% of people with eczema develop asthma, and 35% develop allergic rhinitis (Luoma 1983). However, it is known that atopy does not concurrently occur in all people with atopic eczema. In view of this, it has been proposed that the term 'eczema' should be used to define people both with and without atopy. In agreement with the 'Revised nomenclature for allergy for global use' (Johansson 2003), and similar to other Cochrane Reviews evaluating eczema therapies (Van Zuuren 2017), we will therefore use the term 'eczema' throughout the review.

The main mechanism of this disease is the combination of an epidermal barrier function defect and cutaneous inflammation. Barrier dysfunction can be attributed in part to a genetic susceptibility, such as a mutation in the filaggrin gene (*FLG*). Cutaneous inflammation is demonstrated by inflammatory cell infiltration of the dermis, predominantly by Th2 cells (Weidinger 2016).

Eczema is diagnosed clinically by its appearance and its predilection for certain skin sites, which is age-dependent (Spergel 2003). In a research setting, the most commonly used diagnostic criteria are the UK Working Party Diagnostic Criteria for Atopic Dermatitis (Williams 1994). Prevalence of eczema is reported at up to 20% in children and may be increasing (Flohr 2014). Eczema has a significant impact on the patient and the family. In childhood, eczema is often associated with sleep disturbance and behavioural difficulties. Eczema also significantly impacts the quality of life of parents of affected children. Partaking in their children's treatment can take up to two hours per day, their own sleep is often disturbed along with their child's, and this exacerbates the distress experienced (Carroll 2005). The impact of moderate to severe eczema on family dynamics is comparable to that of other chronic health conditions such as type 1 diabetes (Su 1997). The financial cost of childhood eczema incorporates both the direct cost of the child's care and the indirect costs of parental time off work and decreased productivity due to decreased sleep and increased stress. The total cost of eczema care in the USA has been estimated at over USD 5 billion per annum (Drucker 2017).

Eczema often improves during childhood, with more than 50% of childhood eczema resolving by adolescence (Williams 1998). Recent studies suggest that some aspects of skin barrier and immune dysfunction may persist into adulthood (Abuabara 2018). Adult eczema is estimated at approximately 5% in the USA and 2% in Japan (Barbarot 2018). Adults with eczema have significantly decreased social functioning and greater psychological distress than both the general population and adults with some other long-term conditions (Carroll 2005). In a recent systematic review, a positive association was seen between eczema and suicidal ideation in adults and adolescents. It was proposed that chronic itch, sleep disturbance, and the social stigma of a visible disease contribute to mental health effects (Ronnstad 2018).

As is seen in most disease prevalence studies, reported prevalence of eczema may vary depending on the location of the trial and variation in measurements used for classification and diagnosis. Using consistent measurements, the International Study of Asthma and Allergies in Childhood (ISAAC) has shown an increase in reporting of eczema across different settings and in different populations apart from those with already high prevalence (Asher 2006). Admittedly, the youngest children in this cohort were six to seven years old - not preschool age, at which eczema prevalence can be higher. This variation in reported prevalence between different regions and over time suggests that environmental influences may contribute significantly to disease prevalence. Eczema has been associated with smaller families, higher social class, and urban living. Children of immigrants moving from a country with low eczema prevalence to a country with higher eczema prevalence have a relatively higher prevalence of eczema, supporting a role for environmental factors acting during early life (Martin 2013). Family history of eczema, that is, genetics, is the strongest determinant of eczema, and it cannot be modified (Apfelbacher 2011). However interaction of genes with environmental factors may be influenced by skin barrier interventions.

Food allergy has been defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food (Boyce 2010). Food allergy can be further classified into IgE-mediated, non-IgE-mediated, and mixed

types. IgE-mediated food allergy typically occurs within two hours of exposure to the offending food, and symptoms are well characterised, ranging from minor oral or gastrointestinal symptoms, urticaria, or angioedema to more severe symptoms such as anaphylaxis, which can occasionally result in death (Boyce 2010). IgE-mediated reactions involve degranulation of mast cells, and the condition is diagnosed by a clinical history supported by skin prick or serum-specific IgE testing. A positive test alone indicates sensitisation to the food but does not always predict clinical reactivity. The titre of IgE or the size of the skin prick test wheal is a predictor of clinical reactivity, although not an indication of the severity of a reaction. Oral food challenges - either open or blinded placebo-controlled challenges - are used to confirm the diagnosis in cases where the clinical history and test results are inconclusive (Bock 1988). Non-IgE-mediated food allergy and mixed food allergies have a slower onset and less specific symptoms. Diagnosis is more difficult and relies on clinical history supported by exclusion or reintroduction of suspected foods, or both (Johansson 2003). It is unclear whether non-IgE-mediated allergies have the same association with skin barrier function and eczema; therefore we will not consider non-IgE-mediated food allergies in this review.

Exact prevalence rates for food allergy are difficult to ascertain and are largely dependent on the method used to diagnose food allergy and the population studied. Self-reported food allergy rates are generally higher than those confirmed by specific allergy testing (Woods 2002). Previous population-based studies have suggested that IgE-mediated food allergy affects around 3% to 10% of children (Kelleher 2016; Osbourne 2011; Venter 2008). For some people, food allergy can resolve spontaneously during childhood, particularly for foods such as milk and egg. However a recent US survey study identified a history suggestive of IgE-mediated food allergy in over 10% of adults, demonstrating that it is not just a disease of childhood (Gupta 2019). Like eczema, food allergy is thought to have increased in prevalence in recent decades, although epidemiological data from the 1990s onwards in England and Australia suggest that food allergy prevalence in young children may be stable (Peters 2018 ; Prescott 2013; Sicherer 2003; Venter 2008). Food allergy also varies in prevalence across different regions, with lower prevalence in areas with lower overall rates of allergic disease, such as rural settings in Asia and Africa (Botha 2019; Prescott 2013).

Food allergy is a considerable burden on the individual, the family, and wider society. Acute reactions can cause significant anxiety and when severe may rarely result in a fatal outcome within minutes of food ingestion (Umasunthar 2013). The continuous vigilance required to avoid potential triggers has an adverse impact on quality of life of allergic children and adults and their families (Knibb 2010). People with food allergy and their carers report a negative impact of dietary restrictions, limitations to social activities, and an emotional and financial burden of living with food allergy. For example, in the USA, the financial cost of food allergy for affected families and healthcare providers has been estimated as at least USD 25 billion per annum (Gupta 2013). In recent decades, numbers of hospital admissions for food-related anaphylaxis have increased. It is unclear however whether this represents a true increase in incidence or greater recognition of the potential for acute food allergy as a cause of symptoms, as there has not been a concomitant increase in fatal anaphylaxis (Jerschow 2014; Poulos 2007; Turner 2015).

Eczema and food allergy are closely associated. Both conditions typically begin during the first year of life. Genetic variations that damage skin barrier function are associated with both eczema and food allergy (Palmer 2006; Van den Oord 2009). In particular, *FLG* mutation - a mutation in the gene encoding for filaggrin binding protein in the epidermis - has been the most widely studied of the genes associated with atopy. Those with a mutation have significantly increased prevalence of eczema and food allergy (Irvine 2011). Animal studies demonstrate that exposure to food allergen across a damaged skin barrier predisposes to food sensitisation (Strid 2004; Strid 2005). Human observational studies support an onset timing and severity-dependent relationship between childhood eczema and risk of food allergy. In Martin 2015, over 50% of infants who needed prescription topical steroids before three months of age for treatment of eczema were IgE-sensitised to one or more of egg white, peanut, or sesame. This study was included in a systematic review, which demonstrated a strong dose-dependent relationship between eczema food sensitisation and food allergy, and suggested that eczema may be an important cause of food allergy (Tsakok 2016).

With regards to primary prevention of eczema, some studies have suggested that maternal supplementation with a probiotic supplement during pregnancy and breastfeeding may reduce risk of eczema (Garcia-Larsen 2018). However the mechanism of action of such an intervention is unclear, findings are inconsistent between trials, and few of the relevant studies have published protocols that confirm the absence of selective reporting.

With regards to primary prevention of food allergy, it has been shown that early introduction of allergenic foods such as egg and peanut can decrease the risk of allergy to those foods (Du Toit 2015; Ierodiakonou 2016; Natsume 2017; Perkin 2016). However, it is unclear whether this approach will reduce the prevalence of food allergy at a population level because applying the intervention to multiple foods is likely to be too onerous for some parents (Voorheis 2019), and some children already have allergy to the food before the age when complementary foods are usually introduced (Du Toit 2015).

New approaches are therefore required for prevention of eczema and food allergy; simple interventions designed to promote skin barrier function represent one potential approach.

Description of the intervention

In this review we included all interventions designed to improve the skin barrier in infants, either by enhancement or by promotion of the barrier through hydration via directly applied topical products such as emollients or moisturisers or through reduction of potential damage to the skin barrier and consequent dryness through various means such as avoiding soaps or reducing water hardness. We expected promotion of the skin barrier and skin hydration through topical emollients would be the most widely used intervention. Emollients are described as mainly lipid-based products that smooth the skin, whereas moisturisers give water and moisture to the skin (Penzer 2012). However, sometimes 'emollient' is referred to as an ingredient of 'moisturisers' (Lodén 2012). There is not yet a clear nomenclature for topical preparations for the skin. The terms 'moisturiser' and 'emollient' are used interchangeably in different settings to describe directly applied topical products. Several different 'classes' or 'formulations' of emollients and moisturisers are available, including oil-in-water creams, water-in-

oil creams, ointments, lotions, oils, gels, sprays, and emulsions (Van Zuuren 2017). However these may not reflect accurately the format, ingredient, and effects of the product. Further complicating this is the fact that many skin care products are classed as cosmetics and therefore are not subjected to the same regulations as medicines. A recently proposed classification includes considering the vehicle, the formulation, and the active ingredients (Surber 2017).

Emollients themselves may be categorised by their mode of use, as leave-on emollients that are directly applied to the skin and allowed to dry in; as soap substitutes whereby an emollient may be used instead of a soap to clean; and as bath oils or emollients by which a product is added to the bath water (Van Zuuren 2017). In this review we expect most intervention trials to use leave-on emollients, although the characteristics of emollients may vary.

As part of treatment for established eczema, emollients are recommended to be applied two to three times a day, at up to 150 g to 200 g per week in young children and up to 500 g in adults (Eichenfield 2014; Ring 2012). Overall, emollients are regarded as safe, with few adverse effects. However, daily application of sufficient emollient can be time-consuming and unpleasant, having a negative impact on the child and the family (Carroll 2005). Certain emollients can cause stinging, especially to skin with established eczema (Oakley 2016). There is concern that emollients can actively sensitise to their individual components, leading to cutaneous reactions (Danby 2011), and even systemic allergic reactions (Voskamp 2014). Slippage of infants covered in emollient from the hands of carers is a stated potential adverse reaction in emollient prevention studies such as the BEEP study (Chalmers 2017).

Protection of the skin barrier could also be achieved by limiting water loss across the skin, or by limiting skin contact with potentially harmful substances or irritants. Activities and substances that may harm the skin barrier, at least in people with established eczema, include excessive bathing, wash products, and hard water (Cork 2002). Thus, ameliorating any of these factors in the first months of life may potentially improve hydration and skin barrier function, thereby reducing subsequent eczema prevalence.

Neonatal skin is different from the skin of children and adults, as it takes time to adjust to the dry extrauterine environment during the postnatal period (Cooke 2018). Postnatal maturation of skin structure and physiology can take up to a year, with regional differences in maturation, with cheek skin maturing more slowly than skin at other sites (McAleer 2018). However, very early neonatal skin has decreased water permeability compared to the skin of older children and adults, along with decreased surface pH and stratum corneum formation, demonstrating an effective skin barrier in the first two days of life, which changes rapidly (Yosipovitch 2000). It was previously thought that infant skin beyond the first few weeks following birth was structurally and functionally equivalent to the skin of adults; however skin undergoes a maturation process that can last for several years after birth (Chiou 2004; Stamatas 2011; Visscher 2017). This process involves higher keratinocyte proliferation and desquamation rates with impaired keratinocyte differentiation compared to adults (Liu 2018; Stamatas 2010). The increased keratinocyte cell turnover results in smaller corneocytes and a thinner stratum corneum (Stamatas 2010). These changes in the stratum corneum create a shorter path for penetration of irritants and allergens through the skin of normal babies. The increased permeability of a baby's stratum corneum compared to that of an adult is reflected in higher transepidermal water loss (TEWL) rates (Nikolovski 2008). This higher stratum corneum permeability is likely to be an important factor in the development of eczema early in life. Infants, with their thinner skin and an increased body surface area-to-volume ratio compared with adults, may be more susceptible to percutaneous uptake of any potentially harmful substances (Mancini 2008).

Standard care for neonatal and infant skin differs internationally and is affected by cultural factors. The World Health Organization recommends not bathing newborn infants in the first 24 hours after birth but does not recommend any specific method of infant skin care beyond this time (WHO 2015). In the UK, standard skin care advice given to parents of newborns is to wash in plain water for the first month and to use a mild non-perfumed soap if one is required. What constitutes a 'mild soap' is not described, and there is no set recommendation for bathing frequency or use of moisturisers (NICE 2006). Few emollient studies have included term infants; most have incorporated premature infants, whose skin is different from the skin of term infants (Irvin 2015). Application of an emollient or oil to the skin of newborn infants is practised in some regions and cultures for a variety of reasons often unrelated to allergy prevention (Amare 2015).

Timing of the first bath in neonates may be important. In some areas of the world, infants are washed immediately after birth, but the World Health Organization recommends leaving the vernix caseosa intact and allowing it to wear off with normal handling (WHO 2015). When modes of washing were compared, a comparison of infant bathing with water versus washing with a cotton wash cloth did not demonstrate a significant difference in skin barrier properties after four weeks but did show regional differences in skin barrier properties and demonstrated dynamic adaption of the skin barrier over the first four weeks of life (Garcia Bartels 2009). Among neonates bathed twice weekly, those washed in age-appropriate liquid cleanser with added cream had lower transepidermal water loss (TEWL) than those washed with water only, whereas stratum corneum hydration was similar. Whether this shows improvement in the skin barrier is unclear (Garcia Bartels 2010). Although specific wash products or moisturiser ingredients such as sodium laureth sulfate are thought to be harmful, plain water or wash products without known skin irritants are thought to be safe, other than the risk of slippages with oil-based products (Blume-Peytavi 2016). Some groups recommend pharmaceutical-grade oils or specially formulated baby skin products over locally produced oils that are traditionally used in many parts of the world (Blume-Peytavi 2016). However, such recommendations sometimes come from industry-funded groups, and there is little direct evidence to suggest that traditional local oils are inferior to commercial products. Frequency and timing of infant bathing may vary by culture and region, and although excessively frequent infant bathing is thought to harm skin barrier function and physiology, the optimal frequency of infant washing or bathing is not known.

Hard water is relatively rich in calcium and magnesium, and water hardness varies depending on geographical location. Water of a certain hardness will cause limescale and may corrode pipes (Ewence 2011). Hard water is associated with increased eczema prevalence (Engebretsen 2017). It is thought that the skin barrier disruption associated with hard water is due to the interaction

between surfactants in wash products and hard water itself (Danby 2018).

This review covers all potential skin care interventions designed to promote, or reduce damage to, the skin barrier and to enhance skin hydration for the primary prevention of eczema and food allergy.

How the intervention might work

Emollients, as one intervention, are the mainstay of treatment for those with already established eczema, as detailed in a Cochrane Review (Van Zuuren 2017), because dry skin (xerosis) is a key feature of eczema, and topical moisturisers have an integral role in the standard treatment of eczema of all severities (Eichenfield 2014). Emollients can decrease water loss across the skin (TEWL), increase stratum corneum hydration, improve comfort, and reduce itch when used on skin that already has active eczema (Lodén 2012; Rawlings 2004), and therefore are a key component in treatment of eczema (Ring 2012). They may be more effective than interventions such as less frequent bathing or use of water softeners for eczema prevention.

All moisturisers contain varying amounts of active ingredients such as humectant or ceramide, as well as excipient ingredients such as emulsifiers (Lodén 2012). Humectants, such as glycerol or urea, aid retention and attraction of water by the stratum corneum. Ceramides are intracellular lipids found in the stratum corneum that are reduced in lesional eczematous skin (Meckfessel 2014). Occlusives such as petrolatum form a layer on the skin surface that may prevent TEWL across the stratum corneum and can soften the skin (Eichenfield 2014; Rawlings 2004). Moisturisers can be hydrophilic or lipophilic. Hydrophilic moisturisers attract water and are important for skin hydration, whereas lipophilic moisturisers tend to stay on the surface to aid the skin barrier (Caussin 2009).

Van Zuuren 2017 showed that regular use of emollients for those with eczema can prolong time to eczema flare, can reduce the number of flares, and can reduce the need for topical corticosteroids. In infants, skin barrier dysfunction is seen before the development of clinical eczema (Danby 2011; Flohr 2010). Therefore, applying moisturisers before eczema is noted may offer a route for primary prevention of eczema. Three published pilot studies suggest that applying moisturisers to infant skin might reduce the prevalence of eczema during the application period (Horimukai 2014; Lowe 2018a; Simpson 2014). These pilot studies were small-scale studies testing the feasibility of the intervention or looking for signals of a preventative effect, or both. They were insufficiently powered for confirming a preventative effect. It is not known whether applying moisturisers could lead to a programming effect on the skin, causing longer-term effects on skin physiology, immunology, or clinical manifestations of eczema.

The strong association between eczema and food allergy would suggest that reduced clinical manifestations of eczema could potentially reduce the risk of food allergy, even if it were just to delay the onset of eczema from early infancy, where the association with development of food allergy is strongest (Martin 2015). In a small pilot study of a ceramide-dominant emollient with an action described as a lipid replacement, evidence suggests reduced allergic sensitisation to foods in the per-protocol analysis of the intervention group (Lowe 2018a).

Mechanistic studies within the clinical trials suggest that emollients can increase stratum corneum hydration when used in healthy infants, but trials have not consistently identified changes in skin pH or TEWL (Yonezawa 2018). It is unclear whether this increase in stratum corneum hydration will lead to reduced skin inflammation and associated allergic sensitisation.

Why it is important to do this review

Preliminary data suggest that variations in infant skin care protection interventions, such as application of emollients, might influence the risk of eczema or food sensitisation, at least during the intervention period (Horimukai 2014; Lowe 2018a; Simpson 2014). This raises the possibility of a relatively simple, cheap, and safe intervention for primary prevention of two common and burdensome conditions. This review is important and timely because larger clinical trials are now formally testing the hypothesis that variations in infant skin care can influence the risk of eczema or food allergy (Chalmers 2020; Skjerven 2020).

At the time this systematic review was initiated, two major ongoing interventional trials were assessing whether skin care interventions in the first year of life will reduce the prevalence of eczema or food allergy; these have both been published. The National Institute for Health Research-Health Technology Assessment (NIHR-HTA)-funded Barrier Enhancement for Eczema Prevention (BEEP) study was designed to assess whether daily application of emollients for the first year of life would reduce the prevalence of eczema or allergic disease in the first five years of life (Chalmers 2017; Chalmers 2020; ISRCTN 21528841). Preventing Atopic Dermatitis and Allergies in Children - the PreventADALL study - is a large, prospective, mother-child birth cohort study incorporating a randomised controlled 2 x 2 factorial-designed intervention strategy (skin care and early complementary food introduction) to prevent eczema and food allergy (Lødrup 2018; NCT02449850; Skjerven 2020). This study will report food allergy outcomes after all assessments at age three years have been completed.

The BEEP study was powered to detect a difference in eczema during the second year. However, statistical power within this sample size was limited for other outcomes such as food allergy, and for subgroup analyses. For example, BEEP had 80% power at two-sided alpha of 0.05 for detecting a 50% reduction in food allergy. BEEP was a pragmatic study, which could further limit statistical power if compliance with recommended skin care advice in that setting was low.

PreventADALL was powered to detect a difference in eczema during the second year. PreventADALL also had limited statistical power for other outcomes such as food allergy, and for subgroup analyses. Several other smaller studies of primary prevention of eczema or food allergy were ongoing at the time this systematic review was initiated - in Australia (ACTRN12613000472774), Germany (NCT03376243), Japan,(JPRN-UMIN000004544; JPRN-UMIN000010838; JPRN-UMIN000013260), and the USA (NCT01375205). Many have now published and are included in this review (Dissanayake 2019; Lowe 2018a; McClanahan 2019; Yonezawa 2018).

This systematic review aimed to determine whether infant skin care interventions influence eczema or food allergy prevalence. We undertook an individual participant data (IPD) meta-analysis.

This type of meta-analysis is considered the gold standard for systematic reviews. Database and analysis errors in individual trials can be identified and potentially corrected. IPD meta-analysis also allows (i) fitting of a consistent analysis model to all trial data sets for each outcome to ensure that we are comparing treatment effects that are adjusted for the same covariates across trials; (ii) obtaining more reliable and powerful subgroup analyses; and (iii) better evaluating the relationship between compliance with the intervention and outcomes of interest (Stewart 2002). This systematic review also incorporated a prospectively planned component whereby two of the main studies aligned outcomes and details of the meta-analysis were planned before the results of each trial were known. Prospectively Planned Meta-Analysis (PPMA) aims to reduce bias related to knowledge of existing trial outcomes. Sharing clinical trial data is encouraged as best practice in clinical trials, and sharing of individual participant data maximises knowledge gained through the efforts of trial participants (Taichman 2017).

OBJECTIVES

Primary objective

To assess effects of skin care interventions, such as emollients, for primary prevention of eczema and food allergy in infants.

Secondary objective

To identify features of study populations such as age, hereditary risk and adherence to interventions that are associated with the greatest treatment benefit or harm for both eczema and food allergy.

METHODS

Criteria for considering studies for this review

Types of studies

Parallel-group or factorial randomised controlled trials (RCTs), including both individual and cluster-randomised trials. Quasi-RCTs and controlled clinical trials were excluded. Cross-over trials were also excluded, as the design is inappropriate to the clinical context.

Types of participants

Infants (age 12 months or younger). As this is a primary prevention review, we did not include studies on infants who already had diagnosed eczema or food allergy at the time of randomisation. We excluded study populations defined by a pre-existing health state in the infant, such as preterm birth (less than 37 weeks' gestation) or congenital skin conditions, because findings in these populations may not be generalisable.

We attempted to obtain individual participant data for all included studies. If individual participant data were not available, we obtained aggregate data instead. For studies with only aggregate data available, we excluded the whole study if some participants were not eligible, unless ineligible participants made up an insignificant proportion of the total group, that is, less than 5%. In trials with individual participant data, we planned to include only the data on participants who meet our eligibility criteria; however no exclusions were necessary, as all obtained individual participant data were eligible.

Types of interventions

All skin care interventions that could potentially enhance skin barrier function, reduce dryness, or reduce subclinical inflammation. These include:

1. moisturisers/emollients;
2. bathing products (these may include oils or emollients);
3. advice regarding reducing soap exposure and bathing frequency; and
4. use of water softeners.

Interventions could be simple single interventions; others could be complex interventions that utilise a combination of measures to protect or promote skin barrier function and hydration or to reduce subclinical inflammation. The comparators were no treatment intervention or advice, or standard care, in the study setting. We excluded multi-faceted interventions, whereby the skin care component was only a small part of the study if the skin care component was likely trivial or irrelevant to the outcome. We also planned to assess separately those interventions that primarily aim to enhance the skin barrier through direct application of emollient or moisturiser (skin care intervention A) and those that aim to protect the skin barrier from irritation, that is, through use of water softeners (skin care intervention B). However, we did not find any eligible studies for type B.

Types of outcome measures

No minimum follow-up was required. However, we separately analysed outcomes that related to symptoms during the intervention period and outcomes that occurred and were reported after the intervention period, when appropriate and feasible.

Primary outcomes

1. Eczema. When multiple measures were reported, the hierarchy of diagnosis was investigator assessment as described by the Hanifin and Rajka criteria in their original form (Hanifin 1980), or by the UK Working Party refinement of them (Williams 1994), other modifications of the Hanifin and Rajka criteria, doctor diagnosis of eczema, then patient or parent report of eczema
2. Food allergy. When multiple measures of food allergy were reported, the hierarchy of diagnosis was confirmed IgE-mediated food allergy diagnosed via oral food challenge, with eligibility for oral food challenge decided as per study protocol, although ideally based on current recommendations (Grabenhenrich 2017). If oral food challenge was not available, then food allergy was as diagnosed by investigator assessment using a combination of clinical history and allergy testing: skin prick testing and serum-specific IgE. We defined IgE sensitisation as skin test to a food of 3 mm or more, or specific IgE of 0.35 kUa/L or higher. The primary foods of interest were milk, egg, and peanut; however we collected data on any foods that were available from each study

The time point for all food allergy and eczema outcome analyses was by age one to three years using the closest available time point to two years, from each included trial. Adverse event outcomes were measured during the intervention period only. When pooling data from different trials, we considered the relationship between timing of the intervention and timing of the outcome measure, for example, we pooled separately measures of eczema taken during

the intervention period and measures of eczema taken after the intervention period has ceased.

As we identified multiple measures of eczema across trials, we conducted sensitivity analysis to look separately at eczema measured using the Hanifin and Rajka criteria in their original form (Hanifin 1980), or the UK Working Party refinement of them (Williams 1994), and other modifications of the Hanifin and Rajka criteria only. We had planned to separately look at food allergy measured using secure diagnosis of food allergy by oral food challenge in a sensitivity analysis, if necessary.

Secondary outcomes

1. Adverse events, including skin infection during the intervention period; stinging or allergic reactions to moisturisers; or slippage accidents around the time of bathing or application of emollient. We will report all serious adverse events
2. Eczema severity: clinician-assessed using EASI (Eczema Area and Severity Index) or a similarly validated method (Hanifin 2001)
3. Parent-reported eczema severity using POEM (Patient Orientated Eczema Measure) or a similarly validated patient-reported measure (Charman 2004)
4. Time to onset of eczema
5. Parent report of immediate (less than two hours) reaction to a known food allergen: milk, soya, wheat, fish, seafood, peanut, tree nut, egg, or local common food allergen
6. Allergic sensitisation to foods and inhalants via skin prick test (or, if not available, via serum-specific IgE)

When available, from each trial, we analysed any relevant core outcomes identified as part of the Cochrane Skin COUSIN and HOME initiatives (www.homeforeczema.org). Relevant HOME domains include clinician signs measured using the EASI instrument, patient-reported symptoms using the POEM instrument, long-term disease control, and quality of life. These outcomes were designed for trials involving those with established eczema. There is not yet a set of core outcomes for defining eczema or food allergy in prevention studies; however, for eczema, a modified version of the UK Hanifin and Rajka criteria has been proposed to differentiate between an incident diagnosis of eczema and transient eczematous rashes of infancy (Simpson 2012). When feasible, we contacted trial authors early in the design or set-up of their trial to encourage sharing of outcome assessment methods, instruments used, and timing. We did not include long-term disease control or quality of life outcomes in this review.

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist searched the following databases up to 14 July 2020, using strategies based on the draft strategy for MEDLINE in our published protocol (Kelleher 2020).

1. Cochrane Skin Specialised Register, using the search strategy in Appendix 1.
2. Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 7), in the Cochrane Library, using the strategy in Appendix 2.
3. MEDLINE via Ovid (from 1946 onwards), using the strategy in Appendix 3.
4. Embase via Ovid (from 1974 onwards), using the strategy in Appendix 4.

Trials registers

We (MK, SC, and LT) searched the following trials registers on 25 October 2019, and to update, again on 23 July 2020.

1. ClinicalTrials.gov (www.clinicaltrials.gov), using the draft search strategy in Appendix 5.
2. World Health Organization International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/), using the draft strategy in Appendix 6.

Searching other resources

Conference proceedings: we reviewed the proceedings of Asia Pacific Association of Pediatric Allergy, Respirology & Immunology Conferences (APAPARI) for 2018, 2019, and 2020.

Searching reference lists: we checked the bibliographies of included trials and identified relevant systematic reviews for further references to relevant RCTs.

Adverse effects: we did not perform a separate search for adverse effects of interventions used for prevention of eczema and food allergy. We considered only adverse effects described in included trials.

Data collection and analysis

This systematic review was undertaken according to the methods recommended by Cochrane, including the updated *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.0 (Stewart 2019), with special attention to Chapter 26, 'Individual Patient Data'. A summary record of prospectively planned components of the meta-analysis was registered on PROSPERO (reference 42017056965; registered 10 February 2017) (Boyle 2017).

Selection of studies

Two review authors (from MK, SC, and LT) independently carried out title, abstract, and full-text screening, with arbitration by a third review author (RJB) when necessary. In this systematic review, we combined both retrospective and prospectively acquired data in the meta-analysis. Retrospective data are outcome data acquired, analysed, unblinded, and known to the trial Chief Investigator before registration of the systematic review protocol (PROSPERO reference 42017056965; registered 10 February 2017; Boyle 2017). Prospectively acquired data are those data known to the trial Chief Investigator, in analysed and unblinded form, before 10 February 2017. This systematic review used participant-level data from all trials when possible. We invited the authors of each included trial to collaborate in accordance with Section 26.2 of the updated *Cochrane Handbook for Systematic Reviews of Interventions* (Stewart 2019). We asked all trial authors to provide individual participant data. One review author (from LT and MK) sent a data request email to the first and corresponding authors of the associated trial listing the variables required for the analysis

(Appendix 7). Following completion of a data sharing agreement, selected variables, or full data sets when appropriate permissions were obtained, were exchanged between researchers along with a data dictionary. If study authors were unable to provide participant-level data, we accepted appropriate summary data.

Data extraction and management

We conducted data collection and handling in accordance with guidance provided in Chapter 26.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Stewart 2019). For each of the included trials, descriptive data on trial setting, methods, participants, interventions, comparator, length of follow-up, instruments used for measuring outcomes, funding source, and conflicts of interest were extracted. Two review authors (MK, SC, or LT) independently extracted data using a standardised data collection form, discussing disagreements to reach resolution. When unsuccessful, a third review author (RJB) was consulted. We requested that trial authors who agreed to provide information or data beyond those available in the public sphere share protocol and statistical analysis plan details, along with details of available data fields.

All IPD data used in the systematic review were de-identified. The list of variables that we requested from each trial is provided in Appendix 7. We transferred specific data fields and then cleaned and coded data for analysis for those trials willing to provide individual participant data. Data sources from previously published trials were provided as anonymised whole databases when trial authors preferred. We carried out range and consistency checks for all data. Any missing data, obvious errors, inconsistencies between variables, or extreme values were queried and rectified with individual trial authors as necessary. We also cross-checked summaries of provided data with those in published reports of the trial and contacted original trial authors to resolve identified inconsistencies. A secure record was kept of all correspondence, agreements and data transfers with trial authors, and the systematic review database.

For included trials that were unable to provide individual participant data, we recorded the reason for data unavailability and requested aggregate data on our outcomes. If aggregate data could not be obtained directly from the trial authors, two review authors assessed whether any relevant appropriate aggregate-level data were available in the trial publication or other sources (e.g. clinical trials registry). We recorded aggregate data on a standardised data extraction form. Two review authors (MK, SC) independently extracted data. Any disagreements on extracted aggregate data were discussed and resolved by consensus, and it did not prove necessary for a third review author to arbitrate over data extraction.

The detailed statistical analysis plan for this review was written when data to be collected for the trials providing IPD were known, but before any grouped outcome data from prospective trials had been evaluated (Cro 2020a). The statistical analysis plan was therefore written with consideration of the nature and limitations of the data recorded in trials known to be eligible for inclusion, and the statistician remained blind to intervention and control group outcomes for each data field, so that bias was not introduced by exploring the possible impact of different data analyses and coding decisions on findings.

Assessment of risk of bias in included studies

We assessed risk of bias using the Cochrane 'Risk of bias' 2 tool (Higgins 2018; Higgins 2020b). This tool is designed specifically for RCTs and assesses bias from five domains.

1. Bias arising from the randomisation process.
2. Bias due to deviations from intended interventions.
3. Bias due to missing outcome data.
4. Bias in measurement of the outcome.
5. Bias in selection of the reported result.

We assessed the risk of bias separately for eczema (by age one to three years using the closest time point to two years), food allergy (by age one to three years using the closest time point to two years), slippage accidents (during the intervention period), skin infection (during the intervention period), allergic reactions (during the intervention period), time to onset of eczema, parent report of food allergy reaction (at age one to three years using the closest time point to two years), and allergic sensitisation (at age one to three years using the closest time point to two years). The RoB 2 tool is outcome-specific, and we rated each domain as 'low risk of bias', 'some concerns' or 'high risk of bias'. For bias due to deviations from intended interventions, we were interested in effects of assignment to the interventions at baseline, regardless of whether interventions were received as intended, by an intention-to-treat analysis that included all randomised participants. Bias in selection of the reported result was low risk for all prospectively identified studies, as we obtained the full data set for these trials. Risk of bias assessments were not performed for qualitative narrative information.

At the time of writing of this review, the RoB 2 tool for cluster RCTs was under development. For cluster-RCTs, we therefore similarly assessed risk of bias using the Cochrane 'Risk of bias' tool 2 (Higgins 2018) as outlined above but including an additional domain specific for cluster-RCTs from the archived version of the RoB 2 tool for cluster-RCTs (Eldridge 2016) - 'Domain 1b - Bias arising from the timing and identification and recruitment of participants'.

To reach an overall 'risk of bias' judgement for a specific outcome, we used the following criteria.

1. Overall low risk of bias: all domains considered at low risk for the specific result.
2. Some concerns: some concerns have been raised in at least one domain for the specific result, but no domains are considered at high risk of bias.
3. High risk of bias: at least one domain is considered at high risk for the specific result, or there are some concerns for multiple domains, which substantially lowers confidence in the result.

Two review authors (MK and SC) independently conducted 'Risk of bias' assessments with any disagreements resolved via discussion or through arbitration with a third review author (RJB). For a trial for which MK and RJB were investigators (Chalmers 2020), SC and VC independently conducted risk of bias assessments.

Measures of treatment effect

For binary outcomes when meta-analysis was considered appropriate, we calculated risk ratios (RRs). For continuous outcomes when trials used the same measurement scale,

we calculated mean differences (MDs); when trials used different measurement scales, we calculated standardised mean differences (SMDs). For time-to-event outcomes, we expressed the intervention effect as a hazard ratio (HR). We computed a 95% confidence interval (CI) for each outcome.

Unit of analysis issues

This review included RCTs only. As elaborated on further below (see Data synthesis), we adopted a two-stage approach for this IPD meta-analysis. In stage 1, we separately estimated the treatment effect of interest for each included trial. In stage 2, we pooled treatment effects using methods for meta-analyses of aggregate data.

Factorial RCTs and cluster-RCTs were included. For factorial randomised trials, if we noted a significant interaction between the two active interventions with respect to our primary outcome, we included only the arms 'skin care intervention/control' versus 'control/control'. Sensitivity analysis explored the impact of including data from all arms of factorial trials when an interaction was present, with adjustment for non-skin care interventions.

For other trials with more than two treatment arms (excluding factorial trials, which were handled as described above), which could have multiple intervention groups in a particular meta-analysis, we combined all relevant intervention groups into a single intervention group and all relevant control groups into a single control group.

For all stage 1 analyses for cluster-RCTs providing individual participant data, we used mixed models that allow analysis at the level of the individual while accounting for clustering in the data. Treatment effects from cluster-RCTs were therefore appropriately adjusted for correlation within clusters, before inclusion in the stage 2 (pooled) analysis, following recommendations for analysis of cluster-RCTs (Higgins 2020a).

For cluster-RCTs providing non-individual participant data, we planned to extract data from trial reports that had taken into account the clustering in these data, and to then analyse the data using the generic-inverse variance method in Review Manager 5 (RevMan 5; Review Manager 2014). If data were not adjusted for clustering, we planned to attempt to estimate the intervention effect by calculating an intracluster correlation coefficient (ICC) while following the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a).

Dealing with missing data

We dealt with missing data according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019). To resolve missing information about methodological properties of identified trials, we contacted authors of the included trials. When trial authors were unable to provide the required information, we rated the relevant 'Risk of bias' criterion using Cochrane 'Risk of bias 2' (Higgins 2018). We did not anticipate substantial quantities of missing data for the primary outcomes. For trials providing individual participant data, we naturally handled missing participant data under the assumption of missing-at-random within each trial analysis.

For trials that did not provide individual participant data and reported an MD but no standard deviation (SD) or other statistic that could be used to derive the SD, we planned to use imputation (Furlan 2009). Specifically, we planned to impute SDs for each outcome by using the pooled SD across all other trials within the same meta-analysis by treatment group. This is an appropriate method of analysis if a majority of the trials do not have missing SDs in the meta-analysis. If a large proportion of trials (e.g. ≥ 20%) were missing data on parameter variability for a particular outcome, imputation would not be appropriate, and we planned to conduct analysis using only trials providing complete data and to discuss the implications of this alongside results. However such imputation did not prove necessary.

In risk of bias assessments, to address the impact of non-negligible missing data (≥ 5%) on individual trial outcomes, we conducted sensitivity analyses using individual participant data and best case/worst case scenarios, that is, we conducted analysis by imputing a best case scenario of response in both treatment groups, followed by analysis under a worst case scenario of no response in both treatment groups. Results of sensitivity analyses under these scenarios were compared to primary complete case analyses (conducted under the missing-at-random assumption) to assess the risk of bias due to missing data.

In meta-analysis, we included trials with substantial quantities of missing data (e.g. rated as high risk of bias or some concerns due to missing data), but to investigate the robustness of pooled results, we performed sensitivity analysis while excluding trials rated overall at high risk of bias or with some concerns, which included excluding trials rated at high risk of bias or some concerns due to missing data.

Assessment of heterogeneity

We examined both clinical and statistical heterogeneity and combined data in meta-analysis only when we judged that evaluation would yield a meaningful summary. We assessed clinical heterogeneity by examining characteristics of included participants, types of interventions, primary and secondary outcomes, and the follow-up period. We used the I^2 statistic and the Chi^2 test to quantify the degree of statistical heterogeneity of trials judged as clinically homogeneous (Higgins 2003). For interpretation, we considered an I^2 of 0% to 40% might not be important heterogeneity; 30 to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and I^2 greater than 75% indicative of considerable heterogeneity (Deeks 2019). The observed I^2 value was judged against this guide in combination with its 95% confidence interval, the P value from the Chi^2 test, and the magnitude and direction of effect. When the magnitude and direction of effects and the strength of evidence for heterogeneity based on the P value from the Chi^2 confidence intervals for I^2 revealed heterogeneity, or if we observed considerable heterogeneity, we explored reasons for heterogeneity and when appropriate conducted sensitivity analysis while excluding any trials identified as outlying.

Assessment of reporting biases

By including as many prospective trials as possible in this review, as well as individual participant data, risks of reporting bias and publication bias should be reduced. However, if at least 10 trials were included in the meta-analysis, we planned to formally assess reporting bias using funnel plots to explore the likelihood of any reporting bias or small-study effects. We planned to assess funnel

plot asymmetry visually and to use formal tests for funnel plot asymmetry. For continuous outcomes, we planned to use the test proposed by Egger 1997. For dichotomous outcomes, we planned to use the test proposed by Rucker when estimated between-study heterogeneity variance of log odds ratios, tau^2, is greater than 0.1 (Rucker 2008). Otherwise, when the heterogeneity variance tau^2 was less than 0.1, we planned to use one of the tests proposed in Harbord 2006. If asymmetry was detected in any of these tests or was suggested by a visual assessment, we planned to explore and discuss possible explanations. However, we did not conduct a meta-analysis with 10 or more trials included; therefore we did not undertake any formal assessment of reporting bias.

Data synthesis

We conducted an IPD meta-analysis of both prospective and retrospectively acquired data. Primary meta-analysis used individual participant data only. Aggregate data were not used in the primary meta-analysis when individual participant data could not be provided, as the total proportion of participants that made up aggregate data was less than 10% of the overall number of participants across all trials (i.e. total aggregate data represented a negligible proportion of the data set). We performed a sensitivity analysis by adding in the aggregate data, as described further below, to explore the impact of data availability bias. We undertook a prospectively planned meta-analysis (PPMA) of a more limited number of trials, as a sensitivity analysis. PPMA was limited to those trials in which trial authors were not aware of trial outcomes at the time of PPMA protocol registration on PROSPERO (Boyle 2017).

The main analyses estimated the effect of being assigned to receive the intervention, according to the intention-to-treat principle. We retained all eligible participants in the treatment group to which they were originally assigned who had an outcome, irrespective of the treatment they actually received. To understand the effect of compliance, we included pre-planned secondary supplementary analysis to estimate the complier average causal effect.

We planned to perform all analyses stratified by type of intervention group. Planned comparisons were therefore:

1. skincare intervention versus no treatment or standard care;
2. skincare intervention 'A' versus no treatment or standard care; and
3. skincare intervention 'B' versus no treatment or standard care.

We planned to consider interventions in two broad categories: A interventions promoting hydration and skin barrier mainly through emollients, and B interventions that would protect from harm, such as water softeners or avoidance of irritants. Because our search did not reveal any eligible trials of B-type skin care interventions, it did not prove necessary to stratify comparisons by type of skin care intervention; therefore, we undertook only comparisons of type A. For each outcome, when we judged a sufficient number of trials (two or more) to be clinically similar, we pooled results in a meta-analysis. When we did not undertake meta-analyses owing to clinical heterogeneity or to insufficient data, we narratively discuss the results from individual trials.

We adopted a two-stage approach to analysis for all primary and secondary analyses. In the first stage, we derived individual trial treatment effect estimates from individual participant data. For analyses of binary outcomes, including both primary outcomes (eczema and food allergy), the stage 1 model, fitted to each trial providing individual participant data separately, was a binomial regression model. For analyses of continuous outcomes, the stage 1 model fitted to each trial providing individual participant data was a linear regression model. For time-to-event outcomes, the stage 1 model fitted to each trial providing individual participant data was a binomial regression model with a complementary log-log link, where follow-up time was split into appropriate intervals for the obtained data (3 months, 6 months, 12 months, 18 months, and 24 months). This model was appropriate for time-to-event data of a discrete nature. In addition to the treatment group variable indicating use of a skin care intervention, we included the important prognostic factors of sex and family history of atopic disease within the stage 1 models.

In the second stage, we combined derived treatment effects using methods for meta-analyses of aggregate data. We used random-effects models in stage 2 to derive the pooled treatment effect (DerSimonian 1986). We planned to use random-effects models because we anticipated some level of variability across trials, for example, by types of interventions, length of follow-up, and methods of measurement. A random-effects model incorporates heterogeneity among trials and allows the true treatment effect to be different in each trial. In sensitivity analysis, the second stage also included aggregate data from trials whose authors did not provide individual patient data.

We performed residual analysis for all IPD meta-analyses and PPMAs to assess model assumptions and fit. Meta-analyses also included trial sequential analysis, using two-sided 5% significance and 80% power to estimate optimum heterogeneity-adjusted information sizes needed to identify relative risk reductions of 20% and 30% (Wetterslev 2008). We estimated control event rates using random-effects meta-analyses of pooled proportions from the largest trials included in the meta-analyses and compared them with event rates from large population-based studies. Trial sequential analysis was used to identify when the optimum information size or futility boundaries for pre-defined effect sizes in relation to primary outcomes will be reached. We performed stage 1 of the IPD meta-analysis in Stata 15 or above (Stata), with summary results of these analyses added into RevMan Web (revman.cochrane.org).

To explore the impact of compliance, we estimated the effect of complying with the intended intervention. For the subgroup of trials providing compliance data, we estimated the complier average causal effect (CACE) for each primary outcome. As in the primary analysis, we followed a two-stage approach to analysis. For each trial, we estimated the CACE using instrumental variable (IV) analysis. We used randomisation as an instrumental variable for intervention received, and we estimated the CACE using a two-stage residual inclusion estimator approach (2SRI) (Cook 2018). Randomisation meets the criteria for an adequate instrument in that (i) randomisation predicts the treatment receipt, (ii) randomisation is unconfounded with the outcome, and (iii) we assume no direct effect of randomisation on the outcome (other than via treatment receipt): 'the exclusion restriction'. Here, we initially defined a ‘complier’ as an individual who used the prescribed intervention for three or more days a week over the intervention period. When interventions and the quality of compliance data were sufficiently comparable, we used random-effects models in stage 2 to derive the pooled CACE effect. We

repeated the primary analysis for each of the trials in the subgroup of trials with compliance data to compare pooled CACE estimates against the primary treatment effect (RR) while estimating the effect of being assigned to the intervention for the subgroup of trials for which compliance data were available. Subsequently, we explored the impact of different threshold values for defining compliance (≥ 5 days a week over the intervention period, 7 days over the intervention period, ≥ 3 days a week over the first 3 months of the intervention period, ≥ 5 days a week over the first 3 months of the intervention period, and 7 days a week over the first 3 months of the intervention period).

The detailed statistical analysis plan, which set out all comparisons to be made and the precise model forms and fitting strategy to be used, can be consulted for additional information (Cro 2020a). For trials providing only narrative information, or incomplete measures of effect (i.e. no denominators available) when meta-analysis could not be performed, we summarised available effect estimates or narrative informative alongside meta-analyses for the same groupings of populations, interventions, outcomes, and study design as were used for the quantitative meta-analysis.

Subgroup analysis and investigation of heterogeneity

Subgroups of interest that were identified a priori for analysis were as follows.

1. By participant-level characteristics.
   a. Comparing effects of the intervention on 'high' or 'not high' risk for atopy based on filaggrin genotype.
   b. Comparing effects of the intervention on 'high' or 'not high' risk for atopy based on family history of allergic disease.
2. By study-level characteristics.
   a. Comparing effects of interventions aimed at preventing damage to the skin (e.g. reduced exposure to soaps, wipes, bathing, hard water) versus interventions aimed at promoting skin hydration or barrier function (e.g. emollient cream, lotion, ointment, oil) versus combined treatment.
   b. Intervention timing: comparing effects of intervention on participants advised to commence the skin care intervention within the first four weeks of life versus those who commenced intervention after four weeks.
   c. Intervention duration: comparing duration of intended treatment, when 'short' is regarded as up to six months of treatment compared to 'longer' treatment durations - six months' duration or longer. When feasible, we planned to undertake modelling to assess the relationship between study outcome and timing or duration of intervention.

We calculated subgroup effects for participant-level characteristics on the two primary outcomes by first estimating treatment by covariate interaction terms within studies using individual participant data. We then combined interaction terms across studies in the same way as for the main intervention effects, using a random-effects meta-analysis. For study-level characteristics, we pooled treatment effects separately for each characteristic, and we performed a test for subgroup differences using a Chi^2 test.

Sensitivity analysis

We conducted the following a priori planned sensitivity analyses for the co-primary outcomes when relevant.

1. By overall risk of bias: in primary analysis, we included all trials regardless of overall risk of bias, and we undertook a sensitivity analysis of trial outcomes assessed as having an overall low risk of bias. The 'low risk of bias' sensitivity analysis excluded trial outcomes at overall high risk or those with some concerns, assessed via the Cochrane 'Risk of bias' tool 2 (Higgins 2018). This included omitting trial outcomes with high risk of bias and those with some concerns due to missing data, because inclusion would have led to the trial receiving an overall rating that was not low risk of bias.
2. By outcome measures: we explored the impact of using different definitions of outcome measures by undertaking sensitivity analyses of outcomes that had previously been validated. For the primary outcome eczema, in the absence of agreed core outcomes, we undertook sensitivity analysis of eczema evaluated using only the UK Working Party Criteria (Williams 1994), or other variations of the Hanifin and Rajka criteria (Hanifin 1980). For the primary outcome food allergy, we undertook sensitivity analysis for secure diagnosis of food allergy by oral food challenge or investigator decision using an algorithm developed for the BEEP study.
3. Including aggregate data from trials that do not provide individual participant data: as aggregate data made up less than 10% of the total number of participants across all trials, our primary analysis included individual participant data only, and we conducted a sensitivity analysis *including* aggregate data from trials that did not provide individual participant data.
4. Excluding any data that are not prospectively acquired: prospectively acquired data are data that were not known to the study Chief Investigator, in analysed and unblinded form, before 10 February 2017. PPMA reduces bias related to knowledge of existing trial outcomes, which might influence trial selection in a retrospective study, because trials are included without any knowledge of outcome. Additionally, outcomes across prospectively planned trials were more closely aligned due to awareness of being included in this IPD meta-analysis. Sensitivity analysis of prospectively acquired data was conducted using the same approach to the primary analysis (i.e. using individual participant data only; see Data synthesis section).
5. To explore heterogeneity: when considerable statistical heterogeneity was observed (I^2 > 75%), we explored reasons for heterogeneity and when appropriate conducted sensitivity analysis while excluding any trials identified as outlying. Outlying trials are those with very different trial findings from others reporting comparable interventions/outcomes. Outliers were identified from inspection of individual trial treatment estimates and 95% CIs in forest plots.
6. Including data from all arms of factorial trials with a significant interaction: for factorial trials, when there was a significant interaction between the two active interventions with respect to our primary outcome, we included only the arms ‘skin care intervention/control’ versus ‘control/control’. In such scenarios, an additional sensitivity analysis explored the impact of including data from all arms of factorial trials, with adjustment for the non-skin barrier intervention in stage 1 of the analysis.

Summary of findings and assessment of the certainty of the evidence

We planned our 'Summary of findings' tables to include the following.

1. 'Summary of findings' table 1. Skin care intervention versus no treatment or standard care only.
   a. This table includes primary estimates of treatment effects in addition to key sensitivity analyses for primary outcomes.
2. 'Summary of findings' table 2. Skin care intervention A versus no treatment or standard care only. Intervention A = skin care interventions that aim to promote hydration or barrier function.
   a. This table would have included subgroup analyses of low risk of eczema and food allergy versus high risk of eczema and food allergy, either by *FLG* mutation or by family history of allergic disease.
3. 'Summary of findings' table 3. Skin care intervention B versus no treatment or standard care only. Intervention B = skin care interventions that aim to prevent damage.
   a. This table would have included subgroup analyses of low risk of eczema and food allergy versus high risk of eczema and food allergy, either by *FLG* mutation or by family history of allergic disease.

It did not prove necessary to stratify comparisons by types of skin care interventions because we did not identify any eligible trials of skin care interventions type B. Therefore, our 'Summary of findings' tables include only Summary of findings 1.

Outcomes for 'Summary of findings' tables

Primary outcomes

1. Eczema diagnosis
2. IgE-mediated food allergy

Key secondary outcomes

1. Adverse events during the intervention period, such as slippage, skin infection, stinging or allergic reaction to moisturiser
2. Time to onset of eczema
3. Parental report of immediate reaction to a common food allergen
4. Allergic sensitisation to a food allergen

We included outcomes for sensitivity analyses by method of outcome assessment and by risk of bias in the 'Comments' in Summary of findings 1.

Quality of the evidence

We applied the GRADE approach to our main comparisons listed above (Andrews 2013; Schünemann 2020). The outcomes that we included in our 'Summary of findings' tables are the primary outcomes of eczema and food allergy and adverse events during the intervention period, along with key secondary outcomes of time to onset of eczema, parental report of immediate food allergy, and allergic sensitisation to a food allergen. Two review authors (MK, SC, or RJB) independently assessed each outcome for risk of bias, imprecision, inconsistency, indirectness, and publication bias, and downgraded when appropriate. We graded each outcome as high, moderate, low, or very low quality.

RESULTS

Description of studies

We included 33 RCTs in the review.

Results of the search

Searches of the four databases and two trials registers (see Electronic searches) yielded 7046 records. Our searches of other resources identified no further relevant records. Once duplicates had been removed, we had a total of 6133 records. We excluded 5891 records based on titles and abstracts. We obtained the full text of the remaining 242 records. We excluded 150 studies reported in 152 articles (see Characteristics of excluded studies). We identified eight ongoing studies reported in 11 articles (see Characteristics of ongoing studies), and three studies reported in four articles are awaiting classification (see Characteristics of studies awaiting classification). We included 33 studies reported in 75 articles (see Characteristics of included studies). For a further description of our screening process, see the study flow diagram (Figure 1).

Figure 1. Study flow diagram.

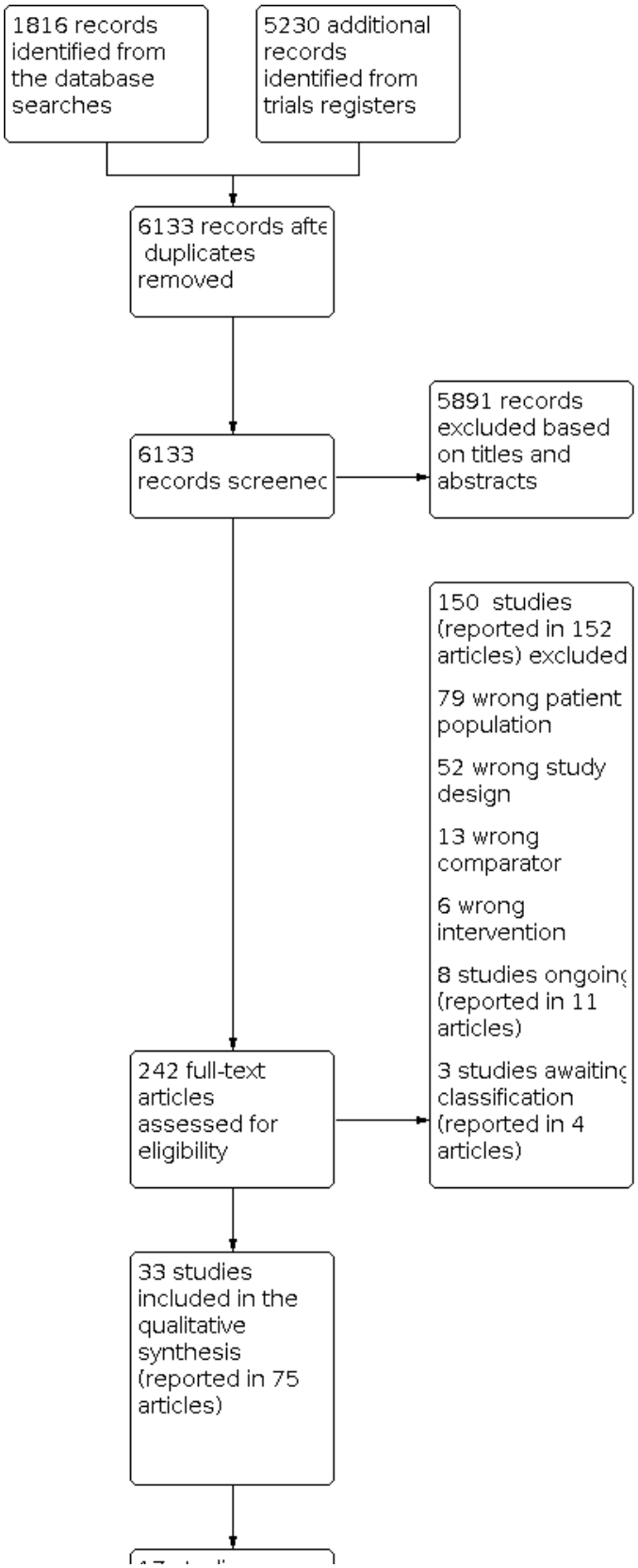
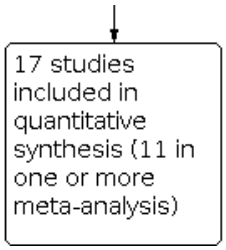


Figure 1. (Continued)



Included studies

Thirty-three studies with 25,827 participants were included. Full details for each trial are summarised in the Characteristics of included studies tables. Of the included studies, only 17 trials, randomising 5823 participants, had outcome data relevant to eczema, food allergy, or the adverse events of interest; these data were IPD, either aggregate or narrative.

The 16 included studies that did not have any outcome data relevant to the review were Abraham 2019; Baldwin 2001; Duan 2019; Garcia Bartels 2010; Garcia Bartels 2011; Garcia Bartels 2012; Garcia Bartels 2014; Lavender 2011; Lavender 2012; Lavender 2013; Lund 2020; Raisi Dehkordi 2010; Rush 1986; Sankaranarayanan 2005; Tielsch 2007; and Zhao 2005. Ten of these studies assessed the impact of short-term application of skin care products in term infants in the first few weeks of life on physiological skin outcomes (Abraham 2019; Duan 2019; Garcia Bartels 2010; Garcia Bartels 2012; Garcia Bartels 2014; Lavender 2011; Lavender 2012; Lavender 2013; Lund 2020; Raisi Dehkordi 2010). Rush 1986 evaluated the impact of daily bathing on *Staphylococcus aureus* colonisation levels. Baldwin 2001 assessed diaper products to prevent diaper dermatitis. Garcia Bartels 2011 looked at effects of swimming and lotion on infant skin, with Zhao 2005 evaluating the impact of swimming alone on neonatal skin barrier. Tielsch 2007 was a cluster-randomised trial including more than 17,000 participants, evaluating effects of chlorhexidine wipes on neonatal mortality and infection in rural Nepal, and Sankaranarayanan 2005 evaluated effects of coconut and mineral oil on weight velocity. For these trials, the longest follow-up period was four weeks, and outcomes were physiological skin measures or non-skin-related outcomes. These trials met the criteria for inclusion; however, they did not include eczema or food allergy outcomes, nor usable adverse event outcomes.

Participant Characteristics

For studies included in the meta-analysis, almost all participants were enrolled in the study before 14 days of age.

Female sex ranged from 43% of participants in Cooke 2015 to 56% in NCT03376243. Vaginal delivery ranged from 26% in Simpson 2014 to 83% in Cooke 2015.

Design

As per the inclusion criteria, all trials were randomised controlled trials of a skin barrier intervention versus standard care or no skin care intervention. Most (25/33) trials recruited infants before one month of age and randomised them to a "control" group, which provided standard care for infant skin in the locality, or an "intervention" group. Both intervention and control groups were then followed up at specified intervals for assessment of outcomes. Because the most common intervention was the application of emollients or changes to skin care, in almost all studies, participants were not blinded to their allocation status. All trials were individually randomised, apart from Skjerven 2020 and Tielsch 2007.

Two studies were factorial RCTs: Skjerven 2020 was a cluster-randomised trial evaluating both a skin barrier intervention and early introduction of solid foods. Due to significant interaction between interventions, only the skin care and control arms of the study were used for IPD analysis. Dissanayake 2019 was an individually randomised factorial trial evaluating both a skin barrier intervention and an oral synbiotic. The following studies included more than two arms but included a control arm: Abraham 2019; Cooke 2015; Dizon 2010; Duan 2019; Garcia Bartels 2010; Garcia Bartels 2014; Raisi Dehkordi 2010; Sankaranarayanan 2005.

Simpson 2014 is the pilot study for Chalmers 2020. Lowe 2018a is the pilot study for an ongoing study, Lowe 2019.

Sample sizes

The three largest studies contributing to data analysis were Skjerven 2020 (n = 2397), Chalmers 2020 (n = 1394), and Dissanayake 2019 (n = 549). Eight studies enrolled between 100 and 250 participants (Bellemere 2018; Cooke 2015; Da Cunha 2008; Dizon 2010; Horimukai 2014; McClanahan 2019; Simpson 2014; Yonezawa 2018), and six studies included fewer than 100 participants (Amer 2017; Kataoka 2010; Lowe 2018a; Migacheva 2018; NCT03376243; Thitthiwong 2019).

Setting

In most trials, women were approached during pregnancy or in the first few weeks after birth and were offered participation. Most studies were conducted from tertiary referral hospitals. All studies that contributed to the meta-analysis were conducted in well-resourced settings. Visits mainly took place at children's hospitals, apart from Chalmers 2020, which was a pragmatic study, and a majority of end of study assessments were conducted in participants' homes. Chalmers 2020 recruited from multiple sites across England. Skjerven 2020 recruited mainly in Oslo, Norway, but also in Sweden. Four studies were based in Japan (Dissanayake 2019; Horimukai 2014; Kataoka 2010; Yonezawa 2018). Remaining trials were based in Australia, France, Germany, and the United States.

Participants

All trials set their own inclusion and exclusion criteria. The meta-analysis protocol set inclusion criteria as infants under one year old; however a vast majority of studies in the meta- analysis that contributed data to meta-analyses enrolled newborns up to

three weeks of age. The only exceptions to this were Garcia Bartels 2011 (infants 3 to 6 months), Dizon 2010 (mean age approximately 5.4 months), Duan 2019 (mean age 3 months), and Garcia Bartels 2014 (infants enrolled at 9 months of age). As this was a primary prevention review, infants who already had eczema diagnosed were excluded, along with infants with a known skin condition. Studies that focused on a pre-specified population such as preterm infants were excluded, as their findings may not be generalisable. Most studies contributing to meta-analyses enrolled participants with a family history of allergy, although this was defined in different ways across studies. Horimukai 2014 included infants with high risk of atopic dermatitis from family history, and Kataoka 2010 included infants with "family history of AD in second degree of kinship". Four studies included infants with at least one first-degree relative with eczema, hay fever, or asthma (Chalmers 2020; McClanahan 2019; NCT03376243; Simpson 2014). Lowe 2018a and Thitthiwong 2019 included infants with a self-reported family history in parent or sibling of any allergic disease, whereas Bellemere 2018 required two atopic first-degree relatives. Dissanayake 2019, Skjerven 2020, and Yonezawa 2018 did not require family history of atopy for enrolment. Key baseline characteristics of participants included in the meta-analyses are summarised in Table 2 and Table 3.

Interventions

Interventions were any skin barrier interventions that could alter the skin barrier in the infant. We did not identify any completed trials of interventions to reduce exposure to substances that might damage the skin barrier, but we did identify one ongoing trial of a water softener with this aim (Jabbar-Lopez 2019). Some included trials used a single intervention, others used a package of skin care interventions, and two were factorial trials. The intervention was compared to standard infant care in the country of the study setting.

i. Emollients

The most common intervention, used in 13 of 33 trials, was emollient with standard care. The type of emollient and the treatment regimen varied.

Five trials compared a commercial daily emollient for a treatment duration of three to six months with standard care (Bellemere 2018; Kataoka 2010; Lowe 2018a; Simpson 2014; Yonezawa 2018). Bellemere 2018 compared the use of a "French cosmetic brand" emollient in neonates, twice daily for the first six months of life, versus control, with outcomes measured at six months of age. Kataoka 2010 randomised newborn infants to an unspecified daily emollient "more than once a day", or to control, for six months, with outcome measured at six months of age. Lowe 2018a randomised 80 newborn infants to a ceramide dominant emollient (EpiCeram™; PuraCap Pharmaceutical LLC, South Plainfield, NJ, USA) or to control (no intervention); participants were advised to apply the emollient all over twice a day for six months. Outcomes were measured at 12 months of age. Simpson 2014 was the pilot study for Chalmers 2020 and randomised 124 infants to once-daily all-over emollient or standard care for six months, starting within three weeks of birth, with outcomes measured at 24 weeks. The emollient was chosen from sunflower oil, Doublebase gel, or paraffin in UK-based participants, and from sunflower oil, Aquaphor, or Cetaphil in US-based participants. In Yonezawa 2018, newborn infants were also randomised to an emollient one or more times per day and reduced bathing to every second day or standard care for the control group. Soap for washing was provided by the team. The intervention period lasted from week 1 to week 12 after birth; outcomes were measured at three months of age.

Five trials compared the use of commercial emollients with standard care over a longer intervention period, between 32 weeks and 12 months (Chalmers 2020; Horimukai 2014; McClanahan 2019; NCT03376243; Thitthiwong 2019). Chalmers 2020 was a pragmatic randomised controlled trial of all-over body, once-daily emollient from enrolment to one year, with outcome assessment one year after treatment ended. This trial used Doublebase Gel or Diprobase Cream, and participants were able to choose between them and to swap during the study. In Horimukai 2014, infants younger than one week were randomised to an all-over, once-daily emulsion-type emollient (2e (Douhet) Emulsion; Shiseido, Tokyo, Japan) or to control for 32 weeks. Participants in the control group were allowed to use petroleum jelly if they wished. Outcomes were measured at 32 weeks. McClanahan 2019 randomised 100 infants under three weeks of age to Cetaphil Restoraderm emollient or to an emollient of choice on an as-needed basis. The intervention group was advised to apply the emollient all over the baby once daily until 12 months of age, with outcomes recorded at two years of age. Thitthiwong 2019 randomised 54 infants less than 10 weeks old to once-daily, all-over body cold cream or control. The skin outcome was assessed at nine months of age; however, it is unclear when the intervention period was completed. NCT03376243 randomised newborn infants to once-daily all-over Lipikaur Baume or control. Both groups received general skin care advice for infants. The intervention was given for 12 months and outcome was assessed at two years of age.

Skjerven 2020 evaluated skin care intervention and early introduction of allergenic food. As Skjerven 2020 reported a significant interaction between interventions for the primary eczema outcome, we used only data from the skin care and control arms for our primary analysis, where infants were bathed using an oil emulsion and had cream applied to the face once daily from age two weeks to eight months. Eczema outcome was measured at 12 months of age, and food allergy was assessed at three years of age.

Two trials compared the use of emollient and synbiotic with standard care (Dissanayake 2019; Migacheva 2018). Dissanayake 2019 was a factorial trial of skin care intervention plus a synbiotic versus normal care for prevention of eczema in infants. The skin care intervention was the use of a lipid-based emollient, which was advised to be put on the cheeks twice daily and on the body if wished. The synbiotic was a combination of 0.5 g (7 × 109 colony-forming units (CFUs)/g) of *Bifidobacterium bifidum* and fructo-oligosaccharides twice a day. The intervention period lasted from birth to six, months with outcome assessment at 12 months of age. One study compared an emollient and an oral synbiotic versus control. Migacheva 2018 randomised 63 infants younger than three weeks of age to twice-daily all-over emollient for six months and two supplements of synbiotic at three and six months, or control.

ii. Topical oils

Cooke 2015 was a three-armed trial of the effect of sunflower oil or olive oil versus control on neonatal skin. Parents were advised to apply 4 drops of oil to their baby's left forearm, left thigh, and abdomen, twice a day. All groups were advised not to use any other skin care products, and the intervention period lasted four

weeks, with outcomes measured at four weeks. Raisi Dehkordi 2010 randomised 120 infants who were 10 to 15 days old to massage with sunflower oil, sesame oil, or no oil. Mothers were advised to massage the oil into infants twice daily for 28 days, with outcomes measured at the end of the 28 days. Sankaranarayanan 2005 randomised 224 babies to coconut oil, mineral oil, or control with four times daily oil massage from birth until 31 days of age; outcomes were measured at 31 days of age.

iii. Bathing products and frequency

In Abraham 2019, 102 children were randomly assigned to bathing with one of chlorhexidine, saline, or standard bath, with outcomes assessed up to 24 hours after the intervention. In Dizon 2010, children younger than one year were randomly assigned to three groups to be bathed for two weeks with Group I - Johnson's Baby Top-to-Toe Wash, Group II - Sebamed Baby Liquid Cleanser, or Group III - clear water. Assessment was done at one and two weeks of treatment. In Duan 2019, 150 infants were randomised to Group I commercial baby wash (Johnson's Baby Wash) and commercial baby lotion (Johnson's Baby Lotion), and Group II to water wash and commercial baby lotion, or water only. Parents were asked to wash their infant daily in the wash and apply the lotion, or to wash their infant daily with water and apply the lotion daily, or to wash their infant daily with water only. This intervention was given for 12 weeks, with outcomes assessed at the end of the 12-week period. In Garcia Bartels 2010, 64 newborn infants were randomised to twice-weekly washing for the first eight weeks of life in one of four groups: Group WG, bathing with wash gel (Top-To-Toe Baby Gel Penaten, Johnson & Johnson); Group C, bathing with clear water and afterwards topical cream (Baby Caring Facial & Body Cream Penaten, Johnson & Johnson); Group WG + C, bathing with wash gel and topical cream; or Group C, bathing with wash only (i.e. control). Outcome assessment was conducted at eight weeks of age. Lavender 2011 randomised newborn infants to be washed with Johnson's Baby Top-To-Toe or water, at least three times a week, for the first eight weeks of life. Skin was assessed at four and eight weeks, the first during and the second at the end of the intervention period. This was a pilot trial; the full trial - Lavender 2013 - randomised 307 infants to washing with commercial product or water alone at least three times a week. The intervention period lasted for four weeks only, with outcome assessment at four weeks - the end of the intervention period. Lund 2020 randomised 100 newborn infants to be washed with Johnson's Baby Top-To-Toe or water, in the first hours of life. Skin was assessed before and "after" this bath. Rush 1986 randomised healthy term newborn infants to daily washing with soap and water versus dry skin care and no bath. The outcome was measured on day 4 of bathing, or immediately before discharge.

iv. Combined skin interventions

Amer 2017 compared detailed instructions to use a combined skin intervention for parents of newborn infants involving delaying the first bath and using daily baby oil on scalp and body or chlorhexidine wash for umbilical cord bathing twice per week versus study shampoo versus standard care. The cream, wash, shampoo, and wipes used were provided to parents for a four-week interval, with outcomes measured at the end of the treatment period. Skjerven 2020 was a factorial randomised trial of 2396 infants evaluating effects of the skin barrier intervention of emollient and bath oil and early introduction of allergenic food on the impact of developing eczema and food allergy. Those randomised to skin barrier intervention were advised to bathe daily with bath oil and to apply emollient to the infant's face from two weeks to eight months of age. Outcomes were assessed at 12 months to three years of age. Garcia Bartels 2011 evaluated effects of infant swimming and applying an emollient after swimming versus swimming alone in three- to six-month-old infants. Both groups participated in the swimming classes once a week for four weeks. The intervention group was instructed to apply a simple emollient all over after swimming. The final outcome was assessed at one week after the end of the intervention period. In another swimming-related intervention, Zhao 2005 evaluated the impact of daily infant swimming in the maternity hospital compared to control. Infants in the swimming group had twice-daily, 10- to 15-minute swimming sessions whilst in the maternity hospital. Outcomes were measured on discharge.

v. Diapers

Baldwin 2001 compared a new zinc oxide diaper to a commercially available diaper for prevention of diaper dermatitis. Previously well children without diaper dermatitis were randomly assigned to control diaper or zinc oxide-based diaper for four weeks. The outcome of diaper dermatitis was measured at the end of the treatment period.

vi. Cleansing products

In Da Cunha 2008, newborn infants were randomised to receive chlorhexidine liquid soap bath versus control liquid soap. Outcome was measured at 24 hours after bath. In Garcia Bartels 2012, newborn infants were randomised to washing of the diaper area with commercial wipes or water-moistened cloths (control) for four weeks. Skin was assessed at four weeks - the end of the intervention period. In Lavender 2012, 280 newborn infants were also randomised to washing of the diaper area with a commercial wipe (Johnson's Baby Skincare Fragrance Free Wipe) or cotton wool and water for four weeks post birth, with outcome assessed at four weeks - the end of the intervention period. Tielsch 2007 was a cluster-randomised study of 17,530 infants in rural Nepal, which compared all-over cleansing at birth with a chlorhexidine wipe versus a wipe without chlorhexidine. This was a one-time intervention provided at birth. The outcome was measured at 28 days.

Follow-up

Our specified primary and secondary outcomes were measured from one to three years, apart from adverse events, which were measured during the intervention period. Studies with emollients and Skjerven 2020 were the only studies with follow-up long enough to meet this outcome timing. Most of the other studies followed up with these infants to a maximum of four weeks, which was too soon to assess whether eczema or food allergy was present.

Comparators

All trials included a comparison arm that provided "routine" skin care for their country. We did not specify what the comparator was, as daily practices on how to treat infant skin vary between countries and within countries according to cultural norms. We excluded any trial that had an active comparator such as an emollient.

Outcomes

Of 33 studies, 17 studies provided data on one or more outcomes relevant to this review, of which 11 could be included in the meta-analysis. Ten trials provided IPD, including nine studies that provided IPD for the primary outcome eczema or food allergy. Cooke 2015 provided IPD for adverse events only. Pre-specified outcome timings were one to three years for both primary and secondary outcomes related to eczema and food allergy. Adverse events were measured during the intervention period.

Eczema data were measured between one and three years of age in eight trials (Chalmers 2020; Dissanayake 2019; Lowe 2018a; McClanahan 2019; Migacheva 2018; NCT03376243; Skjerven 2020; Yonezawa 2018). Two trials had eczema outcomes before one year (Horimukai 2014; Simpson 2014). Four further trials recorded some data on eczema outcomes, which were not usable in the meta-analysis (Amer 2017; Bellemere 2018, Kataoka 2010 Thitthiwong 2019), but these data were included in narrative format in the results. The primary outcome of eczema was measured by Hanifin and Rajka, or by UK Working Party methods, in all trials except one, which used parental report of a doctor diagnosis of eczema (Yonezawa 2018). Three studies measured eczema severity between one and three years by clinician assessment, including Chalmers 2020 and NCT03376243 using the EASI at two years and one year, respectively, and Lowe 2018a using objective SCORAD (clinical tool used to assess the extent and severity of eczema) at one year. Only Chalmers 2020 recorded parental report of eczema severity based on the POEM at two years. Nine studies measured time to onset of eczema (Chalmers 2020; Dissanayake 2019; Horimukai 2014; Lowe 2018a; McClanahan 2019; NCT03376243; Simpson 2014; Skjerven 2020; Yonezawa 2018).

The primary outcome of IgE-mediated food allergy diagnosed by oral food challenge between one and three years was measured in Chalmers 2020 only. Three trials provided data on parental report of doctor diagnosis of food allergy between one and three years: Dissanayake 2019 (by one year), Yonezawa 2018 (by two years), and Chalmers 2020 (by two years). Two trials provided data on parental report of an immediate (< 2 hours) reaction to a common food allergen: Chalmers 2020 (at two years) and NCT03376243 (by one year). Data on allergic sensitisation to foods between one and three years were provided in Chalmers 2020 (at two years) and Lowe 2018a (at one year). Two trials had data on allergic sensitisation to foods at eight months - Horimukai 2014 - and at nine months - Dissanayake 2019 - which were used in sensitivity analysis only. Kataoka 2010 and Thitthiwong 2019 provided narrative information on food allergy that could not be used in the meta-analysis but was included in narrative format in the results.

Adverse event data for the pre-specified adverse events of interest were provided by 10 studies (Amer 2017; Chalmers 2020; Cooke 2015; Da Cunha 2008; Dizon 2010; Lowe 2018a; McClanahan 2019; NCT03376243; Simpson 2014; Skjerven 2020). Nine studies contributed some narrative data on non-specific adverse events, which were not included in the meta-analysis but are presented descriptively in the effects of interventions section (Dissanayake 2019; Garcia Bartels 2011; Horimukai 2014; Lavender 2012; Migacheva 2018; Raisi Dehkordi 2010; Sankaranarayanan 2005; Thitthiwong 2019; Tielsch 2007).

Funding

Of the 11 trials contributing to one or more meta-analyses, two did not specify funding (McClanahan 2019; Migacheva 2018); the other nine contributing trials were funded through higher-level institutions.

Of the six trials that contributed aggregate data that were not relevant for inclusion in one or more meta-analyses, three studies did not specify funding, two were supported by local hospitals, and one was commercially sponsored.

Of the 16 trials that did not contribute any data on outcomes, two did not report on funding, two were sponsored by local hospitals, one was sponsored by a local hospital and the Gates Foundation, and the other 11 were commercially sponsored.

Excluded studies

We excluded 178 studies (see Characteristics of excluded studies). We excluded 93 for including the "wrong patient population". The aim of this review was to evaluate prevention of eczema and food allergy in infants; therefore any population already diagnosed with eczema was excluded, along with participants over the age of 12 months. We also excluded any studies that were primarily looking at preterm infants, as these infants did not have a "normal" neonatal course, with most cared for in neonatal intensive care units, where skin care practices are inherently different. We excluded 63 studies for using the "wrong study design" - mainly if they were not randomised controlled trials. We excluded 14 studies as using a "wrong comparator", as there was no standard control in the study design. Finally, we excluded eight studies as they provided the "wrong intervention" - some including oral probiotics.

Studies awaiting classification

We marked three trials as "awaiting classification" (Studies awaiting classification).

ISRCTN38965585 is a World Health Organization (WHO)-sponsored cluster-randomised trial including over 40,000 infants and assessing effects of newborn massage with cold pressed olive oil on newborn survival in rural India. This study was registered initially in 2014 and is marked as "recruitment complete". This study could have contributed only to adverse events; no results are recorded at the clinical trial registry or in our search. We received no response from study authors when we contacted them via the email addresses provided.

JPRN-UMIN000026877 is a small trial of 50 infants evaluating the efficacy of a foam body cleanser and "lotion" on infant skin; it was sponsored by a Japanese cosmetics company and is marked as "complete" at the clinical trial register. We received no response from study authors when we contacted them via the email addresses provided.

NCT03640897 is a commercial trial of a wipe for infants. It does meet our criteria; however, it could contribute only to adverse events. This study has been marked as "complete" at the trial register since March 2019. No data have been published. We received no response from study authors when we contacted them through their website at www.labogilbert.com/.

Ongoing studies

We classified eight studies as "ongoing studies" (Characteristics of ongoing studies), which could provide further useful information in an update to this review in the future. Specifically for prevention of eczema in infants, NCT02906475 is an RCT of 160 infants undertaken by HIPP Pharmaceuticals to evaluate the impact of use of daily milk lotion in infants for prevention of eczema. Jabbar-Lopez 2019 is a pilot RCT in Kings College London of 80 infants that is evaluating whether families would be willing to be randomised to have domestic ion exchange water softener installed, with a secondary outcome of prevention of eczema in infants. NCT03808532 is an RCT by MYOR Corporation of 290 infants that is evaluating the effect of daily emollient for prevention of eczema. Eichner 2020 is an RCT of 1250 infants conducted in the USA to evaluate the impact of daily lipid-rich emollient from birth to two years on the cumulative incidence of eczema at 24 months. For prevention of eczema and food allergy, NCT03871998 is an RCT in Ireland of 242 infants evaluating the effect of twice-daily all-over emollient in the first two months of life on incidence of eczema at 12 months and of IgE-mediated food allergy at 24 months. Lowe 2019 is an RCT of 760 infants undertaken in Melbourne, Australia, to evaluate the impact of a twice-daily ceramide-dominant emollient for prevention of eczema and food allergy. NCT04398758 is an RCT that is under way in Germany to evaluate twice-daily paraffin-based cream on infants with a family history of diagnosed eczema. The primary outcome is eczema at six months, with food sensitisation at 12 months - one of its secondary outcomes. For evaluation of the skin barrier in infants, NCT03142984 is a study of 160 infants that is exploring effects on the skin barrier of a new baby wash and baby lotion.

Trialists leading the following ongoing trials are all involved in the IPD collaboration and will be involved in an update of this review when planned: NCT02906475, NCT03142984, Jabbar-Lopez 2019, NCT03871998, Lowe 2019, and Eichner 2020.

Risk of bias in included studies

We assessed risk of bias using the Cochrane 'Risk of bias' tool 2 (Higgins 2018) for trials providing outcome data on one or more of eczema, food allergy, slippage accidents, skin infections, stinging or allergic reactions, serious adverse events, time to eczema onset, parent report of immediate reaction to a common allergenic food, and allergic sensitisation. Detailed risk of bias assessment data, with consensus responses to each RoB 2 signalling question, are available at Cro 2020b. Risk of bias assessments by analysis are also summarised in the results level RoB 2 tables. Risk of bias assessments were not performed for trials providing qualitative narrative information.

Risk of bias summary by domain

Most studies (12/17) were at low risk of bias for the randomisation process; we rated five studies as some concerns for risk of bias, as insufficient information on allocation concealment or balance in baseline characteristics was provided (Amer 2017; Bellemere 2018; Dizon 2010; Kataoka 2010; Migacheva 2018).

Most studies (12/17) providing outcome data were judged to be at low risk of bias for deviations from intended interventions for all outcomes, as whilst it was not possible to blind participants or carers in the individual studies due to the nature of the intervention under study, no evidence indicates that deviations arose because of the trial context. Control group rates of skin care application were consistent with those of other trials and observational studies, which have reported that up to 75% of individuals apply a skin care intervention (Rendell 2011). Additionally, analyses were appropriately performed according to the intention-to-treat principle to identify the effect of assignment to the intervention.

Three studies were rated to be at some concerns of bias for deviations from intended interventions for all outcomes (Amer 2017; Migacheva 2018; Thitthiwong 2019), as they provided no information for assessment of whether deviations arose because of trial context. For two other studies, analysis populations were unclear, and we consequently rated these as having high risk of bias (Bellemere 2018; Kataoka 2010).

For missing data on our outcomes of interest, studies were predominantly at low risk of bias or at some concerns if they included a non-negligible quantity of missing data, and if sensitivity analysis using the individual participant revealed that trial conclusions changed (point estimate changed by at least 20% of the complete case estimate). However across most outcomes, whilst missingness could have depended on the true value, it was rated unlikely that missingness in the outcome depended on its true value due to trial circumstances and the fact that rates of missingness did not vary considerably by intervention groups. The one exception to this was a single trial that provided outcome data on food allergy as assessed by oral food challenge and was rated having high risk of bias for missing data (see risk of bias for analysis table for Analysis 1.29) (Chalmers 2020). Data were missing for 398/1394 (29%) randomised participants. Results varied in missing data sensitivity analyses performed using the IPD, and it was judged potentially likely that missingness depending on the value of the outcome (because there was a difference between treatment groups in the proportion of participants who underwent oral food challenge) and recorded reasons for missingness included decline in oral food challenge and unwillingness to participate, which could have depended on the outcome.

For measurement of the outcome, outcomes reported by carers (e.g. adverse events, report of reaction, POEM, eczema for one study) were judged at some concerns for risk of bias, as carers were unblinded due to the nature of the intervention. However, whilst knowledge of the intervention could have influenced the measurement, it was judged unlikely to have impacted measurement. For other outcome measurements judged at low risk of bias, if no information was available on the blinding status of assessors, these were rated as some concerns. One trial supplied no information on how eczema was measured and by whom and was rated as having high risk of bias for this outcome.

Selection of the reported result

Of the 17 studies providing data on one or more of our outcomes assessed for risk of bias, 10 were rated at low risk of bias for selection of reported results; these supplied individual participant data (Chalmers 2020; Cooke 2015; Dissanayake 2019; Horimukai 2014; Lowe 2018a; McClanahan 2019; Simpson 2014; Skjerven 2020; NCT03376243; Yonezawa 2018). For each of these trials, for each outcome, we performed the required analysis using the supplied trial data set in keeping with a pre-specified statistical analysis plan that was finalised before unblinded outcome data were available for analysis (Cro 2020a).

Seven trials contributing some aggregated outcome data were rated as some concerns for selection of reported results (Amer 2017; Bellemere 2018; Da Cunha 2008; Dizon 2010; Kataoka 2010; Migacheva 2018; Thitthiwong 2019). Only Migacheva 2018 was included in the meta-analysis. All seven provided no information on whether a pre-specified statical analysis plan, finalised before unblinding, was followed.

Overall risk of bias

In summary, most of the evidence included in this review was assessed as low risk or some concern of risk of bias. Over all RoB 2 domains, 3/17 studies were rated as low risk of bias across all included outcomes (Cooke 2015; Dissanayake 2019; Horimukai 2014); eight were rated as some concerns for risk of bias across all included outcomes (Da Cunha 2008; Dizon 2010; McClanahan 2019; Migacheva 2018; NCT03376243; Simpson 2014; Thitthiwong 2019; Yonezawa 2018), and one was at high risk of bias for its sole included outcome (Bellemere 2018). Two trials were predominantly rated as some concerns of risk of bias across all included outcomes due to measurement of the outcome or missing data (4/5 and 4/6 outcomes for Skjerven 2020 and Lowe 2018a, respectively) but also included outcomes at low risk of bias (1/5 and 2/6 outcomes for Skjerven 2020 and Lowe 2018a, respectively). One study was at high risk of bias for eczema and of some concerns for risk of bias for the skin infection outcome overall (Amer 2017). Another study was at high risk of bias for allergic sensitisation and of some concerns for risk of bias for the eczema outcome overall (Kataoka 2010). Finally, one study was at low risk of bias for 2/7 outcomes, some concerns for 4/7 outcomes due to unblinded measurement, and at high risk for food allergy due to missing data (Chalmers 2020).

Effects of interventions

See: **Summary of findings 1** Skin care intervention compared to standard skin care or no skin care intervention for the prevention of eczema and food allergy

Primary outcomes

Primary and secondary outcome results are presented for comparison 1: skin care intervention versus no treatment or standard care only. Comparison 2 - "skin care intervention A versus no treatment or standard care only" and "skin care intervention B versus no treatment or standard care only" - was not conducted because our search did not identify any eligible studies of skin care interventions type B. Results are summarised in Summary of findings 1.

Eczema

Individual participant data on eczema diagnosis by age one to three years were available from seven studies including 4800 randomised participants (Chalmers 2020; Dissanayake 2019; Lowe 2018a; McClanahan 2019; NCT03376243; Skjerven 2020; Yonezawa 2018). Eczema was measured using the Hanifin and Rajka criteria (Hanifin 1980), or the UK Working Party refinement of these criteria (Williams 1994), or other modifications of the Hanifin and Rajka criteria for six trials (Chalmers 2020; Dissanayake 2019; Lowe 2018a; McClanahan 2019; NCT03376243; Skjerven 2020), and eczema was doctor diagnosed for one trial (Yonezawa 2018). Eczema was diagnosed cumulatively up to 12 months for four trials - Dissanayake 2019; Lowe 2018a; NCT03376243; Skjerven 2020 - and up to 24 months for three studies - Chalmers 2020; McClanahan 2019; Yonezawa 2018. Pooled individual patient data available from 3075 participants in these studies show no benefit of skin care intervention (risk ratio (RR) 1.03, 95% confidence interval (CI) 0.81 to 1.31; Analysis 1.1). However, the 95% CI for the pooled RR indicates that we cannot rule out potential benefit or harm, extending from 0.81 to 1.31. Results show moderate statistical heterogeneity between studies for this outcome (I^2 = 41%, P = 0.12). This is driven by one trial with an RR favouring standard care (RR 1.57, 95% CI 1.10 to 2.23) (Skjerven 2020). This heterogeneity may be driven by the type of intervention (bathing with oil and emollient applied to the face only) and/or by timing of intervention initiation (initiated from two weeks). When this study was excluded, pooled individual patient data available from 2004 participants in the remaining six studies continued to show no benefit of skin care intervention (RR 0.95, 95% CI 0.81 to 1.12; I^2 = 0%; Analysis 1.12).

A series of pre-planned sensitivity analyses were conducted (see Table 4). Sensitivity analysis including aggregate data from one additional study that did not supply individual participant data involving 63 randomised participants, of which 60 completed the study (Migacheva 2018), did not change the pooled result (RR 0.97, 95% CI 0.75 to 1.25; Analysis 1.3). When only the six studies that used the Hanifin and Rajka criteria (Hanifin 1980), or the UK Working Party refinement of them (Williams 1994), or other modifications of the Hanifin and Rajka criteria to assess eczema were included, the pooled result remained consistent (RR 1.02, 95% CI 0.78 to 1.34; Analysis 1.3). The pooled result also remained consistent in sensitivity analyses that included data from all four arms of Skjerven 2020 (RR 1.03, 95% CI 0.81 to 1.31; Analysis 1.5); included only studies at low risk of bias (RR 0.97, 95% CI 0.81 to 1.17; Analysis 1.6); excluded non-prospectively acquired data (RR 1.08, 95% CI 0.84 to 1.37; Analysis 1.7); incorporated studies assessing eczema by six months to three years (RR 0.89, 95% CI 0.70 to 1.14; Analysis 1.8); and considered eczema only after the intervention period (i.e. at one year or beyond) (RR 1.06, 95% CI 0.77 to 1.47; Analysis 1.8).

Four additional studies randomising a total of 314 participants provided aggregate data on eczema at four weeks - Amer 2017 - six months - Bellemere 2018; Kataoka 2010 - and nine months - Thitthiwong 2019 that were not eligible for meta-analysis due to not supplying individual participant data nor data from the short follow-up period. Amer 2017 reported eczema in 2/35 (5.7%) participants randomised to standard care and 0/35 (0%) randomised to skin care intervention over a four-week follow-up period. At six months, Bellemere 2018 reported eczema in 9.8% of the intervention arm versus 18.3% of the control arm (60 participants were randomised to each treatment group, but the analysis population was not clear); after follow-up of 24 months, seven new cases of atopic dermatitis (AD) were observed in the intervention group and six new cases in the control group. Kataoka 2010 reported 5/35 (14%) versus 6/32 (19%) cases of eczema in the intervention and control arms, respectively. At nine months, Thitthiwong 2019 reported 0/26 (0%) versus 4/27 (15%) cases of eczema in the intervention and control arms, respectively.

Subgroup analysis did not suggest any differences in treatment effects by intervention type or intervention duration. For basic emollients (Chalmers 2020; McClanahan 2019; Skjerven 2020), there was a pooled RR of 1.04 (95% CI 0.66 to 1.65), and for complex emollients (Dissanayake 2019; Lowe 2018a; NCT03376243;

Yonezawa 2018), there was a pooled RR of 1.01 (95% CI 0.75 to 1.37) (Analysis 1.10). Only one study reported a prescribed intervention period < 6 months (Yonezawa 2018), with an RR of 1.01 (95% CI 0.45 to 2.27). For the six studies with an intervention period ≥ 6 months (Chalmers 2020; Dissanayake 2019; Lowe 2018a; McClanahan 2019; NCT03376243; Skjerven 2020), there was a pooled RR of 1.02 (95% CI 0.78 to 1.34) (Analysis 1.11).

The interaction effect between treatments and actual age of treatment initiation (< 4 days, ≥ 4days) for eczema by one to three years could be estimated for two trials (Chalmers 2020; Lowe 2018a), which randomised a total of 1474 participants. Pooled individual patient data available from 1284 participants in these two studies show no impact of age of treatment initiation on treatment effect (RR 1.05, 95% CI 0.64 to 1.73; Analysis 1.12). In one additional study randomising 118 participants (Horimukai 2014), the interaction between treatment and actual age of treatment initiation for eczema by eight months could be estimated for 99 participants. When data from this study are incorporated, pooled individual patient data available from 1383 participants continue to show no impact of age of treatment initiation (RR 1.59, 95% CI 0.56 to 4.51; Analysis 1.13).

The interaction effect between treatment and *FLG* genotype on eczema by one to three years could be estimated for one trial (Chalmers 2020), which randomised 1394 participants. Based on available data from 816 participants in Chalmers 2020, the RR of eczema by two years for having 1/2 *FLG* mutations in the skin care intervention group versus zero mutations was RR 1.22 (95% CI 0.71 to 2.11) (Analysis 1.14). The large width of the 95% confidence interval indicates uncertainty surrounding the direction and magnitude of any effect of *FLG* on treatment effect from this one study. In one additional study randomising 124 participants (Simpson 2014), the interaction between treatment and *FLG* mutations for eczema by six months could be estimated for 63 participants. When data from this study are incorporated, pooled individual patient data available from 879 participants continue to show uncertainty for the impact of *FLG* mutations on treatment effect (RR 1.03, 95% CI 0.42 to 2.51; Analysis 1.15).

The interaction effect between treatment and family history of atopic disease on eczema by one to three years could be estimated for three trials (Dissanayake 2019; Skjerven 2020; Yonezawa 2018), which randomised 3172 participants. Based on available data from 1663 participants, the pooled RR of eczema by two years for having ≥ 1 family member in the skin care intervention group versus 0 did not indicate a notable interaction (RR 0.95, 95% CI 0.35 to 2.61; Analysis 1.16).

The complier average causal effect (CACE) for an individual using skin care intervention for three or more days a week could be estimated for three trials providing adequate compliance and eczema outcome data (Chalmers 2020; Lowe 2018a; Yonezawa 2018). The pooled CACE for an individual using skin care intervention for three or more days a week from 1440 participants in these studies was on average more in favour of skin care intervention (RR 0.65, 95% CI 0.29 to 1.45; Analysis 1.17) in comparison to the pooled intention-to-treat effect for these same three studies (RR 0.93, 95% CI 0.77 to 1.12; Analysis 1.23). However the 95% CI for the CACE estimate is considerably wider than for the intention-to-treat effect and is consistent with the intention-to-treat effect of no difference. Therefore, we cannot infer any difference in treatment effects for a complier. Additional CACE estimates for alternative definitions of a complier are displayed in Table 5 and similarly do not reveal an impact of compliance on treatment effect.

Trial sequential analysis shows that a target sample size of 5534 would be necessary to demonstrate a minimum relative risk reduction of 30% (assuming a control rate of 15% versus skin care intervention 10.5%) with 90% power (Figure 2). However, based on the data accumulated to date and included within the primary eczema meta-analysis (3075 participants), the Z value falls on the boundary of the inner wedge and is well within the two-sided significance testing boundaries, indicating that a conclusion can be made: the intervention effect is not greater than 30%. A target sample size of 13,072 would be necessary to demonstrate a minimum relative risk reduction of 20% (assuming a control rate of 15% versus skin care intervention 12%) with 90% power (Figure 3). Currently, the meta-analysis is inconclusive for an effect size of 20 because it has not yet crossed the upper or lower boundary for statistical significance or non-superiority.

Figure 2. Trial sequential analysis for eczema (RR of 30%).

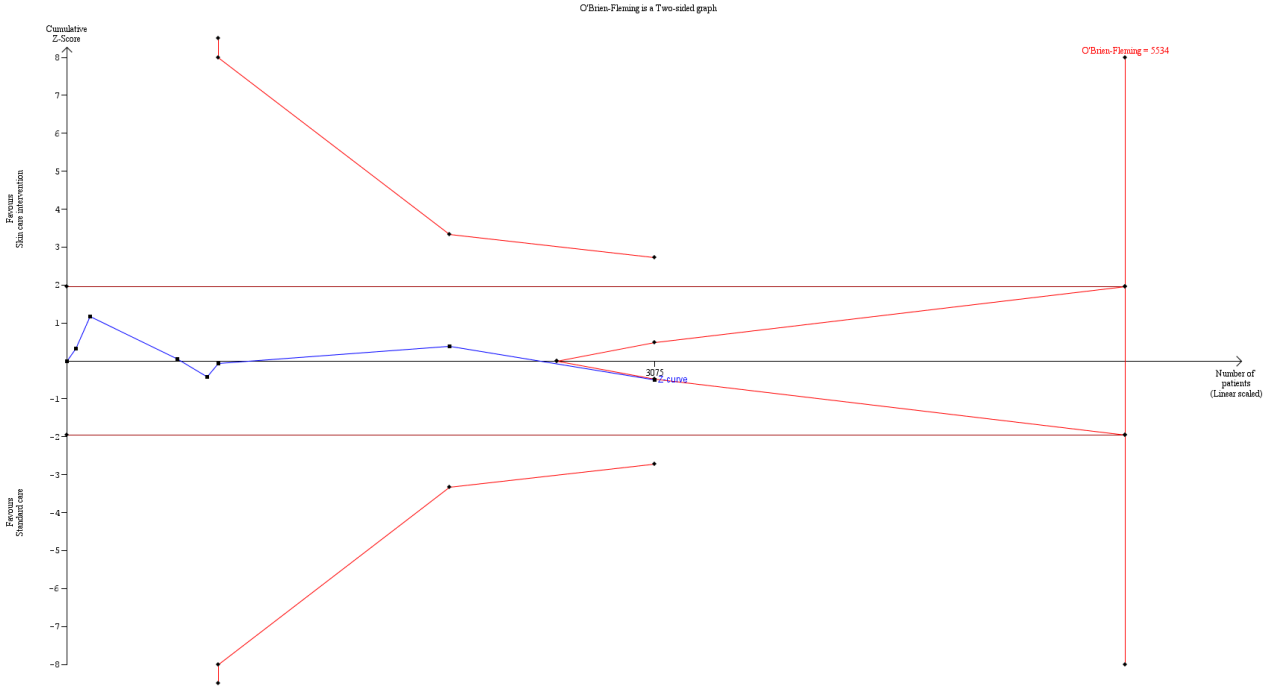
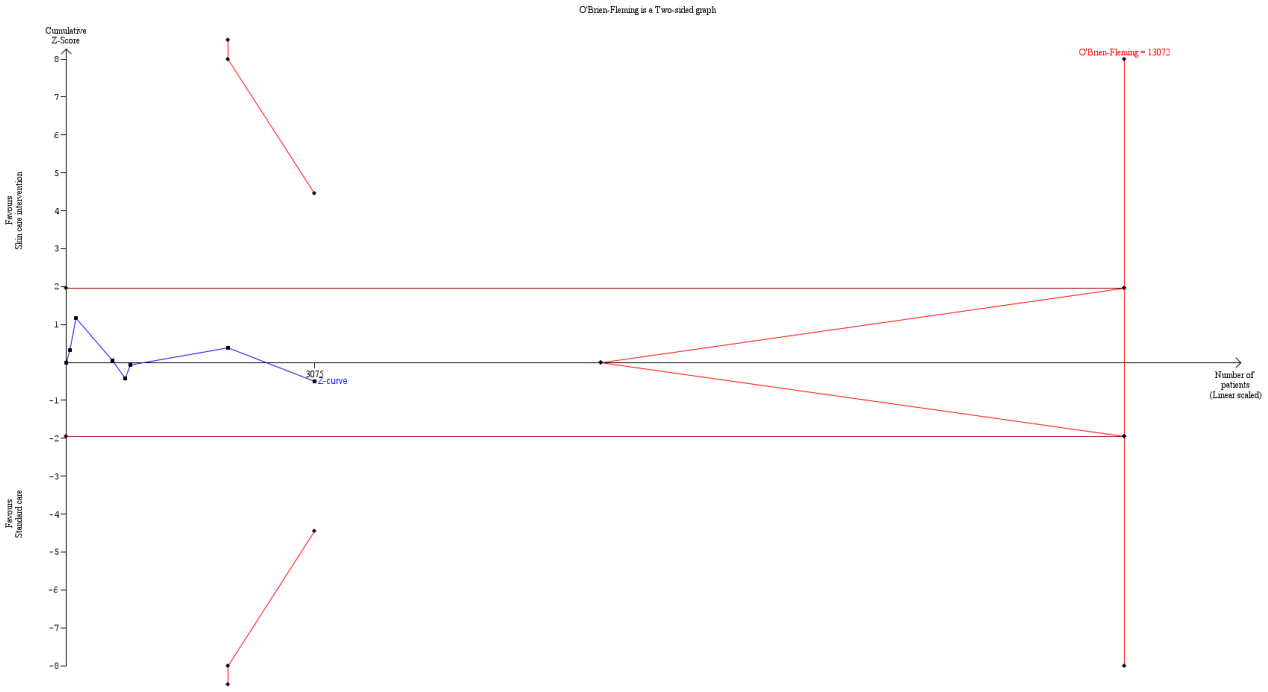


Figure 3. Trial sequential analysis for eczema (RR of 20%).



Food allergy

Individual participant data on IgE-mediated food allergy, confirmed by oral food challenge, by age one to three years were recorded in one study that included 1394 randomised participants (Chalmers 2020). Data on oral food challenge, conducted at two years, was available for 996 participants and favoured standard care (RR 2.53, 95% CI 0.99 to 6.47; Analysis 1.29). The 95% CI for the RR is wide, indicating that we cannot rule out no difference nor small to large harm of skin care intervention based on this one study.

In sensitivity analysis (see Table 6) for IgE-mediated food allergy confirmed by oral food challenge or via an investigator

assessment based on clinical history and/or skin prick tests, data were available for 1115 participants from one study and favoured standard care (RR 1.46, 95% CI 0.91 to 2.34; Analysis 1.30) (Chalmers 2020). The width of the 95% CI for the RR is reduced but it is still wide, indicating that we cannot rule out no difference nor small to large harm of skin care intervention based on this one study.

For food allergy, as measured by a parental report of a doctor diagnosis, individual participant data were available for three studies including 2170 randomised participants (Chalmers 2020; Dissanayake 2019; Yonezawa 2018). Food allergy diagnosis was cumulative up to 12 months for one trial (Dissanayake 2019), and up to 24 months for two trials (Chalmers 2020; Yonezawa 2018). Pooled individual patient data available from 1614 participants in these studies showed no effect of skin care intervention (RR 1.02, 95% CI 0.80 to 1.31; $I^2 = 0$; Analysis 1.31). But uncertainty exists around the true effect value because the 95% CI includes benefit or harm of skin care intervention.

One additional trial randomising a total of 53 participants reported some narrative information on food allergy for only the control group that was not suitable for inclusion in meta-analysis (Thitthiwong 2019). It was narratively reported that "none of the 4 IAD infants developed cow's milk protein allergy or any other food allergy".

As only one study reported the primary food allergy outcome, we did not conduct planned subgroup analysis at the study level. Access to Individual participant data did allow us to assess the interaction between actual age of treatment initiation and treatment. Based on data available for 996 participants in Chalmers 2020, the RR of food allergy for starting skin care treatment at ≥ 4 days of age, in comparison to initiation of skin care treatment < 4 days, was 0.51 (95% CI 0.07 to 3.53). The large width of the 95% confidence interval indicates uncertainty surrounding the direction and magnitude of any effect of age of treatment initiation.

The CACE for an individual using a skin care intervention for three or more days a week could be estimated for one study providing adequate compliance and food allergy outcome data (Chalmers 2020). The CACE on food allergy assessed via an oral food challenge for an individual using a skin care intervention for three or more days a week from 996 participants was accompanied by considerable uncertainty, as reflected by a very wide 95% CI (RR 31.19, 95% CI 0.43 to 2236.62; Analysis 1.32). Whilst the point estimate for the RR was more in favour of standard care in comparison to the intention-to-treat effect of RR 2.53 (95% CI 0.99 to 6.47) (Analysis 1.29), the 95% CI for the CACE estimate is considerably wider than for the intention-to-treat effect and is consistent with the intention-to-treat effect of no difference. Therefore we cannot infer any difference in treatment effect for a complier. Additional CACE estimates for alternative definitions of a complier are displayed in Table 7 and similarly do not demonstrate an impact of compliance on the treatment effect due to a large amount of uncertainty in estimation.

Trial sequential analysis shows that a target sample size of 7602 would be necessary to demonstrate a minimum relative risk reduction of 30% (assuming a control rate of 5% versus skin care intervention 3.5%) with 90% power (Figure 4). A target sample size of 18,063 would be necessary to demonstrate a minimum relative risk reduction of 20% (assuming a control rate of 5% versus skin care intervention 4%) with 90% power (Figure 5). Based on the data accumulated to date included within the primary food allergy meta-analysis (996 participants), the meta-analysis is inconclusive for a relative effect size of 30 or smaller, because it has not yet crossed the upper or lower boundary for statistical significance or non-superiority.

Figure 4. Trial sequential analysis for food allergy (RR of 30%).

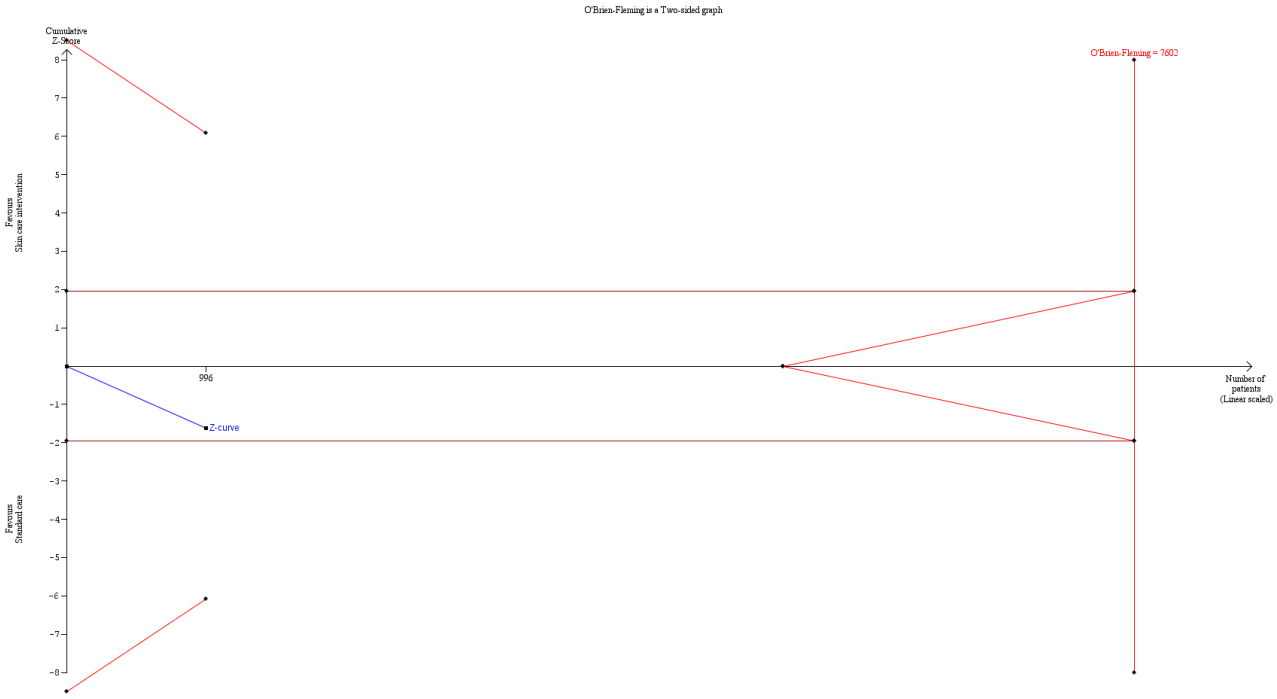
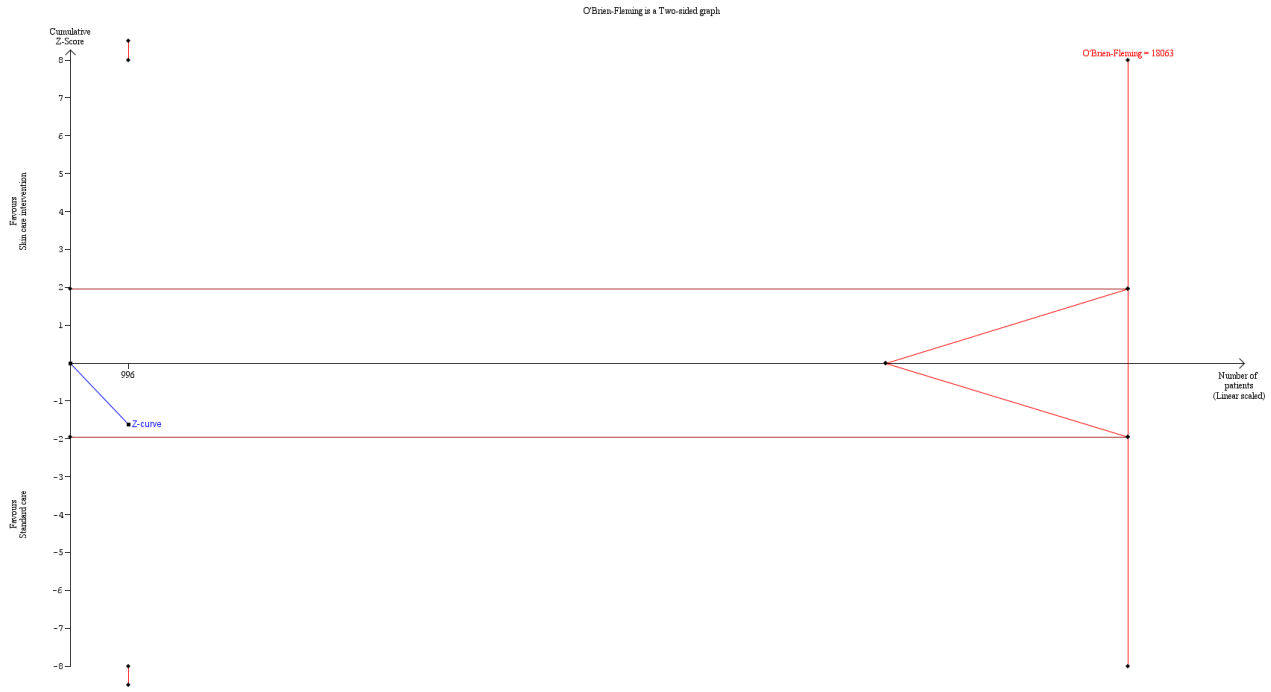


Figure 5. Trial sequential analysis for food allergy (RR of 20%).



Secondary outcomes

Adverse effects

Our adverse events of interest for which we separately report meta-analysis below are skin infections, stinging or allergic reactions, slippages, and serious adverse events recorded over the study intervention period. Ten trials reported some data on one or more of these specific adverse events, including seven trials that could be included in one or more meta-analyses.

An additional nine trials randomising 18,869 participants (one trial randomised 17,530 participants) provided a short general qualitative narrative on adverse events that was not eligible for inclusion in the meta-analysis (Dissanayake 2019; Garcia Bartels 2011; Horimukai 2014; Lavender 2012; Migacheva 2018; Raisi Dehkordi 2010; Sankaranarayanan 2005; Thitthiwong 2019; Tielsch 2007). Of these nine trials, six trials randomising 18,593 participants (9412 control, 9181 intervention) narratively reported no intervention-related adverse events (Dissanayake 2019; Horimukai 2014; Lavender 2012; Migacheva 2018; Thitthiwong 2019; Tielsch 2007). Of the remaining three trials, Sankaranarayanan 2005 (randomised 112 term babies to groups of 38 coconut oil, 37 mineral oil, and 37 placebo) reported, "3 in the coconut oil group, 3 in the mineral oil group and 2 in the placebo group developed mild rash that did not require discontinuation of application"; Garcia Bartels 2011 (randomised 44; 20 lotion and 24 no lotion) reported, "the overall occurrence of adverse events (AEs) was lower in group L *(lotion)* (n = 18) than in group WL *(without lotion)* (n = 33, Table 3)"; and Raisi Dehkordi 2010 (randomised 120) reported, "some adverse events in the oil massage groups; however they were mild rash, which required no cessation".

Skin infections

Individual participant data on skin infections were available from six studies (Chalmers 2020; Cooke 2015; Lowe 2018a; McClanahan 2019; Simpson 2014; Skjerven 2020) including a total of 4209 randomised participants. Pooled individual participant data available from 2728 participants in these studies were in favour of standard care (RR 1.34, 95% CI 1.02 to 1.77; Analysis 1.38) with I^2 = 0 (P = 0.99).

One additional trial that randomised 70 participants (35 to each group) reported weekly infection rates over four weeks of 0 (0%), 3 (8.6%), 7 (20%), and 5 (14.3%) in the control group versus 0 (0%), 0 (0%), 1 (2.9%), and 0 (0%) in the skin care group (Amer 2017).

Stinging or allergic reactions

Individual participant data on stinging or allergic reactions to moisturisers were available from four studies (Cooke 2015; Lowe 2018a; McClanahan 2019; NCT03376243) including a total of 349 randomised participants. Pooled individual patient data available from 343 participants in these studies were in favour of standard care (RR 2.24, 95% CI 0.67 to 7.43; Analysis 1.39) with I^2 = 0 (P = 0.99) but with some uncertainty about the true effect, with the 95% CI including no difference and a benefit of skin care intervention.

One study randomising 120 participants to Johnson's Baby Top-To-Toe wash (group 1, n = 60), Sebamed Baby Liquid Cleanser (group 2, n = 60), and lukewarm tap water (group 3, n = 60) reported, "in group I, 1/60 subjects had mild rashes and redness on the neck and arms that appeared around 4 days after use. The irritation appeared 2-3 hours after bathing and lasted for a few minutes. In group II, 2/60 subjects had irritation in the first week. These were mild rashes on the back and leg and lasted for 1- 2 days. For group II, 1/60 subjects had mild rashes and dryness 3 days after starting use of the

product. No irritation was noted with any of the three compounds in the second week" (Dizon 2010). It was also reported how "no statistically significant irritation was visible to the clinician for all three groups of the study".

One additional study randomised 93 participants to receive the first bath with chlorhexidine (n = 44) or neutral liquid soap in the control group (n = 49) (Da Cunha 2008). No adverse effects were reported for the use of chlorhexidine , including skin irritation.

Slippage accidents

Individual participant data on slippage accidents were available from four studies (Chalmers 2020; Lowe 2018a; Simpson 2014; Skjerven 2020) including a total of 3994 randomised participants. Two studies recorded no slippage events in both treatment groups (Simpson 2014; Skjerven 2020). Pooled individual patient data available from 1242 participants in two studies where the treatment effect could be estimated (Chalmers 2020; Lowe 2018a) favoured standard care (RR 1.42, 95% CI 0.67 to 2.99; Analysis 1.40) with $I^2 = 0$ (P = 0.68) but with some uncertainty about the true effect, with the 95% CI including no difference and a benefit of skin care intervention.

Skjerven 2020 provided data on slippage accidents and was a 2 x 2 factorial trial. Because significant interaction was noted between the two interventions in this trial (food intervention and skin care intervention), we included in our analysis only data from the skin care intervention group versus the control group, in line with our pre-specified statistical analysis plan (Cro 2020a). One accident connected with bathing was reported for a participant in the food and skin care intervention group (1/583, 0.2%).

Serious adverse events

Individual participant data on serious adverse events were available from three studies including a total of 2591 randomised participants (Cooke 2015; Lowe 2018a; Skjerven 2020). Pooled individual patient data available from 1367 participants in these studies favoured standard care (RR 1.80, 95% CI 0.45 to 7.18; Analysis 1.41) but with some uncertainty about the true effect, with the 95% CI including no difference and a benefit of skin care intervention. Evidence shows some heterogeneity ($I^2 = 51$, P = 0.13); however only three trials were included in this comparison, each of which had wide confidence intervals for the effect size, including no difference and a benefit of standard care and a benefit of skin care intervention due to small numbers of events. See Table 8 for a description of reported serious adverse events.

Eczema severity

Individual participant data on eczema severity as assessed by a clinician at one to three years were available from three studies including 1528 randomised participants (Chalmers 2020; Lowe 2018a; NCT03376243). Eczema severity was measured using the EASI at 24 months for Chalmers 2020; the EASI at 12 months for NCT03376243; and the objective SCORAD at 12 months for Lowe 2018a. When no eczema was present, two studies had recorded an eczema severity rating of 0 (Chalmers 2020; NCT03376243). For one study, we imputed an eczema severity rating of 0 for the purpose of analysis when no eczema was reported (Lowe 2018a).

We first assessed the risk of moderate/severe/very severe eczema versus clear/mild eczema. Two studies did not record any incidences of moderate/severe/very severe eczema in either treatment group amongst a total of 108 participants (58 skin care intervention versus 50 standard care) (Lowe 2018a; NCT03376243). In the third study (Chalmers 2020), data on eczema severity, measured by a clinician at two years, were available for 1120 participants and showed no difference between treatment groups (RR 0.92, 95% CI 0.37 to 2.27; Analysis 1.42). The 95% CI for the RR is wide, indicating no difference or small to large harm, and benefit of the skin care intervention for moderate/severe/very severe eczema cannot be ruled out based on this one study.

We subsequently assessed the pooled standardised mean treatment group difference for clinician-assessed eczema severity. Pooled individual participant data available from 1228 participants in the three studies providing participant data on clinician-assessed eczema severity showed no difference between treatment groups (SMD -0.02, 95% CI -0.17 to 0.12; Analysis 1.43) with $I^2 = 7\%$ (P = 0.34) (Chalmers 2020; Lowe 2018a; NCT03376243). When the SMD is re-expressed on the EASI Scale, this is equivalent to an MD of -0.035 (95% CI -0.296 to 0.209), using the pooled SD of 1.74 for EASI as observed in the largest study (Chalmers 2020).

An additional study randomising 63 participants (31 intervention, 32 control) that did not provide individual participant data reported narratively that 60 infants completed the study (29 intervention, 31 control), and that the severity of eczema measured using the SCORAD in the control group was significantly greater than in the intervention group "(22.6 +/- 12.9 vs 17.6 +/- 5.3 respectively, U = 348, P < 0.058)" (Migacheva 2018). Bellemere 2018 reported that amongst 120 randomised participants (60 intervention, 60 control), the frequency of AD during the first six months of life was 9.8% in the prevention group, 18.3% in the control group, and 6.7% in the no-risk group.....Mean SCORAD scores were 24.1 and 23.3 in the at-risk groups".

Parent-assessed eczema severity

Individual participant data on eczema severity as assessed by a parent were available from one study including 1394 randomised participants (Chalmers 2020). Eczema severity was measured using the POEM at 24 months. We first assessed risk of moderate/severe/very severe eczema versus clear/mild eczema as assessed by the parent. Data on eczema severity, as assessed by a parent at two years, were available for 1171 participants and showed no difference between treatment groups (RR 1.17, 95% CI 0.82 to 1.67; Analysis 1.44). The width of the 95% CI for the RR indicates that we cannot rule out no difference or small to large favouring of standard care or skin care intervention for moderate/severe/very severe eczema based on this one study.

We subsequently assessed the mean difference for parent-assessed eczema severity for the only study with available data (Chalmers 2020). Individual participant data available from 1171 participants showed no difference between treatment groups (MD 0.07, 95% CI -0.38 to 0.52; Analysis 1.45).

Time to onset of eczema

Individual participant data on time to eczema onset were available from nine studies, including 5042 randomised participants (Chalmers 2020; Dissanayake 2019; Horimukai 2014; Lowe 2018a; McClanahan 2019; Simpson 2014; Skjerven 2020; NCT03376243; Yonezawa 2018). Eczema was measured using the Hanifin and Rajka criteria (Hanifin 1980), or the UK Working Party refinement of them

(Williams 1994), or other modifications of the Hanifin and Rajka criteria for six studies (Dissanayake 2019; Horimukai 2014; Lowe 2018a; McClanahan 2019; NCT03376243; Skjerven 2020), was doctor diagnosed for two studies (Simpson 2014; Yonezawa 2018), and was assessed by first parent report of a clinical diagnosis for one study (Chalmers 2020). Eczema onset was assessed up to six months for one study (Simpson 2014); up to 8 months (32 weeks) for one study (Horimukai 2014); up to 12 months for four studies (Dissanayake 2019; Lowe 2018a; NCT03376243; Skjerven 2020); and up to 24 months for three studies (Chalmers 2020; McClanahan 2019; Yonezawa 2018). For each trial, data were censored at the trial-specific last measured time point for individuals not experiencing eczema.

Pooled individual patient data available from 3349 participants in these nine studies showed no benefit of skin care intervention (hazard ratio 0.86, 95% CI 0.65 to 1.14; Analysis 1.46). However the 95% CI for the pooled HR indicates that we cannot rule out potential benefit or harm, extending from 0.65 to 1.14. The median time to eczema onset across included studies in the control group was six months. The pooled hazard ratio corresponds to a median time to eczema onset of 6.98 months (95% CI.26 to 9.23 months) in the skin care intervention group. Results show moderate statistical heterogeneity between studies for this outcome (I^2 = 53%, P = 0.03). Post-hoc subgroup analysis, conducted to explore heterogeneity, showed a significant interaction effect (P = 0.03) of trial follow-up (< 1 year versus ≥ 1 year). The pooled HR from the two studies with follow-up less than a year was 0.55 (95% CI 0.35 to 0.87) (I^2 = 0%, P = 0.67) (Analysis 1.48). However, as this result is based upon a total of only 224 participants from two studies that followed up participants for only six months or eight months, there is uncertainty as to whether the skin care intervention delays eczema. The pooled HR from the seven studies with follow-up of at least one year was 1.00 (95% CI 0.75 to 1.33) (I^2 = 44%, P = 0.10) (Analysis 1.48). Remaining heterogeneity amongst studies with follow-up of at least one year is driven by one trial (Skjerven 2020). When Skjerven 2020 was further excluded, the pooled HR with follow-up of at least one year was 0.91 (95% CI 0.78 to 1.07) (I^2 = 0%, P = 0.67), which continues to showing no benefit of skin care intervention. This heterogeneity may be driven by type of intervention (bathing and oil and emollient applied to the face only) and/or by timing of intervention initiation (from two weeks).

One additional study that did not provide individual participant data with a follow-up period of nine months did not identify any diagnoses of eczema in the skin care intervention group and reported four (14.8%) AD diagnoses in the control group, for whom "the mean age of the 4 infants at the onset of IAD was 5.5 ± 0.55 months" (Thitthiwong 2019).

Parent report of immediate reaction to food allergen

Individual participant data on parental report of an immediate reaction (within two hours) to a known common food allergen at one to three years were available from two studies, including 1448 randomised participants (Chalmers 2020; NCT03376243). In one study, no immediate reactions were reported in either treatment group from a total of 41/54 participants who were followed up to one year (NCT03376243). In the the other study, data were available for 1171/1394 participants (Chalmers 2020), who were followed up to two years; reactions were reported for 118/574 (21%) of the skin care intervention group and for 96/597 (16%) of the standard care group, favouring standard care (RR 1.27, 95% CI 1.00 to 1.61; Analysis 1.48).

For one trial (Chalmers 2020), we were able to examine parental reports of an immediate reaction (within two hours) separately for milk, egg, and peanut. Reactions to milk were reported for 61/575 (11%) of the skin care intervention group and for 46/598 (8%) of the standard care group, favouring standard care on average but with some uncertainty about the true effect, with the 95% CI including no difference (RR 1.38, 95% CI 0.95 to 2.00; Analysis 1.49). Reactions to egg were reported for 44/575 (8%) of the skin care intervention group and for 41/598 (7%) of the standard care group, favouring standard care on average but with some uncertainty about the true effect, with the 95% CI including no difference and a benefit of skin care intervention (RR 1.12, 95% CI 0.74 to 1.68; Analysis 1.50). Reactions to peanuts were reported for 8/574 (1.4%) of the skin care intervention group and for 10/598 (2%) of the standard care group, favouring skin care intervention on average but with some uncertainty about the true effect, with the 95% CI including no difference and a benefit of standard care (RR 0.84, 95% CI 0.33 to 2.10; Analysis 1.51).

Allergic sensitisation to foods or inhalants

Allergic sensitisation data on foods or inhalants at one to three years were available from two studies, including 1474 randomised participants (Chalmers 2020; Lowe 2018a). In one study (Chalmers 2020), data were available for 988/1394 participants who were followed up at two years; sensitization was reported for 88/490 (18%) of the skin care intervention group and for 74/498 (15%) of the standard care group. In the second study (Lowe 2018a), data were available for 70/80 participants who were followed up at one year; sensitisation was reported for 6/34 (18%) of the skin care intervention group and for 8/36 (22%) of the standard care group. Pooled individual patient data available from 1058 participants in these studies favoured standard care but there is uncertainty about the true effect, with the 95% CI including a benefit of skin care intervention and no treatment difference (RR 1.09, 95% CI 0.72 to 1.66) (I^2 = 24%; Analysis 1.52).

For allergic sensitisation to food only, data were available for 985/1394 participants in Chalmers 2020 who were followed up at two years; sensitisation was reported for 58/487 (12%) of the skin care intervention group and for 44/498 (9%) of the standard care group. In the second study (Lowe 2018a), data were available for 70/80 participants who were followed up at one year; sensitisation was reported for 3/34 (9%) of the skin care intervention group and for 7/36 (19%) of the standard care group. Pooled individual patient data available from 1055 participants in these two studies showed reduced food sensitisation in the skin care intervention groups but there is uncertainty about the true effect, with the 95% CI including benefit or harm of skin care intervention and no treatment difference (RR 0.86, 95% CI 0.28 to 2.69) (I^2 = 70%; Analysis 1.53). There was a high level of statistical heterogeneity across the two included trials (I^2 = 70%, P = 0.07), which could not be explained. We separately pooled results for milk, egg, and peanut across the two trials providing allergic sensitisation data on foods or inhalants at one to two years. Pooled results for milk were RR 1.16 (95% CI 0.55 to 2.43) (Analysis 1.54), for egg RR 0.75 (95% CI 0.18 to 3.08) (Analysis 1.55), and for peanut RR 1.03 (95% CI 0.53 to 2.01) (Analysis 1.56). Each separate food analysis also showed a high level of heterogeneity across the two included trials.

Two additional studies reported allergic sensitisation to foods at eight months and at nine months (Dissanayake 2019; Horimukai 2014). When data from these two studies were included in sensitivity analyses, the pooled treatment effect was RR 1.08 (95% CI 0.87 to 1.33), with I^2 = 35% (P = 0.20) (Analysis 1.58). Pooled results for milk were RR 0.84 (95% CI 0.59 to 1.21) (Analysis 1.59), for egg RR 1.09 (95% CI 0.88 to 1.37) (Analysis 1.60), and for peanut RR 1.03 (95% CI 0.53 to 2.01) (Analysis 1.61). Again, each separate analysis continued to show a high level of heterogeneity across included trials.

One additional study that did not provide individual participant data with a follow-up period of six months reported eczema onset for "5/35 of the intervention group and 6/32 of the control group. And eczema onset ratio among infants who reacted positive to a prick test were 5/1 vs. 6/8" (Kataoka 2010).

DISCUSSION

Summary of main results

A summary of the main results is shown in Summary of findings 1.

Our key results, presented here, are based on 10 trials that provided individual participant data (IPD). These studies assessed skin care interventions that aim to promote hydration or barrier function: eight assessed emollients; one assessed combined skin interventions, including emollients; and one assessed topical oils, although this study provided IPD only for adverse events.

For our primary outcome of eczema, this review identified data from 3075 participants in seven randomised controlled trials and found that skin care interventions probably do not influence the development of eczema by age one to two years in healthy term infants when compared with standard care. The certainty of this evidence was moderate. One trial - Skjerven 2020 - showed an increase in eczema in the intervention group, leading to some statistical heterogeneity in the main eczema analysis. This was a factorial randomised trial with skin care interventions and early allergenic food introduction. Due to significant interaction between interventions, only the skin care and control arms of the trial could be utilised in the primary analysis. The skin intervention was a combination of daily facial emollient with daily baths with paraffin-based bath oil, which is a somewhat different intervention than was provided in the other trials providing data towards the primary analysis. This difference in intervention may explain the statistical heterogeneity seen in the main eczema analysis, with daily baths potentially having an adverse effect on skin barrier function and risk of eczema development compared with direct emollient application. Our pre-planned subgroup analyses show that the following did not influence the effect of intervention on risk of developing eczema: family history of atopy or *FLG* mutation, classification of intervention type, duration of intervention, and age. We could not evaluate these effects on risk of food allergy. We also found that the skin care interventions used probably do not change time to onset of eczema when compared with standard care (based on 3349 participants in nine trials; moderate-certainty evidence). This is thought to be important in the interaction between eczema and food allergy because increased length of time with eczema is associated with increased likelihood of food sensitisation (Tsilochristou 2019). Overall, evidence from this review demonstrates with moderate certainty that the skin care interventions used in these randomised controlled trials (RCTs) do not impact the development of eczema (Chalmers 2020; Dissanayake 2019; Horimukai 2014; Lowe 2018a; McClanahan 2019; NCT03376243; Simpson 2014; Skjerven 2020; Yonezawa 2018).

For our co-primary outcome of food allergy, we are uncertain whether skin care interventions influence development of immunoglobulin (Ig)E-mediated food allergy when compared with standard care. Unfortunately, due to delays in the progress of trial outcome assessments related to the COVID-19 pandemic, food allergy outcomes from Skjerven 2020 were not available for inclusion in this review. Only one trial with 996 participants had food allergy diagnosed by oral food challenge as an outcome (Chalmers 2020). The certainty of this evidence is very low, and we are thus uncertain whether skin care interventions influence risk of food allergy by age one to two years, compared with standard care. A sensitivity analysis for data from the same trial, using an alternative method for food allergy outcome assessment (combination of oral food challenge and investigator assessment using clinical history and sensitisation data), also favoured standard care (1115 participants, one trial), suggesting that skin care interventions may increase risk of food allergy. The width of the 95% confidence interval (CI) for the risk ratio (RR) is reduced, but it is still wide, indicating that we cannot rule out no difference nor small to large harm of skin care intervention based on this one study.

Data from the same trial (1171 participants) suggest that again when compared with standard care, skin care interventions may slightly increase the risk of parent-reported immediate reaction to a common food allergen at two years, but this association was seen only for parent-reported immediate reaction to cow's milk, which is thought to be an unreliable measure of IgE-mediated cow's milk allergy due to commercially influenced over-reporting of cow's milk allergy in infants (Munblit 2020). Hence, the certainty of this evidence was considered low. Evidence for allergic sensitisation to food was of very low certainty due to statistical heterogeneity and severe imprecision, with increased allergic sensitisation to food in the intervention group in one trial (Chalmers 2020), as well as decreased allergic sensitisation to food in the intervention group in a second trial (Lowe 2018a); both studies compared skin care interventions against standard care, with 1055 participants included in this analysis.

Complier average causal effect (CACE) analysis was utilised to assess whether compliance with the assigned intervention influenced outcomes. For both > 3 days per week and > 5 days per week, although the CACE favoured the intervention for the eczema outcome, the confidence interval ranged from large benefit to moderate harm; therefore, we were unable to demonstrate whether increased adherence to assigned interventions was associated with different outcomes. Insufficient evidence meant that we were unable to ascertain whether treatment adherence affected risk of developing food allergy.

For adverse events, the key adverse events of interest were local infection, stinging or allergic reactions to moisturisers, and slippage accidents. We found that compared to standard care, skin care interventions probably increase the risk of skin infection in an analysis that included IPD from 2728 infants participating in six trials (moderate-certainty evidence). In terms of stinging and allergic reactions (four trials including 343 participants) or slippage accidents (four trials including 2538 participants), there may be an increase in these adverse events with the intervention; however,

the certainty of these findings was low due to very small numbers of events, yielding very wide confidence intervals which include the possibility of no effect or reduced risk.

Overall completeness and applicability of evidence

Although 33 studies were included in the review, only 17 reported outcomes relevant to this review. Of these 17 studies, eight reported our primary outcome cumulative incidence of eczema by one to three years, and three of these studies measured eczema severity between one and three years by clinician assessment, with one of these studies also reporting parent report of eczema severity. Nine studies measured time to onset of eczema. Two studies reported parent report of immediate food allergy, and two studies reported allergic sensitisation to food or inhalant allergen. Ten studies reported adverse event data for our pre-specified adverse events of interest.

Only 10 trials provided IPD analysis. Most of the other identified trials (SCiPAD - Skin Barrier Interventions for Prevention of Allergic Disease) included types of skin barrier interventions other than emollients, such as change in bath routine, but they did not provide follow-up long enough after intervention to identify our primary outcomes, and they were limited to contributing some narrative data on safety outcomes. Therefore, the impact of non-emollient interventions on the development of eczema or food allergy, rather than their short-term impact on skin barrier physiology or safety outcomes, is unknown.

All of the trials reporting eczema as an outcome used an emollient on its own as the intervention, or within a combination of skin care interventions, and commenced within the first month of life. Eczema was largely evaluated by a blinded trained assessor using widely accepted tools such as Hanifin and Rajka or UK Working Party criteria for diagnosis. Therefore, we can be confident in the diagnosis of eczema in these studies. Interventions mainly focused on emollients, with each study using a different emollient with different constituents. Trials also had variable regimens and durations of emollient therapy. The emollients used were a combination of so called simple emollients and more complex emollients that contain lipids. Emollient regimens varied in intensity from twice-daily all-over body emollient to once daily on cheeks in combination with other skin care interventions. Skin care for infants varies by country and culture, and there is no standard recommendation. Thus, our comparison of control (standard skin care or no skin care intervention) may have varied between studies.

We analysed data based on assignment to intervention rather than on adherence to intervention. Compliance with daily emollient, when reported, was low but may have been higher in smaller pilot studies, in which potentially greater input from the research team could have aided compliance. Complier average causal effect was utilised to assess whether compliance with the assigned intervention influenced outcomes. We were, however, unable to identify whether or not adherence to skin care interventions influences risk of eczema.

The prospective portion of this meta-analysis, planned in 2017, ensured that the two largest trials in the series had aligned outcomes and used similar methods of outcome evaluation (Chalmers 2020; Skjerven 2020). Meta-analysis of these two studies and another five studies providing IPD on the development of eczema by one to three years allowed us to assess both study factors and individual participant factors that may influence results. When we evaluated study factors such as type of emollient used and duration of intervention and individual factors such as age, *FLG* genotype, or family history of atopy, we found no evidence for an interaction between these factors and the intervention on eczema risk.

Ongoing studies are randomising newborn healthy infants to a skin care intervention; half are assessing emollients. NCT03871998 is designed to address whether the emollient intervention applied from day one or two of life for a short (two month) time period would influence eczema and IgE-mediated food allergy development. Lowe 2019 and Eichner 2020 are evaluating daily complex emollients and are expected to report in 2022. It is possible that the use of more complex emollient interventions may have different effects on risk of eczema.

Sixteen studies that were eligible for the review did not have relevant outcome measures (i.e. they did not record eczema or food allergy at one to three years or at any time, and they did not comment on adverse events. Infants in these trials were followed up to a maximum of four weeks, which was too soon to assess whether eczema or food allergy was present. These trials mainly involved different timings and mechanisms of bathing infants, along with different types of bathing products. Their follow-up was four weeks or less, and outcomes were skin physiology, such as transepidermal water loss. It is possible that had these infants been followed up for longer, and had eczema outcome been measured, these skin care practices would have an effect on eczema. Furthermore, although "skin care intervention type B - any skin care interventions that aimed to protect the skin barrier from irritation such as water softeners" were pre-specified in our search, they could not be assessed, as no suitable trials were found. A trial of water softeners is currently ongoing (Jabbar-Lopez 2019).

Evidence for effects of skin care interventions in infants on risk of food allergy is incomplete. Only one trial reported food allergy outcomes using oral food challenge, within the time period set out in the protocol (Chalmers 2020); however, these results were inconclusive, as the quality of evidence for food allergy in this study was low or very low due to high risk of bias and imprecision of the result, with wide confidence intervals. Evidently as only one trial had food allergy outcomes, we could not look at the effects of planned subgroup analyses on food allergy. Skjerven 2020 intended to contribute food allergy outcomes to this review; however the clinical trial team experienced delay with final data collection due to the COVID-19 pandemic, which means that these data were not complete in time for this review. It will be important to update this review when food allergy outcomes are available from more trials, including Skjerven 2020. Food allergy is a more difficult outcome to measure reliably than eczema, and it is a less common condition than eczema. Oral food challenge is the currently accepted standard for food allergy diagnosis, but a European initiative is currently working on development of core outcome measures for food allergy in clinical trials (COMFA 2020).

Quality of the evidence

Our confidence in the findings for eczema was moderate. Sensitivity analysis including only studies with low risk of bias was consistent with the primary analysis. We downgraded the certainty of evidence for eczema due to statistical heterogeneity that could not be explained. For the primary eczema outcome, this heterogeneity

was due to one trial (Skjerven 2020), which found increased eczema in the intervention group compared with the control group. One potential cause of this heterogeneity is the nature of the intervention. Skjerven 2020 used a bathing intervention, and other trials contributing to the primary eczema analysis used direct application of a moisturiser to the infant's skin. However, for the outcome time to onset of eczema, we downgraded the certainty of evidence due to statistical heterogeneity, and heterogeneity in this analysis was due to more than one trial.

Our confidence in the findings for food allergy was low or very low. We downgraded the certainty of evidence for food allergy due to severe imprecision, with small numbers of studies and events and wide confidence intervals encompassing both a harmful effect and no effect. For the primary food allergy outcome, we also downgraded due to risk of bias related to missing outcome data. In the only trial contributing to this analysis (Chalmers 2020), participants who were invited for an oral food challenge due to suspected food allergy frequently declined to attend an oral food challenge, and the proportion that did attend differed between intervention group (29%) and control group (17%), suggesting high risk of bias related to missing outcome data. Although the findings are similar if all those with missing outcome data are assumed to not have food allergy, they differ if patients are assumed to have food allergy. Findings also differ in sensitivity analysis when investigator assessment was used for categorising participants with no available oral food challenge data (Analysis 1.30). For the secondary food allergy outcome, allergic sensitisation to a food allergen, we also downgraded due to statistical heterogeneity that could not be explained.

Our confidence in the findings for adverse events was moderate or low. We downgraded the certainty of evidence for skin infection due to imprecision, with wide confidence intervals, which included a harmful effect and no effect. We downgraded the certainty of evidence for slippages and stinging/allergic reactions to moisturisers due to severe imprecision, with small numbers of events and wide confidence intervals, which included both a harmful effect and a beneficial effect. All studies included in the adverse events analyses, except one, were rated at some concerns for risk of bias for the specific adverse events assessed, but this was due to the nature of adverse events being self-recalled by carers, who could not be blinded due to the type of intervention under study. Otherwise there were no concerns for risk of bias for adverse events.

Potential biases in the review process

The meta-analysis collaboration group for this review (SCiPAD - Skin Barrier Interventions for Prevention of Allergic Disease) was formed in 2017 through collaboration between the two largest trials - Chalmers 2020 and Skjerven 2020. The purpose of the prospective collaboration was to increase the alignment of outcomes measured in the two individual trials and to enhance the power of individual trials to identify effects of the interventions on the outcome of food allergy, which is less prevalent than eczema. Other trial groups were invited to join the collaboration between 2017 and 2020, and their data formed the basis of the prospective portion of the meta-analysis. Prospective meta-analysis allows for alignment of outcomes before completion of the trial, so that comparisons and analysis are more readily conducted between trials. Within this collaborative group, trials mainly involved emollients as an intervention and eczema as an outcome. We attempted to reduce any availability bias by conducting a sensitive search, which identified over 6000 potentially eligible studies, and by contacting authors of eligible studies to request their collaboration in the IPD meta-analysis, but follow-up for most studies was too short for inclusion.

We classified collaborating trials when trial outcome data were not analysed and known to study authors before February 2017 as contributing 'prospectively acquired data'. Data from some of these trials became known to the investigators or to the public before the statistical analysis plan (SAP) for this meta-analysis was locked, so that in theory, findings could have influenced the design of the statistical analysis plan. Development of the SAP was led by a statistician (SC) with no detailed knowledge of eligible trial publications at the time of finalising the SAP, and the principles of the SAP and the review protocol were aligned with the February 2017 PROSPERO registration of the prospective meta-analysis (Boyle 2017). The SAP was signed off before any unblinding of individual participant data sets received from individual trials. Due to our close collaboration with trial investigators, they were involved in protocol and SAP development and in interpretation of meta-analysis findings. A strength of this approach was that collaborating trialists had the opportunity to review our analyses of their data sets before stage 2 of the IPD meta-analysis and to correct any misinterpretation of data coding. MK and RB were quite involved with the Chalmers 2020 trial, with RB the principal investigator for food allergy, and MK involved in food allergy diagnosis. Therefore, they were not involved in data extraction nor risk of bias assessment for this trial, other than as investigators commenting on meta-analysis findings.

Use of IPD in this review allowed us to (i) fit a consistent analysis model to trial data sets for each outcome to ensure that we compared treatment effects adjusted for the same covariates across trials; (ii) fully explore the risk of bias due to missing data by conducting additional sensitivity analyses that had not previously been reported; (iii) obtain more reliable and powerful subgroup analyses including estimation of treatment interactions with participant characteristics that had not previously been reported; and (iv) evaluate the relationship between compliance with the intervention and outcomes of interest. However, the method of sharing IPD can result in availability bias. We attempted to limit this by offering all trials administrative assistance in working with their individual institutions for data agreement development and sign-off and for data sharing and extraction. Overall, trials with relevant outcomes from which we did not manage to access IPD were generally small (fewer than 100 participants) or were industry-funded and researchers were concerned about the commercial impact of data sharing. Only one trial, with 60 participants, had primary outcome data eligible for inclusion in the meta-analysis and did not supply IPD; sensitivity analysis including aggregate data from this one trial showed similar findings to the main analysis. One industry-funded trial was involved in the SCiPAD collaboration (NCT02906475); however, this trial is ongoing, and results are expected in 2022.

Overall, the close relationship between trialists and systematic reviewers in this project carries risk of availability bias and academic bias towards individual clinical trial findings, which is mitigated only in part by the prospectively planned nature of the meta-analysis for most studies contributing data.

The interventions used in included trials varied in their composition, and there is no standard classification system for emollients (Surber 2017). This led to difficulty in classification of the intervention for the purpose of subgroup analysis, as different emollients have overlapping constituents, which may have differential effects on the skin barrier or on skin health. We took advice from a member of our collaboration (MC) with expertise in emollient formulation and effects on skin barrier, who classified the interventions used before seeing the meta-analysis results. These were used for the subgroup analysis of 'basic' versus 'complex' skin care interventions, which showed no evidence of an interaction. We acknowledge that other groups may have classified the interventions differently. Similarly, although we planned to stratify interventions as A - "those that primarily aim to enhance the skin barrier through direct application of emollient or moisturiser" - and B - "those that aim to protect the skin barrier from damage" - we did not find any trial results that had used intervention B. Jabbar-Lopez 2019 would be classified as an intervention B but is still ongoing. Similarly, there is no standard recommended skin care for infants, with practices varying by country and by culture; therefore, the comparison of control, taken as standard skin care or no skin care intervention, may have digressed between studies.

Several trials did not contribute data to the meta-analysis, or contributed only narrative data on non-specific adverse events. There were some difficulties in deciding whether some of these trials should be included based on the type of intervention and the type of comparator evaluated. For example, we excluded trials that compared one way of bathing to another (Bryanton 2004), but we included a trial that was using a different product in the bath compared to the control group bath, because this might influence skin barrier function (Lund 2020). We concentrated on a normal healthy term population so that these findings were generalisable and were not impacted by the unique structure of preterm skin and the different skin care practices to which preterm infants are exposed.

Agreements and disagreements with other studies or reviews

This is the first Cochrane Review of skin barrier intervention in term infants. A previous Cochrane Review looked at topical emollients for preventing infection in preterm infants (Cleminson 2016). This review concluded that there was no evidence that emollients prevent invasive infection in preterm infants in high-, middle-, or low-income countries. This review also looked at topical oils - mainly vegetable oils - and showed that there was some evidence that those treated with topical vegetable oils had increased growth compared to those given control treatment, although long-term growth was not measured. This review had invasive infection as a primary outcome. It did not discuss or report on cutaneous infection, so it is unclear whether this was not seen as an adverse effect of the interventions studied, or if it just was not measured. If skin care interventions increase risk of cutaneous infection in term infants, but not in preterm infants, the reason for this difference is unclear. Preterm infants have more permeable skin than term infants and have specific vulnerability to serious bacterial infection. It is possible that hand hygiene for those who apply emollients or oils to the skin of preterm infants may be more thorough than hand hygiene for those who apply emollients or oils to the skin of healthy term infants. If this were the case, then differences in effects on risk of cutaneous infection could potentially be explained by differences in hand hygiene practice.

A previous Cochrane overview of interventions for primary prevention of eczema in children identified systematic reviews of trials evaluating dietary interventions such as maternal dietary antigen avoidance, exclusive breastfeeding for a defined period of time, omega-3 and omega-6 fatty acid supplementation, hydrolysed protein formula, soya formula, and pre-biotics and probiotics. The overview did not identify trials of skin care interventions and did not identify an intervention that effectively prevents the onset of eczema (Foisy 2011).

A systematic review of interventions for prevention of food allergy was undertaken by a European Academy of Allergy and Clinical Immunology committee to inform an update of their guidance on food allergy prevention (DaSilva 2020). This systematic review included Dissanayake 2019 in its section on emollients for food allergy prevention, as other studies reporting eligible food allergy outcomes had not been published at the time this systematic review was conducted. Review authors concluded that emollients may not reduce risk of food allergy (low-certainty evidence). Our review included the larger and more recently published trial using oral food challenge for outcome assessment - Chalmers 2020 - and did not include food challenge outcomes from Dissanayake 2019 in the primary food allergy analysis because oral food challenge was not used for food allergy assessment in this trial. We rated the evidence for this outcome as very low certainty and could not therefore make a conclusion about effects of emollients on risk of food allergy.

Two pilot studies - Simpson 2014 and Horimukai 2014 - were reported as showing significant reductions in eczema risk. Larger, more definitive trials published subsequently found no reduction in eczema, and our meta-analysis results are consistent with the findings from these larger trials (Chalmers 2020; Skjerven 2020). The reason for the difference in findings between small pilot studies and larger trials is not clear, but differences in adherence to treatment, in methods and timing of outcome assessment, and in study population may all be relevant.

Finally, emollients as treatment for already established eczema has been the topic of a previous Cochrane Review (Van Zuuren 2017). This review concluded that although evidence was weak, emollients reduce disease severity compared to no treatment. However, moisturisers reduce flares, prolong time between flares, and decrease the need for topical corticosteroids. Our new review concerns the primary prevention of eczema and does not directly impact the well-established and well-accepted intervention of emollients for people who already have eczema.

AUTHORS' CONCLUSIONS

Implications for practice

This review found that skin care interventions such as emollients probably do not influence the development or time to onset of eczema in healthy term infants by age one to two years and probably increase the risk of skin infection (moderate-certainty evidence). This suggests that regular application of emollients or other skin care interventions probably is not necessary for healthy infants, unless there are other specific reasons for using such products. This information should be taken into account by

guideline developers in this field. Given the probable increase in local skin infection risk, it may be important for carers to practise appropriate hygiene measures when applying emollients to the skin of infants.

This review could not draw conclusions about the impact of skin care interventions on IgE-mediated food allergy by age one to two years (very low-certainty evidence); only one study had food allergy diagnosed by oral food challenges, and in this study, only 29% of eligible participants attended for oral food challenge (OFC). Low-certainty evidence from one trial suggests that skin care intervention may slightly increase parent reports of immediate food allergy (to a common allergen) at two years. However, this outcome was only detected in cow's milk, which may be unreliable as a measure due to the commercially influenced over-reporting of cow's milk allergy in infants. Evidence was insufficient to detect effects of skin care interventions on food sensitisation at age one to two years (very low-certainty evidence). The gold standard for diagnosing food allergy is an OFC; however, these are costly and time consuming for participants and trialists. Alternative modes of diagnosis of food allergy, by standardised questionnaires and documented sensitisation, or even by more complex methods such as basophil activation test, could be considered in further trials.

Infant slippages and stinging/allergic reactions to moisturisers may increase with the use of skin care interventions during infancy (low-certainty evidence), although confidence intervals for slippages and stinging/allergic reactions are wide and include the possibility of no effect or reduced risk. All results presented here are in comparison to standard care.

Subgroup analysis showed that age, hereditary risk, *FLG* mutation, duration of intervention, and classification of intervention type did not have an impact on the risk of developing eczema. We could not evaluate these effects for food allergy risk. We do not know if adherence to treatment effects the relationship between skin care interventions and risk of developing eczema or food allergy.

The common clinical practice of applying emollients to the skin of people who already have eczema is not directly affected by our findings.

Implications for research

In this review, the trials with eczema as an outcome were mainly emollient trials. Other methods of skin barrier intervention in this review had very short follow-up and did not measure eczema as an outcome, so their impact on eczema remains unclear. Potential future studies on bathing practices should have longer follow-up of clinical outcomes that use standard methods of eczema measurement. Trialists may wish to consider using novel interventions that impact skin barrier function, rather than those that have already been evaluated in these trials.

We were unable to identify whether skin care interventions such as emollients have an impact on risk of developing food allergy. More research is needed to identify whether food allergy risk is influenced by early skin care practices. Future trials should measure food allergy using a robust outcome assessment (Asai 2020), and researchers may wish to consider applying published algorithms to evaluate food allergy outcomes in participants who do not undergo oral food challenge (Kelleher 2020b). The paucity of oral food challenge-diagnosed food allergy outcomes in this meta-analysis infers that oral food challenges are difficult to conduct and are infrequently attended in prevention studies. We would suggest that future studies incorporate Core Outcome Measures for Food Allergy. An update of this review with food allergy outcomes from Skjerven 2020 and potentially the other ongoing trials with foods allergy outcomes will be needed to fully address the hypothesis that skin care interventions may impact the risk of food allergy (Lowe 2019; NCT03871998; NCT03808532).

Conclusions on adherence to intervention could not be made, and we would suggest that future studies carefully document adherence and compliance with interventions. Also, collaboration between groups regarding future potential studies may allow for larger numbers with less imprecision.

This review focused on primary prevention of eczema and food allergy, preventing the diagnosis of eczema and food allergy in infants. Given the strong links between early-onset eczema and food allergy, another body of work has begun on secondary prevention of food allergy among infants already diagnosed with eczema. These trials - NCT03742414 and UMIN000028043 - include infants younger than 13 weeks with diagnosed eczema and randomise them to active eczema management from onset with emollient and topical corticosteroids. Both studies have IgE-mediated food allergy as a primary outcome and are ongoing.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abraham 2019

Study characteristics	
Methods	**Study Design:** randomised controlled trial **Study conducted:** not reported **Treatment arms:** 3 **Follow-up:** 24 hours
Participants	**Randomised:** N = 102 (chlorhexidine n = 34, saline n = 34, standard n = 34) **Inclusion criteria:** 1. Admitted to the paediatric ward at a tertiary care hospital, Vellore 2. Informed consent from parents **Exclusion criteria:** not reported
Interventions	**Intervention:** participants were bathed according to treatment group in either chlorhexidine or saline; concentrations were not reported **Comparator:** standard bath of soap and water
Outcomes	**Primary outcome:** skin health status of all participants before and 2 hours and 24 hours after the intervention by an individual who is blinded to the intervention using neonatal skin assessment score **Adverse events:** not reported
Identification	**Country:** India **Setting:** tertiary care hospital, Vellore **Sponsorship Source:** Institutional Review Board, Christian Medical College, Vellore

Abraham 2019 *(Continued)*

Declarations of interest	Nil
Notes	

Amer 2017

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study conducted:** April 2014 and September 2014 **Treatment arms:** 2 **AD follow-up:** 4 weeks
Participants	**Randomised:** N = 70 (group A underwent care n = 35, group B did not undergo care n = 35) **Inclusion criteria:** 1. Healthy and full-term (determined by mothers' obstetrician/gynaecologist) 2. 1 to 7 days old at baseline 3. Mothers of infant participants had to be older than 18 years and were told to refrain from using their infants' current lotion products (if applicable) for the duration of the study 4. Mothers agreed not to introduce fragrances on themselves, on their infant, or in their household for the duration of the study 5. Mothers also agreed to avoid excessive sun exposure on their infants' arms and legs **Exclusion criteria:** 1. Infants suffering from any known abnormal skin conditions (rash), hypersensitivity, or allergic reactivity to fragrances or other ingredients 2. Infants suffering from asthma, upper respiratory tract infection, or other conditions that would affect the evaluation of skin care regimens 3. Infants with any genetic abnormalities 4. Premature infants
Interventions	**Intervention:** Caregivers/mothers were instructed to provide a specific skin care regimen Caregivers (if possible) were instructed to gently dry the baby immediately after birth and to gently remove any blood or meconium and to not rub off the vernix (leave it as intact as possible to absorb into the skin) During the 4 weeks of the study, neonates were bathed at variable frequencies by mothers most often 1 to 2 times per week using shampoo as a cleanser; sometimes baby wipes were used as an alternative to bathing. The first bath was given only when the temperature of the newborn was stabilised, instead of considering only the number of hours after birth, and usually during the first week. Mothers were instructed to apply oil to the skin and the scalp 3 to 4 times per week and after bath time, and that this should be applied daily when signs of dryness (flaking/scaling) were presented. Mothers were instructed to keep the umbilical cord clean and dry by applying chlorhexidine in the first 10 days of life until the cord falls off and 2 days after, and allowing it to be exposed to air as frequently as possible. Mothers were instructed to use the best quality nappy available, to change soiled nappies frequently, to cleanse the nappy area with plain water or unperfumed, alcohol-free baby wipes, to expose the nappy area as often as possible, and to consider using a thin layer of barrier ointment or cream with nappy changes. Mothers were instructed to care for the neonatal intertrigo by keeping it clean and dry.

Amer 2017 *(Continued)*

	A colourful and informative booklet had been designed for the mothers, which clarifies instructions about care of neonatal skin and benign transient neonatal skin disorders for the reassurance of parents **Comparator:** group B: did not undergo care; no specific intervention **Shampoo, baby oil, wipes, and cream ingredients:** Baby shampoo, which is composed of sodium lauroamphoacetate, sodium laureth sulfate, coco glucoside, polyquaternium-10, and sodium benzoate. Baby oil is a mineral oil that contains paraffinum liquidum, isopropyl palmitate, and parfum, which are safe. It is used as a moisturiser and for massage. Baby wipes consist of a non-woven carrier soaked with an emulsion-type watery or oily lotion. Baby cream consists of zinc oxide and olive oil
Outcomes	**Primary outcomes:** optimal skin function, mothers' visual skin assessment questionnaire to evaluate the presence of neonatal skin for erythema and dryness. Clinical examination for skin assessment for appearance of erythema, dryness, and infection or any skin disorders or adverse effects on a weekly-basis **Adverse events:** adverse events were recorded when the baby's skin was assessed during weekly clinical examination The only adverse effect of this study was a case of milaria using emollient because the mother turned on the heater all night, which turns the atmosphere hot and humid; this conclusion is in agreement with a study by Rocha et al., which found that emollient may cause acne, folliculitis, and prickly heat, and may aggravate pruritus when used in extremely hot and humid areas
Identification	**Country:** Egypt **Setting:** outpatient clinics at the Dermatology and Venereology Department, Obstetric Department, and Pediatric Department, Faculty of Medicine, Zagazig University Hospitals **Sponsorship source:** not reported
Declarations of interest	Not reported
Notes	

Baldwin 2001

Study characteristics	
Methods	**Study design:** randomised clinical trial, double-blinded, parallel-group comparison trial **Study conducted:** no date of recruitment or start/end date of trial reported in the study **Treatment arms:** 2 (Study C) **AD follow-up:** 4 weeks (2 visits every week)
Participants	**Randomised:** 304 children (evaluated skin erythema and diaper rash in 268 infants over a 4-week usage period) **Inclusion criteria:** 1. General good health as determined by medical history 2. No evidence of serious or chronic disease upon initial dermatological examination 3. Skin types I to IV on the Fitzpatrick Scale 4. Age range not reported - average participant age: 9.9 months **Exclusion criteria:**

Baldwin 2001 *(Continued)*

	1. Severe diaper rash that appeared to require physician treatment
Interventions	Parents of all eligible children were given a 1-week supply of the control product and were instructed to use only this diaper until the next scheduled visit 6 days later ('washout' period). At completion of the 'washout' period, 304 children were randomly allocated to 1 of 2 treatment groups after a baseline dermatological examination of the diaper area. Randomisation was by gender and diaper rash grade All parents were instructed to diaper their child exclusively with the product assigned to him/her, and to avoid the use of any ointments, creams, powders, or other diaper rash or skin care products on the diapered area of their children for the entire duration of the study. Parents were allowed to maintain normal bathing and hygiene routines for their children except that they were asked to use a standard disposable infant wipe, which was supplied to them in lieu of their usual wipe or wash cloth for diaper changing needs Parents were instructed to change their child into a clean diaper approximately 2 hours before each subsequent scheduled visit to the clinical site. Children returned to the clinical site twice per week (Monday/Thursday or Tuesday/Friday) over the next 4 weeks, for a total of 8 post-baseline visits. At each of these visits, the skin in the diaper area of each child was examined for the presence of rash and erythema **Intervention:** Group 2 was assigned to use the test diaper **Comparator:** Group 1 was assigned to continue on the control product **Diaper and wipes:** control diaper used was a commercially available, premium quality product containing a super-absorbent(AGM)/cellulose core and a breathable outer cover, which was obtained directly from our manufacturing lines (Procter & Gamble Co., Cincinnati, OH, USA) The test diaper was identical in every respect to the control except for the inclusion of a top sheet (inner layer) impregnated with a proprietary formulation containing primarily petrolatum, stearyl alcohol, and zinc oxide in combination (ZnO/Pet). The wipes used were Pampers Baby Fresh™, Proctor & Gamble Co.
Outcomes	Severity of diaper dermatitis (skin erythema and rash), scoring given by Table 1 (Baldwin 2001) **Adverse events:** not reported
Identification	**Country:** USA **Sponsorship source:** Hill Top Laboratories (Cincinnati, OH, USA, and Winnipeg, Canada), for its collaboration in the conduct of the clinical studies
Declarations of interest	Not reported
Notes	

Bellemere 2018

Study characteristics	
Methods	**Study design:** randomised clinical study **Study conducted:** no date of recruitment or start/end date of trial reported in study **Treatment arms:** 2 **AD follow-up:** 6 months
Participants	**Randomised:** N = 120 (n = 60 in the intervention arm, n = 60 in the control arm)

Bellemere 2018 *(Continued)*

	Inclusion criteria: 1. Newborns at risk aged 2 to 3 weeks 2. 2 atopic first-degree relatives **Exclusion criteria:** not reported
Interventions	(D0, D30, D90, D120, D180). In parallel, 60 newborns with no familial history of atopy have been followed. Swabs were taken on forearms, face, and AD lesions in 45 children: quantitative PCR for SA and SE and LC/UV + LC/MS for NMF and ceramides **Intervention:** use balm twice a day, cleansing cream and bath oil twice a week from the same brand for 6 months **Comparator:** control group, no specific intervention **Moisturiser/Emollient:** "a French cosmetic brand" dedicated to children's skin (no other details of formulation reported)
Outcomes	**Primary outcome:** 1. Frequency of AD in the first 6 months of life **Secondary outcomes:** 1. Clinical information on predictive signs and first AD flare 2. To quantify NMFs and ceramides 3. SA and *S epidermidis* (SE) colonisation from birth until first AD flare **Adverse effects:** none reported in conference abstracts
Identification	**Country:** not reported **Setting:** not reported **Sponsorship source:** none reported
Declarations of interest	Not reported
Notes	

Chalmers 2020

Study characteristics	
Methods	**Study design:** multi-centre, pragmatic, parallel-group, randomised controlled trial **Recruitment:** 19 Nov 2014 and 18 Nov 2016 **Treatment arms:** 2 **AD follow-up:** participant follow-up was 2 years, including follow-up at 2 weeks (by telephone), and at 3, 6, 12, and 18 months (online or postal questionnaire), and at a 2-year face-to-face appointment **FA and inhalants follow-up:** 2 years
Participants	**Randomised:** N = 1394 (emollient n = 693, control n = 701) **Inclusion criteria:**

Chalmers 2020 *(Continued)*

1. Term infants (at least 37 weeks' gestation)
2. At least 1 first-degree relative with parent-reported eczema, allergic rhinitis, or asthma diagnosed by a doctor
3. Mother aged 16 years or older
4. Consenting adult with the ability to understand English

Exclusion criteria:

1. Preterm birth (birth before 37 weeks' gestation)
2. Sibling (including twin) randomly assigned in the trial
3. Severe widespread skin condition that would make detection or assessment of eczema difficult
4. Serious health issue that would make it difficult for the family to take part in the trial
5. Condition that would make use of an emollient inadvisable

Interventions	Both groups received advice on general skin care in booklet and video formats at the time of randomisation (Appendix pp 11 to 21). The skin care guidance provided advice to use mild cleansers and shampoos specifically formulated for infants, and to avoid soap, bubble bath, and baby wipes. Infants were randomly assigned to a group within a maximum of 21 days after delivery, and randomisation was stratified by recruiting centre and number of first-degree relatives with atopic disease (1, 2, or > 2) **Intervention:** adherence was captured at each questionnaire time point during year 1 (3, 6, and 12 months) by asking parents about emollient use since the last questionnaire (Appendix p 4), and was defined in the protocol as satisfactory in the intervention group if emollients were applied at least 3 to 4 times per week to most of the child's body (defined as at least 2 of face and neck, arms and legs, or trunk). A similar definition was used for contamination in the control group Parents were advised to apply emollient to the whole body of their child at least once daily (excluding the scalp) until the child reached 1 year of age. They were also advised to apply emollient after every bath, even if they had already applied the emollient that day. Daily application was advised to encourage regular use of emollient several times a week, but because the study was designed to reflect how the intervention might be delivered in normal practice, no prompts or reminders were sent to parents The guidance given to those in the emollient group also showed parents how to apply emollients correctly by dotting over the skin and using gentle downward strokes rather than rubbing in, and contained warnings about the skin being slippery after application and the need to clean up spillages from the floor to avoid slipping **Comparator:** best practice skin care advice only **Moisturiser/Emollient:** Doublebase Gel (Dermal Laboratories, Herts, UK) or Diprobase Cream (Bayer, Berks, UK)
Outcomes	**Primary outcome:** diagnosis of eczema over the past year (defined by the UK Working Party refinement of Hanifin and Rajka diagnostic criteria for eczema) assessed by research nurses masked to treatment allocation at age 2 years **Secondary outcomes:** other eczema definitions - i.e. presence of eczema between birth and 2 years of age (assessed by any parental report of a clinical diagnosis of eczema (up to 2 years) and parent completion of UK Working Party criteria at 1 and 2 years); presence of visible eczema at 2 years recorded by a nurse who was masked to treatment allocation; time to onset of eczema (based on first parent report of clinician diagnosis and time of first topical corticosteroid or immunosuppressant prescription); clinician-reported and patient-reported severity of eczema (Eczema Area and Severity Index (EASI) at 2 years and Patient-Oriented Eczema Measure [POEM] at 1 and 2 years). Other secondary outcomes were presence of other allergic diseases (i.e. parent-reported wheezing and allergic rhinitis (between 1 and 2 years); allergic sensitisation (masked skin prick tests) to milk, egg, peanut, cat dander, grass pollen, or dust mite at 2 years; parent-reported food allergy and parental report of clinical diagnosis of food allergy at 1 and 2 years; and allergy to milk, egg, or peanut at 2 years confirmed by oral food challenge; for cases in which no oral food challenge was done, an expert allergy panel was asked to allocate treatment

Chalmers 2020 *(Continued)*

	Adverse events: safety outcomes were parent-reported skin infections (parents were asked what the doctor called the infection) and emollient-related infant slippages during the intervention period (year 1). Skin infections and slippages were collected via 3, 6, and 12 month questionnaires. No other adverse event information was collected
Identification	**Country:** UK **Setting:** 12 hospitals and 4 primary care sites across the UK **Sponsorship source:** this study was sponsored by the University of Nottingham, was co-ordinated by the Nottingham Clinical Trials Unit (CTU), and was funded by the UK National Institute for Health Research (NIHR) Health Technology Assessment Programme
Declarations of interest	The main funder (NIHR Health Technology Assessment) was involved in refining the trial design through the funding peer review process but had no role in data collection, data analysis, data interpretation, or writing of the report. Funders of the food allergy outcomes and skin prick tests (Goldman Sachs Gives and Sheffield Children's Hospital Research Fund) had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript HCW, AAM, and LEB had full access to all data in the study, and HCW had final responsibility for the decision to submit for publication
Notes	

Cooke 2015

Study characteristics	
Methods	**Study design:** pilot, assessor-blinded RCT **Study data collected:** between September 2013 and July 2014 **Treatment arms:** 3 **AD follow-up:** 4 weeks
Participants	**Randomised:** N = 115 (olive oil n = 38, sunflower oil n = 38, no oil n = 39) **Inclusion criteria:** participants with or without a family history of AE **Exclusion criteria:** 1. Mother 16 years of age or younger or without capacity to consent 2. Admittance to Special Care Baby Unit 3. Receiving phototherapy treatment 4. Participation in another clinical trial 5. Medical history preventing participation to endpoint 6. Limb defects 7. Non-traumatic impairment of epidermal integrity 8. Evidence of skin disorder at first assessment
Interventions	**Intervention:** randomization took place within 72 hours of birth, parents were instructed from the day after initial assessment to apply 4 drops of oil to their baby's left forearm, left thigh, and abdomen, twice a day. Parents in all groups were asked not to use any other skin care products at the 3 study sites; water only was advocated. Intervention period was 4 weeks 1. Group 1: olive oil 2. Group 2: sunflower oil

Cooke 2015 *(Continued)*

	Comparator: the control group was provided no oil and was asked not to use any other skin care products at the 3 study sites; water only was advocated
Outcomes	**Primary outcome:** the change in structure of the lipid lamellae, a determinant of SC permeability (measured using ATR-FTIR spectroscopy) and TEWL (measured via Biox Aquaflux Model AF200) **Secondary outcome:** stratum corneum hydration (measured via a Corneometer® Model CM825); skin surface pH (measured by skin pH meter® Model PH 905); clinical observations around changes in the skin using a modified Neonatal Skin Condition Score; and erythema (measured by a Mexameter® Model MX18 probe) **Adverse effects:** adverse events, including skin infections, skin reactions, and serious adverse events, were prompted for and collected for all participants
Identification	**Country:** England, UK **Setting:** St. Mary's Hospital, Manchester **Sponsorship source:** AC was funded by the NIHR, and this paper was independent research arising from the Doctoral Research Fellowship, supported by NIHR
Declarations of interest	None reported
Notes	

Da Cunha 2008

Study characteristics	
Methods	**Study design:** randomised clinical trial **Recruitment date:** infants delivered between 13 September 2005 and 14 March 2006 **Treatment arms:** 2 **AD follow-up:** time points: first bath (first collection), 30 minutes after bath (second collection), and 24 hours after bath (third collection)
Participants	**Randomised:** N = 112 (chlorhexidine, experimental group n = 56, neutral liquid soap control group n = 56) **Inclusion criteria:** normal term newborns with gestational age 37 and 42 weeks **Exclusion criteria:** 1. Skin breakdown 2. Congenital infection 3. Premature rupture of membranes for over 18 hours 4. Foetid amniotic fluid 5. HIV+ mother 6. Mother with suspicion of or with bacterial infection before delivery or presenting axillary temperature > 37.8C 7. Hospitalisation before the bath at 24 hours 8. Second bath before 24 hours
Interventions	**Intervention:** chlorhexidine liquid soap bath, admission bath between 1 and 1.5 hours after birth **Comparator:** neutral liquid soap bath, admission bath same as above

Da Cunha 2008 *(Continued)*

	Moisturiser/Emollient: neutral liquid soap (ingredients: Texapon SBN (detergent), Dehyton KB (cocamide), Plantaren 2000 (detergent), Glycerin (emollient), Coperlan KDB (thickener), citric acid, deionized water, pH = 7) Chlorhexidine liquid soap bath (chlorhexidine digluconate liquid soap at 0.4%, resulting from dilution of 10 mL of chlorhexidine digluconate liquid soap at 4% in 90 mL of warm water that released 0.25% chlorhexidine)
Outcomes	*Staphylococcus aureus* skin colonisation **Adverse effects:** none reported
Identification	**Country:** Brazil **Setting:** Obstetric Centre of Hospital de Clinicas de Porto Alegre **Sponsorship source:** this study was supported by the Fundo de Incentivo à Pesquisa (Research Incentive Fund) of Hospital de Clínicas de Porto Alegre (FIPE/HCPA), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ)
Declarations of interest	None reported in publication
Notes	

Dissanayake 2019

Study characteristics	
Methods	**Study design:** 2 × 2 factorial, randomised, non-treatment controlled trial **Recruitment:** October 2012 and March 2014 **Treatment arms:** 4 **AD follow-up:** 1, 6, and 9 months
Participants	**Participants:** N = 549 (skin care + synbiotics n = 137; synbiotics n = 137; skin care n = 138; no intervention n = 137) **Inclusion criteria:** 1. Born at full term 2. Written informed consent available from parent(s)/guardian 3. Family history of atopy was not required for inclusion **Exclusion criteria:** 1. Preterm birth 2. Complications due to severe underlying disease 3. HBV or HIV positivity of mother at the time of birth 4. Any other appropriate status as judged by the physician
Interventions	**Intervention:** parents/caregivers were advised on how interventions should be applied at home. Group 1 received a combination of synbiotics and skin care, group 2 received synbiotics only, group 3 received skin care only, and group 4 received no intervention. Interventions were carried out from birth to 6 months of age, and further observation was made for an additional 6 months. Parents/guardian maintained a diary for 6 months of the intervention to record the number of times that the emollient was applied, any illnesses contracted during this period, and the use of antibiotics during this time. Parents/guardians were instructed to apply emollient 2 to 3 times/d, after a bath or on clean skin, par-

Dissanayake 2019 *(Continued)*

	ticularly on the cheeks and the peri-oral area. Parents/guardians were allowed to apply the emollient to other parts of the body at their discretion and were not advised for or against it **Comparator:** the control group was not prevented from applying emollients for ethical reasons. A diary was maintained to record the number of times and the amount of emollient that was applied each month **Moisturiser/Emollient:** all participants receiving skin care (groups 1 and 3) were given Locobase® REPAIR Cream (Daiichi Sankyo, Japan), which contains ceramide, cholesterol, and free fatty acids **Synbiotics :** groups that were given synbiotics (groups 1 and 2) received a combination of 0.5 g (7 × 109 CFU/g) of *Bifidobacterium bifidum* OLB6378 (Meiji Holdings Co. Ltd., Japan) combined with 0.5 g of fructo-oligosaccharides (Meiji Food Materia Co. Ltd., Japan) twice a day
Outcomes	**Primary outcomes:** The primary outcome assessed was development of AD by 1 year of age. AD was diagnosed according to the criteria of the Japanese Dermatological Association, when an itchy rash lasting 2 months or longer was reported in questionnaires returned at 1, 6, and 9 months and at 1 year of the baby's age. In addition, AD was diagnosed using the UK Working Party's diagnostic criteria included in the questionnaire at 1 year **Secondary outcomes:** Prevalence of FA, as reported in the questionnaires at 1 year. Sensitisation to food and/or inhalant allergens – total and allergen-specific IgE levels were determined in blood sampled at 9 months of age. EASI score – babies were examined by Dr. YuT (paediatrician) at 9 months of age. If AD was diagnosed, severity was determined using the EASI score and photography of the body. AD diagnosis was further confirmed blindly by YaT (dermatologist) and NS (paediatrician). AD was diagnosed based on criteria of the Japanese Dermatological Association Thymus- and activation-regulated chemokine (TARC) score – blood samples obtained at 9 months were used for evaluating TARC levels of all participants **Adverse effects:** no adverse effects of the interventions were reported during the study period
Identification	**Country:** Japan **Setting:** antenatal clinic at the Japanese Red Cross Katsushika Maternity **Sponsorship source:** this study was supported by the Environmental Restoration and Conservation Agency of Japan in fiscal years 2014 to 2016 and by grants from the Japan Agency for Medical Research and Development (AMED-CREST) (15652274)
Declarations of interest	Study authors have no conflicts of interest to disclose
Notes	

Dizon 2010

Study characteristics	
Methods	**Study design:** parallel, randomised, controlled trial **Recruitment date:** not reported **Treatment arms:** 3 **Follow-up:** assessment was done at baseline, and after 1 week and 2 weeks of using the products

Dizon 2010 *(Continued)*

Participants	**Randomised:** N = 180 Filipino infants (< 1 year) (JTT n = 60; SEBAMED n = 60; water only n = 60) **Inclusion criteria:** Filipino infants (age 1 day to < 1 year) in good health with normal skin **Exclusion criteria:** prematurely born infants and those with congenital problems
Interventions	**Intervention:** 1. Group I - Johnson's Baby Top-To-Toe Wash 2. Group II - Sebamed Baby Liquid Cleanser (SM) The above products (Group I) were used on the skin of subjects as whole body cleansers at least twice a week for 2 weeks Assessment was done at baseline and after 1 week and 2 weeks of use: (i) clinically by a dermatologist, (ii) instrumentally, and (iii) by the consumer (parent of the participant) **Comparator:** Group III - lukewarm tap water
Outcomes	Clinical assessment (erythema, oedema, dryness, and scaling); skin moisture content; skin surface pH; transepidermal water loss; skin oxyhaemoglobin and deoxyhaemoglobin; and consumer satisfaction were the outcome measures **Adverse effects:** parents did not report any side effects
Identification	**Sponsorship source:** Johnson and Johnson. **Country:** Philippines
Declarations of interest	Not reported
Notes	

Duan 2019

Study characteristics	
Methods	**Study design:** randomised, single-centre, parallel-assignment trial **Study date:** June 2013 to November 2013 **Treatment arms:** 3 **AD follow-up:** 6 weeks and 12 weeks
Participants	**Randomised:** N = 150 (wash + lotion n = 44; water + lotion n = 43; water only n = 43) **Inclusion criteria:** 1. Healthy full-term infant (0 to 6 months old) 2. Male or female 3. Parent/caregiver ≥18 years old 4. Willingness of parent/caregiver to follow study instructions and sign consent forms 5. Willingness of parent/caregiver to avoid prolonged exposure of infant to sun, beach, or swimming pool 6. Willingness of caregiver to attend all scheduled visits **Exclusion criteria:** 1. Pre-existing skin conditions (dermatitis, eczema, psoriasis, rosacea), dry skin

Duan 2019 *(Continued)*

	2. Prescription or over-the-counter topical or oral medication that might impact results (except vitamins) 3. Parent/caregiver or participant with unusual or hypersensitive or allergic response to skin care products 4. Parent/caregiver or participant with asthma 5. Participant with active localised or general infection 6. Other condition that may make the patient inappropriate for trial entry
Interventions	**Intervention:** **Group 1:** Johnson's Baby Top-To-Toe Wash (ideally 7 times a week, at least 5 times a week) + Johnson's Baby Lotion (at least once a day). Products/treatments were used for 3 months, and products were placed on the skin with attention to applying them to the arms, legs, and torso **Group 2:** water (in lieu of bathing products) + Johnson's Baby Lotion (at least once a day). Products/treatments were used for 3 months, and products were placed on the skin with attention to applying the products to the arms, legs, and torso **Comparator:** water (in lieu of bathing products) only. Products/treatments were used for 3 months. Products were placed on skin with attention to applying products to the arms, legs, and torso **Moisturiser/Emollient:** Johnson's® Baby Top-To-Toe® Wash and Johnson's® Baby Lotion, Johnson & Johnson Consumer Inc., Skillman, NJ; wash + lotion
Outcomes	**Primary outcome:** skin surface moisture [Time Frame: 3 months] Skin surface moisture content via capacitance measurements **Secondary outcome:** 1. Skin deep hydration [Time Frame: 3 months] 2. Trans-epidermis water loss (TEWL) [Time Frame: 3 months] 3. Ratio of TEWL/Skin surface moisture to reflect skin barrier function [Time Frame: 3 months] 4. Skin pH value [Time Frame: 3 months] 5. Skin roughness [Time Frame: 3 months] 6. Dermatological assessments [Time Frame: 3 months] 7. Parent/Caregiver assessments [Time Frame: 3 months] 8. Skin microbiome [Time Frame: 3 months] 9. Skin biomarker [Time Frame: 3 months] **Adverse effects:** none reported
Identification	**Country:** China **Setting:** Beijing Children's Hospital, Xicheng District **Sponsorship source:** this study was funded by Johnson & Johnson International Pte. Ltd (Singapore)
Declarations of interest	YYD, CG, and F-QK were employees of Johnson & Johnson at the time this study was conducted. YYD and F-QK are no longer employed at Johnson & Johnson. C-PS and LM received research support in association with this study. Study authors report no other conflicts of interests in this work
Notes	

Garcia Bartels 2010

Study characteristics

Garcia Bartels 2010 *(Continued)*

Methods	**Study design:** monocentric, prospective, randomised study **Study conducted:** October 2006 to May 2007 **Treatment arms:** 4 **AD follow-up:** day 2; weeks 2, 4, and 8 of life
Participants	**Randomised:** N = 64 (WG, bathing with wash gel n = 16; C, bathing and cream n = 16; WG + C, bathing with wash gel plus cream n = 16; B, bathing with water n = 16) **Inclusion criteria:** 1. Healthy full-term newborns with 37 completed weeks of gestation, aged 48 hours **Exclusion criteria:** 1. Sepsis 2. Serious congenital malformations 3. Asphyxia 4. Hydronephrosis 5. Severe intracranial haemorrhage 6. Immunodeficiency 7. Pre-existing skin disease with eruptions covering more than 50% of body surface 8. Relevant skin maceration or inflammation/irritation 9. Urticaria 10. Acute or chronic disease with temperature below 35°C or above 40°C
Interventions	**Intervention:** full-term neonates (32 girls, 32 boys) aged ≤ 48 hours were randomly assigned to 4 groups (including one comparator group, each n = 16) receiving treatment twice weekly from day 7 until week 8 of life. 1. Group WG, bathing with pH 5.5 wash gel (Top-To-Toe Baby Gel Penaten, Johnson & Johnson GmbH, Duesseldorf, Germany). 2. Group C, bathing with clear water and afterwards topical cream (Baby Caring Facial & Body Cream Penaten, Johnson & Johnson GmbH, Duesseldorf, Germany). 3. Group WG + C, bathing with wash gel and topical cream. All neonates were washed 3 times with a cotton wash cloth, moistened with water, until day 7 Bathing lasted about 5 minutes using tap water at temperature 37 to 38°C, pH 7.9 to 8.2, hardness 13.4 dH (range 7 to 25 dH). Diapers from Pampers Baby Dry for Newborns were provided. Parents were instructed to avoid treating skin with any other skin care products. Topical products were allowed on areas of skin trauma or diaper dermatitis, including: triclosan 1% cream, octenidin/phenoxyethanol solution, zinc paste (optional with nystatin). To remove meconium: oil and vaseline were allowed. **Comparator:** Group B, bathing with clear water
Outcomes	1. Transepidermal water loss 2. Stratum corneum hydration 3. Skin pH 4. Sebum **Adverse effects:** no adverse events reported
Identification	**Country:** Germany **Setting:** Department of Dermatology, Clinic for Neonatology CCM at Charité-Universitätsmedizin Berlin, and Department of Gynaecology, Clinic Dahme-Spreewald

Garcia Bartels 2010 *(Continued)*

	Sponsorship source: the work of Franziska Prosch was supported by an unrestricted medical grant from Johnson & Johnson
Declarations of interest	The funders had no input regarding study design or conduct, data analysis or interpretation, manuscript preparation, or the decision to submit the results for publication
Notes	

Garcia Bartels 2011

Study characteristics	
Methods	**Study design:** monocentric, prospective, randomised, clinical non-pharmaceutical study **Study conducted:** September to December 2009 **Treatment arms:** 2 **AD follow-up:** 4 weeks
Participants	**Randomised:** N = 44 (Group L using lotion n = 20; Group WL without lotion n = 24) **Inclusion criteria:** 1. Healthy full-term infant (37 weeks+) 2. Aged 3 to 6 months 3. Parental consent **Exclusion criteria:** 1. Immunocompromised infant 2. Severe illness 3. Congenital skin disorder 4. Skin irritation that could have affected measurements or was contagious 5. Current or previous atopic dermatitis in both parents 6. Acute or chronic illness with increased or decreased body temperature 7. Participation in another study
Interventions	Both groups went swimming weekly for 4 weeks for 25 to 40 minutes at the Charité-Universitätsmedizin Berlin physiotherapy facilities. Both groups received a standard skin care regimen: weekly bathing in tap water, diaper care with water and cotton cloth or Bübchen® Comfort sensitive wipes. No skin care was performed 12 hours before evaluations **Intervention:** in group L (lotion group), baby skin care lotion was applied to the entire body once weekly after swimming and the skin was dried with a towel **Comparator:** no lotion or other skin care product was applied in Group WL (without lotion) **Moisturiser/Emollient ingredients:** Bübchen® Pflege Lotion: aqua, *Helianthus annuus* seed oil, isopropyl palmitate, dicaprylyl ether, ethylhexyl stearate, polyglyceryl-3 polyricinoleate, glycerin, butylene glycol, octyldodecanol, polyglyceryl-3 diisostearate, parfum, zinc stearate, chamomilla-recutita extract, tocopheryl acetate, glyceryloleate, magnesium sulfate, tocopherol
Outcomes	1. Transepidermal water loss 2. Stratum corneum hydration 3. Skin pH 4. Sebum

Garcia Bartels 2011 *(Continued)*

	Measured on 4 anatomical test areas (forehead, abdomen, buttock, thigh), using the non-invasive Multi-Probe Adapter System MPA® (Courage & Khazaka Electronic, GmbH, Cologne, Germany) at 6 study visits. Baseline visit (V0) was within 4 weeks before the first swimming session. After baseline, visits were performed weekly before swimming sessions (V1 to V4). No swimming took place at follow-up, 1 week after the last swimming session (V5) **Adverse events:** method of collection of adverse events is not recorded "Neonatal skin condition score (NSCS) was found to be mainly normal (score 3). A mildly elevated NSCS (4) was found in < 7.5% of infants per visit, and depending on area, an NSCS of 5 was found only once at baseline visit on the thigh (data not shown). NSCS was statistically comparable at all test regions in both groups throughout the study period (n = 44). The overall occurrence of adverse events (AEs) was lower in group L (n = 18) than in group WL(n = 33, Table 3). The occurrence of diaper dermatitis, however, was similar in both groups (n = 9). After dichotomisation of subjects into the two groups "no AE at all" vs "at least one AE", χ^2 test showed significantly less occurrence of AEs in group L compared to group WL (55.0% vs 83.3%; P = 0.04; Figure 8)"
Identification	**Country:** Germany **Setting:** Charité-Universitätsmedizin Berlin, Germany, physiotherapy facilities **Sponsorship source:** the clinical study was sponsored by Bübchen Deutschland
Declarations of interest	Prof. Blume-Peytavi has received presentation fees from Bübchen Deutschland, which sponsored the study
Notes	

Garcia Bartels 2012

Study characteristics	
Methods	**Study design:** monocentric, prospective, randomised pilot study **Study conducted:** May 2007 to October 2007 **Treatment arms:** 2 **AD follow-up:** baseline second day of life at neonatal ward, followed by 14th and 28th days of life
Participants	**Randomised:** N = 44 (skin care with baby wipes n = 21; water-moistened washcloth n = 23 at each diaper change) **Inclusion criteria:** healthy full-term newborns with 37 completed weeks of gestation **Exclusion criteria:** 1. Sepsis 2. Congenital malformation 3. Asphyxia 4. Hydronephrosis 5. Intracranial haemorrhage 6. Immunodeficiency 7. Skin disease with eruptions covering more than 50% of body surface 8. Skin maceration or inflammation, or both 9. Urticaria 10. Acute/chronic disease with temperatures

Garcia Bartels 2012 *(Continued)*

Interventions	Treatments were applied approximately 8 times per 24 hours by parents over 4 weeks Both groups obtained a standard skin care regimen, with twice-weekly bathing in clear tap water without use of a cleanser as described. No additional skin care was given, except for areas of skin trauma or diaper dermatitis **Intervention:** skin care with baby wipes (BW). Infants were cleansed with baby wipes during each diaper change **Comparator:** water-moistened washcloth (cotton washcloth moistened with tap water) **Wipes and diaper ingredients:** skin care with baby wipes (BW), Penaten (Procter & Gamble Manufacturing GmbH, Euskirchen, Germany), baby wet wipes with aloe vera (aqua, myristyl alcohol, stearyl alcohol, propylene glycol, epilobium angustifolium extract, aloe barbadensis, PEG-4 laurate, tocopherol, citric acid, lactic acid, tetrasodium-EDTA phenoxyethanol, iodopropyynyl butylcarbamate, parfum, Johnson & Johnson GmbH, Duesseldorf, Germany), Pampers Diapers ''newborn'' size, cotton washcloths provided. Tap water pH 7.9 to 8.2
Outcomes	**Primary outcome:** transepidermal water loss **Secondary outcomes:** skin pH, SCH, epidermal desquamation, Neonatal Skin Condition Score (NSCS), IL-1 alpha level **Adverse effects:** not reported
Identification	**Country:** Germany **Setting:** Charité -Universitätsmedizin Berlin **Sponsorship source:** Lida Massoudy's work was supported by an unrestricted medical grant from Johnson & Johnson GmbH. We thank Dr. Gaelle Bellemere (Johnson & Johnson, Research and Development, France) for support in the IL-1a analysis and in the D-Squame technique of blinded samples
Declarations of interest	Not reported
Notes	

Garcia Bartels 2014

Study characteristics	
Methods	**Study design:** single-centre, prospective, randomised trial **Study conducted:** November 2010 to April 2012 **Treatment arms:** 3 **Follow-up:** 4 weeks and 8 weeks
Participants	**Randomised:** N = 89 (group 1 n = 30, group 2 n = 28, group 3 n = 31) **Inclusion criteria:** Healthy infants aged 9 months (±8 weeks) **Exclusion criteria:** 1. Immunocompromised infant 2. Infant with severe illness 3. Congenital disorder

Garcia Bartels 2014 *(Continued)*

4. Contagious or irritated skin affecting measurements
5. Current or previous atopic dermatitis in both parents
6. Acute or chronic illness with high or low body temperature
7. Participating in another study

Interventions	**Intervention:** Daily use of wet wipes or water-moistened washcloths and diaper cream in the diaper area. Group 2 received cleansing with water-moistened washcloths and diaper cream twice per day. Group 3 received cleansing with wet wipes (Penaten Baby-Lotion Tucher, Johnson & Johnson) at each diaper change and diaper cream twice per day In addition, all groups were advised a twice-weekly skin care regimen, which includes bathing with a baby cleanser (Pentanen Baby Bad & Shampoo, Johnson & Johnson) and applying baby lotion after bathing (Penaten Baby Intensive Lotion, Johnson & Johnson) except for the diaper region Parents advised to wash the water-moistened washcloths at 60°C in the washing machine without fabric softener Clinical measurements were performed at inclusion (week 0 (W0)), week 4 (W4), and week 8 (W8) at the CRC. Diapers were removed 10 minutes before measurements. The minimum duration between last diaper change and measurements was 1 hour; bathing or skin care was allowed 12 hours before measurements. A minimum of 4 diaper changes every 24 hours was required, and if DD occurred, a topical therapy was allowed on affected areas as needed. Ambient conditions were standardised (temperature 22°C to 26°C, relative humidity 40% to 60%). During the study period, DD occurred in the perianal and genital areas but not in investigational areas, that is, the outer upper quadrant of the buttock (diapered area) and the upper leg (non-diapered area). When DD occurred, extra measurements were taken in the affected area Skin condition was evaluated using a modified NSCS 2, 3, 11, and in the diaper area using a modified DRG 1 (7-point scale; none = 0, severe = 3). Clinically relevant DD was defined as DRG of 1.5 or greater Parents were advised to document in a diary any changes in skin care and the health status of the infant, which they were given and was explained at the inclusion visit. The investigator verified diary entries at each visit **Comparator:** Group 1 received cleansing with water-moistened washcloths at each diaper change
Outcomes	**Primary outcome**: transepidermal water loss **Secondary outcomes:** 1. Skin surface pH 2. Stratum corneum hydration 3. Interleukin-1 alpha (IL-1α) 4. Neonatal skin condition score 5. Diaper rash grade **Adverse events:** no adverse events reported
Identification	**Country:** Germany **Setting:** Clinical Research Center for Hair and Skin Science (CRC), Charité-Universitätsmedizin Berlin **Sponsorship source:** the trial was sponsored by Johnson & Johnson Consumer EMEA. The sponsor had input into the study design and blinded analysis of interleukin. The sponsor had no influence on conduct of the trial, collection of data, or statistical evaluations

Garcia Bartels 2014 *(Continued)*

Declarations of interest	U. Blume-Peytavi is a consultant to Johnson & Johnson GmbH. N. Garcia Bartels has been speaker for Johnson & Johnson Consumer GmbH
Notes	

Horimukai 2014

Study characteristics	
Methods	**Study design:** randomised, controlled, parallel-group, investigator-blinded trial **Recruitment date:** November 2010 to November 2013 **Treatment arms:** 2 **AD follow-up:** 4 weeks, 12 weeks, 24 weeks, 32 weeks **FA follow-up:** sensitisation to food and inhalants at 32 weeks
Participants	**Randomised:** N = 118 (intervention n = 59; control n = 59) **Inclusion criteria:** 1. Infant within the first week after birth 2. High-risk infant from atopic dermatitis (family history) 3. Infant without treatment with corticosteroids 4. Infant whose parents gave informed consent **Exclusion criteria:** 1. Infant treated with corticosteroid ointment (except genital and anal areas) 2. Infant with skin lesions such as dyskeratosis or bullosa diagnosed by specialists in dermatology 3. Small-for-gestational-age (< 37 weeks) 4. Infant with hepatic disease, convulsion, cardiac disease, haemophilia, diabetes, or autoimmune disease 5. Inappropriate case as evaluated by doctors
Interventions	**Intervention:** emollient was applied each day for 32 weeks. Hanifin-Rajka criteria were used to diagnose AD **Comparator:** control group applied petroleum jelly if desired **Moisturiser/Emollient:** emulsion-type emollient (2e (Douhet) emulsion) from the first week of life; petroleum jelly was prescribed to each infant in both groups on request by the institutional review board
Outcomes	**Primary outcomes:** the cumulative rate of incidence of AD, eczema, or both by temporal observation. Modified UKWP criteria were applied by a dermatology specialist **Secondary outcomes:** 1. Specific IgE antibodies 2. Transepidermal water loss (TEWL) 3. Stratum corneum water concentration 4. Stratum corneum pH 5. *Staphylococcus aureus* on skin 6. Onset of allergic disease such as asthma and food allergy

Horimukai 2014 *(Continued)*

	Adverse events: "the dermatology specialist stopped giving the emollient to 3 infants whose skin lesions seemed to be the result of urticaria or contact dermatitis caused by emulsion-type emollients (related adverse events). After several days, however, the doctor judged that these skin lesions were not adverse events because they disappeared rapidly, and similar lesions were not seen when the same emollients were used again. These 3 infants did not have AD/eczema or skin rash when they were followed for 32 weeks. There were no infants from families that withdrew consent who had skin lesions. In summary, adverse events caused by this emulsion-type emollient were not observed during this RCT" No IPD are available on adverse events
Identification	**Sponsorship source:** supported in part by Health and Labour Sciences Research Grants for Research on Allergic Diseases and Immunology from the Ministry of Health, Labour and Welfare of Japan (H22-Men'eki-Ippan-002 to H.S.; H25-Nanchito-Ippan-001 to M.A. and H.S. as principal investigators) and grants from the National Center for Child Health and Development (20S-1 to Y.O. and 23S-3 to H.S.) **Country:** Japan **Setting:** National Center for Child Health and Development, the only national hospital for mothers and children in Tokyo
Declarations of interest	Extensive list in the trial publication
Notes	

Kataoka 2010

Study characteristics	
Methods	**Study design:** randomised trial **Recruitment date:** not reported **Treatment arms:** 2 **Follow-up:** 6 months for AD, 6 months for food allergen sensitivity
Participants	**Randomised:** N = 71 **Inclusion criteria:** family history of AD in second degree of kinship **Exclusion criteria:** none reported
Interventions	**Intervention:** apply prescribed emollient more than once a day and do not wash infant's face with any other detergent **Comparator:** parent preference in skin care ("do what they like")
Outcomes	1. Eczema and skin barrier function 2. Food allergen sensitivity 3. Transepidermal water loss **Adverse events:** adverse effects not reported
Identification	**Country:** Japan **Sponsorship source:** not reported
Declarations of interest	Not reported

Kataoka 2010 *(Continued)*

Notes	

Lavender 2011

Study characteristics	
Methods	**Study design:** a pilot randomised, assessor-blinded controlled trial **Recruitment date:** November 2008 to November 2009 **Treatment arms:** 2 **AD follow-up:** 4 weeks and 8 weeks
Participants	**Randomised:** N = 80 (recruit a sample of babies with family history of atopic eczema (n = 30) and a sample of babies without this family history (n = 50)) **Inclusion criteria:** 1. Born at 37 weeks' gestation or later 2. Good general health (determined by investigator) **Exclusion criteria:** 1. Admittance to the neonatal unit 2. Having phototherapy 3. Limb defects 4. Non-traumatic impairment of epidermal integrity 5. Evidence of skin disorder at first visit 6. Participation in another clinical trial For the purposes of this study, the following normal variations were not considered skin disorders: erythema neonatorum, erythema toxicum, and milia
Interventions	All participating parents were supplied with written guidance on baby bathing. These instructions included guidance on regularity of bathing and the non-use of other products (e.g. oils, sponges, flannels, baby wipes). Participating women were requested to bathe their baby a minimum of 3 times per week. The number of times babies were bathed was recorded by the women. They were also instructed to avoid any rubbing of the baby's skin and were asked not to use any additional products A baseline assessment was made before maternal transfer into the community and before the first bath. A second assessment was made at 4 weeks and at 8 weeks post birth. Measurements were taken on the upper abdomen (above nappy area), upper leg, and forearm **Intervention:** for those allocated to the wash product (experimental) arm, parents were provided with sufficient baby wash and were advised to use the product as per instructions **Comparator:** for those allocated to the water only (control) arm, parents were not provided with any products and were advised to bathe their baby with water and cotton wool only **Moisturiser/Emollient:** bathed in water only or bathed with the baby wash product. The wash product was the commercially available Johnson's® Baby Top-To-Toe™ Wash (Johnson & Johnson Consumer Companies, Inc.). This wash is a soap-free liquid cleanser specifically designed for newborns' skin. It is sodium lauryl sulphate-free and consists of a proprietary blend of non-ionic and amphoteric surfactants that, when combined, result in large, gentle-cleansing micelles. The formula contains only strictly necessary levels of well-tolerated preservatives and a very low level of fragrance; it is pH-adjusted (around 5.5) and hypoallergenic. The INCI list comprised aqua, coco glucoside, cocamidopropyl

Lavender 2011 *(Continued)*

	betaine, citric acid, acrylates/C10-30 alkyl acrylate crosspolymer, sodium chloride, glyceryl oleate, p-Anisic acid, sodium hydroxide, phenoxyethanol, sodium benzoate, and parfum
Outcomes	1. Transepidermal water loss 2. Skin surface pH 3. Hydration **Adverse effects:** the skin was observed and recorded by the assessing midwife, at 4 and 8 weeks post birth using a validated rating scale that records erythema, dryness, scaling, and the need for medical products/attention. Any skin treatments were recorded by the mother
Identification	**Country:** UK **Setting:** teaching hospital in the North West of England **Sponsorship source:** this study was funded by Johnson and Johnson. However, the study was investigator led. TL, CB, and MC previously acted as temporary advisors to J & J
Declarations of interest	As above
Notes	

Lavender 2012

Study characteristics	
Methods	**Study design:** prospective, assessor-blinded, randomised, controlled trial **Recruitment date:** February and October 2010 **Treatment arms:** 2 **AD follow-up:** 4 weeks
Participants	**Randomised:** N = 280 (napkin area cleansed with an alcohol-free baby wipe n = 140 babies; cotton wool and water n = 140 babies) **Inclusion criteria:** 1. Infants born at 37 weeks' gestation or later and using disposable nappies **Exclusion criteria:** 1. Admitted to the neonatal unit 2. Receiving phototherapy 3. Limb defects 4. Non-traumatic impairment of epidermal integrity 5. Evidence of skin disorder at first visit 6. Chromosomal abnormality or other syndromic diagnosis 7. Baby going for adoption
Interventions	**Intervention:** napkin cleansing regimen using a specific type of baby wipe. Participating mothers were given a cleansing demonstration by a healthcare assistant. All mothers were advised to use nappies that were supplied by researchers for the duration of the study to ensure similar absorbency - a factor likely to influence skin hydration. Mothers were also advised to avoid using napkin cream, other than that supplied by the research team as a rescue treatment. Parents were provided with cotton wool or baby wipes, according to their allocated trial arm

Lavender 2012 *(Continued)*

	Comparator: napkin cleansing regimen using cotton wool and water **Wipe and emollient:** Johnson's Baby Skincare Fragrance Free Wipe (Johnson & Johnson Ltd., Maidenhead SL6 3UG, UK). The emollients contained glycerin and glyceryl oleate. The baby wipes also contained citric acid, which can have dual functionality as pH adjuster and chelator. Additionally, it was important to have a wipe with a pH close to the skin pH (around 4.9 in this case); if the pH is too low, this could be an irritant; if too high, this would increase protease activity and inhibit lipid lamellar synthesis in the skin barrier. Wipes contained 97% water and were free of alcohol, fragrance, essential oils, soap, and other harsh detergents; they were appropriately preserved to prevent growth of micro-organisms. Cloth material of the wipes was a rayon viscose and polyester non-woven fibre blend, entangled in a matrix of trough water jets without chemical binders. This is designed to reduce friction when wiped across the skin surface
Outcomes	**Primary outcome:** change in stratum corneum hydration scores on the buttocks from first assessment (within 48 hours of birth) to 4 weeks post birth, using a Corneometer **Secondary outcomes:** change in erythema measurements using a Mexameter (W MX 18) (27); change in transepidermal water loss (TEWL) using an Aquaflux (AF200) (28); change in skin surface pH (using a pH meter). Measurements were taken on the babies' buttocks at first assessment (within 48 hours of birth) and 4 weeks post birth **Adverse effects:** study group found no evidence of any adverse effects of using these wipes
Identification	**Country:** UK **Setting:** North West of England
Declarations of interest	None reported
Notes	

Lavender 2013

Study characteristics	
Methods	**Study design:** assessor-blinded, randomised, controlled, non-inferiority trial **Recruitment date:** between February 2010 and March 2011 **Treatment arms:** 2 **AD follow-up:** 2 weeks and 4 weeks for AD
Participants	**Randomised:** N = 307 (wash product n = 159; bathing with water alone n = 148) **Inclusion criteria:** 1. Newborn infants born at 37 weeks' gestation or later **Exclusion criteria:** 1. Admitted to the neonatal unit 2. Receiving phototherapy 3. Limb defects 4. Non-traumatic impairment of epidermal integrity 5. Evidence of skin disorder at first visit 6. Chromosomal abnormality or other syndromic diagnosis 7. Infant going for adoption

Lavender 2013 *(Continued)*

Interventions	Bathing regimen using a newborn wash product or water alone before the first bath. Participating mothers were instructed to bathe their neonate at least 3 times per week and to avoid rubbing the skin. On the day of assessment, mothers were requested to delay bathing their neonate until measurements had been taken **Intervention:** those allocated to the wash product (experimental) were provided with sufficient newborn wash and were advised to dilute the product at a ratio of 3 squirts per bath **Comparator:** control group used water alone; parents were not provided with any products. If these mothers wished to use shampoo on their neonates' hair, they were requested to do this outside of the bath, and to ensure that the neonate's body was wrapped in a towel to prevent contact with the skin **Cleanser:** Johnson's Baby Top-To-Toe Bath (Johnson & Johnson Limited, Maidenhead SL6 3UG, UK) is a soap-free liquid cleanser designed for newborns' skin. It is sodium lauryl sulphate-free and consists of a proprietary blend of non-ionic and amphoteric surfactants that when combined result in large micelles that clean via dispersal of fats without disrupting the skin barrier. The formula contains well-tolerated preservatives and a low level of fragrance; it is pH-adjusted (around 5.5) and hypoallergenic. The International Nomenclature Cosmetic Ingredients list comprised aqua, coco glucoside, coca midopropyl betaine, citric acid, acrylates/C10-30 alkyl acrylate crosspolymer, sodium chloride, glyceryl oleate, p-Anisic acid, sodium hydroxide, phenoxyethanol, sodium benzoate, and parfum
Outcomes	**Primary outcomes:** the average of TEWL measurements, using a closed chamber system, over 3 sites (outer forearm, midpoint between wrist and elbow; front of thigh, midpoint between knee and groin; abdomen, midpoint between umbilicus and sternum) at 14 days following birth using AquaFlux Model AF200 (Biox Systems Ltd, London, UK) **Secondary outcomes:** TEWL at 4 weeks post birth, skin surface pH using Courage + Khazaka Skin-pH-MeterR PH 900, and stratum corneum hydration scores using CorneometerR CM 820 (Courage + Khazaka Electronic GmbH, Cologne, Germany) from baseline (within 48 hours of birth). Because of the sensitivity of the neonate's skin in the early weeks following birth, this is an ideal time to investigate the effects of wash products. Any differences in these outcomes are likely to be greater than later in an infant's life, when the skin barrier is more stable **Adverse events:** not reported
Identification	**Country:** UK **Setting:** teaching hospital in the North West of England **Sponsorship source:** funded by Johnson & Johnson Consumer Companies, Inc.
Declarations of interest	None reported
Notes	

Lowe 2018a

Study characteristics	
Methods	**Study design:** a pilot randomised, parallel, single-blinded (outcome assessor), controlled trial **Recruitment date:** 1 May 2013 to 2 July 2014 **Treatment arms:** 2 **AD follow-up:** 6 weeks, 6 months, and 12 months of age for AD **FA follow-up:** 6 months and 12 months

Lowe 2018a *(Continued)*

Participants	**Randomised:** N = 80 (treatment group n = 41; control group n = 39) **Inclusion criteria:** 1. Self-reported family history (either parent or older siblings) of allergic disease (asthma, eczema/atopic dermatitis, allergic rhinitis/hay fever, or food allergy) 2. Single birth **Exclusion criteria:** 1. Either parent had known hypersensitivity to any of the ingredients of EpiCream 2. Born prematurely (< 36 weeks) 3. Required admission into a neonatal special or intensive care nursery 4. Parents with insufficient English language skills or not able to comply with all protocol required visits and procedures 5. Infant with a major birth or early life medical complications 6. Parents not able to comply with all protocol required visits and procedures
Interventions	**Intervention:** parents of infants were shown how to apply the emollient to the full skin surface of their child twice a day for the first 6 months of life. Treatment commenced within the first 3 weeks of life (neonatal period). Approximately 6 grams per application 1. Adherence was high. 76% applied EpiCeram ≥ 5 days per week 2. 18% used other emollients on average ≥ 3 days per week **Comparator:** control group - no other skin care instructions were provided **Emollient:** EpiCeram is a ceramide-dominant emollient cream
Outcomes	**Primary outcomes:** 1. Presence of observed eczema within the first 6 weeks and 6 months of life using UKWP criteria for eczema and assessed by study investigators 2. Skin barrier function, transepidermal water loss at 6 weeks and 6 months 3. Measurement tools: UK Working Party criteria **Secondary outcomes:** 1. Presence of observed eczema from 6 to 12 months of age, Hanifin and Rajka standardised criteria, assessed by study investigators 2. Presence of probably eczema (based on diagnosis in the community but not verified by the study investigator) up to 12 months of age 3. Parent-reported or community doctor-diagnosed eczema 4. Eczema severity assessed using SCORAD (Scoring of Atopic Dermatitis) Scale 5. Skin prick test reactivity to 6 allergens (egg white, cows' milk, peanut, dust mite, cat dander, and rye grass) 6. Skin pH 7. Skin hydration 8. Skin oiliness
Identification	**Country:** Australia **Setting:** Royal Women's Hospital and Frances Perry House (recruitment) Murdoch Children's Research Institute (assessment and storage of biological samples) University of Melbourne (data storage) **Sponsorship source:** this trial was supported by the Financial Markets Foundation for Children and the Asthma Foundation of Victoria. Additional support was obtained via an NHMRC equipment grant

Lowe 2018a *(Continued)*

	to purchase instruments used to measure biophysical aspects of skin. PuraCap, the manufacturer of EpiCeram at the time, provided the study with the interventional product free of charge
Declarations of interest	None declared
Notes	

Lund 2020

Study characteristics	
Methods	**Study design:** randomised, controlled trial **Recruitment date:** September 2012 to May 2013 **Treatment arms:** 2 **Follow-up:** 1 post-bath measurement
Participants	**Randomisation:** N = 100 (vaginal delivery n = 50, caesarean section (C/S) n = 50) (intervention n = 49, control n = 51); randomised according to a balanced block design and stratified according to delivery mode **Inclusion criteria:** 1. Healthy full-term infant 2. English-speaking parents 3. Parental consent **Exclusion criteria:** 1. Respiratory symptoms requiring oxygen 2. Intravenous antibiotics 3. Maternal chorioamnionitis 4. Congenital anomalies 5. Admission to the newborn intensive care unit
Interventions	All participants were bathed according to the study protocol: immersion bath with water temperature 101°F, depth 5 inches(12.7 cm), which has been shown to be safe even with the umbilical cord in place- and swaddle technique to reduce infant distress. The infant was stabilised under a radiant warmer- with the 2 study sites - volar forearm and beneath the sternum - exposed for 10 minutes **Intervention:** bathed using cleanser **Comparator:** bathed with water only **Cleanser ingredients:** Johnson & Johnson's Head-To-Toe™ was used, as this product was used at the time at this facility. It is a soap-free liquid cleanser designed for newborn and infant skin; it is sodium lauryl sulfate-free and pH-adjusted
Outcomes	**Primary outcome:** skin barrier function, measured by skin surface pH **Secondary outcomes:** transepidermal water loss (TEWL), hydration of the stratum corneum (SCH) **Adverse events:** not reported
Identification	**Country:** USA **Setting:** UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA

Lund 2020 *(Continued)*

	Sponsorship Source: this study was supported by a grant from Johnson & Johnson Consumer Co. Inc., and by the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 TR000004
Declarations of interest	This study was supported by a grant from Johnson & Johnson Consumer Co. Inc., and by the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 TR000004
Notes	

McClanahan 2019

Study characteristics	
Methods	**Study design:** single-centred, investigator-blinded RCT **Recruitment dates:** June 2011 and January 2014 **Treatment arms:** 2 **AD follow-up:** study visits occurred at 2, 6, and 12 months. Two phone calls were performed at 18 to 24 months to discuss development of AD, provide education on emollient use, and supply additional product
Participants	**Randomisation:** N = 100 (intervention n = 54, control n = 46) **Inclusion criteria:** 1. Parent/guardian over 18 years of age 2. Newborn within 21 days considered at high risk for AD development (first-degree relative with history of AD, asthma, or allergic rhinitis) 3. Parents/guardians of participants willing to comply with study procedures **Exclusion criteria:** 1. Premature newborn (born before 37 weeks' gestational age) 2. Diagnosed with major congenital anomaly 3. Significant dermatitis at birth (excluding seborrhoeic dermatitis) 4. Immunodeficiency disorder 5. Serious medical problem making emollient use inadvisable by increasing the risk of adverse events or inhibiting outcomes assessment
Interventions	**Intervention group:** instructed to apply moisturiser daily to all body surfaces excluding the scalp and diaper area and to use the cleanser only as needed during bathing **Comparator:** control group was given no specific instructions regarding use of emollients except to use emollients of their choice on an as needed basis **Moisturiser/ Emollient :** Cetaphil Restoraderm (Galderma, Baie d'Urfé, Montreal, Canada); key ingredients include shea butter as a lipid source, pseudoceramide-5, and 2 FLG breakdown products. A cleanser was also provided. No bathing frequency instructions were provided. Both products were to be used within 21 days of birth
Outcomes	**Primary outcomes:** cumulative incidence of AD at 12 months diagnosed by a blinded investigator ('investigator-confirmed AD'). UK Working Party Criteria adapted to identify incident cases of AD were used rather than a 12-month period of prevalence

McClanahan 2019 *(Continued)*

	Secondary outcomes: a post-hoc secondary analysis of the primary outcome was also performed: cumulative incidence of AD defined as AD diagnosed by an investigator and/or an outside paediatrician or chart review within 12 or 24 months (any AD) **Adverse events:** intervention group vs control group: bacterial skin infections (7.4% vs 6.5%); hypersensitivity reactions including irritant contact dermatitis and urticaria (14.8% vs 8.7%). No serious adverse events were reported in either group
Identification	**Country:** Oregon, USA **Setting:** maternal hospital wards **Sponsorship source:** all funding sources supported the work
Declarations of interest	Dr. Simpson has received consulting fees from Galderma, which supplied emollient for this study
Notes	

Migacheva 2018

Study characteristics	
Methods	**Study design:** randomised, controlled trial **Treatment arms:** 2 **AD follow-up:** 12 months
Participants	**Randomised:** N = 63 **Inclusion criteria:** 1. Family history of allergy **Exclusion criteria:** 1. Prematurity 2. Supplementation (including short-term use of children milk formulas in the maternity hospital) 3. Appointment of probiotics 4. Use of drugs by nursing mother 5. Use of special means of baby skin care (emollients)
Interventions	**Intervention:** infants in the intervention group received full-body emollient therapy (cream) twice a day starting within 3 weeks of birth in combination with supplementation of synbiotic containing LGG and fructo-oligosaccharides at the age of 3 to 6 months **Comparator:** parents in the control group were asked to use no emollients and no pro/prebiotics during the study period Adherence to the application came in at 95.2% by the end of the study, which reassured that the process was feasible
Outcomes	Cumulative incidence of AD at 12 months, as assessed by a trained investigator **Adverse events:** no intervention-related adverse events occurred
Identification	**Country:** Russia **Sponsorship source:** not reported

Migacheva 2018 *(Continued)*

Declarations of interest	Not reported
Notes	

NCT03376243

Study characteristics	
Methods	**Study design:** pragmatic, parallel-group, assessor-blind, randomised, open-label, prospective study **Study start date:** 1 February 2017 **Treatment arms:** 2 **Follow-up:** patients were followed up until they had eczema or 12 months or were lost to follow-up
Participants	**Participants:** N = 54 **Inclusion criteria:** 1. Participant (i.e. the newborn baby) must have a parent or sibling with a history of atopic eczema, allergic rhinitis, or asthma 2. Infant in overall good health 3. Term-born babies 4. Mother at least 18 years of age at delivery and capable of giving informed consent **Exclusion criteria:** 1. Preterm birth (defined as birth before 37 weeks' gestation) 2. Child previously randomised to this trial 3. Major congenital anomaly 4. Significant inflammatory skin disease at birth (except seborrhoeic dermatitis) 5. Any immunodeficiency disorder or severe genetic skin disorder 6. Any condition that would make the use of emollients inadvisable or not possible
Interventions	**Intervention:** in the experimental arm, daily application of Lipikar Baume AP+ emollient and structured parent education **Comparator:** control group had no emollient intervention - only structured parent education
Outcomes	**Primary outcomes:** 1. Feasibility, safety, and tolerability, and preventive effectiveness 2. Willingness to participate [Time Frame: 2 years] 3. Willingness of parents to have their child randomised and to adhere to the regimen **Secondary outcomes:** 1. Development of AE [Time Frame: 2 years] 2. Cumulative incidence of AE 3. Transepidermal water loss [Time Frame: 2 years] 4. Development of transepidermal water loss over time 5. Microbiome diversity [Time Frame: 2 years] 6. Development of microbiome diversity over time

NCT03376243 *(Continued)*

	Adverse events: skin reactions with study product prompted for at follow-up visits (month 1, month 3, month 6, and month 12)
Identification	**Country:** Germany **Sponsorship source:** University of Schleswig-Holstein
Declarations of interest	Not reported
Notes	

Raisi Dehkordi 2010

Study characteristics	
Methods	**Study design:** triple-blind clinical trial **Recruitment start dates:** 9 April 2010 and 23 Aug 2010 **Treatment arms:** 2 **Follow-up:** weekly up to 4 weeks
Participants	**Randomised:** 120 infants who were 10 to 15 days old, full-term, single, exclusively breastfed, and with no history of hospitalisation **Inclusion criteria:** 1. Term infants (37 to 42 weeks) 2. Birth weight 2500 to 4000 grams 3. Singleton 4. Fed exclusively with breast milk 5. Absence of obvious disease or birth abnormalities 6. Minimal maternal education in secondary school 7. Lack of maternal disease such as hypertension, diabetes, pregnancy, postpartum depression, or any psychiatric illness and no history of hospitalisation due to disease 8. Lack of separation of infant from mother **Exclusion criteria:** 1. Sensitivity to any of the oils used for massage 2. Disease public or skin infant during the study [sic] 3. No intervention in 4 sessions consecutive or intermittent (48 hours) 4. Failure to complete the application form for at least 24 hours 5. Infant feeding with artificial milk 6. Mother's illness
Interventions	Mothers administered 15 minutes of massage to their infants twice per day (morning and afternoon) for 28 days. Times of crying and sleep were measured by parents' information forms at baseline, and at the end of the first, second, third, and fourth weeks of the study **Intervention:** sunflower oil massage or sesame oil massage **Comparator:** massage with no oil
Outcomes	**Main outcomes:** crying time and sleeping time

Raisi Dehkordi 2010 *(Continued)*

	Adverse events: none reported
Identification	**Country:** Iran **Sponsorship Source:** Vice Chancellor, Tehran University for Medical Sciences
Declarations of interest	None reported
Notes	

Rush 1986

Study characteristics	
Methods	**Study design:** randomised controlled trial **Recruitment date:** 19 March to 7 May 1984 **Treatment arm:** 2 **Follow-up:** not reported
Participants	**Randomised:** N = 186 (Group I n = 99, Group II n = 87) **Inclusion criteria:** 1. At least 37 weeks' gestational age 2. Apgar score ≥ 9 at 5 minutes **Exclusion criteria:** 1. Neonatal intensive care unit stay longer than 24 hours
Interventions	**Intervention:** washed daily with soap and water **Comparator:** no bath, dry skin care
Outcomes	*Staphylococcus aureus* colonisation rate **Adverse events:** infection rate reported but no details re: adverse events
Identification	**Country:** Canada **Setting:** Maternity Unit **Sponsorship source:** not reported
Declarations of interest	Not reported
Notes	

Sankaranarayanan 2005

Study characteristics	
Methods	**Study design:** open randomised, controlled trial

Sankaranarayanan 2005 *(Continued)*

	Recruitment date: 1 August 2003 to 31 January 2004 **Treatment arms:** 3 **Follow-up:** 31 days, daily during hospital stay, weekly thereafter
Participants	**Randomised:** a total of 224 babies (112 preterm and 112 term babies) were enrolled. In each gestation stratum, coconut oil n = 38, mineral oil n = 37, placebo n = 37 **Inclusion criteria:** full-term neonates weighing 2500 grams or more were included if they fulfilled the following inclusion criteria: 1. Apgar score > 7 at 1 and 5 minutes with no resuscitation required at birth 2. Medically stable with no requirement of drugs (other than mineral and vitamin supplements for preterm babies) or any interventions/procedures 3. Breastfeeding or feeding with expressed breast milk (preterm) 4. Adequate family support **Exclusion criteria:** 1. Congenital anomaly or neuromuscular disorder 2. Parents staying far away from the hospital and therefore less likely to follow up 3. Parents who refused consent for the study
Interventions	Sessions began an hour after a feed. The total duration of each session was 5 minutes, and sessions were done 4 times a day. Term infants were massaged in a draught-free room. Massage was given in prone and supine positions to include head, neck, trunk, and extremities. At completion of the massage, kinaesthetic stimulation was provided in the supine position by passive flexion and extension movements of the limbs at each large joint (shoulder, elbow, hip, knee, and ankle) as 5 events of 2 seconds. Massage was given by a trained person from day 2 of life until discharge, and thereafter by the mother until 31 days of age, 4 times a day. Babies were followed up daily until discharge and every week after discharge for anthropometry **Intervention:** coconut oil or mineral oil massage **Comparator:** massage using baby powder; methods of application and monitoring the same as in the oil groups **Moisturiser/Emollient:** coconut oil, mineral oil, and baby powder. No details of ingredients reported
Outcomes	**Primary outcome:** weight gain velocity over first 31 days of life **Secondary outcomes:** length gain velocity, head growth, neurobehavioural outcome, incidence of adverse events **Adverse events:** in the preterm group, adverse events occurred in 6 babies, 2 each in the coconut oil, mineral oil, and placebo groups. All adverse events were mild rash and did not require discontinuation of application. Among term babies, 3 in the coconut oil group, 3 in the mineral oil group, and 2 in the placebo group developed mild rash that did not require discontinuation of application
Identification	**Country:** India **Setting:** premature unit and postnatal wards of a major tertiary care centre in a metropolitan city in Mumbai **Sponsorship source:** Marico Industries Ltd. provided oils and placebo for the study
Declarations of interest	Marico Industries Ltd. is involved in the production of coconut oil. BM, AM, and RS Mohile are employees of Marico Industries. None of the authors from Sion Hospital have any shares in the company
Notes	

Simpson 2014

Study characteristics	
Methods	**Study design:** multi-centre, multi-national, assessor-blind, randomised (1:1), controlled pilot trial (6 months) **Recruitment date:** May 2010 and May 2011 **Treatment arms:** 2 **Follow-up:** 6 months; research nurse contacted parents by telephone at 10 days and 6 weeks, with a face-to-face visit at 12 weeks (usually at home in the UK and as a clinic visit in the USA). A further telephone call was made at 18 weeks, and the final contact was a clinic visit at 24 weeks
Participants	**Randomised:** N = 124 (intervention n = 64, control n = 60) **Inclusion criteria:** 1. High risk of eczema with a first-degree relative with a clinical diagnosis of atopic dermatitis, asthma, or allergic rhinitis **Exclusion criteria:** 1. Mother had taken *Lactobacillus rhamnosus* supplements during pregnancy 2. Born before 37 weeks' gestation 3. Major congenital anomaly 4. Hydrops fetalis 5. Immunodeficiency syndrome 6. Severe genetic skin disorder 7. Serious skin condition that would make the use of emollients inadvisable
Interventions	All parents were given a skin care advice booklet, which reflected current guidelines. Parents were advised to: 1. avoid soap and bubble bath; 2. use a mild, fragrance-free synthetic cleanser designed specifically for babies; 3. avoid bath oils and additives; 4. use a mild, fragrance-free shampoo designed specifically for babies, and avoid washing the suds over the baby's body; and 5. avoid using baby wipes, when possible. **Intervention:** parents were offered a choice of 3 emollients of different viscosities (an oil, a cream/gel, or an ointment) 1. In the UK, sunflower seed oil, Doublebase Gel, and liquid paraffin 2. In the USA, sunflower seed oil, Cetaphil Cream, or Aquaphor Healing Ointment Preferred emollient used in the intervention group: cream/gel formulations (67.2%), oil (23.4%), ointment (9.4%). Parents were asked to apply the emollient to the baby's entire body surface, except for the scalp, starting as soon as possible after birth (within a maximum of 3 weeks) and continuing until the infant was 6 months of age **Comparator:** control arm was asked to use no emollients and was given the infant skin care advice booklet **Oil/Moisturiser/Emollient ingredients:** sunflower seed oil (a high ratio of linoleic/oleic acid, William Hodgson and Co., Congleton, UK), Doublebase Gel (Dermal Laboratories, Hitchin, United Kingdom), liquid paraffin 50% in white soft paraffin (Cetaphil Cream, Galderma Laboratories, Fort Worth, Texas, USA), Aquaphor Healing Ointment (Beiersdorf, Chester, OH, USA)

Simpson 2014 *(Continued)*

Outcomes	Age of onset of eczema and proportion of transient cases Incidence of emollient-related adverse events Cumulative incidence of eczema at 6 months, as determined by an investigator **Adverse events:** adverse events, including accidents, infections, and reactions, were prompted for at all patient visits. Three superficial cutaneous infections occurred in each group; all were considered mild in nature. There were no reports of irritant or allergic contact dermatitis (p 821). There were no emollient-related adverse events and no differences in adverse events between groups (Results section, Abstract). IPD contains 2 participants who had skin infections
Identification	**Country:** UK and the USA **Setting:** UK: acute NHS hospital trusts (Nottingham University Hospitals, Derby Hospitals, and United Lincolnshire Hospitals) and 1 GP surgery (Surgery @Wheatbridge, Chesterfield) USA: Oregon Health & Science University Hospital and Clinics (Portland, Oregon) **Sponsorship source:** National Institute for Health Research (NIHR) under its programme grants for Applied Research Programme (RP-PG-0407-10177). United States–based contributions were made possible with funding from a Mentored Patient-oriented Research Career Development Award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases at the National Institutes of Health (5K23AR057486). Support was also obtained from the Oregon Clinical and Translational Research Institute (OCTRI) and by grant number 5 KL2 RR024141-04 from the National Center for Research Resources (NCRR; 5 KL2 RR024141-04), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Research in the McLean Laboratory is funded by the Wellcome Trust (Programme Grant 092530/Z/10/Z and Strategic Award 098439/Z/12/Z). SJB holds a Wellcome Trust Intermediate Clinical Fellowship - WT086398MA
Declarations of interest	This study was funded by the National Institute for Health Research (RPPG-0407-10177). MJ Cork has received compensation from Almirall Pharmaceuticals for membership on its advisory board; has received or has grants pending from Almirall Pharmaceuticals; and has received payment for delivering lectures, as well as compensation for travel and other meeting-related expenses, from Almirall, Astellas Pharma, and Steifel (a GlaxoSmithKline company). WHI McLean's institution has received funding from the Wellcome Trust (WT086398MA), as has that of SJ Brown, who also received an honorarium for speaking at the AAAAI Annual Meeting in 2012 and 2013. Remaining study authors declare that they have no relevant conflicts of interest
Notes	

Skjerven 2020

Study characteristics	
Methods	**Study design:** population-based, 2 x 2 factorial, cluster-randomised clinical trial **Recruitment date:** 9 December 2014 and 31 October 2016 **Treatment arms:** 4 **Follow-up:** 12 months - UK Working Party diagnostic criteria used at 3 month, 6 month, and 12 month follow-up investigations, with additional use of Hanifin and Rajka diagnostic criteria at age 12 months
Participants	**Randomised:** N = 2396 (no intervention group n = 5967 infants, skin intervention group n = 575, food intervention group n = 642, combined intervention group n = 583) **Inclusion criteria:** 1. All newborn babies of women recruited during pregnancy and born at a minimum gestational age > 35 weeks

Skjerven 2020 *(Continued)*

Exclusion criteria:

1. Pregnancy with more than 2 foetuses
2. Lack of sufficient Scandinavian language skills
3. Plans to move outside a reasonable travel distance within 1 year postpartum
4. Severe maternal, foetal, or neonatal disease that could potentially influence adherence to the interventions

Interventions	**Intervention characteristics:** 1. The skin intervention group. Baths for 5 to 10 minutes with added emulsified oil (0·5 dL of bath oil per 8 L of water) and cream applied to the entire face after the bath on at least 4 days per week, from week 2 through to age 8 months. Parents were carefully instructed at the maternity ward on safe baby handling during bathing, including written instructions with illustrations. Flasks of bath oil were handed out to participants assigned to the skin intervention, together with tubes of Ceridal every 3 months, during the clinical investigations from time of birth. Use of soaps was discouraged 2. The food intervention group. Complementary feeding was introduced between 12 and 16 weeks of age in breastfed or formula-fed babies as follows: peanut butter was given for the first time at the scheduled 3 month clinical follow-up investigation, followed by cow's milk 1 week later, wheat porridge the next week, and finally scrambled eggs in the fourth week of introduction. Parents were instructed to let the infant taste each of the foods from the finger of a parent or from a teaspoon at least 4 days per week and to continue to include the foods in the infant's diet to at least 6 months of age 3. Combined intervention group. Skin intervention + food intervention as above Adherence: bath oil additive was used at least 4 days per week in 497 (43%) of 1158 infants assigned to a skin intervention and facial cream on at least 4 days per week in 514 (44%); 316 (27%) were fully protocol adherent for use of both emollients. Between age 13 weeks and 18 weeks, peanut butter was introduced to 966 (79%) of 1225 infants assigned to food intervention, cow's milk to 838 (68%), wheat to 820 (67%), and egg to 677 (55%). 431 (35%) were fully protocol adherent up to week 26 for peanut butter, 530 (43%) for cow's milk, 543 (44%) for wheat, and 289 (24%) for egg. Full protocol adherence to the overall food intervention was reported in 387 (32%) **Comparator characteristics:** No intervention group: no specific advice on feeding practices or skin care was given to parents of infants except regular advice from well-baby clinics and national guidelines for infant nutrition. Exclusive breastfeeding is generally recommended until age 6 months Adherence: IPD show regular use of emollient (Ceridal cream) (≥ 3 days a week averaged over intervention period) by only 1 control participant Cream/Oil/ Ingredients: cream (Ceridal; GlaxoSmithKline Consumer Healthcare, Philadelphia, PA, USA), bath oil (paraffinum liquidum and trilaureth-4-phosphate only were produced specifically for the PreventADALL trial by Pharmatech (Østfold, Norway))
Outcomes	The main outcome of food allergy will first be assessed at 36 months of age. Rationale: due to recent reports, published after the PreventADALL study was well in progress, we reassessed the appropriateness of time of the first report for the main outcomes. The LEAP46 and EAT47 studies, both assessing introduction of allergenic foods from infancy in high-risk and general populations, recruited babies, respectively, published in the NEJM in 2015 and 2016. Both studies assessed food allergy at 36 months of age, in part because natural tolerance development is likely in some children up to this age. The PreventADALL is important and unique in terms of food introduction as well as skin care in infancy in a large mother-child general cohort; we therefore believe that assessing food allergy at the same time as these 2 pivotal studies will improve the likelihood of solid evidence as to the effectiveness of preventing food allergy by 3 years of age, albeit with different strategies Likewise, the main outcome of atopic dermatitis (AD) will be assessed first at 12 months of age. Rationale: 2 clinical trials of daily emollients from shortly after birth assessed their main outcomes in high-risk babies first at 6 months or 32 weeks of age, in line with the end of their intervention. With the PreventADALL study being the first large study in a general population birth cohort, we find it important to have the first main outcome endpoint after the intervention has stopped (9 months). Infants are inves-

Skjerven 2020 *(Continued)*

	tigated at 12 months of age, with detailed skin examination. Although for factorially designed interventions, both intervention outcomes should ideally be assessed at the same time, we find it ethically challenging to delay outcome assessment for 2 years, in case of significant improvement of the intervention. It is unlikely that reporting the effect of primary prevention use of specifically produced bath oil in infancy will affect behaviour of mothers of 2- to 3-year-old children in terms of skin care, in a way that interferes with assessment at 3 years of age. Also, we have detailed blinded assessments of skin disease at 6, 12, 24, and 36 months of age to adjust for potential behaviour modification **Adverse events:** adverse events: recorded in weekly electronic diaries up to week 26, in electronic questionnaires every 3 months, and in specific forms by personnel at the discretion of study personnel
Identification	**Country:** Sweden **Setting:** Oslo University Hospital and Østfold Hospital Trust, Norway, and Karolinska University Hospital, Stockholm **Sponsorship source:** this study was funded by several public and private funding bodies: Regional Health Board South East, Norwegian Research Council, Health and Rehabilitation Norway, Foundation for Healthcare and Allergy Research in Sweden-Vårdalstiftelsen, Swedish Asthma and Allergy Association's Research Foundation, Swedish Research Council—Initiative for Clinical Therapy Research, Swedish Heart-Lung Foundation, SFO-V at the Karolinska Institute, Freemason Child House Foundation in Stockholm, Swedish Research Council for Health, Working Life and Welfare—FORTE, Oslo University Hospital, University of Oslo, and Østfold Hospital Trust
Declarations of interest	EMR has received honoraria for presentations from Sanofi Genzyme, Novartis, MEDA, and Omega Pharma. KCLC has received honoraria for presentation from Thermo-Fisher Scientific. All other study authors declare no competing interests
Notes	

Thitthiwong 2019

Study characteristics	
Methods	**Study design:** prospective, randomised, controlled trial **Recruitment date:** January 2016 to April 2017 **Treatment arms:** 2 **Follow-up:** clinic visits at 2, 4, 6, and 9 months old
Participants	**Randomised:** N = 53 (intervention n = 26; control n = 27) **Inclusion criteria:** 1. Healthy term infants, less than 10 weeks old 2. Parent(s) or sibling(s) with history of any allergic disease such as atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, food allergy, or other allergic condition **Exclusion criteria:** 1. Congenital anomaly 2. Immunodeficiency syndrome 3. Any skin disease other than infantile seborrhoeic dermatitis or neonatal acne
Interventions	Verbal advice for good skin care practice were repeatedly given to all caregivers (in both groups) during every clinic visit. This comprised bathing for 5 to 10 minutes with tap or lukewarm water, bathing not

Thitthiwong 2019 *(Continued)*

	more than twice daily, and using only a minimal amount of gentle liquid baby cleansers of any manufacturers. Bath oil, bubble bath, or any bath additives were not allowed to be used in both groups **Intervention:** cold cream applied all over the infant's body except peri-orbital and peri-oral areas at least once daily shortly within 3 to 5 minutes after bathing and padding dry baby skin **Comparator:** control group was asked not to apply any skin care products to the baby's skin except to use gentle liquid cleansers during bathing and barrier ointment or cream on diaper areas as needed. This group also received good skin care advice during every visit **Moisturiser/Emollient:** emollient called cold cream: white petrolatum, stearyl alcohol, propylene glycol, and glycerin
Outcomes	**Primary outcomes:** 1. Cumulative incidence of AD in both groups 2. Diagnostic criteria based on AD guidelines by Eichenfield et al. 2014 Study endpoints were defined when infants developed AD, or when infants were 9 months old Food allergy outcomes are not mentioned as part of the outcomes, but in the results, study authors reported, "none of the 4 IAD infants developed cows' milk protein allergy or any other food allergy' **Secondary outcome:** mean onset of AD, adverse reaction to cold cream application, factors associated with developing AD **Adverse events:** no ADs were reported by caregivers
Identification	**Country:** Thailand **Setting:** Paediatric Outpatient Department of Phramongkutklao Hospital in Bangkok **Sponsorship source:** Phramongkutklao Hospital
Declarations of interest	No conflict of interest reported
Notes	

Tielsch 2007

Study characteristics	
Methods	**Study design:** cluster-randomised, placebo-controlled, community-based trial **Recruitment date:** between 1 September 2002 and 8 March 2005 **Treatment arms:** 2 **Follow-up:** 28 days. Assessed at 2, 3, 4, 6, 8, 10, 12, 14, 21, and 28 days since birth (not eczema or AD related but for assessment of infant vital status and morbidity)
Participants	**Randomised:** N = 17,530 (intervention n = 8650, control n = 8880) **Inclusion criteria:** all liveborn infants born in the study area **Exclusion criteria:** newborn infants who died before study staff arrived to conduct interventions
Interventions	**Intervention:** 1-time skin cleansing of newborn infants, wiping of the total body excluding eyes and ears with Pampers Infant Wipes (Procter and Gamble Co., Cincinnati, OH, USA) that released a solution that contained 0.25% free chlorhexidine (equivalent to 0.44% chlorhexidine digluconate)

Tielsch 2007 *(Continued)*

	Newborn skin cleansing occurred soon after delivery at a median time of 5.8 hours after birth (interquartile range 2.1 to 11.8 hours); 91.4% of infants were cleansed within the first 24 hours **Comparator:** wiping with the same infant wipes that lacked chlorhexidine (placebo) **Wipes:** all wipes were alcohol-free, produced by Procter and Gamble Co., and were packaged in sterile plastic sachets that contained 6 wipes. Pampers Infant Wipes (Procter and Gamble Co., Cincinnati, OH, USA) that released a solution that contained 0.25% free chlorhexidine (equivalent to 0.44% chlorhexidine digluconate)
Outcomes	All-cause mortality by 28 days **Adverse events:** none reported
Identification	**Country:** Nepal **Setting:** Sarlahi District in south-central Nepal (> 95% of births delivered in the home) **Sponsorship source:** this study was conducted by the Department of International Health, Bloomberg School of Public Health, Johns Hopkins University (Baltimore, MD, USA), under grants HD 44004 and HD 38753 from the National Institutes of Health (Bethesda, MD, USA); grant 810 −2054 from the Bill and Melinda Gates Foundation (Seattle, WA, USA); and Cooperative Agreements HRN-A-00−97−00015−00 and GHS-A-00−03−000019−00 between Johns Hopkins University and the Office of Health and Nutrition, US Agency for International Development (Washington, DC, USA). Commodity support was provided by Procter and Gamble Co. (Cincinnati, OH, USA)
Declarations of interest	Financial supporters and the commodity supplier played no role in design, conduct, management, analysis, or interpretation of results, nor in preparation, review, or approval of this article
Notes	

Yonezawa 2018

Study characteristics	
Methods	**Study design:** randomised, parallel, controlled trial **Study conducted:** March 2014 and June 2015 **Treatment arms:** 2 **Follow-up:** 24 months (eczema, AD, and food allergy)
Participants	**Randomised:** N = 227 (intervention n = 113, control n = 114) **Inclusion criteria:** 1. Newborn born at the institution at minimum gestational age of 35 weeks 2. Newborn born to Asian parents 3. Newborn who received no medical treatment in the paediatric ward 4. Newborn who had a mother who was able to speak Japanese **Exclusion criteria:** not reported
Interventions	Each group performed skin care from week 1 to week 12 after birth **Intervention:** moisturising skin care (bathing every 2 days and using lotion daily). The intervention group performed moisturising skin care as follows: (i) routine bathing every 2 days; and (ii) use of a moisturiser 1 or more times per day. If parents were resistant to reducing the frequency of bathing,

Yonezawa 2018 *(Continued)*

	they were allowed to bathe their newborn daily, but they could use soap only every other day. The researcher provided soap. Parents were also allowed to choose a moisturiser of their choice **Comparator:** the control group performed the skin care regimen commonly used in Japan as follows: (i) routine bathing daily; and (ii) no moisturiser. Midwives recommended that all mothers routinely bathe their newborn daily. The researcher provided soap. The control group was allowed to apply a moisturiser to their newborn if they wanted to
Outcomes	**Primary outcomes:** 3-month outcomes: skin barrier function, by measuring values of transepidermal water loss **Secondary outcomes:** 3-month outcomes: skin problems and skin conditions in the diaper area, face, and body recorded in parents'/infants' skin diaries Skin conditions assessed in terms of redness, erythema, dryness, and breakdown Presence of diaper dermatitis assessed using the diaper rash and erythema scoring scale, which rates diaper dermatitis on 7 levels from none to severe Skin problems on the face or the body were assessed by an original score scale that refers to the Neonatal skin Condition Score, which rates a skin condition between 3 and 9 points Infants with skin problems for at least 1 day were considered to have skin problems (p 25). Two year outcomes: parent report of diagnosis of eczema and parent report of diagnosis of food allergy **Adverse events:** not formally collected
Identification	**Country:** Japan **Setting:** Tokyo-Kita Medical Center **Sponsorship source:** this study was supported by the Mitsubishi Foundation (Grants for Social Welfare Activities on 2013) and the Mishima Kaiun Memorial Foundation
Declarations of interest	None declared
Notes	

Zhao 2005

Study characteristics	
Methods	**Study design:** randomised controlled trial **Recruitment date:** October 2002 and February 2003 (babies delivered between these dates) **Treatment arms:** 2 **Follow-up:** from delivery to discharge; no further details reported
Participants	**Randomised:** N = 377 (Group 1 was the swimming (study) group, comprising a total of 223 newborns including 127 babies delivered after spontaneous vaginal delivery and 96 babies after Cesarean section. Group 2 was the bathing (control) group, comprising 154 newborns including 109 babies delivered after spontaneous vaginal delivery and 45 babies after Cesarean section) **Inclusion criteria:** no details reported **Exclusion criteria:** no details reported
Interventions	**Intervention:** the study group (swimming) included 223 cases (127 babies delivered after spontaneous vaginal delivery and 96 babies after Cesarean section). During hospitalisation (from delivery to discharge), newborns in the study group swam twice a day for 10 to 15 minutes each time

Zhao 2005 *(Continued)*

	Comparator: bathing
Outcomes	Outcomes not relevant to SCiPAD
Identification	**Sponsorship source:** not reported **Country:** China **Setting:** Guangdong Provincial Maternal and Child Health Hospital
Declarations of interest	Not reported
Notes	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12607000466448	Wrong study design
Ahmed 2007	Wrong patient population
Alonso 2013	Wrong patient population
Baer 2006	Wrong study design
Barria 2004	Wrong comparator
Baudouin 2014	Wrong patient population
Baudouin 2014a	Wrong patient population
Berger 2009	Wrong patient population
Bhakoo 1969	Wrong study design
Blume Peytavi 2010	Wrong study design
Blume Peytavi 2012	Wrong study design
Blume Peytavi 2014	Wrong study design
Blume Peytavi 2016	Wrong study design
Brandon 2010	Wrong patient population
Bryanton 2004	Wrong comparator
Chaithirayanon 2016	Wrong comparator
Chen 2009	Wrong patient population
Cleminson 2015	Wrong study design

Study	Reason for exclusion
Cleminson 2016	Wrong study design
Conner 2004	Wrong study design
Cooke 2014	Wrong study design
Cooke 2018	Wrong study design
Cowan 1986	Wrong comparator
CTRI201208002876	Wrong study design
CTRI201709009890	Wrong patient population
Da Cunha 2005	Wrong patient population
Da Cunha 2005a	Wrong patient population
Darmstadt 2004	Wrong patient population
Darmstadt 2005	Wrong patient population
Darmstadt 2005a	Wrong patient population
Darmstadt 2007	Wrong patient population
Darmstadt 2008	Wrong patient population
Darmstadt 2014	Wrong patient population
Duggan 2015	Wrong study design
Erdemir 2015	Wrong patient population
Ernest 1995	Wrong intervention
EUCTR2005-001269-32-AT	Wrong patient population
Fernandez 2018	Wrong study design
Field 2008	Wrong intervention
Fluhr 2012	Wrong study design
Foisy 2011	Wrong intervention
Franck 2000	Wrong patient population
Friscia 2019	Wrong patient population
Gao 2008	Wrong patient population
Garcia Bartels 2009	Wrong intervention
Gezon 1964	Wrong comparator

Study	Reason for exclusion
Gfatter 1997	Wrong patient population
Gleiss 1965	Wrong comparator
Gunt 2018	Wrong patient population
Hauk 2008	Wrong study design
Hawkins 2017	Wrong patient population
Hnatko 1977	Wrong comparator
Horimukai 2016	Wrong study design
Hu 2014	Wrong patient population
IRCT201306164617N	Wrong patient population
IRCT201306164617N7	Wrong patient population
IRCT2013090814594N1	Wrong patient population
IRCT2016111530903N	Wrong patient population
IRCT20170911036118N1	Wrong patient population
ISRCTN71423189	Wrong patient population
ISRCTN89579779	Wrong patient population
Jabraeile 2016	Wrong patient population
Jensen 1971	Wrong intervention
JPRN UMIN000005158	Wrong patient population
JPRN-UMIN000018110	Wrong study design
JPRN-UMIN000025302	Wrong study design
JPRN UMIN000032181	Wrong study design
JPRN UMIN000032798	Wrong study design
JPRN UMIN000035357	Wrong study design
JPRN UMIN000035412	Wrong study design
Kadar 1974	Wrong study design
Kanti 2014	Wrong patient population
Kanti 2017	Wrong comparator
Kiechl Kohlendorfer 2008	Wrong patient population

Study	Reason for exclusion
Konar 2019	Wrong patient population
Koplin 2019	Wrong study design
Kottner 2017	Wrong patient population
Kvenshagen 2014	Wrong patient population
Lane 1993	Wrong patient population
Larson 2005	Wrong study design
Lee 2018	Wrong patient population
LeFevre 2010	Wrong patient population
Leung 2015	Wrong study design
Li 2016	Wrong study design
Ling 2011	Wrong patient population
Linnamaa 2010	Wrong patient population
Lowe 2012	Wrong study design
Lowe 2018b	Wrong study design
Lund 2001	Wrong study design
Lund 2001a	Wrong study design
Marenholz 2015	Wrong study design
Muggli 2009	Wrong comparator
Nangia 2015	Wrong patient population
Natsume 2018	Wrong study design
NCT00162747	Wrong patient population
NCT00257569	Wrong patient population
NCT00806221	Wrong study design
NCT00917085	Wrong intervention
NCT01131403	Wrong study design
NCT01177111	Wrong comparator
NCT01364948	Wrong patient population
NCT01396642	Wrong patient population

Study	Reason for exclusion
NCT01758068	Wrong patient population
NCT02120833	Wrong patient population
NCT02403999	Wrong comparator
NCT02404493	Wrong patient population
NCT02557698	Wrong patient population
NCT02614248	Wrong patient population
NCT02857062	Wrong patient population
NCT03089476	Wrong study design
NCT03112876	Wrong study design
NCT03143504	Wrong study design
NCT03719742	Wrong study design
NCT03738163	Wrong study design
NCT03742414	Wrong patient population
NCT03813472	Wrong patient population
NCT04001855	Wrong patient population
NCT04099602	Wrong patient population
Nesmiyanov 2018	Wrong comparator
Nopper 1996	Wrong patient population
Noviello 2005	Wrong study design
Pupala 2017	Wrong study design
Pupala 2018	Wrong patient population
Pupala 2019	Wrong study design
Qiu 2008	Wrong patient population
Quinn 2005	Wrong patient population
RBR 93996y	Wrong patient population
Rehbinder 2018	Wrong study design
Rosenstock 2007	Wrong patient population
Sach 2019	Wrong study design

Study	Reason for exclusion
Salam 2013	Wrong study design
Salam 2015	Wrong patient population
Sarkar 2010	Wrong study design
Sawatzky 2016	Wrong patient population
Solanki 2005	Wrong patient population
Soll 2000	Wrong study design
Soriano 2000	Wrong patient population
Summers 2017	Wrong comparator
TCTR20161209001	Wrong patient population
Thomas 1979	Wrong study design
Vaivre Douret 2009	Wrong patient population
Visscher 2009	Wrong patient population
Wananukul 2001	Wrong patient population
Wananukul 2002	Wrong patient population
Wang 2009	Wrong patient population
Waserman 2016	Wrong study design
Xatzopoulou 2010	Wrong patient population
Xiao 2009	Wrong patient population
Yamamoto 1996	Wrong patient population
Zhang 2016	Wrong patient population

Characteristics of studies awaiting classification *[ordered by study ID]*

ISRCTN38965585

Methods	Single-centre cluster-randomised controlled trial
Participants	Aim: 41,072 newborns from 276 clusters
Interventions	**Intervention:** 1. The product, cold-pressed sunflower seed oil 2. Directions for newborn massage. The directions for newborn massage further consist of the following aspects 2.1. Dosage of SSO, comprising frequency of use, quantity per use, and duration of use

ISRCTN38965585 *(Continued)*

	2.1.1. Dose: 10 g per application, applied 3x daily 2.1.2. Duration: 0 to 27 days of life 2.2. Improvements in overall massage practice: 2.2.1. Encourage handwashing before massage 2.2.2. Encourage gently massaging the vernix into the newborn skin, rather than forcefully removing it 2.2.3. Promote gentle massage of newborns 2.2.4. Delay use of mustard oil and skin-scrubbing substances such as bukwa (coarse-grained paste made of mustard/wheat seeds along with additives) past the newborn period 2.2.5. Ensure that the newborn is kept warm during and after massage **Comparator:** control group, which will continue following the same traditional massage practices, including the type of oil used. No further information
Outcomes	**Primary outcomes were infant mortality rate** SCiPAD outcome of interests in this study is: 1. Infections and hospitalisation: signs and symptoms of infection during the newborn period, along with episodes of hospitalisation, would be recorded through parent recall. These will include local infections such as pyoderma and umbilical cord infection Skin barrier function: barrier property of stratum corneum (assessed as transepidermal water loss or TEWL) Adherence to intervention: information on continued oil use and adherence to massage technique would be obtained from families (mothers). This would also be applicable to a subsample (5%) of the population
Notes	No response from study author, emailed on 14.01.2020. Link to trial: http://www.isrctn.com/ISRCTN38965585

JPRN-UMIN000026877

Methods	Factorial randomised
Participants	Target sample size: 50
Interventions	Use the foaming cleanser and lotion every single day for 4 weeks Use the foaming cleanser and cream every single day for 4 weeks
Outcomes	Change in skin symptoms by dermatological diagnosis before and after topical application of 4 weeks Change in water content, transepidermal water loss, skin pH, and composition of stratum corneum before and after topical application for 4 weeks
Notes	Clinical trial link: https://apps.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000026877

NCT03640897

Methods	Monocentric, prospective, randomised, comparator-controlled, parallel-group study
Participants	133 participants
Interventions	**Experimental:** Liniderm Oleocalcareous liniment Liniderm:

NCT03640897 *(Continued)*

	The product will be applied on the diaper area by parents/caregivers at each diaper change **Active comparator:** wipes Free-fragrance baby wipes. The product will be used on the diaper area by parents/caregivers at each diaper change **Active comparator:** water Water and cotton pads. The product will be used on the diaper area by parents/caregivers at each diaper change
Outcomes	**Primary outcomes:** Number of infants who had at least 1 episode of diaper rash [Time Frame: 28 days] Every day, in a daily log, parents/caregivers will report the presence or not of a diaper rash At the end of follow-up, the investigator must identify infants who have had at least 1 episode of diaper rash **Secondary outcomes:** 1. Severity of diaper rash episodes: rating [Time Frame: Continuously for 28 days] 2. Severity of diaper rash episodes: extent [Time Frame: Continuously for 28 days] 3. Safety of the cleaning method [Time Frame: Continuously for 28 days] 4. Skin evaluation on the genital area [Time Frame: 0, 14, and 28 days] 5. Paediatrician satisfaction [Time Frame: 14 and 28 days] 6. Well-being [Time Frame: 0, 14, and 28 days] 7. Parent satisfaction [Time Frame: 14 and 28 days]
Notes	

Supported by Johnson & Johnson Consumer Inc.

Characteristics of ongoing studies *[ordered by study ID]*

Eichner 2020

Study name	A Community-based Assessment of Skin Care, Allergies, and Eczema (CASCADE)
Methods	Pragmatic, multi-site, randomised, community-based trial
Participants	Estimated enrolment: 1250
Interventions	Experimental: daily emollient Parents assigned to the intervention arm will receive a lipid-rich emollient and educational materials promoting once-daily full-body emollient use until the infant is 24 months old. Parents will select 1 of 5 emollients to be mailed to the dyad's home at enrolment and approximately every 6 months for the duration of the study. These emollients include (1) CeraVe Healing Ointment, (2) Vaseline, (3) Cetaphil Cream, (4) CeraVe Cream, and (5) Vanicream Intervention: other: participant choice of over-the-counter emollients: Vaseline, Vanicream, CeraVe Healing Ointment, CeraVe Cream, Cetaphil Cream Comparator: no Intervention, natural skin

Eichner 2020 *(Continued)*

	Parents assigned to the control arm will receive educational materials promoting general infant skin care guidelines only and will be asked to refrain from emollient use unless dry skin develops (current standard of care guidelines)
Outcomes	**Primary outcome** Cumulative incidence of AD [Time Frame: 24 months] **Secondary outcomes** 1. Parental report [Time Frame: 3, 6, 9, 12, 15, 18, and 24 months] 2. Children's Eczema Questionnaire [Time Frame: 12 and 24 months] 3. Sleep loss [Time Frame: 12 and 24 months] 4. Prescription topical skin medication [Time Frame: 3, 6, 9, 12, 15, 18, 21, and 24 months] 5. Asthma risk [Time Frame: 12 and 24 months] 6. Food allergy symptoms [Time Frame: 12 and 24 months] 7. Food allergy clinician diagnosed [Time Frame: 12 and 24 months] 8. Global Health Status [Time Frame: 12 and 24 months] 9. Atopic dermatitis severity 1 [Time Frame: 12 and 24 months] 10.Atopic dermatitis severity 2 [Time Frame: 12 and 24 months] 11.Atopic dermatitis severity 3 [Time Frame: 12 and 24 months] 12.Atopic dermatitis severity 4 [Time Frame: 12 and 24 months] 13.Atopic dermatitis severity 5 [Time Frame: 12 and 24 months]
Starting date	3 July 2018
Contact information	LeAnn Michaels - michaell@ohsu.edu Clara Stemwedel - stemwedc@ohsu.edu
Notes	

Jabbar-Lopez 2019

Study name	Softened Water for Eczema Prevention Pilot Trial (SOFTER)
Methods	Assessor-blinded pilot randomised controlled trial
Participants	N = 80 estimated enrolment
Interventions	Intervention group will have a domestic ion-exchange water softener installed before birth Comparator: usual hard water supply; control group will receive the usual domestic water supply
Outcomes	Primary outcome: 1. Proportion of eligible families screened who are willing and able to be randomised [Time Frame: Before birth] Secondary outcomes: 1. Proportion with patient-reported, doctor-diagnosed eczema [Time Frame: by 6 months of age] 2. Proportion with visible eczema according to UK diagnostic criteria-based photographic protocol [Time Frame: 4 weeks, 3 and 6 months] 3. Severity of eczema (if present) using Eczema Area and Severity Index (EASI) [Time Frame: 4 weeks, 3 and 6 months]

Jabbar-Lopez 2019 *(Continued)*

	4. Patient-reported eczema symptoms (Patient-Orientated Eczema Measure - POEM) [Time Frame: Monthly from 4 weeks to 6 months of age] 5. Time to onset of patient-reported doctor-diagnosed eczema [Time Frame: from birth to end of follow up (6 months of age)] 6. Proportion of participants with visible eczema status (yes/no) recorded [Time Frame: Baseline, 4 weeks, 3 and 6 months] 7. Proportion with filaggrin null mutations [Time Frame: at birth, 4 weeks, 3 and 6 months of age] 8. Effect of filaggrin (*FLG*) gene mutation status on TEWL, cytokine levels, NMF levels, and skin microbiota diversity [Time Frame: at birth, 4 weeks, 3 and 6 months of age]
Starting date	12 February 2018 to June 2019
Contact information	Carsten Flohr - carsten.flohr@kcl.ac.uk
Notes	

Lowe 2019

Study name	PEBBLES study protocol: a randomised controlled trial to prevent atopic dermatitis, food allergy and sensitisation in infants with a family history of allergic disease using a skin barrier improvement strategy
Methods	Multi-centre, phase III, outcome assessor-blinded, randomised, controlled trial
Participants	Aim: to recruit 760
Interventions	**Intervention:** 2 times per day treatment with EpiCeram (intervention group). EpiCeram has been approved for use by patients with AD or eczema by the Food and Drug Administration (FDA) in the USA but does not yet have Australian Therapeutic Goods Administration (TGA) approval and is not currently available in Australia. Parents will be instructed to apply approximately 6 g of EpiCeram per application 2 times per day from birth until the infant is 6 months of age Comparator: standard skin care advice (control group) Parents of children in the control group will be managed as per existing practice and will not be given any emollients. For ethical reasons, parents of children in the control group will not be told to withhold skin care from their infant, and information related to use of emollients will be collected from all participants Compliance: a weekly diary will be completed online by parents, who will document the frequency of EpiCeram application and use of any other creams
Outcomes	**Primary outcomes:** 1. Presence of AD in the first 12 months of life assessed using UK Working Party criteria and/or visible AD at the time of examinations 2. Food allergy, based on skin prick tests, history of reactions, and food challenge at 12 months **Secondary outcomes:** 1. Adverse reaction to EpiCeram 2. Skin barrier function as assessed by TEWL at 6 weeks and 12 months 3. Food sensitisation (positive skin prick test) at 12 months of age 4. Presence of observed AD that first presents from 6 to 12 months (incident after intervention period) 5. Presence of probable AD within first year of life based on parent report of doctor-diagnosed AD 6. IgE-associated AD (AD in the context of a positive skin prick test)

Lowe 2019 *(Continued)*

	7. AD severity assessed using the Eczema Area and Severity Index (EASI) score
Starting date	October 2005
Contact information	Adrian Lowe - lowea@unimelb.edu.au
Notes	

NCT02906475

Study name	Atopic Dermatitis in Atopy Predisposed Infants (ADAPI)
Methods	Randomised, pragmatic, parallel-group trial
Participants	Aim: N = 160
Interventions	Compilation: standardised skin care regimen **Intervention:** milk lotion will be applied once daily on the total body including the face by parents or caregivers at home. If bathing is needed, the bathing addendum is used in addition to water **Comparator:** for the control group, no predetermined or standardised skin care regimen is prescribed
Outcomes	**Primary outcomes:** 1. Cumulative incidence of atopic dermatitis [Time Frame: 12 months] 2. Cumulative incidence of AD at week 52, with AD diagnosis based on criteria by Simpson et al. 2012 **Secondary outcomes:** 1. Cumulative incidence of atopic dermatitis [Time Frame: 24 months] 2. AD incidence density [Time Frame: 12 months] 3. AD incidence density [Time Frame: 24 months] 4. Eczema Area and Severity Index (EASI) [Time Frame: 12 months] 5. Eczema Area and Severity Index (EASI) [Time Frame: 24 months] 6. Infant Dermatitis Quality of Life (IDQoL) [Time Frame: 12 months] 7. Infant Dermatitis Quality of Life (IDQoL) [Time Frame: 24 months] 8. Transepidermal water loss (TEWL) on the midvolar forearm [Time Frame: at ages of 14 days, 1, 3, 6, 12 months and 2 years] 9. Skin surface pH on the midvolar forearm [Time Frame: at ages of 14 days, 1, 3, 6, 12 months, and 2 years] 10. Stratum corneum hydration (SCH) on the forearm [Time Frame: at ages of 14 days, 1, 3, 6, 12 months, and 2 years]
Starting date	Study start date: October 2016 Estimated study completion date: December 2020
Contact information	Stephanie Meyer - stephanie.meyer@hipp.de]
Notes	

NCT03142984

Study name	Randomized Controlled Trial of Gentle Touch/Early Massage With a New Wash and Lotion Regimen for Improved Skin Barrier Strength, Parental Bonding, and Physical Development in Newborn Babies: The Barrier Optimizing Skincare for Newborn Development (BOND) Trial
Methods	Randomised, single-group assignment
Participants	150 participants
Interventions	Experimental: phase 1 An open-use test in a cohort of newborn babies to confirm tolerability and evaluate acceptability of a new Baby Wash & Shampoo product and Baby Lotion Baby Wash & Shampoo (F# 13217-070), Baby Lotion (F# 13217-071) Experimental: phase 2 An evaluator-blind, randomised, controlled trial to determine whether a wash and lotion regimen used for 12 weeks can strengthen the skin barrier in newborns when compared to standard skin care practices without massage Baby Wash & Shampoo (F# 13217-070), Baby Lotion (F# 13217-071), Alternative Baby Wash & Shampoo (GTIN/UPC # 5011451106260)
Outcomes	Primary outcomes: 1. Change in neonatal skin condition score from baseline to 3 weeks [Time Frame: 3 weeks] 2. Change in transepidermal water loss (TEWL) from baseline to 12 weeks [Time Frame: 12 weeks] 3. Change in stratum corneum hydration (corneometer) from baseline to 12 weeks [Time Frame: 12 weeks] 4. Number of adverse events reported related to investigational products [Time Frame: 3 weeks] Secondary outcomes: 1. Product questionnaires [Time Frame: 3 weeks] 2. Change in neonatal skin condition score from baseline to 12 weeks [Time Frame: 12 weeks] 3. Change in stratum corneum surface water content (ATR-FTIR) from baseline to 12 weeks [Time Frame: 12 weeks] 4. Change in stratum corneum lipid structure (ATR-FTIR) from baseline to 12 weeks [Time Frame: 12 weeks] 5. Change in stratum corneum carboxylate levels (ATR-FTIR, marker of natural moisturising factor levels and filaggrin expression) from baseline to 12 weeks [Time Frame: 12 weeks]
Starting date	4 July 2017 to 17 March 2021
Contact information	No contact details on clinical trials
Notes	https://clinicaltrials.gov/ct2/show/NCT03142984

NCT03808532

Study name	Moisturizer to Prevent Atopic Dermatitis (ACE-AD)
Methods	Randomised parallel assignment
Participants	290 participants

NCT03808532 *(Continued)*

Interventions	Experimental: high-risk with moisturiser No intervention: high-risk without moisturiser
Outcomes	**Primary outcomes:** 1. Cumulative incidence of AD at 12 months of age in the intervention group compared to the control group [Time Frame: 12 months] a. Evaluated using UK refinement of Hanifin and Rajka diagnostic criteria for atopic eczema and by parental report of a medical diagnosis of AD by the infant's paediatrician and/or dermatologist **Secondary outcomes:** 1. Cumulative incidence of AD at 6 months of age in the intervention group compared to the control group [Time Frame: 6 months] 2. Cumulative incidence of AD at 24 months of age in the intervention group compared to the control group [Time Frame: 24 months] 3. Timing of onset of AD in the intervention group compared to the control group [Time Frame: 12 months] 4. Severity of AD in the intervention group compared to the control group [Time Frame: 12 months] 5. Cumulative incidence of food allergies at 12 months of age in the intervention group compared to the control group [Time Frame: 12 months] 6. Cumulative incidence of food allergies at 24 months of age in the intervention group compared to the control group [Time Frame: 24 months]
Starting date	June 2020
Contact information	Michael Brandwein - michael@myor.me
Notes	

NCT03871998

Study name	Short-term Topical Application to Prevent Atopic Dermatitis (STOP AD)
Methods	Single-centre, randomised, open-label, controlled study
Participants	242 participants
Interventions	**Experimental:** intervention arm Skin barrier protection in the first 2 months of life **No intervention:** control arm Standard skin care advice. No moisturiser in the first 2 months
Outcomes	Primary outcomes 1. Cumulative incidence of atopic dermatitis at 12 months [Time Frame: 12 months] 2. Cumulative incidence of IgE-mediated food allergy at 2 years [Time Frame: 2 years] Secondary outcomes 1. Longitudinal changes in transepidermal water loss (TEWL) from birth to 12 months [Time Frame: Birth to 12 months]

NCT03871998 *(Continued)*

2. Longitudinal changes in natural moisturising factor (NMF) in the stratum corneum from birth to 12 months [Time Frame: Birth to 12 months]
3. Microbial diversity and richness of the cheek and antecubital fossa (study subset) [Time Frame: Skin swabs for microbiome analysis will be taken at baseline (0 to 4 days), 8 weeks, and 12 months]
4. Changes in skin microbial diversity and richness over the first year of life [Time Frame: Skin swabs for microbiome analysis will be taken at baseline (0 to 4 days), 8 weeks, and 12 months]
5. Comparison of microbial diversity and richness between intervention and control groups [Time Frame: Skin swabs for microbiome analysis will be taken at baseline (0 to 4 days), 8 weeks, and 12 months]
6. Skin biomarker profile analysis of the cheek and antecubital fossa (study subset) [Time Frame: Skin swabs for biomarker analysis will be taken at baseline (0 to 4 days), 8 weeks, and 12 months]
7. Changes in skin biomarker profile between studies over the first year of life [Time Frame: Skin swabs for biomarker analysis will be taken at baseline (0 to 4 days), 8 weeks, and 12 months]
8. Comparison of skin biomarker profiles between intervention and control groups [Time Frame: Skin swabs for biomarker analysis will be taken at baseline (0 to 4 days), 8 weeks, and 12 months]

Starting date	12 March 2019
Contact information	Carol Ní Chaoimh - cnichaoimh@ucc.ie Mairead Murray - mairead.murray@ucc.ie
Notes	

NCT04398758

Study name	Moisturizer Mediated Prevention of Symptoms of Atopic Dermatitis in Early Childhood (MOPAD)
Methods	Randomised controlled trial
Participants	Healthy newborns, < 3 weeks of age, one first-degree relative with medically diagnosed AD N = 360
Interventions	"SanaCutan Basiscreme" applied all over body twice daily for 6 months (main phase) or 12 months (follow-up phase)
Outcomes	Cumulative incidence of children with atopic dermatitis at 6 months of age
Starting date	21 May 2020
Contact information	Dr Wehran - studien@infectopharm.com PI Dr Kristen Beyer, Charité University, Berlin, Germany
Notes	

RISK OF BIAS

Legend: Low risk of bias High risk of bias Some concerns

Risk of bias for analysis 1.1 Eczema by 1-3 years

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	✓	✓	✓
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓
McClanahan 2019	✓	✓	~	✓	✓	~
NCT03376243	✓	✓	~	✓	✓	~
Skjerven 2020	✓	✓	~	✓	✓	~
Yonezawa 2018	✓	✓	~	~	✓	~

Risk of bias for analysis 1.2 Sensitivity analysis: Eczema by 1-3 years including aggregate trial data

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	✓	✓	✓
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓
McClanahan 2019	✓	✓	~	✓	✓	~
Migacheva 2018	~	~	~	~	~	~
NCT03376243	✓	✓	~	✓	✓	~
Skjerven 2020	✓	✓	~	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Yonezawa 2018	✓	✓	~	~	✓	~

Risk of bias for analysis 1.3 Sensitivity analysis: Eczema by 1-3 years (UKWP only)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	✓	✓	✓
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓
McClanahan 2019	✓	✓	~	✓	✓	~
NCT03376243	✓	✓	~	✓	✓	~
Skjerven 2020	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.4 Sensitivity analysis: Eczema by 1-3 years (including data from all 4 arms of PreventADALL)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	✓	✓	✓
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓
McClanahan 2019	✓	✓	~	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
NCT03376243	✓	✓	~	✓	✓	~
Skjerven 2020	✓	✓	~	✓	✓	~
Yonezawa 2018	✓	✓	~	~	✓	~

Risk of bias for analysis 1.5 Sensitivity analysis: Eczema by 1-3 years - low risk of bias

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	✓	✓	✓
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.6 Sensitivity analysis: Eczema by 1-3 years - excluding non-prospectively acquired data

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	✓	✓	✓
Dissanayake 2019	✓	✓	✓	✓	✓	✓
McClanahan 2019	✓	✓	~	✓	✓	~
NCT03376243	✓	✓	~	✓	✓	~
Skjerven 2020	✓	✓	~	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Yonezawa 2018	✓	✓	~	~	✓	~

Risk of bias for analysis 1.7 Sensitivity analysis: Eczema by 6 months-3 years

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	✓	✓	✓
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Horimukai 2014	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓
McClanahan 2019	✓	✓	~	✓	✓	~
NCT03376243	✓	✓	~	✓	✓	~
Simpson 2014	✓	✓	~	✓	✓	~
Skjerven 2020	✓	✓	~	✓	✓	~
Yonezawa 2018	✓	✓	~	~	✓	~

Risk of bias for analysis 1.9 Subgroup analysis (study level): Eczema by 1-3 years by intervention type

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.9.1 Basic emolient						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	✓	✓	✓
McClanahan 2019	✓	✓	~	✓	✓	~
Skjerven 2020	✓	✓	~	✓	✓	~
Subgroup 1.9.2 Complex emolient						
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓
NCT03376243	✓	✓	~	✓	✓	~
Yonezawa 2018	✓	✓	~	~	✓	~

Risk of bias for analysis 1.10 Subgroup analysis (study level): Eczema by 1-3 years by prescribed intervention duration

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.10.1 Intervention prescribed for <6 months						
Yonezawa 2018	✓	✓	~	~	✓	~
Subgroup 1.10.2 Intervention prescribed for ≥6 months						
Chalmers 2020	✓	✓	✓	✓	✓	✓
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓
McClanahan 2019	✓	✓	~	✓	✓	~
NCT03376243	✓	✓	~	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Skjerven 2020	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.11 Subgroup analysis (study level): Eczema by 1-3 years, by prescribed intervention timing

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.11.1 Intervention prescribed to start in first week of life						
Chalmers 2020	✓	✓	✓	✓	✓	✓
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓
McClanahan 2019	✓	✓	~	✓	✓	~
NCT03376243	✓	✓	~	✓	✓	~
Yonezawa 2018	✓	✓	~	~	✓	~
Subgroup 1.11.2 Intervention prescribed to start after first week of life						
Skjerven 2020	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.29 Food allergy by 1-3 years

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✗	✓	✓	✗

Risk of bias for analysis 1.30 Sensitivity analysis: Food allergy by 1-3 years (diagnosed by oral food challenge or investigator assessment)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.38 Adverse event: skin infection

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	~	✓	~
Cooke 2015	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	~	✓	~
McClanahan 2019	✓	✓	✓	~	✓	~
Simpson 2014	✓	✓	✓	~	✓	~
Skjerven 2020	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.39 Adverse event: stinging or allergic reaction to moisturisers

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Cooke 2015	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	~	✓	~
McClanahan 2019	✓	✓	✓	~	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
NCT03376243	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.40 Adverse event: slippage accidents

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	~	✓	~
Lowe 2018a	✓	✓	✓	~	✓	~
Simpson 2014	✓	✓	✓	~	✓	~
Skjerven 2020	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.41 Serious Adverse Events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Cooke 2015	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓
Skjerven 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.46 Time to onset of eczema

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	~	✓	~
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Horimukai 2014	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓
McClanahan 2019	✓	✓	~	✓	✓	~
NCT03376243	✓	✓	~	✓	✓	~
Simpson 2014	✓	✓	~	✓	✓	~
Skjerven 2020	✓	✓	~	✓	✓	~
Yonezawa 2018	✓	✓	~	~	✓	~

Risk of bias for analysis 1.47 Subgroup analysis: Time to onset of eczema (< 1 year follow-up versus ≥ 1 year follow-up)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.47.1 Follow-up ≥ 1 year						
Chalmers 2020	✓	✓	✓	~	✓	~
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	✓	✓	✓	✓
McClanahan 2019	✓	✓	~	✓	✓	~
NCT03376243	✓	✓	~	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Skjerven 2020	✓	✓	~	✓	✓	~
Yonezawa 2018	✓	✓	~	~	✓	~
Subgroup 1.47.2 Follow-up < 1 year						
Horimukai 2014	✓	✓	✓	✓	✓	✓
Simpson 2014	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.48 Parent report of immediate (< 2 hours) reaction to a known common food allergen

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	~	✓	~
NCT03376243	✓	✓	~	~	✓	~

Risk of bias for analysis 1.52 Allergic sensitisation to common foods or inhalants at 1-3 years

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.53 Allergic sensitisation to common foods at 1-3 years

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.58 Sensitivity analysis: Allergic sensitisation to common foods at 6 months-3 years

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chalmers 2020	✓	✓	✓	✓	✓	✓
Dissanayake 2019	✓	✓	✓	✓	✓	✓
Horimukai 2014	✓	✓	✓	✓	✓	✓
Lowe 2018a	✓	✓	~	✓	✓	~

DATA AND ANALYSES

Comparison 1. Skin care intervention versus standard skin care or no skin care intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Eczema by 1-3 years	7	3075	Risk Ratio (IV, Random, 95% CI)	1.03 [0.81, 1.31]
1.2 Sensitivity analysis: Eczema by 1-3 years including aggregate trial data	8	3135	Risk Ratio (IV, Random, 95% CI)	0.97 [0.75, 1.25]
1.3 Sensitivity analysis: Eczema by 1-3 years (UKWP only)	6	2919	Risk Ratio (IV, Random, 95% CI)	1.02 [0.78, 1.34]
1.4 Sensitivity analysis: Eczema by 1-3 years (including data from all 4 arms of PreventADALL)	7	3075	Risk Ratio (IV, Random, 95% CI)	1.03 [0.81, 1.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Sensitivity analysis: Eczema by 1-3 years - low risk of bias	3	1739	Risk Ratio (IV, Random, 95% CI)	0.97 [0.81, 1.17]
1.6 Sensitivity analysis: Eczema by 1-3 years - excluding non-prospectively acquired data	6	3001	Risk Ratio (IV, Random, 95% CI)	1.08 [0.84, 1.37]
1.7 Sensitivity analysis: Eczema by 6 months-3 years	9	3223	Risk Ratio (IV, Random, 95% CI)	0.89 [0.70, 1.14]
1.8 Sensitivity analysis: Eczema after the intervention period (at 1 year or beyond - up to 2 years)	4	2381	Risk Ratio (IV, Random, 95% CI)	1.06 [0.77, 1.47]
1.9 Subgroup analysis (study level): Eczema by 1-3 years by intervention type	7	3075	Risk Ratio (IV, Random, 95% CI)	1.03 [0.81, 1.31]
1.9.1 Basic emolient	3	2341	Risk Ratio (IV, Random, 95% CI)	1.04 [0.66, 1.65]
1.9.2 Complex emolient	4	734	Risk Ratio (IV, Random, 95% CI)	1.01 [0.75, 1.37]
1.10 Subgroup analysis (study level): Eczema by 1-3 years by prescribed intervention duration	7	3075	Risk Ratio (IV, Random, 95% CI)	1.03 [0.81, 1.31]
1.10.1 Intervention prescribed for <6 months	1	156	Risk Ratio (IV, Random, 95% CI)	1.01 [0.45, 2.26]
1.10.2 Intervention prescribed for ≥6 months	6	2919	Risk Ratio (IV, Random, 95% CI)	1.02 [0.78, 1.34]
1.11 Subgroup analysis (study level): Eczema by 1-3 years, by prescribed intervention timing	7	3075	Risk Ratio (IV, Random, 95% CI)	1.03 [0.81, 1.31]
1.11.1 Intervention prescribed to start in first week of life	6	2004	Risk Ratio (IV, Random, 95% CI)	0.95 [0.81, 1.12]
1.11.2 Intervention prescribed to start after first week of life	1	1071	Risk Ratio (IV, Random, 95% CI)	1.57 [1.10, 2.23]
1.12 Participant level treatment interaction: Eczema by 1-3 years for treatment initiation < 4 days versus ≥ 4 days of age	2	1284	Risk Ratio (IV, Random, 95% CI)	1.05 [0.64, 1.73]
1.13 Participant level treatment interaction: Eczema by 6 months-3 years for treatment initiation < 4 days versus ≥ 4 days of age	3	1383	Risk Ratio (IV, Random, 95% CI)	1.59 [0.56, 4.51]
1.14 Participant level treatment interaction: Eczema by 1-3 years by *FLG* genotype (0 mutations versus 1/2 mutations)	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.15 Participant level treatment interaction: Eczema by 6months-3 years by *FLG* genotype (0 mutations versus 1/2 mutations)	3	926	Risk Ratio (IV, Random, 95% CI)	1.03 [0.42, 2.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16 Participant level treatment interaction: Eczema by 1-3 years by ≥ 1 first degree relative with history of allergic disease	3	1663	Risk Ratio (IV, Random, 95% CI)	0.95 [0.35, 2.61]
1.17 CACE: Eczema by 1-3 years for use over intervention period ≥ 3 days a week	3	1440	Risk Ratio (IV, Random, 95% CI)	0.65 [0.29, 1.45]
1.18 CACE Sensitivity: Eczema by 1-3 years for use over intervention period ≥ 5 days a week	2	1366	Risk Ratio (IV, Random, 95% CI)	0.74 [0.26, 2.09]
1.19 CACE Sensitivity: Eczema by 1-3 years for use over intervention period 7 days a week	3	1415	Risk Ratio (IV, Random, 95% CI)	0.78 [0.23, 2.71]
1.20 CACE Sensitivity: Eczema by 1-3 years for use over first 3 months ≥ 3 days a week	2	1366	Risk Ratio (IV, Random, 95% CI)	1.02 [0.79, 1.31]
1.21 CACE Sensitivity: Eczema by 1-3 years for use over first 3 months ≥ 5 days a week	2	1366	Risk Ratio (IV, Random, 95% CI)	0.84 [0.46, 1.52]
1.22 CACE Sensitivity: Eczema by 1-3 years for use over first 3 months 7 days a week	3	1415	Risk Ratio (IV, Random, 95% CI)	0.83 [0.34, 2.03]
1.23 Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over intervention period ≥ 3 days a week	3	1440	Risk Ratio (IV, Random, 95% CI)	0.93 [0.77, 1.12]
1.24 Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over intervention period ≥ 5 days a week	2	1366	Risk Ratio (IV, Random, 95% CI)	0.95 [0.79, 1.15]
1.25 Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over intervention period 7 days a week	3	1415	Risk Ratio (IV, Random, 95% CI)	0.95 [0.79, 1.15]
1.26 Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over first 3 months ≥ 3 days a week	2	1366	Risk Ratio (IV, Random, 95% CI)	0.95 [0.79, 1.15]
1.27 Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over first 3 months ≥ 5 days a week	2	1366	Risk Ratio (IV, Random, 95% CI)	0.95 [0.79, 1.15]
1.28 Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over first 3 months 7 days a week	3	1415	Risk Ratio (IV, Random, 95% CI)	0.95 [0.79, 1.15]
1.29 Food allergy by 1-3 years	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
1.30 Sensitivity analysis: Food allergy by 1-3 years (diagnosed by oral food challenge or investigator assessment)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
1.31 Sensitivity analysis: Food allergy by 1-3 years (parent report of doctor diagnosis)	3	1614	Risk Ratio (IV, Fixed, 95% CI)	1.02 [0.80, 1.31]
1.32 CACE: Food allergy by 1-3 years for use over intervention period ≥ 3 days a week	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

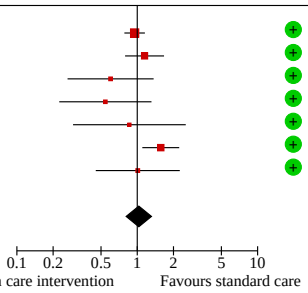
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.33 CACE Sensitivity: Food allergy by 1-3 years for use over intervention period ≥ 5 days a week	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.34 CACE Sensitivity: Food allergy by 1-3 years for use over intervention period 7 days a week	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.35 CACE Sensitivity: Food allergy by 1-3 years for use over first 3 months ≥ 3 days a week	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.36 CACE Sensitivity: Food allergy by 1-3 years for use over first 3 months ≥ 5 days a week	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.37 CACE Sensitivity: Food allergy by 1-3 years for use over first 3 months 7 days a week	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.38 Adverse event: skin infection	6	2728	Risk Ratio (IV, Random, 95% CI)	1.34 [1.02, 1.77]
1.39 Adverse event: stinging or allergic reaction to moisturisers	4	343	Risk Ratio (IV, Random, 95% CI)	2.24 [0.67, 7.43]
1.40 Adverse event: slippage accidents	4	2538	Risk Ratio (IV, Random, 95% CI)	1.42 [0.67, 2.99]
1.41 Serious Adverse Events	3	1367	Risk Ratio (IV, Random, 95% CI)	1.80 [0.45, 7.18]
1.42 Clinician-assessed eczema severity at 1-3 years (clear/mild versus moderate/severe/very severe)	3		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.43 Clinician-assessed eczema severity at 1-3 years (standardised mean difference)	3	1228	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.17, 0.12]
1.44 Parent-reported eczema severity at 1-3 years (clear/mild versus moderate/severe/very severe)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.45 Parent-reported eczema severity at 1-3 years (mean difference)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.46 Time to onset of eczema	9	3349	Hazard Ratio (IV, Random, 95% CI)	0.86 [0.65, 1.14]
1.47 Subgroup analysis: Time to onset of eczema (< 1 year follow-up versus ≥ 1 year follow-up)	9	3349	Hazard Ratio (IV, Random, 95% CI)	0.86 [0.65, 1.14]
1.47.1 Follow-up ≥ 1 year	7	3125	Hazard Ratio (IV, Random, 95% CI)	1.00 [0.75, 1.33]
1.47.2 Follow-up < 1 year	2	224	Hazard Ratio (IV, Random, 95% CI)	0.55 [0.35, 0.87]
1.48 Parent report of immediate (< 2 hours) reaction to a known common food allergen	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.49 Parent report of immediate (< 2 hours) reaction to milk	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.50 Parent report of immediate (< 2 hours) reaction to egg	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.51 Parent report of immediate (< 2 hours) reaction to peanut	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.52 Allergic sensitisation to common foods or inhalants at 1-3 years	2	1058	Risk Ratio (IV, Random, 95% CI)	1.09 [0.72, 1.66]
1.53 Allergic sensitisation to common foods at 1-3 years	2	1055	Risk Ratio (IV, Random, 95% CI)	0.86 [0.28, 2.69]
1.54 Allergic sensitisation to milk at 1-3 years	2	1056	Risk Ratio (IV, Random, 95% CI)	1.16 [0.55, 2.43]
1.55 Allergic sensitisation to egg at 1-3 years	2	1059	Risk Ratio (IV, Random, 95% CI)	0.75 [0.18, 3.08]
1.56 Allergic sensitisation to peanut at 1-3 years	2	1062	Risk Ratio (IV, Random, 95% CI)	1.03 [0.53, 2.01]
1.57 Allergic sensitisation to inhalants at 1-3 years	2	1061	Risk Ratio (IV, Random, 95% CI)	1.09 [0.76, 1.57]
1.58 Sensitivity analysis: Allergic sensitisation to common foods at 6 months-3 years	4	1605	Risk Ratio (IV, Random, 95% CI)	1.08 [0.87, 1.33]
1.59 Sensitivity analysis: Allergic sensitisation to milk at 6 months-3 years	4	1604	Risk Ratio (IV, Random, 95% CI)	0.84 [0.59, 1.21]
1.60 Sensitivity analysis: Allergic sensitisation to egg at 6 months-3 years	4	1607	Risk Ratio (IV, Random, 95% CI)	1.09 [0.88, 1.37]
1.61 Sensitivity analysis: Allergic sensitisation to peanut at 6 months-3 years	3	1154	Risk Ratio (IV, Random, 95% CI)	1.03 [0.53, 2.01]

Analysis 1.1. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 1: Eczema by 1-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Chalmers 2020	-0.05	0.1	598	612	32.1%	0.95 [0.78 , 1.16]	+ + + + + +
Dissanayake 2019	0.14	0.19	232	223	20.7%	1.15 [0.79 , 1.67]	+ + + + + +
Lowe 2018a	-0.51	0.42	38	36	7.1%	0.60 [0.26 , 1.37]	+ + + + + +
McClanahan 2019	-0.61	0.45	31	29	6.3%	0.54 [0.22 , 1.31]	+ + ? + + ?
NCT03376243	-0.15	0.55	22	27	4.5%	0.86 [0.29 , 2.53]	+ + ? + + ?
Skjerven 2020	0.45	0.18	499	572	21.8%	1.57 [1.10 , 2.23]	+ + ? + + ?
Yonezawa 2018	0.01	0.41	69	87	7.4%	1.01 [0.45 , 2.26]	+ + ? ? + ?
Total (95% CI)			**1489**	**1586**	**100.0%**	**1.03 [0.81 , 1.31]**	

Heterogeneity: Tau² = 0.04; Chi² = 10.20, df = 6 (P = 0.12); I² = 41%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable

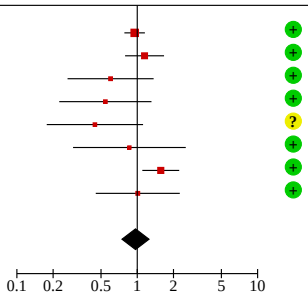


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Eczema by 1-3 years
(C) Bias due to missing outcome data: Eczema by 1-3 years
(D) Bias in measurement of the outcome: Eczema by 1-3 years
(E) Bias in selection of the reported result: Eczema by 1-3 years
(F) Overall bias: Eczema by 1-3 years

Analysis 1.2. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 2: Sensitivity analysis: Eczema by 1-3 years including aggregate trial data

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Chalmers 2020	-0.05	0.1	598	612	27.2%	0.95 [0.78 , 1.16]	+ + + + + +
Dissanayake 2019	0.14	0.19	232	223	19.3%	1.15 [0.79 , 1.67]	+ + + + + +
Lowe 2018a	-0.51	0.42	38	36	7.5%	0.60 [0.26 , 1.37]	+ + + + + +
McClanahan 2019	-0.61	0.45	31	29	6.8%	0.54 [0.22 , 1.31]	+ + ? + + ?
Migacheva 2018 (1)	-0.81	0.47	29	31	6.3%	0.44 [0.18 , 1.12]	? ? ? ? ? ?
NCT03376243	-0.15	0.55	22	27	4.9%	0.86 [0.29 , 2.53]	+ + ? + + ?
Skjerven 2020	0.45	0.18	499	572	20.1%	1.57 [1.10 , 2.23]	+ + ? + + ?
Yonezawa 2018	0.01	0.41	69	87	7.8%	1.01 [0.45 , 2.26]	+ + ? ? + ?
Total (95% CI)			**1518**	**1617**	**100.0%**	**0.97 [0.75 , 1.25]**	

Heterogeneity: Tau² = 0.05; Chi² = 13.36, df = 7 (P = 0.06); I² = 48%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



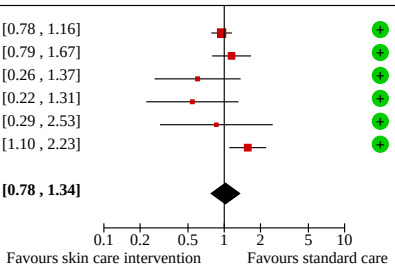
Footnotes
(1) Aggregate trial data (unadjusted)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Sensitivity analysis: Eczema by 1-3 years including aggregate trial data
(C) Bias due to missing outcome data: Sensitivity analysis: Eczema by 1-3 years including aggregate trial data
(D) Bias in measurement of the outcome: Sensitivity analysis: Eczema by 1-3 years including aggregate trial data
(E) Bias in selection of the reported result: Sensitivity analysis: Eczema by 1-3 years including aggregate trial data
(F) Overall bias: Sensitivity analysis: Eczema by 1-3 years including aggregate trial data

Analysis 1.3. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 3: Sensitivity analysis: Eczema by 1-3 years (UKWP only)

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Chalmers 2020	-0.05	0.1	598	612	32.3%	0.95 [0.78 , 1.16]	+	+	+	+	+	+
Dissanayake 2019	0.14	0.19	232	223	22.5%	1.15 [0.79 , 1.67]	+	+	+	+	+	+
Lowe 2018a	-0.51	0.42	38	36	8.5%	0.60 [0.26 , 1.37]	+	+	+	+	+	+
McClanahan 2019	-0.61	0.45	31	29	7.7%	0.54 [0.22 , 1.31]	+	+	?	+	+	?
NCT03376243	-0.15	0.55	22	27	5.5%	0.86 [0.29 , 2.53]	+	+	?	+	+	?
Skjerven 2020	0.45	0.18	499	572	23.5%	1.57 [1.10 , 2.23]	+	+	?	+	+	?
Total (95% CI)			**1420**	**1499**	**100.0%**	**1.02 [0.78 , 1.34]**						

Heterogeneity: Tau² = 0.05; Chi² = 10.19, df = 5 (P = 0.07); I² = 51%
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable

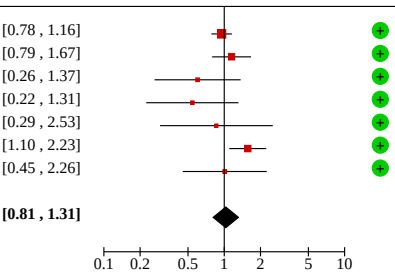


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Sensitivity analysis: Eczema by 1-3 years (UKWP only)
(C) Bias due to missing outcome data: Sensitivity analysis: Eczema by 1-3 years (UKWP only)
(D) Bias in measurement of the outcome: Sensitivity analysis: Eczema by 1-3 years (UKWP only)
(E) Bias in selection of the reported result: Sensitivity analysis: Eczema by 1-3 years (UKWP only)
(F) Overall bias: Sensitivity analysis: Eczema by 1-3 years (UKWP only)

Analysis 1.4. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 4: Sensitivity analysis: Eczema by 1-3 years (including data from all 4 arms of PreventADALL)

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Chalmers 2020	-0.05	0.1	598	612	32.1%	0.95 [0.78 , 1.16]	+	+	+	+	+	+
Dissanayake 2019	0.14	0.19	232	223	20.7%	1.15 [0.79 , 1.67]	+	+	+	+	+	+
Lowe 2018a	-0.51	0.42	38	36	7.1%	0.60 [0.26 , 1.37]	+	+	+	+	+	+
McClanahan 2019	-0.61	0.45	31	29	6.3%	0.54 [0.22 , 1.31]	+	+	?	+	+	?
NCT03376243	-0.15	0.55	22	27	4.5%	0.86 [0.29 , 2.53]	+	+	?	+	+	?
Skjerven 2020	0.45	0.18	499	572	21.8%	1.57 [1.10 , 2.23]	+	+	?	+	+	?
Yonezawa 2018	0.01	0.41	69	87	7.4%	1.01 [0.45 , 2.26]	+	+	?	?	+	?
Total (95% CI)			**1489**	**1586**	**100.0%**	**1.03 [0.81 , 1.31]**						

Heterogeneity: Tau² = 0.04; Chi² = 10.20, df = 6 (P = 0.12); I² = 41%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable

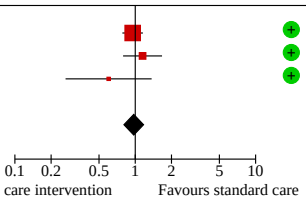


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Sensitivity analysis: Eczema by 1-3 years (including data from all 4 arms of PreventADALL)
(C) Bias due to missing outcome data: Sensitivity analysis: Eczema by 1-3 years (including data from all 4 arms of PreventADALL)
(D) Bias in measurement of the outcome: Sensitivity analysis: Eczema by 1-3 years (including data from all 4 arms of PreventADALL)
(E) Bias in selection of the reported result: Sensitivity analysis: Eczema by 1-3 years (including data from all 4 arms of PreventADALL)
(F) Overall bias: Sensitivity analysis: Eczema by 1-3 years (including data from all 4 arms of PreventADALL)

Analysis 1.5. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 5: Sensitivity analysis: Eczema by 1-3 years - low risk of bias

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Chalmers 2020	-0.05	0.1	598	612	71.4%	0.95 [0.78 , 1.16]	+ + + + + +
Dissanayake 2019	0.14	0.19	232	223	23.5%	1.15 [0.79 , 1.67]	+ + + + + +
Lowe 2018a	-0.51	0.42	38	36	5.1%	0.60 [0.26 , 1.37]	+ + + + + +
Total (95% CI)			**868**	**871**	**100.0%**	**0.97 [0.81 , 1.17]**	

Heterogeneity: Tau² = 0.00; Chi² = 2.15, df = 2 (P = 0.34); I² = 7%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable

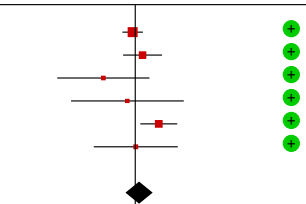


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Sensitivity analysis: Eczema by 1-3 years - low risk of bias
(C) Bias due to missing outcome data: Sensitivity analysis: Eczema by 1-3 years - low risk of bias
(D) Bias in measurement of the outcome: Sensitivity analysis: Eczema by 1-3 years - low risk of bias
(E) Bias in selection of the reported result: Sensitivity analysis: Eczema by 1-3 years - low risk of bias
(F) Overall bias: Sensitivity analysis: Eczema by 1-3 years - low risk of bias

Analysis 1.6. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 6: Sensitivity analysis: Eczema by 1-3 years - excluding non-prospectively acquired data

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Chalmers 2020	-0.05	0.1	598	612	35.6%	0.95 [0.78 , 1.16]	+ + + + + +
Dissanayake 2019	0.14	0.19	232	223	22.2%	1.15 [0.79 , 1.67]	+ + + + + +
McClanahan 2019	-0.61	0.45	31	29	6.5%	0.54 [0.22 , 1.31]	+ + ? + + ?
NCT03376243	-0.15	0.55	22	27	4.6%	0.86 [0.29 , 2.53]	+ + ? + + ?
Skjerven 2020	0.45	0.18	499	572	23.4%	1.57 [1.10 , 2.23]	+ + ? + + ?
Yonezawa 2018	0.01	0.41	69	87	7.6%	1.01 [0.45 , 2.26]	+ + ? ? + ?
Total (95% CI)			**1451**	**1550**	**100.0%**	**1.08 [0.84 , 1.37]**	

Heterogeneity: Tau² = 0.03; Chi² = 8.45, df = 5 (P = 0.13); I² = 41%
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable

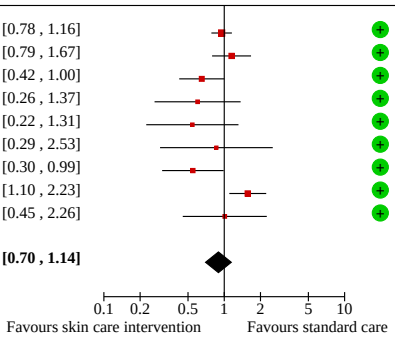


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Sensitivity analysis: Eczema by 1-3 years - excluding non-prospectively acquired data
(C) Bias due to missing outcome data: Sensitivity analysis: Eczema by 1-3 years - excluding non-prospectively acquired data
(D) Bias in measurement of the outcome: Sensitivity analysis: Eczema by 1-3 years - excluding non-prospectively acquired data
(E) Bias in selection of the reported result: Sensitivity analysis: Eczema by 1-3 years - excluding non-prospectively acquired data
(F) Overall bias: Sensitivity analysis: Eczema by 1-3 years - excluding non-prospectively acquired data

Analysis 1.7. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 7: Sensitivity analysis: Eczema by 6 months-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Chalmers 2020	-0.05	0.1	598	612	20.9%	0.95 [0.78 , 1.16]	+ + + + + +
Dissanayake 2019	0.14	0.19	232	223	15.5%	1.15 [0.79 , 1.67]	+ + + + + +
Horimukai 2014	-0.43	0.22	50	49	13.9%	0.65 [0.42 , 1.00]	+ + + + + +
Lowe 2018a	-0.51	0.42	38	36	6.5%	0.60 [0.26 , 1.37]	+ + + + + +
McClanahan 2019	-0.61	0.45	31	29	5.9%	0.54 [0.22 , 1.31]	+ + ? + + ?
NCT03376243	-0.15	0.55	22	27	4.3%	0.86 [0.29 , 2.53]	+ + ? + + ?
Simpson 2014	-0.6	0.3	22	27	10.1%	0.55 [0.30 , 0.99]	+ + ? + + ?
Skjerven 2020	0.45	0.18	499	572	16.1%	1.57 [1.10 , 2.23]	+ + ? + + ?
Yonezawa 2018	0.01	0.41	69	87	6.7%	1.01 [0.45 , 2.26]	+ + ? ? + ?
Total (95% CI)			**1561**	**1662**	**100.0%**	**0.89 [0.70 , 1.14]**	

Heterogeneity: Tau² = 0.07; Chi² = 17.85, df = 8 (P = 0.02); I² = 55%
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable

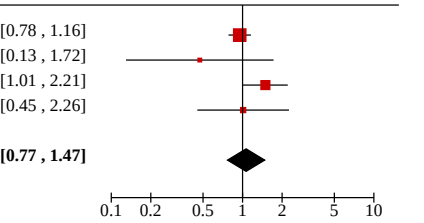


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Sensitivity analysis: Eczema by 6 months-3 years
(C) Bias due to missing outcome data: Sensitivity analysis: Eczema by 6 months-3 years
(D) Bias in measurement of the outcome: Sensitivity analysis: Eczema by 6 months-3 years
(E) Bias in selection of the reported result: Sensitivity analysis: Eczema by 6 months-3 years
(F) Overall bias: Sensitivity analysis: Eczema by 6 months-3 years

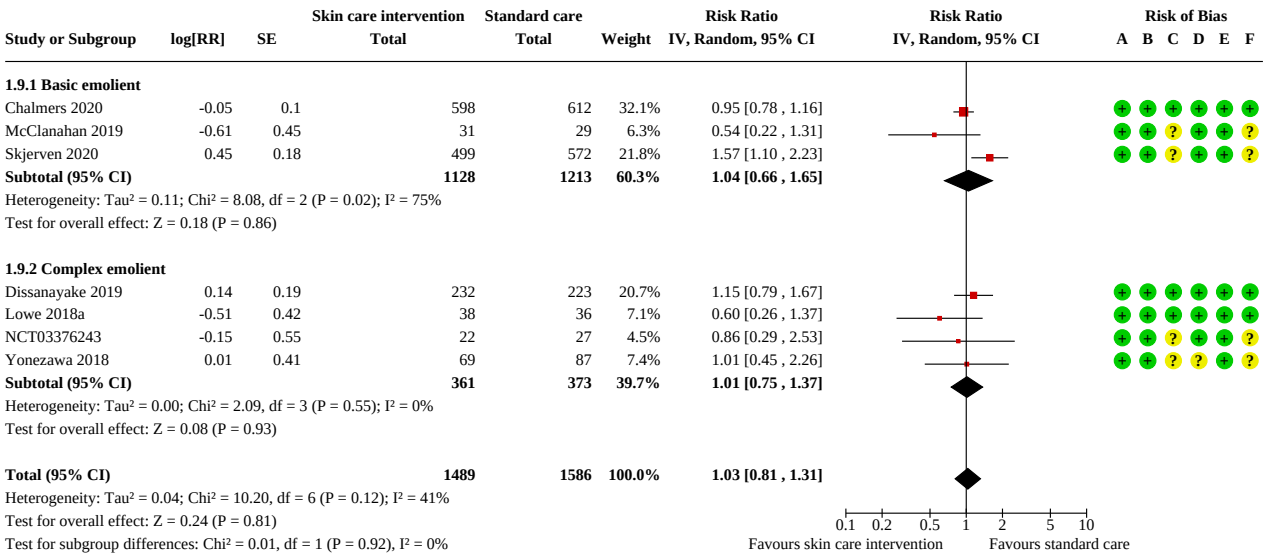
Analysis 1.8. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 8: Sensitivity analysis: Eczema after the intervention period (at 1 year or beyond - up to 2 years)

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.05	0.1	598	612	49.2%	0.95 [0.78 , 1.16]
Lowe 2018a	-0.75	0.66	37	36	5.7%	0.47 [0.13 , 1.72]
Skjerven 2020	0.4	0.2	426	516	32.1%	1.49 [1.01 , 2.21]
Yonezawa 2018	0.01	0.41	69	87	12.9%	1.01 [0.45 , 2.26]
Total (95% CI)			**1130**	**1251**	**100.0%**	**1.06 [0.77 , 1.47]**

Heterogeneity: Tau² = 0.05; Chi² = 5.46, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 9: Subgroup analysis (study level): Eczema by 1-3 years by intervention type

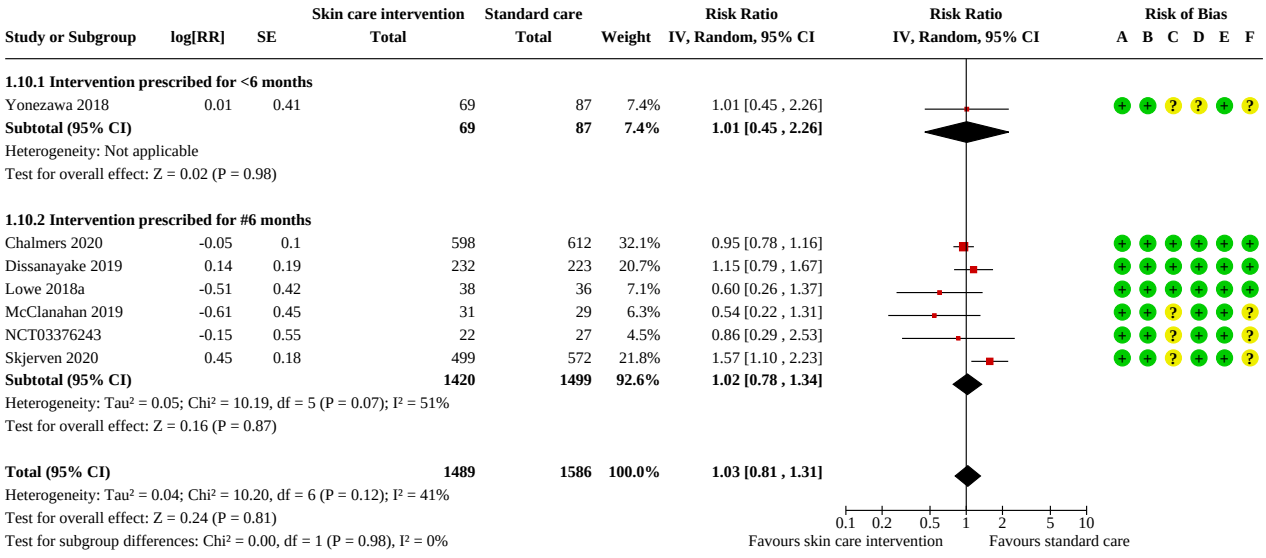


Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
1.9.1 Basic emolient							
Chalmers 2020	-0.05	0.1	598	612	32.1%	0.95 [0.78 , 1.16]	+ + + + + +
McClanahan 2019	-0.61	0.45	31	29	6.3%	0.54 [0.22 , 1.31]	+ + ? + + ?
Skjerven 2020	0.45	0.18	499	572	21.8%	1.57 [1.10 , 2.23]	+ + ? + + ?
Subtotal (95% CI)			**1128**	**1213**	**60.3%**	**1.04 [0.66 , 1.65]**	
Heterogeneity: Tau² = 0.11; Chi² = 8.08, df = 2 (P = 0.02); I² = 75%							
Test for overall effect: Z = 0.18 (P = 0.86)							
1.9.2 Complex emolient							
Dissanayake 2019	0.14	0.19	232	223	20.7%	1.15 [0.79 , 1.67]	+ + + + + +
Lowe 2018a	-0.51	0.42	38	36	7.1%	0.60 [0.26 , 1.37]	+ + + + + +
NCT03376243	-0.15	0.55	22	27	4.5%	0.86 [0.29 , 2.53]	+ + ? + + ?
Yonezawa 2018	0.01	0.41	69	87	7.4%	1.01 [0.45 , 2.26]	+ + ? ? + ?
Subtotal (95% CI)			**361**	**373**	**39.7%**	**1.01 [0.75 , 1.37]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 3 (P = 0.55); I² = 0%							
Test for overall effect: Z = 0.08 (P = 0.93)							
Total (95% CI)			**1489**	**1586**	**100.0%**	**1.03 [0.81 , 1.31]**	
Heterogeneity: Tau² = 0.04; Chi² = 10.20, df = 6 (P = 0.12); I² = 41%							
Test for overall effect: Z = 0.24 (P = 0.81)							
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%							

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Subgroup analysis (study level): Eczema by 1-3 years by intervention type
(C) Bias due to missing outcome data: Subgroup analysis (study level): Eczema by 1-3 years by intervention type
(D) Bias in measurement of the outcome: Subgroup analysis (study level): Eczema by 1-3 years by intervention type
(E) Bias in selection of the reported result: Subgroup analysis (study level): Eczema by 1-3 years by intervention type
(F) Overall bias: Subgroup analysis (study level): Eczema by 1-3 years by intervention type

Analysis 1.10. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 10: Subgroup analysis (study level): Eczema by 1-3 years by prescribed intervention duration



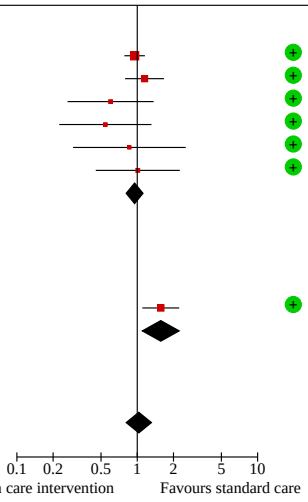
Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
1.10.1 Intervention prescribed for <6 months							
Yonezawa 2018	0.01	0.41	69	87	7.4%	1.01 [0.45 , 2.26]	+ + ? ? + ?
Subtotal (95% CI)			**69**	**87**	**7.4%**	**1.01 [0.45 , 2.26]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.02 (P = 0.98)							
1.10.2 Intervention prescribed for #6 months							
Chalmers 2020	-0.05	0.1	598	612	32.1%	0.95 [0.78 , 1.16]	+ + + + + +
Dissanayake 2019	0.14	0.19	232	223	20.7%	1.15 [0.79 , 1.67]	+ + + + + +
Lowe 2018a	-0.51	0.42	38	36	7.1%	0.60 [0.26 , 1.37]	+ + + + + +
McClanahan 2019	-0.61	0.45	31	29	6.3%	0.54 [0.22 , 1.31]	+ + ? + + ?
NCT03376243	-0.15	0.55	22	27	4.5%	0.86 [0.29 , 2.53]	+ + ? + + ?
Skjerven 2020	0.45	0.18	499	572	21.8%	1.57 [1.10 , 2.23]	+ + ? + + ?
Subtotal (95% CI)			**1420**	**1499**	**92.6%**	**1.02 [0.78 , 1.34]**	
Heterogeneity: Tau² = 0.05; Chi² = 10.19, df = 5 (P = 0.07); I² = 51%							
Test for overall effect: Z = 0.16 (P = 0.87)							
Total (95% CI)			**1489**	**1586**	**100.0%**	**1.03 [0.81 , 1.31]**	
Heterogeneity: Tau² = 0.04; Chi² = 10.20, df = 6 (P = 0.12); I² = 41%							
Test for overall effect: Z = 0.24 (P = 0.81)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%							

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Subgroup analysis (study level): Eczema by 1-3 years by prescribed intervention duration
(C) Bias due to missing outcome data: Subgroup analysis (study level): Eczema by 1-3 years by prescribed intervention duration
(D) Bias in measurement of the outcome: Subgroup analysis (study level): Eczema by 1-3 years by prescribed intervention duration
(E) Bias in selection of the reported result: Subgroup analysis (study level): Eczema by 1-3 years by prescribed intervention duration
(F) Overall bias: Subgroup analysis (study level): Eczema by 1-3 years by prescribed intervention duration

Analysis 1.11. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 11: Subgroup analysis (study level): Eczema by 1-3 years, by prescribed intervention timing

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
1.11.1 Intervention prescribed to start in first week of life						
Chalmers 2020	-0.05	0.1	598	612	32.1%	0.95 [0.78 , 1.16]
Dissanayake 2019	0.14	0.19	232	223	20.7%	1.15 [0.79 , 1.67]
Lowe 2018a	-0.51	0.42	38	36	7.1%	0.60 [0.26 , 1.37]
McClanahan 2019	-0.61	0.45	31	29	6.3%	0.54 [0.22 , 1.31]
NCT03376243	-0.15	0.55	22	27	4.5%	0.86 [0.29 , 2.53]
Yonezawa 2018	0.01	0.41	69	87	7.4%	1.01 [0.45 , 2.26]
Subtotal (95% CI)			**990**	**1014**	**78.2%**	**0.95 [0.81 , 1.12]**
Heterogeneity: Tau² = 0.00; Chi² = 3.80, df = 5 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
1.11.2 Intervention prescribed to start after first week of life						
Skjerven 2020	0.45	0.18	499	572	21.8%	1.57 [1.10 , 2.23]
Subtotal (95% CI)			**499**	**572**	**21.8%**	**1.57 [1.10 , 2.23]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.50 (P = 0.01)						
Total (95% CI)			**1489**	**1586**	**100.0%**	**1.03 [0.81 , 1.31]**
Heterogeneity: Tau² = 0.04; Chi² = 10.20, df = 6 (P = 0.12); I² = 41%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: Chi² = 6.40, df = 1 (P = 0.01), I² = 84.4%						



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Subgroup analysis (study level): Eczema by 1-3 years, by prescribed intervention timing

(C) Bias due to missing outcome data: Subgroup analysis (study level): Eczema by 1-3 years, by prescribed intervention timing

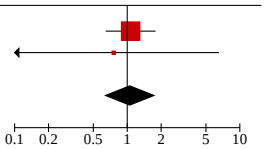
(D) Bias in measurement of the outcome: Subgroup analysis (study level): Eczema by 1-3 years, by prescribed intervention timing

(E) Bias in selection of the reported result: Subgroup analysis (study level): Eczema by 1-3 years, by prescribed intervention timing

(F) Overall bias: Subgroup analysis (study level): Eczema by 1-3 years, by prescribed intervention timing

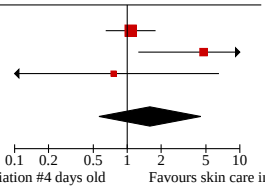
Analysis 1.12. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 12: Participant level treatment interaction: Eczema by 1-3 years for treatment initiation < 4 days versus ≥ 4 days of age

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	0.07	0.26	598	612	94.7%	1.07 [0.64 , 1.79]
Lowe 2018a	-0.28	1.1	38	36	5.3%	0.76 [0.09 , 6.53]
Total (95% CI)			**636**	**648**	**100.0%**	**1.05 [0.64 , 1.73]**
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Not applicable						



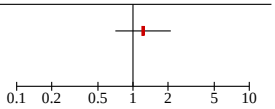
Analysis 1.13. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 13: Participant level treatment interaction: Eczema by 6 months-3 years for treatment initiation < 4 days versus ≥ 4 days of age

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	0.07	0.26	598	612	52.8%	1.07 [0.64 , 1.79]
Horimukai 2014	1.56	0.68	50	49	30.4%	4.76 [1.26 , 18.04]
Lowe 2018a	-0.28	1.1	38	36	16.8%	0.76 [0.09 , 6.53]
Total (95% CI)			**686**	**697**	**100.0%**	**1.59 [0.56 , 4.51]**
Heterogeneity: Tau² = 0.47; Chi² = 4.42, df = 2 (P = 0.11); I² = 55%						
Test for overall effect: Z = 0.87 (P = 0.38)						
Test for subgroup differences: Not applicable						



Analysis 1.14. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 14: Participant level treatment interaction: Eczema by 1-3 years by *FLG* genotype (0 mutations versus 1/2 mutations)

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chalmers 2020	0.2	0.28	402	414	1.22 [0.71 , 2.11]	
McClanahan 2019 (1)	0	0	24	23	Not estimable	



Favours skin care intervention with 1/2 *FLG* mutations | Favours skin care intervention with 0 *FLG* mutations

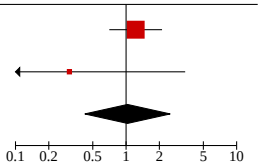
Footnotes

(1) Not estimable as all standard care participants with *FLG* mutations (1 or 2 mutations) had eczema – i.e. the interaction predicts eczema perfectly. In the standard care group 5/22 and 1/1 (mutations) had

Analysis 1.15. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 15: Participant level treatment interaction: Eczema by 6months-3 years by *FLG* genotype (0 mutations versus 1/2 mutations)

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chalmers 2020	0.2	0.28	402	414	87.7%	1.22 [0.71 , 2.11]	
McClanahan 2019 (1)	0	0	24	23		Not estimable	
Simpson 2014	-1.18	1.23	35	28	12.3%	0.31 [0.03 , 3.42]	
Total (95% CI)			**461**	**465**	**100.0%**	**1.03 [0.42 , 2.51]**	

Heterogeneity: Tau² = 0.16; Chi² = 1.20, df = 1 (P = 0.27); I² = 16%
Test for overall effect: Z = 0.07 (P = 0.95)
Test for subgroup differences: Not applicable



Favours skin care intervention with 1/2 *FLG* mutations | Favours skin care intervention with 0 *FLG* mutations

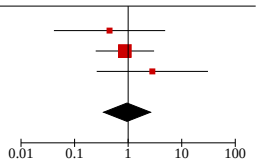
Footnotes

(1) Not estimable as all standard care participants with FLG mutations (1 or 2 mutations) had eczema – i.e. the interaction predicts eczema perfectly. In the standard care group 5/22 and 1/1 (mutations) had eczema ot

Analysis 1.16. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 16: Participant level treatment interaction: Eczema by 1-3 years by ≥ 1 first degree relative with history of allergic disease

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Dissanayake 2019	-0.8	1.22	232	223	17.8%	0.45 [0.04 , 4.91]	
Skjerven 2020	-0.14	0.64	490	562	64.5%	0.87 [0.25 , 3.05]	
Yonezawa 2018	1.04	1.22	69	87	17.8%	2.83 [0.26 , 30.91]	
Total (95% CI)			**791**	**872**	**100.0%**	**0.95 [0.35 , 2.61]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable

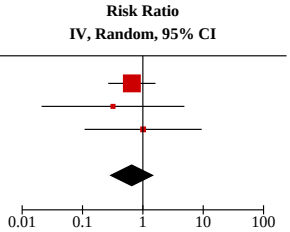


Favours skin care intervention with #1 first degree relative history | Favours skin care intervention with 0 first degree relative history

Analysis 1.17. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 17: CACE: Eczema by 1-3 years for use over intervention period ≥ 3 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.42	0.46	598	612	78.6%	0.66 [0.27 , 1.62]	
Lowe 2018a	-1.14	1.39	38	36	8.6%	0.32 [0.02 , 4.88]	
Yonezawa 2018	0.01	1.14	69	87	12.8%	1.01 [0.11 , 9.43]	
Total (95% CI)			**705**	**735**	**100.0%**	**0.65 [0.29 , 1.45]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.30)
Test for subgroup differences: Not applicable

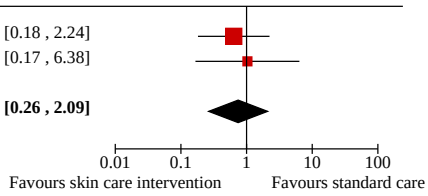


Favours skin care intervention for compliers | Favours standard care for compliers

Analysis 1.18. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 18: CACE Sensitivity: Eczema by 1-3 years for use over intervention period ≥ 5 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.45	0.64	598	612	67.9%	0.64 [0.18 , 2.24]
Yonezawa 2018	0.03	0.93	69	87	32.1%	1.03 [0.17 , 6.38]
Total (95% CI)			**667**	**699**	**100.0%**	**0.74 [0.26 , 2.09]**

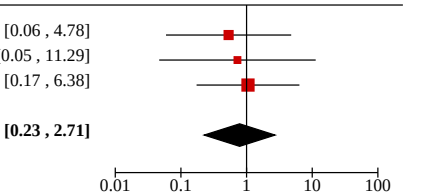
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.57)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 19: CACE Sensitivity: Eczema by 1-3 years for use over intervention period 7 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.63	1.12	598	612	32.0%	0.53 [0.06 , 4.78]
NCT03376243	-0.32	1.4	22	27	20.5%	0.73 [0.05 , 11.29]
Yonezawa 2018	0.05	0.92	69	87	47.5%	1.05 [0.17 , 6.38]
Total (95% CI)			**689**	**726**	**100.0%**	**0.78 [0.23 , 2.71]**

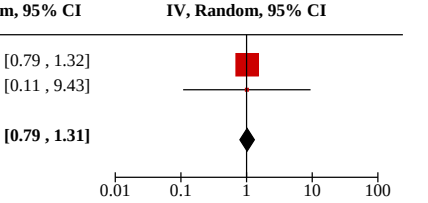
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 20: CACE Sensitivity: Eczema by 1-3 years for use over first 3 months ≥ 3 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	0.02	0.13	598	612	98.7%	1.02 [0.79 , 1.32]
Yonezawa 2018	0.01	1.14	69	87	1.3%	1.01 [0.11 , 9.43]
Total (95% CI)			**667**	**699**	**100.0%**	**1.02 [0.79 , 1.31]**

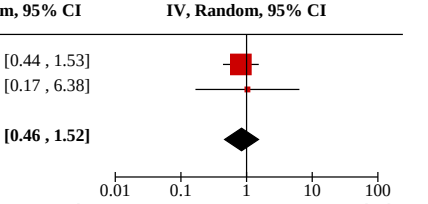
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 21: CACE Sensitivity: Eczema by 1-3 years for use over first 3 months ≥ 5 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.2	0.32	598	612	89.4%	0.82 [0.44 , 1.53]
Yonezawa 2018	0.03	0.93	69	87	10.6%	1.03 [0.17 , 6.38]
Total (95% CI)			**667**	**699**	**100.0%**	**0.84 [0.46 , 1.52]**

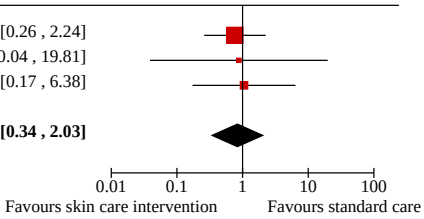
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 22: CACE Sensitivity: Eczema by 1-3 years for use over first 3 months 7 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.27	0.55	598	612	67.7%	0.76 [0.26 , 2.24]
NCT03376243	-0.13	1.59	22	27	8.1%	0.88 [0.04 , 19.81]
Yonezawa 2018	0.05	0.92	69	87	24.2%	1.05 [0.17 , 6.38]
Total (95% CI)			**689**	**726**	**100.0%**	**0.83 [0.34 , 2.03]**

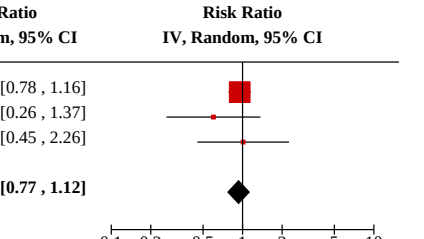
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 2 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 1.23. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 23: Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over intervention period ≥ 3 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.05	0.1	598	612	89.6%	0.95 [0.78 , 1.16]
Lowe 2018a	-0.51	0.42	38	36	5.1%	0.60 [0.26 , 1.37]
Yonezawa 2018	0.01	0.41	69	87	5.3%	1.01 [0.45 , 2.26]
Total (95% CI)			**705**	**735**	**100.0%**	**0.93 [0.77 , 1.12]**

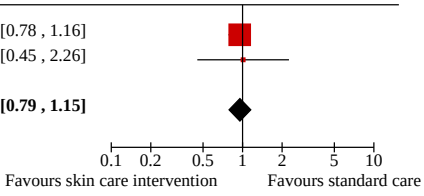
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 1.24. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 24: Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over intervention period ≥ 5 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.05	0.1	598	612	94.4%	0.95 [0.78 , 1.16]
Yonezawa 2018	0.01	0.41	69	87	5.6%	1.01 [0.45 , 2.26]
Total (95% CI)			**667**	**699**	**100.0%**	**0.95 [0.79 , 1.15]**

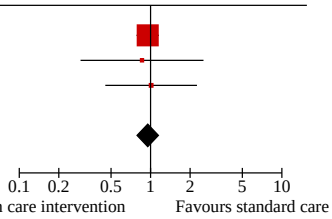
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 1.25. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 25: Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over intervention period 7 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.05	0.1	598	612	91.5%	0.95 [0.78 , 1.16]
NCT03376243	-0.15	0.55	22	27	3.0%	0.86 [0.29 , 2.53]
Yonezawa 2018	0.01	0.41	69	87	5.4%	1.01 [0.45 , 2.26]
Total (95% CI)			**689**	**726**	**100.0%**	**0.95 [0.79 , 1.15]**

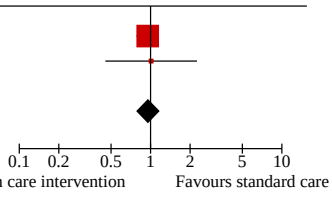
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable



Analysis 1.26. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 26: Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over first 3 months ≥ 3 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.05	0.1	598	612	94.4%	0.95 [0.78 , 1.16]
Yonezawa 2018	0.01	0.41	69	87	5.6%	1.01 [0.45 , 2.26]
Total (95% CI)			**667**	**699**	**100.0%**	**0.95 [0.79 , 1.15]**

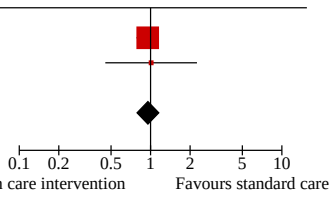
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 1.27. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 27: Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over first 3 months ≥ 5 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.05	0.1	598	612	94.4%	0.95 [0.78 , 1.16]
Yonezawa 2018	0.01	0.41	69	87	5.6%	1.01 [0.45 , 2.26]
Total (95% CI)			**667**	**699**	**100.0%**	**0.95 [0.79 , 1.15]**

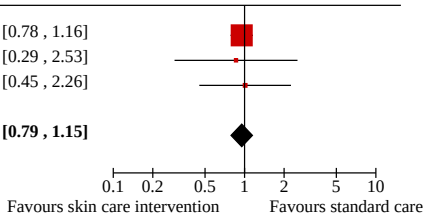
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 1.28. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 28: Sensitivity analysis: Eczema by 1-3 years for studies included in CACE for use over first 3 months 7 days a week

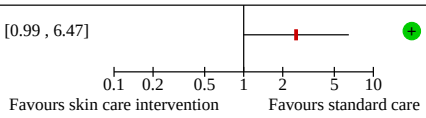
Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.05	0.1	598	612	91.5%	0.95 [0.78 , 1.16]
NCT03376243	-0.15	0.55	22	27	3.0%	0.86 [0.29 , 2.53]
Yonezawa 2018	0.01	0.41	69	87	5.4%	1.01 [0.45 , 2.26]
Total (95% CI)			**689**	**726**	**100.0%**	**0.95 [0.79 , 1.15]**

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable



Analysis 1.29. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 29: Food allergy by 1-3 years

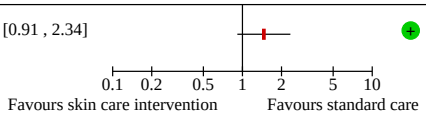
Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Chalmers 2020	0.93	0.47807	491	505	2.53 [0.99 , 6.47]	+	+	-	+	+	-



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Food allergy by 1-3 years
(C) Bias due to missing outcome data: Food allergy by 1-3 years
(D) Bias in measurement of the outcome: Food allergy by 1-3 years
(E) Bias in selection of the reported result: Food allergy by 1-3 years
(F) Overall bias: Food allergy by 1-3 years

Analysis 1.30. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 30: Sensitivity analysis: Food allergy by 1-3 years (diagnosed by oral food challenge or investigator assessment)

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Chalmers 2020	0.38	0.24	547	568	1.46 [0.91 , 2.34]	+	+	?	+	+	?

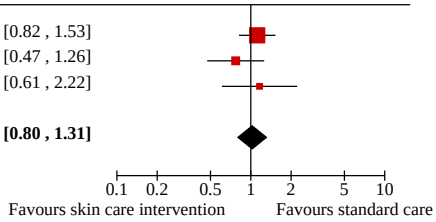


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Sensitivity analysis: Food allergy by 1-3 years (diagnosed by oral food challenge or investigator assessment)
(C) Bias due to missing outcome data: Sensitivity analysis: Food allergy by 1-3 years (diagnosed by oral food challenge or investigator assessment)
(D) Bias in measurement of the outcome: Sensitivity analysis: Food allergy by 1-3 years (diagnosed by oral food challenge or investigator assessment)
(E) Bias in selection of the reported result: Sensitivity analysis: Food allergy by 1-3 years (diagnosed by oral food challenge or investigator assessment)
(F) Overall bias: Sensitivity analysis: Food allergy by 1-3 years (diagnosed by oral food challenge or investigator assessment)

Analysis 1.31. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 31: Sensitivity analysis: Food allergy by 1-3 years (parent report of doctor diagnosis)

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Fixed, 95% CI
Chalmers 2020 (1)	0.11	0.16	493	502	60.8%	1.12 [0.82 , 1.53]
Dissanayake 2019 (2)	-0.26	0.25	232	223	24.9%	0.77 [0.47 , 1.26]
Yonezawa 2018 (3)	0.15	0.33	73	91	14.3%	1.16 [0.61 , 2.22]
Total (95% CI)			**798**	**816**	**100.0%**	**1.02 [0.80 , 1.31]**

Heterogeneity: Chi² = 1.73, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable

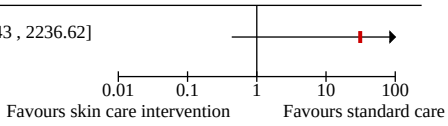


Footnotes

(1) Parent report of doctor diagnosed food allergy by 24 months
(2) Parent report of doctor diagnosed food allergy to common allergen by 12 months
(3) Parent report of doctor diagnosed food allergy by 24 months

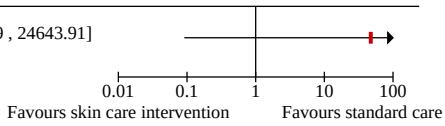
Analysis 1.32. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 32: CACE: Food allergy by 1-3 years for use over intervention period ≥ 3 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI
Chalmers 2020	3.44	2.18	491	505	31.19 [0.43 , 2236.62]



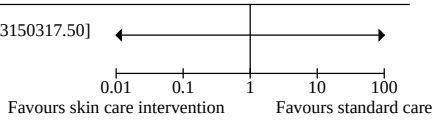
Analysis 1.33. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 33: CACE Sensitivity: Food allergy by 1-3 years for use over intervention period ≥ 5 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI
Chalmers 2020	3.86	3.19	491	505	47.47 [0.09 , 24643.91]



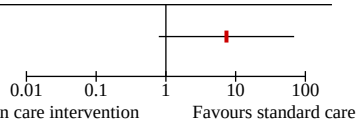
Analysis 1.34. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 34: CACE Sensitivity: Food allergy by 1-3 years for use over intervention period 7 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI
Chalmers 2020	4.83	5.17	491	505	125.21 [0.00 , 3150317.50]



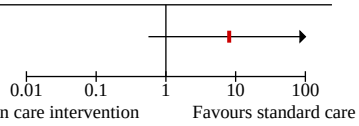
Analysis 1.35. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 35: CACE Sensitivity: Food allergy by 1-3 years for use over first 3 months ≥ 3 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chalmers 2020	2	1.14	491	505	7.39 [0.79 , 69.02]	



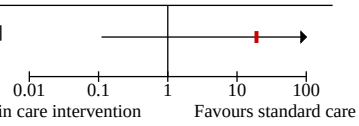
Analysis 1.36. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 36: CACE Sensitivity: Food allergy by 1-3 years for use over first 3 months ≥ 5 days a week

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chalmers 2020	2.09	1.36	491	505	8.08 [0.56 , 116.23]	



Analysis 1.37. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 37: CACE Sensitivity: Food allergy by 1-3 years for use over first 3 months 7 days a week

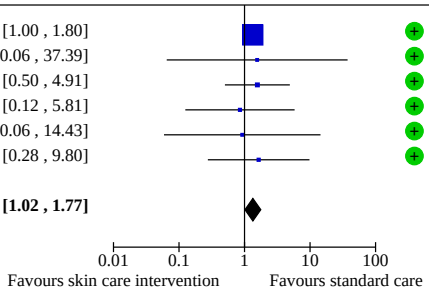
Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chalmers 2020	2.95	2.63	491	505	19.11 [0.11 , 3310.01]	



Analysis 1.38. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 38: Adverse event: skin infection

Study or Subgroup	Skin care intervention Events	Skin care intervention Total	Standard care Events	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Chalmers 2020	89	585	67	589	87.8%	1.34 [1.00 , 1.80]		+	+	+	?	+	?
Cooke 2015	1	76	0	39	0.8%	1.56 [0.06 , 37.39]		+	+	+	+	+	+
Lowe 2018a	7	39	4	35	5.9%	1.57 [0.50 , 4.91]		+	+	+	?	+	?
McClanahan 2019	2	54	2	46	2.1%	0.85 [0.12 , 5.81]		+	+	+	?	+	?
Simpson 2014	1	65	1	60	1.0%	0.92 [0.06 , 14.43]		+	+	+	?	+	?
Skjerven 2020	3	544	2	596	2.4%	1.64 [0.28 , 9.80]		+	+	+	?	+	?
Total (95% CI)		**1363**		**1365**	**100.0%**	**1.34 [1.02 , 1.77]**							
Total events:	103		76										

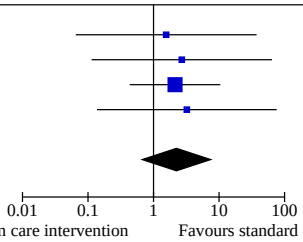
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 5 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Adverse event: skin infection
(C) Bias due to missing outcome data: Adverse event: skin infection
(D) Bias in measurement of the outcome: Adverse event: skin infection
(E) Bias in selection of the reported result: Adverse event: skin infection
(F) Overall bias: Adverse event: skin infection

Analysis 1.39. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 39: Adverse event: stinging or allergic reaction to moisturisers

Study or Subgroup	Skin care intervention Events	Total	Standard care Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Cooke 2015	1	76	0	39	14.3%	1.56 [0.06 , 37.39]		+ + + + + +
Lowe 2018a	1	39	0	35	14.4%	2.70 [0.11 , 64.20]		+ + + ? + ?
McClanahan 2019	5	54	2	46	56.9%	2.13 [0.43 , 10.46]		+ + + ? + ?
NCT03376243	1	26	0	28	14.5%	3.22 [0.14 , 75.75]		+ + + ? + ?
Total (95% CI)		**195**		**148**	**100.0%**	**2.24 [0.67 , 7.43]**		
Total events:	8		2					

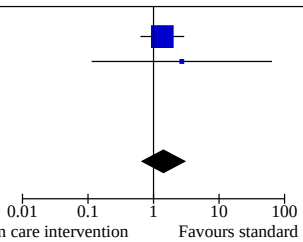


Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 3 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Adverse event: stinging or allergic reaction to moisturisers
(C) Bias due to missing outcome data: Adverse event: stinging or allergic reaction to moisturisers
(D) Bias in measurement of the outcome: Adverse event: stinging or allergic reaction to moisturisers
(E) Bias in selection of the reported result: Adverse event: stinging or allergic reaction to moisturisers
(F) Overall bias: Adverse event: stinging or allergic reaction to moisturisers

Analysis 1.40. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 40: Adverse event: slippage accidents

Study or Subgroup	Skin care intervention Events	Total	Standard care Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Chalmers 2020	15	584	11	584	94.4%	1.36 [0.63 , 2.94]		+ + + ? + ?
Lowe 2018a	1	39	0	35	5.6%	2.70 [0.11 , 64.20]		+ + + ? + ?
Simpson 2014	0	64	0	60		Not estimable		+ + + ? + ?
Skjerven 2020 (1)	0	575	0	597		Not estimable		+ + + ? + ?
Total (95% CI)		**1262**		**1276**	**100.0%**	**1.42 [0.67 , 2.99]**		
Total events:	16		11					



Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable

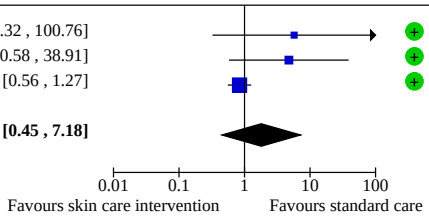
Footnotes
(1) PreventADALL reported 0 slippages in each treatment group included in the IPD meta-analysis. There was one accident connected with bathing for a participant in the food and s

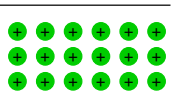
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Adverse event: slippage accidents
(C) Bias due to missing outcome data: Adverse event: slippage accidents
(D) Bias in measurement of the outcome: Adverse event: slippage accidents
(E) Bias in selection of the reported result: Adverse event: slippage accidents
(F) Overall bias: Adverse event: slippage accidents

Analysis 1.41. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 41: Serious Adverse Events

Study or Subgroup	Skin care intervention Events	Total	Standard care Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Cooke 2015	5	76	0	39	16.8%	5.71 [0.32 , 100.76]
Lowe 2018a	5	41	1	39	25.3%	4.76 [0.58 , 38.91]
Skjerven 2020	38	575	47	597	57.8%	0.84 [0.56 , 1.27]
Total (95% CI)		**692**		**675**	**100.0%**	**1.80 [0.45 , 7.18]**
Total events:	48		48			

Heterogeneity: Tau² = 0.82; Chi² = 4.09, df = 2 (P = 0.13); I² = 51%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable

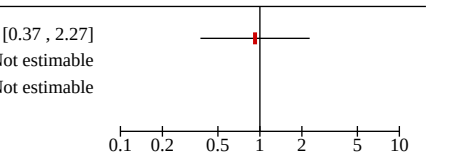




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious Adverse Events
(C) Bias due to missing outcome data: Serious Adverse Events
(D) Bias in measurement of the outcome: Serious Adverse Events
(E) Bias in selection of the reported result: Serious Adverse Events
(F) Overall bias: Serious Adverse Events

Analysis 1.42. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 42: Clinician-assessed eczema severity at 1-3 years (clear/mild versus moderate/severe/very severe)

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI
Chalmers 2020 (1)	-0.08	0.46	553	567	0.92 [0.37 , 2.27]
Lowe 2018a (2)	0	0	35	32	Not estimable
NCT03376243 (3)	0	0	23	18	Not estimable

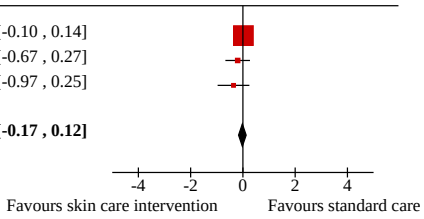


Footnotes
(1) EASI at 24 months
(2) objective SCORAD at 12 months
(3) EASI at 12 months

Analysis 1.43. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 43: Clinician-assessed eczema severity at 1-3 years (standardised mean difference)

Study or Subgroup	SMD	SE	Skin care intervention Total	Standard care Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chalmers 2020 (1)	0.02	0.06	553	567	85.4%	0.02 [-0.10 , 0.14]
Lowe 2018a (2)	-0.2	0.24	35	32	9.1%	-0.20 [-0.67 , 0.27]
NCT03376243 (3)	-0.36	0.31	18	23	5.5%	-0.36 [-0.97 , 0.25]
Total (95% CI)			**606**	**622**	**100.0%**	**-0.02 [-0.17 , 0.12]**

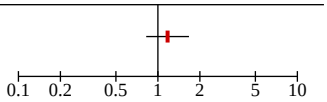
Heterogeneity: Tau² = 0.00; Chi² = 2.15, df = 2 (P = 0.34); I² = 7%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable



Footnotes
(1) EASI at 24 months
(2) objective SCORAD at 12 months
(3) EASI at 12 months

Analysis 1.44. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 44: Parent-reported eczema severity at 1-3 years (clear/mild versus moderate/severe/very severe)

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chalmers 2020 (1)	0.16	0.18	576	595	1.17 [0.82 , 1.67]	

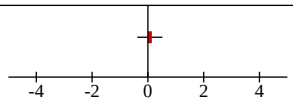


Footnotes

(1) POEM at 24 months as very severe/severe/moderate versus clear/mild

Analysis 1.45. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 45: Parent-reported eczema severity at 1-3 years (mean difference)

Study or Subgroup	MD	SE	Skin care intervention Total	Standard care Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Chalmers 2020 (1)	0.07	0.23	576	595	0.07 [-0.38 , 0.52]	



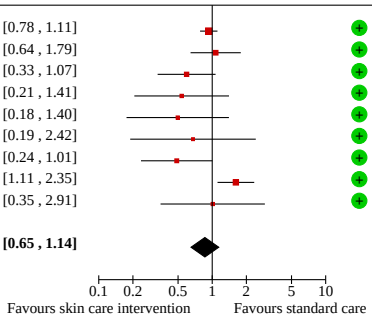
Footnotes

(1) POEM at 24 months

Analysis 1.46. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 46: Time to onset of eczema

Study or Subgroup	log[Hazard Ratio]	SE	Skin care intervention Total	Standard care Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Chalmers 2020	-0.07	0.09	618	618	24.0%	0.93 [0.78 , 1.11]		+ + + ? + ?
Dissanayake 2019	0.07	0.26	217	214	14.2%	1.07 [0.64 , 1.79]		+ + + + + +
Horimukai 2014	-0.52	0.3	58	58	12.3%	0.59 [0.33 , 1.07]		+ + + + + +
Lowe 2018a	-0.62	0.49	41	38	6.5%	0.54 [0.21 , 1.41]		+ + + + + +
McClanahan 2019	-0.7	0.53	54	46	5.7%	0.50 [0.18 , 1.40]		+ + ? + + ?
NCT03376243	-0.39	0.65	26	28	4.1%	0.68 [0.19 , 2.42]		+ + ? + + ?
Simpson 2014	-0.72	0.37	55	53	9.6%	0.49 [0.24 , 1.01]		+ + ? + + ?
Skjerven 2020	0.48	0.19	499	572	18.1%	1.62 [1.11 , 2.35]		+ + ? + + ?
Yonezawa 2018	0.01	0.54	68	86	5.6%	1.01 [0.35 , 2.91]		+ + ? ? + ?
Total (95% CI)			**1636**	**1713**	**100.0%**	**0.86 [0.65 , 1.14]**		

Heterogeneity: Tau² = 0.08; Chi² = 16.91, df = 8 (P = 0.03); I² = 53%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable

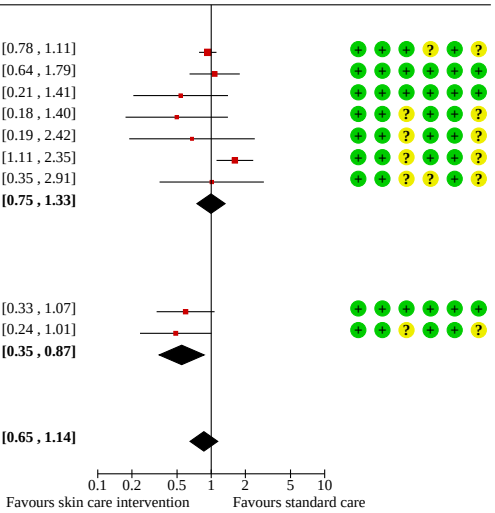


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Time to onset of eczema
(C) Bias due to missing outcome data: Time to onset of eczema
(D) Bias in measurement of the outcome: Time to onset of eczema
(E) Bias in selection of the reported result: Time to onset of eczema
(F) Overall bias: Time to onset of eczema

Analysis 1.47. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 47: Subgroup analysis: Time to onset of eczema (< 1 year follow-up versus ≥ 1 year follow-up)

Study or Subgroup	log[Hazard Ratio]	SE	Skin care intervention Total	Standard care Total	Weight	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
1.47.1 Follow-up # 1 year							
Chalmers 2020	-0.07	0.09	618	618	24.0%	0.93 [0.78 , 1.11]	+ + + ? + ?
Dissanayake 2019	0.07	0.26	217	214	14.2%	1.07 [0.64 , 1.79]	+ + + + + +
Lowe 2018a	-0.62	0.49	41	38	6.5%	0.54 [0.21 , 1.41]	+ + + + + +
McClanahan 2019	-0.7	0.53	54	46	5.7%	0.50 [0.18 , 1.40]	+ + ? + + ?
NCT03376243	-0.39	0.65	26	28	4.1%	0.68 [0.19 , 2.42]	+ + ? + + ?
Skjerven 2020	0.48	0.19	499	572	18.1%	1.62 [1.11 , 2.35]	+ + ? + + ?
Yonezawa 2018	0.01	0.54	68	86	5.6%	1.01 [0.35 , 2.91]	+ + ? ? + ?
Subtotal (95% CI)			**1523**	**1602**	**78.1%**	**1.00 [0.75 , 1.33]**	
Heterogeneity: Tau² = 0.05; Chi² = 10.77, df = 6 (P = 0.10); I² = 44%							
Test for overall effect: Z = 0.03 (P = 0.98)							
1.47.2 Follow-up < 1 year							
Horimukai 2014	-0.52	0.3	58	58	12.3%	0.59 [0.33 , 1.07]	+ + + + + +
Simpson 2014	-0.72	0.37	55	53	9.6%	0.49 [0.24 , 1.01]	+ + ? + + ?
Subtotal (95% CI)			**113**	**111**	**21.9%**	**0.55 [0.35 , 0.87]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%							
Test for overall effect: Z = 2.57 (P = 0.01)							
Total (95% CI)			**1636**	**1713**	**100.0%**	**0.86 [0.65 , 1.14]**	
Heterogeneity: Tau² = 0.08; Chi² = 16.91, df = 8 (P = 0.03); I² = 53%							
Test for overall effect: Z = 1.04 (P = 0.30)							
Test for subgroup differences: Chi² = 4.68, df = 1 (P = 0.03), I² = 78.6%							

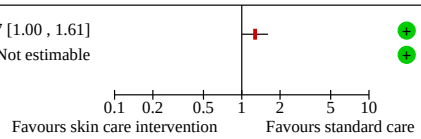


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Subgroup analysis: Time to onset of eczema (< 1 year follow-up versus # 1 year follow-up)
(C) Bias due to missing outcome data: Subgroup analysis: Time to onset of eczema (< 1 year follow-up versus # 1 year follow-up)
(D) Bias in measurement of the outcome: Subgroup analysis: Time to onset of eczema (< 1 year follow-up versus # 1 year follow-up)
(E) Bias in selection of the reported result: Subgroup analysis: Time to onset of eczema (< 1 year follow-up versus # 1 year follow-up)
(F) Overall bias: Subgroup analysis: Time to onset of eczema (< 1 year follow-up versus # 1 year follow-up)

Analysis 1.48. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 48: Parent report of immediate (< 2 hours) reaction to a known common food allergen

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Chalmers 2020 (1)	0.24	0.12	574	597	1.27 [1.00 , 1.61]	+ + + ? + ?
NCT03376243	0	0	18	23	Not estimable	+ + ? ? + ?



Footnotes

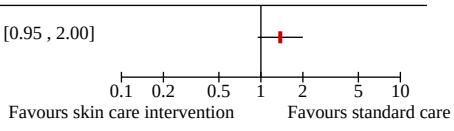
(1) milk, egg, peanut, other nut or other common food allergen at 2 years

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Parent report of immediate (< 2 hours) reaction to a known common food allergen
(C) Bias due to missing outcome data: Parent report of immediate (< 2 hours) reaction to a known common food allergen
(D) Bias in measurement of the outcome: Parent report of immediate (< 2 hours) reaction to a known common food allergen
(E) Bias in selection of the reported result: Parent report of immediate (< 2 hours) reaction to a known common food allergen
(F) Overall bias: Parent report of immediate (< 2 hours) reaction to a known common food allergen

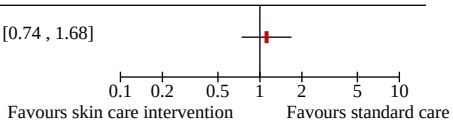
Analysis 1.49. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 49: Parent report of immediate (< 2 hours) reaction to milk

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI
Chalmers 2020	0.32	0.19	575	598	1.38 [0.95 , 2.00]



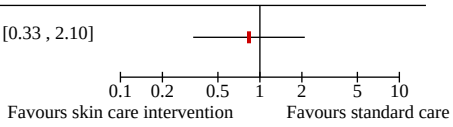
Analysis 1.50. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 50: Parent report of immediate (< 2 hours) reaction to egg

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chalmers 2020	0.11	0.21	575	598	1.12 [0.74 , 1.68]	



Analysis 1.51. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 51: Parent report of immediate (< 2 hours) reaction to peanut

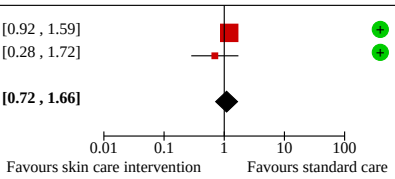
Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chalmers 2020	-0.18	0.47	574	598	0.84 [0.33 , 2.10]	



Analysis 1.52. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 52: Allergic sensitisation to common foods or inhalants at 1-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Chalmers 2020 (1)	0.19	0.14	490	498	81.7%	1.21 [0.92 , 1.59]		+ + + + + +
Lowe 2018a (2)	-0.36	0.46	34	36	18.3%	0.70 [0.28 , 1.72]		+ + ? + + ?
Total (95% CI)			**524**	**534**	**100.0%**	**1.09 [0.72 , 1.66]**		

Heterogeneity: Tau² = 0.04; Chi² = 1.31, df = 1 (P = 0.25); I² = 24%
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Not applicable



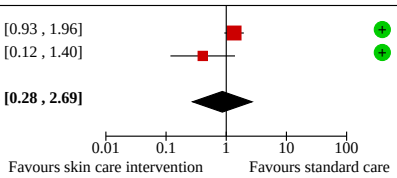
Footnotes
(1) Milk, egg, peanut, cat, dust mite or grass pollen at 24 months via SPT
(2) Milk, egg, peanut, cat, dust mite or rye at 12 months via SPT

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Allergic sensitisation to common foods or inhalants at 1-3 years
(C) Bias due to missing outcome data: Allergic sensitisation to common foods or inhalants at 1-3 years
(D) Bias in measurement of the outcome: Allergic sensitisation to common foods or inhalants at 1-3 years
(E) Bias in selection of the reported result: Allergic sensitisation to common foods or inhalants at 1-3 years
(F) Overall bias: Allergic sensitisation to common foods or inhalants at 1-3 years

Analysis 1.53. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 53: Allergic sensitisation to common foods at 1-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Chalmers 2020 (1)	0.3	0.19	487	498	62.5%	1.35 [0.93 , 1.96]	+ + + + + +
Lowe 2018a (2)	-0.9	0.63	34	36	37.5%	0.41 [0.12 , 1.40]	+ + ? + + ?
Total (95% CI)			**521**	**534**	**100.0%**	**0.86 [0.28 , 2.69]**	

Heterogeneity: Tau² = 0.50; Chi² = 3.33, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 0.26 (P = 0.80)
Test for subgroup differences: Not applicable



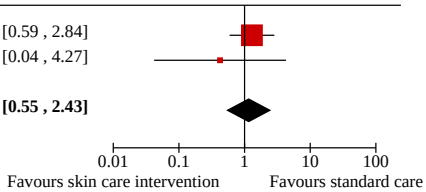
Footnotes
(1) milk, egg or peanut at 24 months via SPT
(2) milk, egg or peanut at 12 months via SPT

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Allergic sensitisation to common foods at 1-3 years
(C) Bias due to missing outcome data: Allergic sensitisation to common foods at 1-3 years
(D) Bias in measurement of the outcome: Allergic sensitisation to common foods at 1-3 years
(E) Bias in selection of the reported result: Allergic sensitisation to common foods at 1-3 years
(F) Overall bias: Allergic sensitisation to common foods at 1-3 years

Analysis 1.54. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 54: Allergic sensitisation to milk at 1-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020 (1)	0.26	0.4	488	498	89.7%	1.30 [0.59 , 2.84]
Lowe 2018a (2)	-0.86	1.18	34	36	10.3%	0.42 [0.04 , 4.27]
Total (95% CI)			**522**	**534**	**100.0%**	**1.16 [0.55 , 2.43]**

Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)
Test for subgroup differences: Not applicable

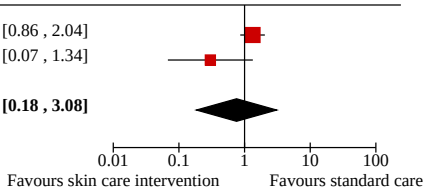


Footnotes
(1) at 24 months via SPT
(2) at 12 months via SPT

Analysis 1.55. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 55: Allergic sensitisation to egg at 1-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020 (1)	0.28	0.22	490	499	62.1%	1.32 [0.86 , 2.04]
Lowe 2018a (2)	-1.2	0.76	34	36	37.9%	0.30 [0.07 , 1.34]
Total (95% CI)			**524**	**535**	**100.0%**	**0.75 [0.18 , 3.08]**

Heterogeneity: Tau² = 0.78; Chi² = 3.50, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Not applicable

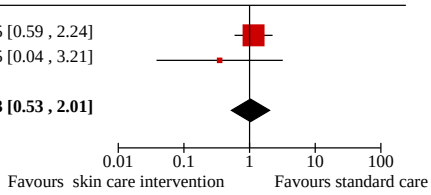


Footnotes
(1) at 24 months via SPT
(2) at 12 months via SPT

Analysis 1.56. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 56: Allergic sensitisation to peanut at 1-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020 (1)	0.14	0.34	490	502	91.0%	1.15 [0.59 , 2.24]
Lowe 2018a (2)	-1.05	1.13	34	36	9.0%	0.35 [0.04 , 3.21]
Total (95% CI)			**524**	**538**	**100.0%**	**1.03 [0.53 , 2.01]**

Heterogeneity: Tau² = 0.01; Chi² = 1.02, df = 1 (P = 0.31); I² = 2%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable

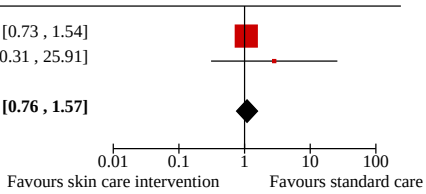


Footnotes
(1) at 24 months via SPT
(2) at 12 months via SPT

Analysis 1.57. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 57: Allergic sensitisation to inhalants at 1-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020 (1)	0.06	0.19	492	499	97.3%	1.06 [0.73 , 1.54]
Lowe 2018a (2)	1.04	1.13	34	36	2.7%	2.83 [0.31 , 25.91]
Total (95% CI)			**526**	**535**	**100.0%**	**1.09 [0.76 , 1.57]**

Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable

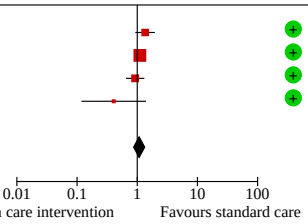


Footnotes
(1) Cat, dust mite or grass pollen at 24 months via SPT
(2) Cat, dust mite or rye at 12 months via SPT

Analysis 1.58. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 58: Sensitivity analysis: Allergic sensitisation to common foods at 6 months-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Chalmers 2020 (1)	0.3	0.19	487	498	22.2%	1.35 [0.93 , 1.96]	+ + + + + +
Dissanayake 2019 (2)	0.1	0.08	235	223	51.0%	1.11 [0.94 , 1.29]	+ + + + + +
Horimukai 2014 (3)	-0.081	0.18	48	44	23.9%	0.92 [0.65 , 1.31]	+ + + + + +
Lowe 2018a (4)	-0.9	0.63	34	36	2.8%	0.41 [0.12 , 1.40]	+ + ? + + ?
Total (95% CI)			**804**	**801**	**100.0%**	**1.08 [0.87 , 1.33]**	

Heterogeneity: Tau² = 0.02; Chi² = 4.61, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



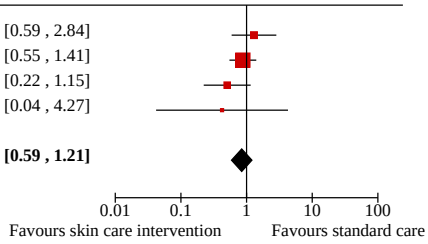
Footnotes
(1) milk, egg or peanut at 24 months
(2) milk, egg at 9 months via IgE testing
(3) milk, egg or peanut at 8 months (32 weeks) via IgE testing
(4) milk, egg or peanut at 12 months via SPT

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Sensitivity analysis: Allergic sensitisation to common foods at 6 months-3 years
(C) Bias due to missing outcome data: Sensitivity analysis: Allergic sensitisation to common foods at 6 months-3 years
(D) Bias in measurement of the outcome: Sensitivity analysis: Allergic sensitisation to common foods at 6 months-3 years
(E) Bias in selection of the reported result: Sensitivity analysis: Allergic sensitisation to common foods at 6 months-3 years
(F) Overall bias: Sensitivity analysis: Allergic sensitisation to common foods at 6 months-3 years

Analysis 1.59. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 59: Sensitivity analysis: Allergic sensitisation to milk at 6 months-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020 (1)	0.26	0.4	488	498	20.8%	1.30 [0.59 , 2.84]
Dissanayake 2019 (2)	-0.13	0.24	233	223	57.9%	0.88 [0.55 , 1.41]
Horimukai 2014 (3)	-0.68	0.42	48	44	18.9%	0.51 [0.22 , 1.15]
Lowe 2018a (4)	-0.86	1.18	34	36	2.4%	0.42 [0.04 , 4.27]
Total (95% CI)			**803**	**801**	**100.0%**	**0.84 [0.59 , 1.21]**

Heterogeneity: Tau² = 0.00; Chi² = 3.00, df = 3 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable

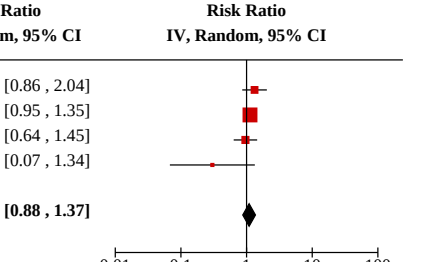


Footnotes
(1) at 24 months via SPT
(2) at 9 months via IgE testing
(3) at 8 months (32 weeks) via IgE testing
(4) at 12 months via SPT

Analysis 1.60. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 60: Sensitivity analysis: Allergic sensitisation to egg at 6 months-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020 (1)	0.28	0.22	490	499	20.3%	1.32 [0.86 , 2.04]
Dissanayake 2019 (2)	0.12	0.09	233	223	55.7%	1.13 [0.95 , 1.35]
Horimukai 2014 (3)	-0.04	0.21	48	44	21.8%	0.96 [0.64 , 1.45]
Lowe 2018a (4)	-1.2	0.76	34	36	2.2%	0.30 [0.07 , 1.34]
Total (95% CI)			**805**	**802**	**100.0%**	**1.09 [0.88 , 1.37]**

Heterogeneity: Tau² = 0.01; Chi² = 4.09, df = 3 (P = 0.25); I² = 27%
Test for overall effect: Z = 0.78 (P = 0.43)
Test for subgroup differences: Not applicable

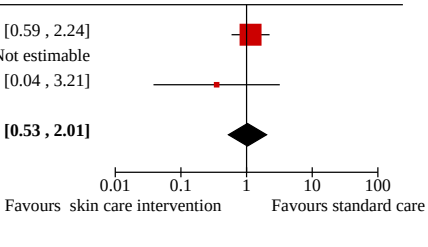


Footnotes
(1) at 24 months via SPT
(2) at 9 months via IgE testing
(3) at 8 months (32 weeks) via IgE testing
(4) at 12 months via SPT

Analysis 1.61. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 61: Sensitivity analysis: Allergic sensitisation to peanut at 6 months-3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI
Chalmers 2020 (1)	0.14	0.34	490	502	91.0%	1.15 [0.59 , 2.24]
Horimukai 2014 (2)	0	0	48	44		Not estimable
Lowe 2018a (1)	-1.05	1.13	34	36	9.0%	0.35 [0.04 , 3.21]
Total (95% CI)			**572**	**582**	**100.0%**	**1.03 [0.53 , 2.01]**

Heterogeneity: Tau² = 0.01; Chi² = 1.02, df = 1 (P = 0.31); I² = 2%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable



Footnotes
(1) at 12 months via SPT
(2) at 8 months (32 weeks) via IgE testing

ADDITIONAL TABLES

Table 1. Glossary of terms

Term	Definition
Adolescence	A period in development, roughly between ages 10 and 19 years, between onset of puberty and acceptance of adult identity and behaviour
Allergic (atopic) march	Typical pattern of onset of allergic disease from eczema, to food allergy, to asthma and allergic rhinitis
Allergic rhinitis	Rhinitis is a group of symptoms affecting the nose, typically by sneezing, itching, or congestion. Allergic rhinitis occurs when these symptoms are due to environmental allergies
Allergic sensitisation	Demonstrated by a positive skin prick test of specific IgE to a known allergen
Anaphylaxis	Acute, potentially life-threatening immediate reaction to an allergen
Angioedema	Pronounced swelling of the deep dermis, subcutaneous or submucosal tissue
Atopic dermatitis (atopic eczema)	Eczema with IgE sensitisation, either by IgE antibody or by skin prick test, is classified as atopic eczema
Atopy	Genetic predisposition to develop allergic diseases such as eczema, food allergy, asthma, and allergic rhinitis, often associated with production of IgE antibodies
Ceramides	Lipid (fatty) molecules found in the lipid bilayer of the intercellular matrix
Eczema	Complex chronic skin condition characterised by itch, a form of dermatitis
Filaggrin gene (*FLG*)	Gene encoding for filaggrin, which is a filament-binding protein in the skin
Flare	In eczema, a period of worsening of signs and symptoms of eczema
Food allergy	Adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food. Can be IgE-mediated or non-IgE-mediated
Food sensitisation	Production of IgE to a food, in the form of a positive skin prick test or immunoglobulin E; may not equate to food allergy
Humectant	Substance or product that draws water towards it
Immunoglobulin E (IgE)	Class of antibody that plays a key role in allergic disease. Signs and symptoms of IgE-mediated disease include urticaria, angioedema, wheeze, anaphylaxis
Infant	A baby in the first year of life
Inhalant allergen	Allergen that typically enters the immune system via the respiratory tract and is airborne, such as house dust mite or pollen
Mast cell	Granular basophil cell present in connective tissue that releases histamine and other mediators in allergic reactions
Neonate	A baby in the first 28 days of life

Table 1. Glossary of terms *(Continued)*

Phenotype	Observable characteristics from an interaction between genes and the environment
Prevalence	In statistics, refers to the number of cases of a disease, present in a particular population at a given time
Quality of life	Defined by WHO as individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns
Transepidermal water loss (TEWL)	Non-invasive measurement of water loss across the epidermis used as a measure of skin barrier function
Urticaria	Rash that is a transient erythematous itchy swelling of skin

Table 2. Baseline characteristics of participants included in meta-analysis

Characteristic	Chalmers 2020	Cooke 2015	Dissanayake 2019	Horimukai 2014	Lowe 2018a	Migacheva 2018	McClanahan 2019	Simpson 2014	Skjerven 2020
Gestational age: mean (SD)	40 (1.3)	40 (1.3)	39 (1.1)	39.1 (1)	39.3 (1.6)			40.3 (1.3)	39.3 (1.6)
Female: n (%)	661 (47)	49 (43)	275 (50)	50 (42)	41 (51)	29 (48)	49 (49)	41 (53)	1134 (47)
Birth weight: mean g (SD)		3405 (452)	3048 (322)	3054 (363)	3356 (442)				3577 (480)
Vaginal delivery: n (%)	954 (68)	95 (83)	420 (77)	89 (75)	31 (41)		80 (80)	32 (26)	1999 (83)
Age intervention began: mean days (SD)	13 (10)	All < 3		2 (2)	12 (7)		13 (14)	14 (6)	
Family history atopy: n (%)	1394 (100)	37 (79)	457 (83)	118 (100)	80 (100)		100 (100)	124 (100)	1814 (78)
FLG (1/2 mutations): n (%)	125 (15)						5 (9)	17 (27)	
Sample size	**1394**	**115**	**549**	**118**	**80**	**60**	**100**	**124**	**2396**

Please note that a blank cell indicates that the study report did not provide relevant information.

Table 3. Baseline characteristics of participants included in meta-analysis (continued)

Characteristic	NCT03376243	Yonezawa 2018
Gestational age: mean (SD)		39.4 (1.3)
Female: n (%)	30 (56)	98 (43)
Birth weight: mean g (SD)	3547 (497)	3017 (362)
Vaginal delivery: n (%)	34 (63)	194 (85)
Age intervention began: mean days (SD)		6 (2)
Family history atopy: n (%)	54 (100)	62 (27)
FLG (1/2 mutations): n (%)		
Sample Size	54	227

Table 4. Sensitivity analysis for eczema

Analysis	N trials	N intervention	N control	Pooled risk ratio	95% CI
Primary: **Eczema by 1 to 2 years**	**7** [a]	**1489**	**1586**	**1.03**	**0.81 to 1.31**
Sensitivity: Eczema by 1 to 2 years including aggregate data	8[b]	1518	1617	0.97	0.75 to 1.25
Eczema by 1 to 2 years using UK Working Party Criteria only	6[c]	1420	1499	1.02	0.78 to 1.34
Eczema by 1 to 2 years including all 4 arms from the PreventADALL trial	7[a]	1993	2183	1.03	0.81 to 1.31
Eczema by 1 to 2 years, low risk of bias data only	3[d]	868	871	0.97	0.81 to 1.17
Eczema by 1 to 2 years, excluding non-prospectively acquired data	6[e]	1451	1550	1.08	0.84 to 1.37
Eczema by 6 months to 2 years	9[f]	1549	1688	0.89	0.70 to 1.14

[a] Chalmers 2020; Dissanayake 2019; Lowe 2018a; McClanahan 2019; Skjerven 2020; NCT03376243; Yonezawa 2018. [b] Chalmers 2020; Dissanayake 2019; Lowe 2018a; McClanahan 2019; Migacheva 2018; Skjerven 2020; NCT03376243; Yonezawa 2018. [c] Chalmers 2020; Dissanayake 2019; Lowe 2018a; McClanahan 2019; Skjerven 2020; NCT03376243. [d] Chalmers 2020; Dissanayake 2019; Lowe 2018a. [e] Chalmers 2020; Dissanayake 2019; McClanahan 2019; Skjerven 2020; NCT03376243; Yonezawa 2018. [f] Chalmers 2020; Dissanayake 2019; Horimukai 2014; Lowe 2018a; McClanahan 2019; Simpson 2014; Skjerven 2020; NCT03376243; Yonezawa 2018.

Table 5. Complier average causal effect analyses for eczema

Complier	N trials	N intervention	N control	CACE		Intention-to-treat	
				Pooled RR	95% CI	Pooled RR	95% CI
Primary CACE: **≥ 3 days of use over intervention period**	**3[a]**	**705**	**735**	**0.65**	**0.29 to 1.45**	**0.93**	**0.77 to 1.12**
Sensitivity CACE: ≥ 5 days of use over intervention period	2[b]	667	699	0.74	0.26 to 2.09	0.95	0.79 to 1.15
7 days use over intervention period	3[c]	689	699	0.78	0.23 to 2.71	0.95	0.79 to 1.15
≥ 3 days of use over *first 3 months* of intervention period	2[b]	667	669	1.02	0.79 to 1.31	0.95	0.79 to 1.15
≥ 5 days of use over *first 3 months* of intervention period	2[b]	667	669	0.84	0.46 to 1.52	0.95	0.79 to 1.15
7 days use over *first 3 months* of intervention period	3[c]	689	726	0.83	0.34 to 2.03	0.95	0.79 to 1.15

[a] Chalmers 2020; Lowe 2018a; Skjerven 2020; Yonezawa 2018. [b] Chalmers 2020; Skjerven 2020; Yonezawa 2018. [c] Chalmers 2020; NCT03376243; Yonezawa 2018.

Table 6. Sensitivity analysis for food allergy

Analysis	N trials	N intervention	N control	Pooled risk ratio	95% CI
Primary: **Food allergy (oral food challenge) by 1 to 2 years**	**1** [a]	**491**	**505**	**2.53**	**0.99 to 6.47**
Sensitivity: Food allergy (oral food challenge + panel assessment) by 1 to 2 years	1[a]	547	568	1.46	0.91 to 2.34
Food allergy (parent report of doctor diagnosis) by 1 to 2 years	3[b]	798	816	1.02	0.80 to 1.31

[a] Chalmers 2020. [b] Chalmers 2020; Dissanayake 2019; Yonezawa 2018.

Table 7. Complier average causal effect analyses for food allergy

Complier	N trials	N intervention	N control	CACE		Intention-to-treat	
				Pooled RR	95% CI	Pooled RR	95% CI
Primary CACE: **≥ 3 days of use over intervention period**	**1** [a]	**491**	**505**	**31.19**	**0.43 to 2236.62**	2.53	0.99 to 6.47
Sensitivity: ≥ 5 days of use over intervention period	1[a]	491	505	47.49	0.09 to 24643.91	2.53	0.99 to 6.47
7 days use over intervention period	1[a]	491	505	125.21	0.00 to 315317.50	2.53	0.99 to 6.47
≥ 3 days of use over *first 3 months* of intervention period	1[a]	491	505	7.39	0.79 to 69.02	2.53	0.99 to 6.47
≥ 5 days of use over *first 3 months* of intervention period	1[a]	491	505	8.08	0.56 to 116.23	2.53	0.99 to 6.47
7 days use over *first 3 months* of intervention period	1[a]	491	505	19.11	0.11 to 3310.01	2.53	0.99 to 6.47

[a]One study is included across all presented analyses: Chalmers 2020.

Table 8. Serious adverse events

Trial	Serious adverse event	Skin care (N events)	Control (N events)	Total (N events)
Cooke 2015	Jaundice	3	0	3
	Viral lung infection	1	0	1
	Seizure (benign myoclonic jerks)	1	0	1
	Total events	**5**	**0**	**5**
Lowe 2018a	Bronchiolitis	3	1	4
	Fever infection	1	0	1
	Respiratory distress	1	0	1
	Total events	**5**	**1**	**6**
Skjerven 2020	Allergic reaction	1	2	3
	Seizure (non-febrile)	1	1	2
	Other	13	18	31
	Bronchiolitis (RS virus or other)	9	6	15
	Croup	0	1	1
	Foreign body aspiration	0	1	1
	Influenza	0	1	1
	Surgery (operation)	1	5	6
	Pneumonia	2	1	3
	Flu/diarrhoea	3	1	4
	Injury or accident	3	4	7
	Urinary infection	2	3	5
	Unspecified reaction	6	10	16
	Total events	**41**	**54**	**95**

APPENDICES

Appendix 1. Search strategy for Cochrane Skin Specialised Register (CRSW)

1. (Emollient* or moisturis* or moisturiz* or cream*):ti,ab AND INREGISTER
2. (Petrolatum or emulsion* or lubrica* or ointment* or lotion* or oil or oils or gel or gels or paste or pastes or salve* or unguent*):ti,ab AND INREGISTER
3. (Bath or baths or bathing or bathe* or soap* or water soften* or hard water or water hardness or skin care):ti,ab AND INREGISTER
4. #1 OR #2 OR #3
5. MESH DESCRIPTOR infant EXPLODE ALL AND INREGISTER
6. MESH DESCRIPTOR infant newborn EXPLODE ALL AND INREGISTER
7. (new next born*):ti,ab AND INREGISTER
8. (newly next born*):ti,ab AND INREGISTER
9. (neo next nat*):ti,ab AND INREGISTER
10. (Infant* or infancy or newborn* or perinat* or neonat* or baby* or babies):ti,ab,kw AND INREGISTER
11. #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. #4 AND #11

Appendix 2. Search strategy for CENTRAL (Cochrane Library)

#1 MeSH descriptor: [Emollients] explode all trees
#2 emollient*:ti,ab,kw
#3 moisturis*:ti,ab,kw
#4 moisturiz*:ti,ab,kw
#5 MeSH descriptor: [Skin Cream] explode all trees
#6 cream*:ti,ab,kw
#7 {OR #1-#6}
#8 MeSH descriptor: [Petrolatum] explode all trees
#9 petrolatum:ti,ab,kw
#10 MeSH descriptor: [Emulsions] explode all trees
#11 emulsion*:ti,ab,kw
#12 MeSH descriptor: [Lubricants] explode all trees
#13 lubrica*:ti,ab,kw
#14 MeSH descriptor: [Ointments] explode all trees
#15 ointment*:ti,ab,kw
#16 lotion*:ti,ab,kw
#17 MeSH descriptor: [Oils] explode all trees
#18 (oil or oils):ti,ab,kw
#19 (gel or gels):ti,ab,kw
#20 (paste or pastes or salve* or unguent*):ti,ab,kw
#21 {OR #8-#20}
#22 skin:ti,ab,kw
#23 MeSH descriptor: [Skin] explode all trees
#24 #22 or #23
#25 #21 and #24
#26 (bath? or bathe? or bathing):ti,ab,kw
#27 MeSH descriptor: [Baths] explode all trees
#28 MeSH descriptor: [Soaps] explode all trees
#29 soap*:ti,ab,kw
#30 MeSH descriptor: [Water Softening] explode all trees
#31 water soften*:ti,ab,kw
#32 (hard water or water hardness):ti,ab,kw
#33 MeSH descriptor: [Skin Care] explode all trees
#34 {OR #26-#33}
#35 #7 or #25 or #34
#36 MeSH descriptor: [Infant] explode all trees
#37 MeSH descriptor: [Infant, Newborn] explode all trees
#38 (Infant? or infancy or newborn* or perinat* or neonat* or baby* or babies or new next born* or newly next born* or neo next nat*):ti,ab
#39 #36 or #37 or #38
#40 #35 and #39

Appendix 3. Search strategy for MEDLINE (Ovid)

1. exp Emollients/
2. emollient$.ti,ab.
3. moisturis$.ti,ab.
4. moisturiz$.ti,ab.
5. exp Skin Cream/
6. cream$.ti,ab.
7. or/1-6
8. exp Petrolatum/
9. petrolatum.ti,ab.
10. Emulsions/
11. emulsion$.ti,ab.
12. exp Lubricants/
13. lubrica$.ti,ab.
14. exp Ointments/
15. ointment$.ti,ab.
16. lotion$.ti,ab.
17. exp Oils/
18. oil$1.ti,ab.
19. (gel or gels).ti,ab.
20. (paste$1 or salve$ or unguent$).ti,ab.
21. or/8-20
22. skin.mp.
23. exp Skin/
24. or/22-23
25. 21 and 24
26. bath$3.ti,ab.
27. exp Baths/
28. exp Soaps/
29. soap$.ti,ab.
30. exp Water Softening/
31. water soften$.ti,ab.
32. (hard water or water hardness).ti,ab.
33. exp Skin Care/
34. or/26-33
35. 7 or 25 or 34
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. randomized.ab.
39. placebo.ab.
40. clinical trials as topic.sh.
41. randomly.ab.
42. trial.ti.
43. 36 or 37 or 38 or 39 or 40 or 41 or 42
44. exp animals/ not humans.sh.
45. 43 not 44
46. exp infant/ or exp infant, newborn/
47. (Infan$ or newborn$ or new next born$ or newly next born$ or perinat$ or neonat$ or neo next nat$ or baby$ or babies).mp.
48. 46 or 47
49. 35 and 45 and 48

[Lines 36-45: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format, from section 3.6.1 in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook]

Appendix 4. Search strategy for Embase (Ovid)

1. exp emollient agent/
2. emollient$.ti,ab.
3. moisturis$.mp.

4. moisturiz$.mp.
5. skin cream/
6. cream$.ti,ab.
7. or/1-6
8. exp petrolatum/
9. petrolatum.ti,ab.
10. exp emulsion/
11. emulsion$.ti,ab.
12. exp lubricating agent/
13. lubrica$.ti,ab.
14. exp ointment/
15. ointment$.ti,ab.
16. exp lotion/
17. lotion$.mp.
18. oil$1.ti,ab.
19. (gel or gels).mp.
20. (paste$1 or salve$ or unguent$).ti,ab.
21. exp paste/
22. exp salve/
23. or/8-22
24. exp skin/
25. skin.mp.
26. 24 or 25
27. 23 and 26
28. exp bath/
29. bath$3.ti,ab.
30. exp soap/
31. soap$.ti,ab.
32. water soften$.ti,ab.
33. exp skin care/
34. exp water hardness/
35. (hard water or water hardness).ti,ab.
36. or/28-35
37. 7 or 27 or 36
38. crossover procedure.sh.
39. double-blind procedure.sh.
40. single-blind procedure.sh.
41. (crossover$ or cross over$).tw.
42. placebo$.tw.
43. (doubl$ adj blind$).tw.
44. allocat$.tw.
45. trial.ti.
46. randomized controlled trial.sh.
47. random$.tw.
48. or/38-47
49. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
50. human/ or normal human/
51. 49 and 50
52. 49 not 51
53. 48 not 52
54. infant/ or baby/ or exp newborn/
55. (Infan$ or newborn$ or new next born$ or newly next born$ or perinat$ or neonat$ or neo next nat$ or baby$ or babies).mp.
56. 54 or 55
57. 37 and 53 and 56

[Lines 38-53: Based on terms suggested for identifying RCTs in Embase (section 3.6.2) in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook]

Appendix 5. Search strategy for clinicaltrials.gov register

emollient OR emollients OR moisturiser OR moisturisers OR moisturizer OR moisturizers OR barrier OR skin OR skincare OR bath OR bathing OR water softener OR water softeners OR water treatment

Appendix 6. Search strategy for WHO ICTRP trials register

emollient OR emollients OR moisturiser OR moisturisers OR moisturizer OR moisturizers OR barrier OR skin OR skincare OR bath OR bathing OR water softener OR water softeners OR water treatment

Appendix 7. Variables requested from trials for the individual participant data meta-analysis (IPDMA)

Patient identifiers for analysis inclusion
1. Unique patient ID (anonymous - or please give a new SCiPAD ID and keep log of the corresponding trial ID)
2. Randomised treatment allocation
3. Date of randomisation
4. Received randomised treatment (yes/no)
5. Included in the trials' primary analysis (yes/no)
Primary outcomes
6. Eczema (at all time points collected and using all recorded measures of eczema or eczema symptoms, e.g. UK Working Party definition and investigator-assessed – please send all eczema measures used and additional variables on skin condition (itch etc) pre formal eczema diagnosis and time point)
7. Food allergy (at all time points collected and using all recorded measures, e.g. using oral food challenge and investigator-assessed – please send all food allergy measures used)
Secondary outcomes
8. Slippage accidents around the time of bathing or application of emollient[a]
9. Skin infections during the intervention period[a]
10. Stinging or allergic reactions to moisturisers[a]
11. Serious adverse events[a]
12. Time of eczema onset (first report of a diagnosis of eczema as a specific date or first visit date eczema recorded)
13. Eczema severity - clinician-assessed: EASI or similar validated measure (at all time points collected) 14. Eczema severity - parent-assessed: POEM or similar validated measure (at all time points collected) 15. Parent-reported of immediate (< 2 hours) reaction to a known food allergen: milk, soya, wheat, fish, seafood, peanut, tree nut, egg, or local common food allergen (at all time points collected and for each food allergen recorded) 16. Allergic sensitisation to foods and inhalants via skin prick test (at all time points collected and for each food and inhalant recorded)
Infant baseline characteristics
17. Gestational age at birth
18. Sex[b]
19. Birth weight
20. Pre-existing health state in the infant, such as very preterm birth (less than 32 weeks' gestation) or congenital skin condition

(Continued)

21. Infant already diagnosed with eczema at the time of randomisation

22. Infant already diagnosed with food allergy at the time of randomisation

23. Age intervention began (e.g. number of days between birth and randomisation)

24. *FLG* genotype (method of analysis and what *FLG* mutations were genotyped)

25. Ethnicity

26. Mode of delivery (e.g. caesarean, vaginal)

27. Method of feeding (e.g. breastfeeding at all time points recorded)

28. Any additional trial randomisation stratification factors

Family baseline characteristics

29. Age of mother at randomisation or enrolment

30. Age of father at randomisation or enrolment

31. Ethnicity of mother

32. Ethnicity of father

33. Educational status of mother

34. Educational status of father

35. Socioeconomic group

36. Singleton or multiple pregnancy

37. Number of other children living at home (without new child – or indicate if this includes the new child)

38. Whether any cats living in the household/living environment?

39. Whether any dogs living in the household/living environment?

40. Mother took any antibiotics during pregnancy?

41. Mother took any regular probiotic supplements during pregnancy?

42. Smoking status of mother

43. Smoking status of father

Family history of atopic disease

44. Number of first-degree relatives with atopic disease (0, 1, 2, or more)[b] [Please indicate how atopic disease is defined]

45. Number of first-degree relatives with eczema (0, 1, 2, or more)

46. Number of first-degree relatives with food allergy (0, 1, 2, or more)

47. Number of first-degree relatives with asthma (0, 1, 2, or more)

48. Number of first-degree relatives with rhinitis/hay fever (0, 1, 2, or more)

Compliance data

49. Data on compliance with intervention, including measures such as grams per day and total number of grams of product dispensed over the study

(Continued)

50. Duration of treatment
51. Dates of treatment withdrawal and reason(s) for treatment withdrawal
Non-assigned skin care
52. Frequency of bathing
53. Product used for bathing (if not part of intervention)
54. Prescribed topical treatment use
55. Any other skin treatments
For cluster-randomised trials
56. Cluster-randomisation factors
Food introduction
57. Any data on the time/age when allergenic foods were introduced
58. Any data on the time/age when solid foods were introduced

EASI: Eczema Area and Severity Index; ***FLG*:** filaggrin gene; **POEM:** Patient-Oriented Eczema Measure

[a]Adverse events of interest. All adverse events may be sent if trials do not have these separated out.
[b]Critical baseline variables required for covariate adjustment within primary and secondary analyses.

HISTORY

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CONTRIBUTIONS OF AUTHORS

MK was the contact person with the editorial base.
RJB and HW conceived of the meta-analysis.
SC and VC wrote the Statistical Analysis Plan; RJB, MK, and AL contributed to this; and all authors reviewed and contributed to the final version of the SAP.
LA and LD provided advice and expertise on conducting a prospective individual participant data (IPD) meta-analysis.
RJB, SC, MK, and EVV co-ordinated contributions from the co-authors and wrote the final draft of the review.
SC, MK, LT, and RJB screened papers against eligibility criteria; EVV and MK screened grey literature.
SC, MK, and LT obtained data on ongoing and unpublished studies.
KLC, HS, ER, AL, ED, NS, KY, YO, KYH, KM, JS, ES, DM, MC, AC, JC, SW, and HW provided IPD from their individual trials, reviewed and contributed to the protocol, reviewed and contributed to the SAP, and reviewed the final version of the review.
RJB, SC, and MK appraised the quality of papers.
SC, MK, and LT extracted data for the review and sought additional information about papers.
SC and LT entered data into RevMan.
SC analysed and interpreted data. RJB and MK reviewed and commented on data analyses, conducted GRADE evaluations, and drafted the 'Summary of findings' table.
RJB, SC, and MK wrote the text of the review and responded to feedback from other authors and peer reviewers.
SC and VC responded to the methods and statistics comments of the referees.
MC provided expert advice on formulation of topical emollients.
CS provided expert advice on classification of topical skin interventions.
EA developed the methods section with SC and VC and reviewed the protocol and review and 'Summary of findings' tables to ensure alignment with Cochrane requirements.
EVV reviewed the full report to ensure that it corresponded to MECIR standards, and co-ordinated the final review with all co-authors.

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DECLARATIONS OF INTEREST

Maeve Kelleher: I have received honoraria (personal payment) for speaking at educational conferences organised by Allergy UK, University of Oslo, and Nutricia, which does not manufacture/market any of the interventions or potential comparators in this review.

Suzie Cro: None known.

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Håvard Ove Skjerven: My institution received money for the PreventADALL study from the two largest governmental grant agencies in Norway, The South-Eastern Norway Regional Health Authority and the Norwegian Research Council, which are not commercial sponsors (Lødrup 2018).

Eva Maria Rehbinder: I declare no real or perceived conflict of interest for the present review; however, I have personally received honoraria in the last 36 months for presentations on atopic dermatitis and psoriasis from Sanofi Genzyme, Perrigo, MEDA, Novartis, and Norwegian patient organisations for atopic dermatitis and psoriasis.

Adrian Lowe: My institution has received National Health and Medical Research Council grant and fellowship funding to undertake a skin barrier intervention study. I also declare that Primus Pharmaceuticals and PuraCap Pharmaceuticals have donated EpiCream (a skin barrier treatment) for use in these studies, free of charge.

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Michael Cork: My institution received a grant from Hyphens Pharma for 'An investigation of the effects of a barrier repair cream on the structure and function of the skin (BARRIER)' (clinical trial).

My institution received a grant from L'Oreal (La Roche Possay) for 'An investigation of the skin barrier restoring effects of a cream containing ceramides in a multi vesicular emulsion in people with dry, eczema-prone, skin (RESTORE)' (clinical trial).

My institution received a grant from Johnson & Johnson for 'A randomised controlled trial of a specially designed wash product and lotion for the maintenance of healthy skin and mind in babies (BOND)'.

My institution and I personally received payment for study design and steering, for travel to meetings for study or other purposes, and for participation in review activities (such as data monitoring boards, statistical analysis, end point committees) from Hyphens Pharma, L'Oreal (La Roche Possay), and Johnson & Johnson.

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My institution and I personally received payment for review preparation from Regeneron in collaboration with Sanofi Genzyme with regard to biologic drug trials for atopic eczema; Pfizer with regard to biologic and topical drug trials for atopic eczema; and Galapagos and Kymab with regard to Biologic drug trials for atopic eczema.

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I am or have been an Investigator and Consultant for the following organisations: Astellas, Boots, Dermavant, Galapagos, Galderma, Hyphens, Johnson & Johnson, Kymab, LEO Pharma, L'Oreal, Menlo, Novartis, Oxagen, Pfizer, Procter & Gamble, Reckitt Benckiser, Regeneron, and Sanofi Genzyme.

Alison Cooke: I was funded by a National Institute for Health Research Doctoral Research Fellowship paid to my institution for the OBSeRvE (Oil in Baby Skincare) study (Cooke 2015). This work was independent research supported by the National Institute for Health Research (Doctoral Research Fellowship DRF-2012-05-160). The views expressed in any Cochrane publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. I was an invited expert to an advisory panel on infant skin care; my consultancy fee from Johnson and Johnson was paid to my institution. I was an invited expert speaker at a neonatal skin care symposium at the Royal College of Midwives Annual Conference and at the European Midwives Association Conference, for which I received personal payment from Johnson and Johnson.

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Eric Simpson: I have received personal payment for the following: board membership (from TARGET-DERM, LEO, and Pfizer); consultancy (from AbbVie, Eli Lilly, and Pfizer); travel/accommodations/meeting expenses unrelated to activities listed (from Lilly, LEO Pharmaceutical, and Sanofi Genzyme); and review preparation (from Regeneron, Dermira, and Sanofi Genzyme). My institution received grants/grants pending from Eli Lilly, Incyte, and Kyowa Hakko Kirin. My institution and I personally received payment for lectures including service on speakers bureaus from Forte Bio Rx, Incyte, and Sanofi Genzyme. For more than 17 years, I have been actively involved in epidemiological, clinical and translational research centered on atopic dermatitis (AD). My experience leading multi-centre AD clinical trials and directing our clinical research center for over 10 years shows my commitment to AD research and specifically disease prevention, clinical trial quality, and team science regardless of any previous financial support and activities.

Stephan Weidinger: My institution received grants from La Roche Posay for investigator-initiated study NCT03376243 and from LEO Pharma for investigator-initiated study 2019-000598-22. I received personal payment for advisory board membership from Sanofi Genzyme, Regeneron, LEO Pharma, AbbVie, Pfizer, Kymab, and Eli Lilly. I received personal payment for lectures from Sanofi Genzyme,

Regeneron, LEO Pharma, AbbVie, Eli Lilly, and Novartis, as well as a personal payment for development of educational presentations from Sanofi Genzyme. I am an investigator in a number of clinical trials in atopic dermatitis and psoriasis sponsored by a wide range of pharmaceutical companies. I have received institutional research grants from Sanofi Genzyme, LEO Pharma, and L'Oreal. I have acted as a consultant for Sanofi Genzyme, Regeneron, LEO Pharma, Eli Lilly, AbbVie, Pfizer, Kymab, and Novartis. I have lectured at educational events sponsored by Sanofi Genzyme, Regeneron, LEO Pharma, AbbVie, and Galderma, outside of the submitted work.

Joanne R Chalmers: My institution received money from NIHR for a research for patient benefit grant to conduct this IPD, on which I am a co-applicant. I am co-applicant on the BEEP trial and the BEEP pilot trial, both of which are included in this review (Chalmers 2020).

Hywel C Williams: I was director of the NIHR Health Technology Assessment (HTA) Programme until 1 October 2020. HTA is part of the NIHR, which also supports the NIHR systematic reviews programme from which this work is funded. I am chief investigator for the BEEP study (Chalmers 2020), which was funded by NIHR HTA and is included in this review. Funds go to my University (Nottingham) from the National Institute for Health Research (public funds) as a result of open competition.

Robert J Boyle: I have received personal payment for participating in advisory boards for DBV Technologies and Prota Therapeutics, which develop allergy diagnostics or treatments; have received payment for designing a clinical trial for Dairy Goat Co-operative; and have received personal payment for providing expert testimony in a class action related to an infant formula health claim concerning the development of allergic conditions.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Objectives: We clarified our Objectives, which included removing some redundant text.

Types of outcome measures: We clarified that the time point for all food allergy and eczema outcome analyses (not just the primary outcomes) was by age one to three years, using the closest available time point to two years from each included trial.

Sensitivity and subgroup analysis

We pre-specified sensitivity analysis by outcome measures for the co-primary outcomes of eczema and food allergy by one to three years. This included sensitivity analysis for secure diagnosis of food allergy by oral food challenge or investigator decision using an algorithm developed for the BEEP study. Since only one trial could be included in the primary outcome and in this pre-specified sensitivity analysis for food allergy, but three trials reported data on food allergy as measured by parental report of a doctor diagnosis, we conducted sensitivity analysis using this additional measure of food allergy - parental report of a doctor diagnosis - to utilise the obtained data.

In subgroup analysis, for co-primary outcomes, we planned that we would compare the effects of intervention on participants advised to commence the skin care intervention within the first four weeks of life compared to those who commenced intervention after four weeks. Since all identified trials advised skin care commencement during the first four weeks of life, we compared the effects of intervention on participants advised to commence skin care intervention within the first week of life compared to those who commenced intervention

after the first week of life. We were able to utilise the obtained IPD and to explore the interaction between treatment effects of skin care intervention and actual age at treatment initiation as < 4 days versus ≥ 4 days. We conducted unplanned sensitivity analysis including outcomes measured at earlier time points for the primary outcome of eczema (6 months to 3 years) and the secondary outcome of allergic sensitisation (8 months to 3 years) to fully utilise the obtained individual participant data and to fully explore the implications of excluding from the main analysis data on early-onset eczema or allergic sensitisation.

Complier average causal effect analysis

For the complier average causal effect analysis, we were unable to provide thresholds for defining compliance in the protocol, as it was unknown exactly what interventions and data fields would be available across trials. As pre-specified in the statistical analysis plan (Cro 2020a), before commencement of any meta-analysis, we held a SCiPAD Investigators meeting to establish alternative thresholds for defining compliance based on available data fields. The primary definition of a complier was use of skin care intervention ≥ 3 days a week over the intervention period, which corresponded to the definition used in the largest trial reporting compliance data (Chalmers 2020). Secondary definitions of a complier included use ≥ 5 days a week, 7 days a week over the intervention period, and ≥ 3 days a week, ≥ 5 days a week, and 7 days a week over the first three months of the intervention period.