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Skincare interventions in infants for preventing eczema and food allergy (Protocol)

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[Intervention Protocol]

Skincare interventions in infants for preventing eczema and food allergy

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

Primary objective

1. To assess the effects of skincare interventions, such as emollients, for prevention of eczema and food allergy in infants.

Secondary objectives

1. To ascertain whether active skincare interventions, commenced in early infancy, influence risk of developing eczema or food allergy
2. To identify features of the study populations such as age, hereditary risk and adherence to the interventions, which are associated with the greatest treatment benefit or harm for both eczema and food allergy

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, though there are treatments to alleviate symptoms. The burden of allergic disease on the individual, the family and society is significant (Gupta 2004; Pawankar 2014). The prevalence of such allergic diseases appears to have increased over the last few decades; traditionally this higher prevalence was seen in high-income countries, but there is now an increasing prevalence of allergic diseases 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 IgE sensitisation, either by IgE antibody or by skin prick test, is classified as atopic eczema (Johansson 2003).

Atopic eczema (atopic dermatitis) is most 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 including 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 immunoglobulin E (IgE) antibodies in response to small amounts of common environmental proteins such as pollen, house dust mite, 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, there have been recent proposals to use the term 'eczema' 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 the disease is the combination of both an epidermal barrier function defect along with cutaneous inflammation. Barrier dysfunction can be in part attributed 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 are 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 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 97). The financial cost of childhood eczema incorporates both the direct cost of their care, and the indirect cost of parental time off work, and decreased productivity due to decreased sleep and increased stress. The estimated total cost of eczema care in the USA has been estimated at over USD 5 billion per annum (Drucker 2017).

Eczema typically improves during childhood, with more than 50% of childhood eczema resolving by adolescence (Williams 1998). However more 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 2.1% in Japan (Barbarot 2018). Adults with eczema also 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).

Like most disease prevalence studies, reported prevalence of eczema may vary depending on location of trial and variation in the 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). 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 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, which cannot be modified (Apfelbacher 2011). However genes' interaction 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 including 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. 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, and 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 of diagnosing 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). Food allergy can resolve spontaneously during childhood, so is thought to be less common in adulthood, affecting just 2% to 3%. However a recent US survey study identified a history suggestive of IgE-mediated food allergy in over 10% of adults (Gupta 2019). Like eczema, food allergy is thought to have increased in prevalence in recent decades, although strong and consistent epidemiological data to support this increase are lacking (Prescott 2013; Sicherer 2003). Food allergy also varies in prevalence across different regions, with lower prevalence in areas with lower overall rates of allergic disease, such as parts of Asia and Africa (Prescott 2013).

Food allergy is a considerable burden on both the individual, the family and wider society. Acute reactions can cause significant anxiety, and when severe may rarely result in 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, 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 to affected families and healthcare providers of food allergy has been estimated as at least USD 25 billion per annum (Gupta 2013). In recent decades there have been increased numbers of hospital admissions for food-related anaphylaxis. It is unclear however whether this represents a true increase in incidence 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 and severity-dependent relationship between childhood eczema and risk of food allergy (Martin 2015). Taken together, these studies suggest that eczema may be an important cause of food allergy (Tsakok 2016).

With regards to prevention of food allergy, it has been shown that early introduction of allergenic food can decrease the risk of food allergy, with the strongest evidence for peanut allergy (Du Toit 2015). However, even in this study, a proportion of participants were excluded at screening because they were already sensitised and likely allergic to peanut, with skin tests of over 5 mm. These children were older at age of screening and had worse eczema. This study suggests that early, high-dose oral exposure causes tolerance, and low-dose cutaneous exposure leading to allergic sensitisation suggests that preventing eczema will lead to a decrease in food allergy sensitisation, known as the dual allergen exposure hypothesis (Du Toit 2016). We do not comment further on early introduction, as this occurs in later infancy, whereas skin barrier interventions will begin from early infancy, most often in the first month of life.

Description of the intervention

In this review we will include all interventions designed to improve the skin barrier in infants, either by enhancement or promotion of the barrier through hydration by directly applied topical products such as emollients or moisturisers, or by reduction of potential damage to the skin barrier and consequent dryness through various means such as avoiding soaps or reducing water hardness. We expect that promotion of the skin barrier and skin hydration through topical emollients will 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. There are a number of different 'classes' or 'formulations' of emollients and moisturisers, 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 effect of the product. Further complicating this is the fact that many skincare products are classed as cosmetics and therefore 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 which are directly applied to the skin and allowed to dry in; soap substitutes where an emollient may be used instead of a soap to clean; and bath oils or emollients where 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 the emollients may vary.

Emollients are recommended to be applied two to three times a day, using up to 150g to 200g per week in young children and up to 500g in adults with eczema (Eichenfield 2014; Ring 2012). Overall, emollients are regarded as being safe, with few adverse effects. However, the application of sufficient emollient daily can be time-consuming and unpleasant, having a negative impact on the child and their family (Carroll 2005). Certain emollients can also 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), though there are not documented cases in the literature.

Protection of the skin barrier could also be achieved by limiting water loss across the skin, or through 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 and thereby reduce subsequent eczema prevalence.

Neonatal skin is different from that of children and adults, as it takes time to adjust to the dry extra-uterine 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 other sites (McAleer 2018). However, early neonatal skin has decreased water permeability compared to older children and adults, along with decreased surface pH and stratum corneum formation, demonstrating an effective skin barrier in the early weeks of life (Yosipovitch 2000). Infants have thinner skin with an increased body surface area to volume ratio compared with adults, therefore 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 influences. In the UK, standard skincare advice given to parents of newborns is to wash in plain water for the first month, and 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). There are few emollient studies in term infants, with most studies incorporating premature infants, whose skin is different to term infants (Irvin 2015). Application of an emollient or oil to the skin of newborn infants is practiced in some regions and cultures, for a variety of reasons often unrelated to allergy prevention (Amare 2015).

Timing of 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 caseous intact and allowing it to wear off with normal handling (WHO 2015). When comparing modes of washing, 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 2009). In neonates bathed twice weekly, those washed in age-appropriate liquid cleanser with added cream had a lower transepidermic water loss (TEWL) than those washed with water only, whereas the stratum corneum hydration was similar. Whether this shows improvement in skin barrier is unclear (Garcia 2010). Overall there is no evidence to suggest that the use of age-appropriate wash products or water for bathing is harmful, keeping in mind basic safety principles such as slippages, particularly if using oil based products (Blume-Peytavi 2016). Frequency and timing of infant bathing may vary by culture and region. It is recommended that babies are bathed at least twice per week. Frequency of bathing was addressed in the previous version of the European round table review on infant skincare. In the context of bathing with water only, twice-daily bathing led to increased drying of skin. However it is unclear if this frequency of bathing is harmful on its own or because of the drying effect of water (Blume-Peytavi 2009).

Hard water is relatively rich in calcium and magnesium and 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).

Although this review will cover all potential skincare interventions designed to promote, or reduce damage to, skin barrier and skin hydration, we will also examine leave-on emollients as a separate subgroup analysis.

How the intervention might work

Emollients, as one intervention, are the mainstay of treatment in those with already established eczema as detailed in a Cochrane Review (Van Zuuren 2017). This is because dry skin (xerosis) is a key feature of eczema, and topical moisturisers have an integral role in the standard treatment of all severities of eczema (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 are therefore a key component of treatment of eczema (Ring 2012). They may be more effective than interventions such as less frequent bathing, or water softeners, for eczema prevention.

All moisturisers contain a varying amount of active ingredients such as humectant or ceramide, and excipient ingredients such as emulsifiers (Lodén 2012). Humectants, such as glycerol or urea, aid the retention and attraction of water by the stratum corneum. Ceramides are intracellular lipids found in the stratum corneum, which are reduced in lesional eczematous skin (Meckfessel 2014). Occlusives such as petrolatum form a layer on the skin surface which may prevent TEWL across the stratum corneum and can soften the skin (Eichenfield 2014; Rawlings 2004). Moisturisers can either 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 the regular use of emollients in those with eczema can prolong time to eczema flare, can reduce the number of these flares, and reduce the need for topical corticosteroids. In infants, skin barrier dysfunction is seen prior to the development of clinical eczema (Danby 2011; Flohr 2010). Therefore, applying moisturisers prior to the development of eczema may be a route for primary prevention of eczema. Three pilot studies have been published that suggest that applying moisturisers to infant skin can reduce the prevalence of eczema during the application period (Horimukai 2014; Lowe 2018; Simpson 2014). The pilot studies were small-scale studies testing the feasibility of the intervention or 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 manifestation of eczema could potentially also reduce risk of food allergy, even if it were just to delay the onset of eczema from early infancy, where the association with the development of food allergy is strongest (Martin 2015). In a study pilot of a ceramide-dominant emollient, with an action described as a lipid replacement, there was evidence to suggest reduced allergic sensitisation to foods in the per-protocol analysis of the intervention group (Lowe 2018). Future and ongoing trials can demonstrate whether this effect is confirmed in adequately powered studies.

Why it is important to do this review

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

There are two major ongoing interventional trials assessing whether skincare interventions in the first year of life will reduce the prevalence of eczema or food allergy. The National Institute for Health Research-Health Technology Assessment (NIHR-HTA)-funded Barrier Enhancement for Eczema Prevention (BEEP) study is designed to assess whether daily application of emollients for the first year of life will reduce the prevalence of eczema or allergic disease in the first five years of life (Chalmers 2017; 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 2x2 factorial-designed intervention strategy (skin care and early complementary food introduction) to prevent eczema and food allergy (Lødrup 2018; NCT02449850).

The BEEP study is powered to detect a difference in eczema during the second year. However, there is limited statistical power within this sample size for other outcomes such as food allergy, and for subgroup analyses. For example, BEEP has 80% power at 2-sided alpha of 0.05 for detecting a 50% reduction in food allergy. BEEP is a pragmatic study, which may further limit statistical power given the likely lower level of compliance with recommended skincare advice in that setting.

PreventADALL is powered to detect a difference in eczema during the second year. PreventADALL also has limited statistical power for other outcomes such as food allergy, and for subgroup analyses. There are other smaller studies of primary prevention of eczema or food allergy ongoing in Australia (ACTRN12613000472774), Germany (NCT03376243), Japan, (JPRN-UMIN000004544; JPRN-UMIN000010838; JPRN-UMIN000013260) and the USA (NCT01375205) that may be eligible for inclusion in this systematic review.

This systematic review protocol aims to determine if infant skincare interventions influence eczema or food allergy prevalence. We will include individual participant data meta-analysis (IPDMA). This type of meta-analysis is considered the gold standard of systematic reviews. Database and analysis errors in individual trials can potentially be identified, leading to increased internal validity of the individual studies.

An IPDMA may allow us to (i) fit a consistent analysis model to all trial data sets for each outcome to ensure we are comparing treatment effects that are adjusted for the same covariates across trials; (ii) obtain more reliable and powerful subgroup analyses; and (iii) better evaluate the relationship between compliance with the intervention and our outcomes of interest.

This systematic review will also incorporate a prospectively planned meta-analysis (PPMA), which involves planning the details of the meta-analysis before the results of each trial are known. PPMA reduces bias related to knowledge of existing trial outcomes. Sharing clinical trials data is encouraged as best practice in clinical trials, and the sharing of individual participant data maximises knowledge gained from the efforts of trial participants (Taichman 2017).

OBJECTIVES

Primary objective

1. To assess the effects of skincare interventions, such as emollients, for prevention of eczema and food allergy in infants.

Secondary objectives

1. To ascertain whether active skincare interventions, commenced in early infancy, influence risk of developing eczema or food allergy
2. To identify features of the study populations such as age, hereditary risk and adherence to the interventions, which 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

We will include parallel-group or factorial randomised controlled trials (RCTs). We will not include quasi-RCTs and controlled clinical trials. We will include both individual and cluster-randomised trials. We will not include cross-over trials as the design is inappropriate to the clinical context.

Types of participants

Infants (age 12 months or under). As this is a primary intervention study, we will not include studies on infants who already have diagnosed eczema or food allergy at the time of randomisation. We will also exclude 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, since findings in these populations may not be generalisable.

We will attempt to obtain individual participant data for all included studies. If individual participant data are not available, we will obtain aggregate data instead. For studies with only aggregate data available, we will exclude the whole study if some participants are

not eligible, unless ineligible participants make up an insignificant proportion of the total group, that is, less than 5%. In trials with individual participant data we will only include the data on participants that meet our eligibility criteria.

Types of interventions

We will include all skincare 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;
4. use of water softeners.

Some will be simple single interventions, while others are likely to be complex interventions that utilise a combination of measures to protect or promote skin barrier function, hydration or reduce subclinical inflammation. The comparators will be a no-treatment intervention of advice, or standard care in the study setting; we will analyse these comparators analysed separately. We will exclude multifaceted interventions, where the skincare component is only a small part of the study, if the skincare component is likely trivial or irrelevant to the outcome. We will also assess separately those interventions that primarily aim to enhance the skin barrier through direct application of emollient or moisturiser (skincare intervention A) and those that aim to protect the skin barrier from irritation, that is, use of water softeners (skincare intervention B).

Types of outcome measures

No minimum follow-up rate is required. However, we will separately analyse outcomes that relate to symptoms during the intervention period, and outcomes that occur and are reported after the intervention period, where appropriate and feasible.

Primary outcomes

1. Eczema. Where multiple measures are reported the hierarchy of diagnosis will be investigator assessment as described by the Hanifin and Rajka criteria in their original form (Hanifin 1980), or 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. Where multiple measures of food allergy are reported, we will combine measures of confirmed IgE-mediated food allergy diagnosis made using oral food challenge; eligibility for oral food challenge will be decided as per study protocol, though ideally based on current recommendations (Grabenhenrich 2017). If oral food challenge is not available, then food allergy will be diagnosed by investigator assessment using a combination of clinical history and allergy testing: skin prick testing and serum-specific IgE. We will define 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 are milk, egg and peanut, however we will collect data on any foods that are available from each study.

The time point for primary outcome analysis is by age one to three years using the closest available time point to two years, from each included trial. When pooling data from different trials, we will consider the relationship between the timing of the intervention and the timing of the outcome measure, for example, we will pool measures of eczema taken during the intervention period, and pool measures of eczema taken after the intervention period has ceased separately.

If we identify multiple measures of eczema across trials, we plan a 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. Additionally if we identify multiple measures of food allergy assessment, we will separately look at food allergy measured using secure diagnosis of food allergy by oral food challenge only.

Secondary outcomes

1. Adverse events during intervention period, such as 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 similar validated method (Hanifin 2001)
3. Parent-reported eczema severity using POEM (Patient Orientated Eczema Measure) or similar 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)

Where available, from each trial, we will analyse 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). Where feasible we will aim to contact trial authors early in the design or set-up of their trial, to encourage sharing of outcome assessment methods, instruments used and timing. We will not include long-term disease control and quality of life outcomes in this review.

Search methods for identification of studies

We aim 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 will search the following databases for relevant trials with no restriction by date:

1. the Cochrane Skin Specialised Register;

2. the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
3. MEDLINE via Ovid (from 1946 onwards); and
4. Embase via Ovid (from 1974 onwards).

A draft search strategy has been devised for RCTs for MEDLINE (Ovid), which is displayed in Appendix 1. This will be used as the basis for search strategies for the other databases listed.

Trials registers

We (MK, SC, and LT) will search the following trials registers:

1. ClinicalTrials.gov (www.clinicaltrials.gov) using the draft search strategy in Appendix 2; and
2. the World Health Organization International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/) using the draft strategy in Appendix 3.

Searching other resources

1. Searching by contacting relevant individuals or organisations: we will contact experts in the field of paediatrics, allergy and dermatology, and manufacturers of infant skincare products in order to identify planned trials and to seek information about unpublished or incomplete trials.
2. Conference proceedings: we will review the proceedings of the Asia Pacific Association of Pediatric Allergy, Respirology & Immunology conference (APAPARI) for the most recent three years.
3. Searching reference lists: we will check the bibliographies of included trials and any relevant systematic reviews identified for further references to relevant RCTs.
4. Correspondence with trial authors/experts/organisations: we will contact original trial authors for clarification and further data if trial reports are unclear.
5. Adverse effects: we will not perform a separate search for adverse effects of interventions used for the prevention of eczema and food allergy. We will consider adverse effects described in included trials only.

Data collection and analysis

The trial investigators will undertake this systematic review according to the methods recommended by Cochrane, including chapters 18 (Stewart 2011), and 19 (Ghersi 2011), of the *Cochrane Handbook for Systematic Reviews of Interventions*, written by the Prospective Meta-Analysis Methods Group. The *Cochrane Handbook for Systematic Reviews of Interventions* was updated during the development of this protocol and Version 6.0, and this protocol is in line with the updates (Higgins 2019). A summary record of the prospectively planned component of the meta-analysis has been registered on PROSPERO (reference 42017056965 registered 10 February 2017; Boyle 2017).

Selection of studies

Two review authors (from MK, SC and LT) will independently carry out title, abstract and full-text screening will be done independently, with arbitration by a third review author (RJB) where necessary. In this systematic review we will combine both retrospective and prospectively acquired data in meta-analysis. Retrospective data are those outcome data acquired, analysed, unblinded and known to the trial Chief Investigator prior to registration of the systematic review protocol (PROSPERO reference 42017056965 registered 10 February 2017; Boyle 2017). Prospectively acquired data are those data that were not known to their trial Chief Investigator, in analysed and unblinded form, prior to 10 February 2017. The intention of this systematic review is to use participant-level data from all trials where possible. We will invite 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 will ask all trial authors to provide individual participant data. If the authors of some trials are unable to provide participant-level data, we will accept appropriate summary data.

Data extraction and management

We will conduct data collection and handling in accordance with the guidance in chapter 26.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Stewart 2019). For each of the included trials we plan to extract descriptive data on the trial setting, methods, participants, interventions, comparator, length of follow-up, instruments used for measuring outcomes, funding source, and conflicts of interest. Two review authors (MK, SC, or LT) will independently extract data by using a standardised collection form, discussing any disagreements to reach a resolution. Should this be unsuccessful, they will consult a third review author (RJB). We will request that trial authors, who have agreed to provide information or data beyond that available in the public sphere, share protocol and statistical analysis plan details, and details of available data fields.

All data used in the systematic review will be de-identified. The list of variables we will particularly request is provided in Appendix 4. We will transfer specific data fields and then clean and code them for analysis by those trials willing to provide individual participant data. Data sources from previously published trials may be provided as anonymised whole databases if those trial authors prefer. We will carry out range and consistency checks for all data. Any missing data, obvious errors, inconsistencies between variables or extreme values will be queried and rectified with the individual trial authors as necessary. A secure record will be kept of all correspondence, agreements and data transfers with trial authors, and the systematic review database.

For included trials that are unable to provide individual participant data we will record the reason for data unavailability and request aggregate data on our outcomes. If aggregate data cannot be obtained directly from the trial authors, two review authors will assess whether any relevant appropriate aggregate-level data are available in the trial publication or other sources (e.g. clinical trials registry). We will record aggregate data on a standardised extraction form. Two review authors (MK, SC, or LT) will independently extract data. We will discuss any disagreements on extracted aggregate data and resolve them by consensus, including a third review author if necessary (RJB).

The detailed statistical analysis plan for this review was written when the Case Report Forms (CRF) and data fields for the trials providing individual participant data were known, but before any grouped outcome data from the prospective trials had been evaluated (Cro 2020). The statistical analysis plan was therefore written taking into consideration the nature and limitations of the data recorded in trials that were known to be eligible for inclusion.

Whilst 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 analysis and coding decisions on findings.

Assessment of risk of bias in included studies

We will assess risk of bias using the Cochrane 'Risk of bias' tool 2 (RoB 2; Higgins 2018). This tool is 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 will assess 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 closest time point to two years), slippage accidents (during intervention period), skin infection (during intervention period), allergic reactions (during intervention period), time to onset eczema, parent report food allergy (by age one to three years using the closest time point to two years) and allergic sensitisation (by age one to three years using the closest time point to two years). The tool is outcome-specific and we will rate each domain as 'low risk of bias', 'some concerns' or 'high risk of bias'. For bias due to deviations from intended interventions, we are interested in the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended by an intention-to-treat analysis that includes all randomised participants. Bias in selection of the reported result will likely be low risk for all prospectively identified studies as we intend to obtain the full dataset for these trials.

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

1. Overall low risk of bias: all domains considered 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 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) will independently conduct 'Risk of bias' assessments, with any disagreements resolved via discussion or through arbitration with a third review author (RJB).

Measures of treatment effect

For binary outcomes where meta-analysis is considered appropriate we will calculate risk ratios (RR). For continuous outcomes where trials use the same measurement scale, we will calculate the mean difference (MD); when trials use different measurement scales, we will calculate the standardised mean difference (SMD). For time-to-event outcomes we will express the intervention effect as a hazard ratio (HR). We will also compute a 95% confidence interval (CI) for each outcome.

Unit of analysis issues

This review will include RCTs only. As elaborated on further below (see Data synthesis), we will be adopting a two-stage approach for this IPDMA. This entails in stage 1 first separately estimating the treatment effect of interest for each included trial. In stage 2, we will pool together the treatment effects using methods for meta-analyses of aggregate data.

Factorial and cluster-RCTs can be included. For factorial randomised trials, if there is a significant interaction between the two active interventions with respect to our primary outcome, then we will only include the arms 'skin barrier intervention/ control' versus 'control/control'. Where data collection across trials allows, additional analysis will explore the impact of including data from all arms of factorial trials where interaction is present, with adjustment for the non-skin barrier intervention.

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

For cluster-RCTs providing non-individual participant data we will extract data from trial reports that have taken into account the clustering in these data; we can then analyse the data using the generic-inverse variance method in Review Manager 5 (RevMan 5; Review Manager 2014). If data are not adjusted for clustering, then we will attempt to estimate the intervention effect by calculating an intracluster correlation coefficient (ICC) following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We may analyse cluster-RCTs with individually randomised trials if we consider it appropriate, but we will conduct a sensitivity analysis to investigate the robustness of combining two different trial designs.

For trials with more than two treatment arms, which could have multiple intervention groups in a particular meta-analysis, we will combine all relevant intervention groups into a single group and all relevant control groups into a single control group.

Dealing with missing data

We will deal with missing data according to recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), along with update version 6.0 (Deeks 2019). To resolve missing information about methodological properties of identified trials we will contact authors of the included trials. Where the trial authors are unable to provide the required information, we will rate the relevant 'Risk of bias' criterion using Cochrane 'Risk of Bias 2' (Higgins 2018). We do not anticipate substantial amounts of missing data for the primary outcomes. For trials providing individual participant data, we will naturally handle missing participant data under the assumption of missing-at-random within each trial analysis.

For trials that do not provide individual participant data and report a MD but no SD or other statistic that can be used to derive the SD we will use imputation (Furlan 2009). Specifically, we will 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 the majority of trials do not have

missing SDs in the meta-analysis. If a large proportion of trials (e.g. ≥ 20%) are missing data on parameter variability for a particular outcome, imputation will not be appropriate and we will conduct analysis using only the trials providing complete data, and we will discuss the implications of this alongside results.

We will include trials with substantial amounts of missing data (e.g. rated as high risk of bias or some concerns due to missing data), but to investigate the robustness of results we will perform a sensitivity analysis excluding these trials and any others rated at high risk of bias or with some concerns.

Assessment of heterogeneity

We will examine both clinical and statistical heterogeneity and we will only synthesise data where we judge that the evaluation will provide a meaningful summary. We will assess clinical heterogeneity by examining the characteristics of included participants, types of interventions, primary and secondary outcomes and follow-up period. We will use the I^2 statistic (Higgins 2003), to quantify the degree of statistical heterogeneity of trials judged as clinically homogeneous. An I^2 greater than 75% will be indicative of considerable heterogeneity (Deeks 2019). Where the magnitude and direction of effects, and the strength of evidence for heterogeneity based on confidence intervals for I^2 reveal heterogeneity, or we observe considerable heterogeneity, we will explore reasons for heterogeneity and where appropriate conduct sensitivity analysis excluding any trials identified as outlying.

Assessment of reporting biases

By aiming to include as many prospective trials as possible in this review, as well as individual participant data, the risk of reporting bias and publication bias should be reduced. However, when there are at least 10 trials included in the meta-analysis we will use funnel plots to explore the likelihood of any reporting bias or small study effects. We will assess funnel plot asymmetry visually and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997. For dichotomous outcomes we will use the test proposed by Rucker when estimated between-study heterogeneity variance of log odds ratios, tau^2, is more than 0.1 (Rucker 2008). Otherwise, when the heterogeneity variance tau^2 is less than 0.1, we will use one of the tests proposed by Harbord (Harbord 2006). If asymmetry is detected in any of these tests or is suggested by a visual assessment we will explore and discuss possible explanations.

Data synthesis

Our intention is to conduct an IPDMA of both prospective and retrospectively acquired data. Primary meta-analysis will use all data, including individual participant data where available, and aggregate data where individual participant data could not be provided if the total proportion of participants that make up aggregate data is greater than 10% of the overall number of participants across all trials (i.e. when the total aggregate data represents a non-negligible proportion of the data set). We will perform a sensitivity analysis of trials providing individual participant data only. This sensitivity analysis may be biased as it would exclude the trials providing aggregate data but it would be of interest to look at the results using individual participant data that we have analysed directly.

If aggregate data represents only an insignificant proportion of the dataset, less than 10%, then the primary analysis will be on individual participant data only. In this scenario we will undertake a sensitivity analysis adding in the aggregate data, as described further below to explore the impact of data availability bias. We will undertake PPMA of a more limited number of trials, as a sensitivity analysis. PPMA will be limited to those trials where the trial authors were not aware of trial outcomes at the time of PPMA protocol registration on PROSPERO (10 February 2017; Boyle 2017).

Analyses will estimate the effect of being assigned to receive the intervention. Analysis will follow the intention-to-treat principle. We will retain all participants eligible in the treatment group to which they were originally assigned who have an outcome, irrespective of the treatment they actually received. We have pre-planned a secondary supplementary analysis to estimate the Complier Average Causal Effect to understand the effect of compliance.

We will perform all analyses stratified by the type of control group. Comparisons will therefore be:

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

For each outcome, where we judge a sufficient number of trials (two or more) to be clinically similar, we will pool results in meta-analysis. When we do not undertake meta-analyses owing to clinical heterogeneity or to insufficient data, we will narratively discuss the results from individual trials.

We will take a two-stage approach to analysis for all primary and secondary analyses. In the first stage, we will derive individual trial treatment effect estimates from the individual participant data. For the analyses of the binary outcomes, including both primary outcomes (eczema and food allergy), the stage 1 model, fitted to each trial providing individual participant data separately, will be a binomial regression model. For the analyses of the continuous outcomes, the stage 1 model fitted to each trial providing individual participant data will be a linear regression model. For time-to-event outcomes, the stage 1 model fitted to each trial providing individual participant data will be a binomial regression model with a complementary log-log link, where follow-up time has been split into appropriate intervals for the obtained data, for example, as three intervals (3 months, 6 months, 12 months). This model is appropriate for discrete time-to-event data. In addition to the treatment group variable indicating use of skincare intervention, we will include important prognostic factors such as sex and family history within the stage 1 models.

In the second stage, we will combine the derived treatment effects using methods for meta-analyses of aggregate data. For the primary analysis, the second stage will also include aggregate data from trials providing aggregate data only. We will use random-effects models in stage 2 to derive the pooled treatment effect (DerSimonian 1986). We plan to use random-effects models because we anticipate some level of variability across trials, for example, by the types of interventions, length of follow-up, and methods of measurement. A random-effects model will incorporate heterogeneity among trials and allows the true treatment effect to be different in each trial.

We will perform residual analysis for all IPDMA and PPMA to assess model assumptions and fit. Meta-analyses will include 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 will estimate control event rates using random-effects meta-analyses of the pooled proportions from the largest trials included in the meta-analyses and comparing them with event rates from large population-based studies. Trial sequential analysis will identify when the optimum information size or futility boundaries for pre-defined effect sizes in relation to primary outcomes have been reached. We will perform IPDMA in Stata 15 or above (Stata), with summary results of these analyses added into RevMan 5 (Review Manager 2014).

To explore the impact of compliance we will estimate the effect of complying with the intended intervention. For the subgroup of trials providing compliance data we will estimate the complier average causal effect (CACE) for each primary outcome. As in the primary analysis, we will follow a two-stage approach to analysis. For each trial, we will estimate the CACE using instrumental variable (IV) analysis. We will use randomisation as an instrumental variable for intervention received and we will estimate the CACE using a two-stage residual inclusion estimator approach (2SRI) (Cook 2018). Randomisation meets the criteria for an adequate instrument since (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 will initially define a 'complier' using the individual trials' definition of a complier. Where interventions and the quality of compliance data are sufficiently comparable, we will use random-effects models in stage 2 to derive the pooled CACE effect. We will repeat the primary analysis for each of the trials in the subgroup of trials with compliance data and we will compare the pooled CACE estimates against the primary treatment effect (RR) estimating the effect of being assigned to the intervention for the subgroup of trials where compliance data is available. Subsequently, we will explore the impact of different threshold values for defining compliance.

The detailed statistical analysis plan sets out all the comparisons to be made and the precise model forms and fitting strategy. It specifies the statistical models with regard to which covariates will be included (Cro 2020).

Subgroup analysis and investigation of heterogeneity

Subgroups of interest that we have identified a priori for analysis are as follows.

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

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

Sensitivity analysis

We will conduct a priori planned sensitivity analyses.

1. By risk of bias: we will aim to include all trials regardless of risk of bias, and will undertake a sensitivity analysis of trials, and outcomes within trials, which are assessed as having a low risk of bias. The low 'risk of bias' sensitivity analysis will exclude trials at high risk or those with some concerns, assessed using the Cochrane Risk of Bias tool 2 (Higgins 2018). This will include omitting trials with a high risk of bias or those with some concerns due to missing data.
2. By outcome measures: we will explore the impact of using different definitions of outcome measures by undertaking sensitivity analyses of outcomes that have previously been validated. For the primary outcome eczema, in the absence of agreed core outcomes, we will undertake sensitivity analysis of eczema evaluated using 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 will undertake sensitivity analysis for secure diagnosis of food allergy by oral food challenge or investigator decision using an algorithm developed for the BEEP study.
3. Excluding aggregate trials that do not provide individual participant data. We intend to include all data, both individual participant data and aggregate, in the primary analysis. In this case a sensitivity analysis will be conducted *excluding* trials that do not provide individual participant data. If aggregate data makes up to less then < 10% of the total number of participants across all trials then our primary analysis will include individual participant data only and we will conduct a sensitivity analysis *including* aggregate trials that do not provide individual participant data.
4. Excluding any data that are not prospectively acquired. Prospectively acquired data are data which were not known to their study Chief Investigator, in analysed and unblinded form, prior to 10 February 2017. PPMA reduces bias related to knowledge of existing trial outcomes, which might influence trial selection in a retrospective study, since trials are included without any knowledge of outcome. Additionally, outcomes across the prospectively planned trials will be more closely aligned due to awareness of being included in this IPDMA. Propective meta-analysis will be conducted using the same

approach to the primary analysis (i.e. individual participant data only or individual participant data plus aggregate data, see Data synthesis section)

5. To explore heterogeneity: where considerable statistical heterogeneity is observed (I^2 > 75%) we will explore reasons for heterogeneity and where appropriate conduct sensitivity analysis excluding any trials identified as outlying. Outlying trials are those with very different trial findings to others reporting comparable interventions/outcomes. Outliers will be identified from an inspection of the 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, if there is a significant interaction between the two active interventions with respect to our primary outcome, then we will only include the arms 'skincare intervention/control' versus 'control/control'. In such scenarios an additional sensitivity analysis will explore the impact of including data from all arms of factorial trials, with adjustment for the non-skin barrier intervention in stage 1 for the factorial trial.

Summary of findings and assessment of the certainty of the evidence

Our 'Summary of findings' tables will include:

1. 'Summary of findings' table 1. Skincare intervention versus no skincare intervention
   a. The table will include primary estimates of treatment effects in addition to the effect of complying with the intervention for the primary outcomes.
2. 'Summary of findings' table 2. Skincare intervention A versus no skincare intervention
   a. Low risk of eczema and food allergy versus high risk of eczema and food allergy, either by FLG mutation or family history of allergic disease.
   b. (Intervention A = skincare interventions that aim to promote hydration or barrier function)
3. 'Summary of findings' table 3. Skincare intervention B versus no skincare intervention
   a. Low risk of eczema and food allergy versus high risk of eczema and food allergy, either by FLG mutation or family history of allergic disease.
   b. (Intervention B = skincare interventions that aim to prevent damage)

For other sensitivity and subgroup analyses we plan to include outcomes in the 'Comments' in 'Summary of findings' table 1, so that if there are important findings there, they can be commented on with the relevant risk ratio in the Abstract.

Outcomes for 'Summary of findings' tables

Primary outcomes

1. Eczema diagnosis
2. IgE-mediated food allergy

Key secondary outcomes

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

For sensitivity and subgroup analyses we plan to include outcomes in the 'Comments' in 'Summary of findings' table 1, so that if there are important findings there, they can be commented on with the relevant risk ratio in the Abstract.

Quality of the evidence

We will apply the GRADE approach to our main comparisons listed above (Andrews 2013). The outcomes we shall include in our 'Summary of findings' tables are the primary outcomes of eczema and food allergy, adverse events during the intervention period and 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) will independently assess each outcome for trial limitations, imprecision, inconsistency, indirectness and publication bias, and downgrade where appropriate. We will grade each outcome as either high, moderate, low or very low quality.

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REFERENCES

Additional references

Abuabara 2018

Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: a systematic review and meta-analysis of longitudinal studies. *Allergy* 2018;**73**(3):696-704.

ACTRN12613000472774

ACTRN12613000472774. The PEBBLES study: prevention of eczema by a barrier lipid equilibrium strategy [Does twice daily application of a ceramide dominant cream (EpiCeram) for the first six months of life reduce the incidence of eczema by six months of age, when compared to standard skin care, in infants who have a family history of allergic disease]. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=364115 (first received 26 April 2013).

Amare 2015

Amare Y, Shamba DD, Manzi F, Bee MH, Omotara BA, Iganus RB, et al. Current neonatal skin care practices in four African sites. *Journal of Tropical Pediatrics* 2015;**61**(6):428-34. [DOI: 10.1093/tropej/fmv053]

Andrews 2013

Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *Journal of Clinical Epidemiology* 2013;**66**(7):726-35. [DOI: 10.1016/j.jclinepi.2013.02.003]

Apfelbacher 2011

Apfelbacher CJ, Diepgen TL, Schmitt J. Determinants of eczema: population-based cross-sectional study in Germany. *Allergy* 2011;**66**(2):206-13.

Asher 2006

Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**(9537):733-43.

Bai 2017

Bai G, Herten MH, Landgraf JM, Korfage IJ, Raat H. Childhood chronic conditions and health-related quality of life: findings from a large population-based study. *PloS one* 2017;**12**(6):e0178539.

Barbarot 2018

Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy* 2018;**73**(6):1284-93.

Blume-Peytavi 2009

Blume-Peytavi U, Cork M, Faergemann J, Szczapa J, Vanaclocha F, Gelmetti C. Bathing and cleansing in newborns from day 1 to first year of life: recommendations from a European round table meeting. *Journal of the European Academy of Dermatology and Venereology* 2009;**23**(7):751-9.

Blume-Peytavi 2016

Blume-Peytavi U, Lavender T, Jenerowicz D, Ryumina I, Stalder JF, Torrelo A, et al. Recommendations from a European roundtable meeting on best practice healthy infant skin care. *Pediatric Dermatology* 2016;**33**(3):311-21.

Bock 1988

Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *Journal of Allergy and Clinical Immunology* 1988;**82**(6):986-97.

Boyce 2010

Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *Journal of Allergy and Clinical Immunology* 2010;**126**(6):S1-58.

Boyle 2017

Boyle R, Williams H, Askie L, Lodrup-Carlsen K, Montgomery A, Chalmers J, et al. Prospectively planned meta-analysis of skin barrier studies for the prevention of eczema and associated health conditions. www.crd.york.ac.uk/prospero/display_record.php?RecordID=56965 (first received 10 February 2017).

Carroll 2005

Carroll CL, Balkrishnan R, Feldman SR, Fleischer AB, Manuel JC. The burden of atopic dermatitis: impact on the patient, family, and society. *Pediatric Dermatology* 2005;**22**(3):192-9.

Caussin 2009

Caussin J, Rozema E, Gooris GS, Wiechers JW, Pavel S, Bouwstra JA. Hydrophilic and lipophilic moisturizers have similar penetration profiles but different effects on SC water distribution in vivo. *Experimental Dermatology* 2009;**18**(11):954-61.

Chalmers 2017

Chalmers JR, Haines RH, Mitchell EJ, Thomas KS, Brown SJ, Ridd M, et al. Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (the BEEP trial): protocol for a randomised controlled trial. *Trials* 2017;**18**(1):343.

Charman 2004

Charman CR, Venn AJ, Williams HC. The Patient-Oriented Eczema Measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Archives of Dermatology* 2004;**140**(12):1513-9.

Cook 2018

Cook JA, MacLennan GS, Palmer T, Lois N, Emsley R. Instrumental variable methods for a binary outcome were used

to informatively address noncompliance in a randomized trial in surgery. *Journal of Clinical Epidemiology* 2018;**96**:126-32.

Cooke 2018

Cooke A, Bedwell C, Campbell M, McGowan L, Ersser SJ, Lavender T. Skin care for healthy babies at term: a systematic review of the evidence. *Midwifery* 2018;**56**:29-43.

Cork 2002

Cork MJ, Murphy R, Carr J, Buttle D, Ward S, Båvik C, et al. The rising prevalence of atopic eczema and environmental trauma to the skin. *Dermatology in Practice* 2002;**10**(3):22-6.

Cro 2020

Cro S, Boyle R, Kelleher M, Tran L, Cornelius V. Skin care interventions for preventing eczema and food allergy: a statistical analysis plan for a systematic review and individual participant data meta-analysis. zenodo.org/record/3610604#.XiGKU8j7SUk (accessed 16 January 2020). [DOI: 10.5281/zenodo.3610604]

Danby 2011

Danby SG, Al-Enezi T, Sultan A, Chittock J, Kennedy K, Cork MJ. The effect of aqueous cream BP on the skin barrier in volunteers with a previous history of atopic dermatitis. *British Journal of Dermatology* 2011;**165**(2):329-34.

Danby 2018

Danby SG, Brown K, Wigley AM, Chittock J, Pyae PK, Flohr C, et al. The effect of water hardness on surfactant deposition after washing and subsequent skin irritation in atopic dermatitis patients and healthy control subjects. *Journal of Investigative Dermatology* 2018;**138**(1):68-77.

Deckers 2012

Deckers IA, McLean S, Linssen S, Mommers M, Van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990–2010: a systematic review of epidemiological studies. *PloS One* 2012;**7**(7):e39803.

Deeks 2019

Deeks JJ, Higgins JP, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177-88.

Drucker 2017

Drucker AM, Wang AR, Li W-Q, Sevetson E, Block JK, Qureshi AA. The burden of atopic dermatitis: summary of a report for the National Eczema Association. *Journal of Investigative Dermatology* 2017;**137**(1):26-30.

Du Toit 2015

Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *New England Journal of Medicine* 2015;**372**(9):803-13.

Du Toit 2016

du Toit G, Tsakok T, Lack S, Lack G. Prevention of food allergy. *Journal of Allergy and Clinical Immunology* 2016;**137**(4):998-1010.

Egger 1997

Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

Eichenfield 2014

Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis: Part 2: Management and treatment of atopic dermatitis with topical therapies. *Journal of the American Academy of Dermatology* 2014;**71**(1):116-32.

Engebretsen 2017

Engebretsen KA, Bager P, Wohlfahrt J, Skov L, Zachariae C, Nybo Andersen AM, et al. Prevalence of atopic dermatitis in infants by domestic water hardness and season of birth: cohort study. *Journal of Allergy and Clinical Immunology* 2017;**139**(5):1568-1574.e1.

Ewence 2011

Ewence A, Rumsby P, Danby S, Cork MJ, Williams HC. A review of skin irritation and tap water. www.dwi.defra.gov.uk/research/completed-research/reports/dwi70-2-257.pdf. Wrc. Swindon. UK, accessed prior to 24 January 2019; Vol. DWI8375.01.

Flohr 2010

Flohr C, England K, Radulovic S, McLean WH, Campbell LE, Barker J, et al. Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. *British Journal of Dermatology* 2010;**163**(6):1333-6.

Flohr 2014

Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. *Allergy* 2014;**69**(1):3-16.

Furlan 2009

Furlan AD, Pennick V, Bombardier C, Van Tulder M, Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* 2009;**34**(18):1929-41.

Garcia 2009

Garcia Bartels N, Mleczko A, Schink T, Proquitté H, Wauer RR, Blume-Peytavi U. Influence of bathing or washing on skin barrier function in newborns during the first four weeks of life. *Skin Pharmacology and Physiology* 2009;**22**(5):248-57.

Garcia 2010

Garcia Bartels N, Scheufele R, Prosch F, Schink T, Proquitté H, Wauer RR, et al. Effect of standardized skin care regimens on neonatal skin barrier function in different body areas. *Pediatric Dermatology* 2010;**27**(1):1-8.

Ghersi 2011

Ghersi D, Berlin J, Askie L. Chapter 19: Prospective meta-analysis. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Grabenhenrich 2017

Grabenhenrich LB, Reich A, Bellach J, Trendelenburg V, Sprikkelman AB, Roberts G, et al. A new framework for the documentation and interpretation of oral food challenges in population-based and clinical research. *Allergy* 2017;**72**(3):453-61.

Gupta 2004

Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: secondary analyses of national databases. *Clinical & Experimental Allergy* 2004;**34**(4):520-6.

Gupta 2013

Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. *JAMA Pediatrics* 2013;**167**(11):1026-31.

Gupta 2019

Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and severity of food allergies among US adults. *JAMA Network Open* 2019;**2**(1):e185630.

Hanifin 1980

Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermato-Venereologica* 1980;**60 Suppl 92**:44-7.

Hanifin 2001

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M, et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. *Experimental Dermatology* 2001;**10**(1):11-8.

Harbord 2006

Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**(20):3443-57.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2011

Higgins JP, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Higgins 2018

Higgins JP, Savovic J, Page MJ, Sterne JA, ROB2 development group. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2 (accessed 5 February 2019).

Higgins 2019

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Horimukai 2014

Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *Journal of Allergy and Clinical Immunology* 2014;**134**(4):824-830.e6.

Irvin 2015

Irvin EJ, Miller HD. Emollient use in the term newborn: a literature review. *Neonatal Network : NN* 2015;**34**(4):227-30.

Irvine 2011

Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *New England Journal of Medicine* 2011;**365**(14):1315-27.

ISRCTN 21528841

ISRCTN 21528841. Barrier enhancement for eczema prevention. www.isrctn.com/ISRCTN21528841 (first received 25 July 2014).

Jerschow 2014

Jerschow E, Lin RY, Scaperotti MM, McGinn AP. Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations. *Journal of Allergy and Clinical Immunology* 2014;**134**(6):1318-28 e7.

Johansson 2003

Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization. *Journal of Allergy and Clinical Immunology* 2003;**113**(5):832-6.

JPRN-UMIN000004544

JPRN-UMIN000004544. Effect of emollients on the prevention of infantile eczema and atopic dermatitis. upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000005429 (first received 11 November 2010).

JPRN-UMIN000010838

JPRN-UMIN000010838. Skin care and synbiotics for prevention of atopic dermatitis or food allergy in newborn infants: a 2 x 2 factorial, randomized, non-treatment controlled trial. upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000012665 (first received 30 May 2013).

JPRN-UMIN000013260

JPRN-UMIN000013260. Effects of moisturizing skin care from the neonatal stage for improving skin barrier function and preventing skin trouble. upload.umin.ac.jp/cgi-open-bin/ctr_e/

ctr_view.cgi?recptno=R000014285 (first received 25 February 2014).

Kelleher 2016

Kelleher MM, Dunn-Galvin A, Gray C, Murray DM, Kiely M, Kenny L, et al. Skin barrier impairment at birth predicts food allergy at 2 years of age. *Journal of Allergy and Clinical Immunology* 2016;**137**(4):1111-1116.e8.

Knibb 2010

Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. *Allergy* 2010;**65**:933-45.

Lefebvre 2019

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.

Leung 2004

Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *Journal of Clinical Investigation* 2004;**113**(5):651-7.

Lodén 2012

Lodén M. Effect of moisturizers on epidermal barrier function. *Clinics in Dermatology* 2012;**30**(3):286-96.

Lowe 2018

Lowe AJ, Su JC, Allen KJ, Abramson MJ, Cranswick N, Robertson CF, et al. A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: the PEBBLES pilot study. *British Journal of Dermatology* 2018;**178**(1):e19-21.

Luoma 1983

Luoma R, Koivikko A, Viander M. Development of asthma, allergic rhinitis and atopic dermatitis by the age of five years. A prospective study of 543 newborns. *Allergy* 1983;**38**(5):339-46.

Lødrup 2018

Lødrup Carlsen KC, Rehbinder EM, Skjerven HO, Carlsen MH, Fatnes TA, Fugelli P, et al. Preventing atopic dermatitis and allergies in children—the PreventADALL study. *Allergy* 2018;**73**(10):2063-70.

Mancini 2008

Mancini A, Lawley L. Structure and function of newborn skin. Neonatal Dermatology. 2nd Edition. Philadelphia: Elsevier Saunders, 2008:19-31.

Martin 2013

Martin PE, Koplin JJ, Eckert JK, Lowe AJ, Ponsonby AL, Osborne NJ, et al. The prevalence and socio-demographic risk factors of clinical eczema in infancy: a population-based observational study. *Clinical and Experimental Allergy* 2013;**43**(6):642-51.

Martin 2015

Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrin LC, Dharmage SC, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clinical and Experimental Allergy* 2015;**45**(1):255-64.

McAleer 2018

McAleer MA, Jakasa I, Raj N, O'Donnell CP, Lane ME, Rawlings AV, et al. Early-life regional and temporal variation in filaggrin-derived natural moisturizing factor, filaggrin-processing enzyme activity, corneocyte phenotypes and plasmin activity: implications for atopic dermatitis. *British Journal of Dermatology* 2018;**179**(2):431-41.

Meckfessel 2014

Meckfessel MH, Brandt S. The structure, function, and importance of ceramides in skin and their use as therapeutic agents in skin-care products. *Journal of the American Academy of Dermatology* 2014;**71**(1):177-84.

NCT01375205

NCT01375205. Comparing cetaphil restoraderm system versus standard skin care in infants. clinicaltrials.gov/ct2/show/results/NCT01375205 (first received 17 June 2011).

NCT02449850

NCT02449850. Preventing atopic dermatitis and allergies in children (PreventADALL). clinicaltrials.gov/ct2/show/NCT02449850 (first received 20 May 2015).

NCT03376243

NCT03376243. EARLYEMOLLIENT - Feasibility of early emollient use in children with atopic eczema (EARLYemo). clinicaltrials.gov/ct2/show/NCT03376243 (first received 18 December 2017).

NICE 2006

NICE. Postnatal care up to 8 weeks after birth. www.nice.org.uk/guidance/cg37 (accessed prior to 24 January 2019).

Oakley 2016

Oakley R, Lawton S. Views on unwanted effects of leave-on emollients and experiences surrounding their incidence. *Dermatological Nursing* 2016;**15**(4):38-43.

Osbourne 2011

Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *Journal of Allergy and Clinical Immunology* 2011;**127**(3):668-76 e1-2.

Palmer 2006

Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nature Genetics* 2006;**38**(4):441-6.

Pawankar 2014

Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. *World Allergy Organization Journal* 2014;**7**(1):12.

Penzer 2012

Penzer R. Best practice in emollient therapy: a statement for healthcare professionals December 2012. *Dermatological Nursing* 2012;**11**(4):60-79.

Poulos 2007

Poulos LM, Waters A-M, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005. *Journal of Allergy and Clinical Immunology* 2007;**120**(4):878-84.

Prescott 2013

Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JKh, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. *World Allergy Organization Journal* 2013;**6**(1):21.

Rawlings 2004

Rawlings AV, Canestrari DA, Dobkowski B. Moisturizer technology versus clinical performance. *Dermatologic Therapy* 2004;**17**(Suppl 1):49-56.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ring 2012

Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *Journal of the European Academy of Dermatology and Venereology* 2012;**26**(8):1045-60.

Ronnstad 2018

Rønnstad AT, Halling-Overgaard A-S, Hamann CR, Skov L, Egeberg A, Thyssen JP. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: a systematic review and meta-analysis. *Journal of the American Academy of Dermatology* 2018;**79**(3):448-56.e30.

Rucker 2008

Rucker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Statistics in Medicine* 2008;**27**(5):746-63.

Sicherer 2003

Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *Journal of Allergy and Clinical Immunology* 2003;**112**(6):1203-7.

Simpson 2012

Simpson EL, Keck LE, Chalmers JR, Williams HC. How should an incident case of atopic dermatitis be defined? A systematic review of primary prevention studies. *Journal of Allergy and Clinical Immunology* 2012;**130**(1):137-44.

Simpson 2014

Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WHI, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention.. *Journal of Allergy and Clinical Immunology* 2014;**134**(4):818-23.

Spergel 2003

Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *Journal of Allergy and Clinical Immunology* 2003;**112**(6 Suppl):S118-27.

Stata [Computer program]

StataCorp. Stata. Version 15. College Station, TX, USA: StataCorp, 2017.

Stewart 2011

Stewart LA, Tierney JF, Clarke M. Chapter 18. Reviews of individual patient data. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Stewart 2019

Tierney JF, Stewart LA, Clarke M. Chapter 26, Individual patient data. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Stone 2002

Stone KD. Atopic diseases of childhood. *Current Opinion in Pediatrics* 2002;**145**(5):634-46.

Strid 2004

Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Disruption of the stratum corneum allows potent epicutaneous immunization with protein antigens resulting in a dominant systemic Th2 response. *European Journal of Immunology* 2004;**34**(8):2100-9.

Strid 2005

Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Epicutaneous exposure to peanut protein prevents oral tolerance and enhances allergic sensitization. *Clinical and Experimental Allergy* 2005;**35**(6):757-66.

Su 97

Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. *Archives of Disease in Childhood* 1997;**76**(2):159-62.

Surber 2017

Surber C, Kottner J. Skin care products: what do they promise, what do they deliver. *Journal of Tissue Viability* 2017;**26**(1):29-36.

Taichman 2017

Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data sharing statements for clinical trials — a requirement

of the International Committee of Medical Journal Editors. *New England Journal of Medicine* 2017;**376**(23):2277-9.

Thomsen 2015

Thomsen SF. Epidemiology and natural history of atopic diseases. *European Clinical Respiratory Journal* 2015;**2**(1):24642.

Tsakok 2016

Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. *Journal of Allergy and Clinical Immunology* 2016;**137**(4):1071-8.

Turner 2015

Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *Journal of Allergy and Clinical Immunology* 2015;**135**(4):956-63.e1.

Umasunthar 2013

Umasunthar T, Leonardi-Bee J, Hodes M, Turner PJ, Gore C, Habibi P, et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. *Clinical and Experimental Allergy* 2013;**43**(12):1333-41.

Van Cleave 2010

Van Cleave J, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. *JAMA* 2010;**303**(7):623-30.

Van den Oord 2009

Van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ* 2009;**339**:b2433.

Van Zuuren 2017

Van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen AP, Arents BW. Emollients and moisturisers for eczema. *Cochrane Database of Systematic Reviews* 2017, Issue 2. [DOI: 10.1002/14651858.CD012119.pub2]

Venter 2008

Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B, et al. Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. *Allergy* 2008;**63**(3):354-9.

Voskamp 2014

Voskamp AL, Zubrinich CM, Abramovitch JB, Rolland JM, O'Hehir RE. Goat's cheese anaphylaxis after cutaneous sensitization by moisturizer that contained goat's milk. *Journal of Allergy and Clinical Immunology* 2014;**2**(5):629-30.

Weidinger 2016

Weidinger S, Novak N. Atopic Dermatitis. *Lancet* 2016;**387**(10023):1109-22.

Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75.

WHO 2015

World Health Organization. Pregnancy, Childbirth, Postpartum and Newborn Care: A Guide for Essential Practice. www.ncbi.nlm.nih.gov/books/NBK326678/ (accessed prior to 11 March 2019).

Williams 1994

Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *British Journal of Dermatology* 1994;**131**(3):383-96.

Williams 1998

Williams HC, Strachan DP. The natural history of childhood eczema: observations from the British 1958 birth cohort study. *British Journal of Dermatology* 1998;**139**(5):834-9.

Woods 2002

Woods RK, Stoney RM, Raven J, Walters EH, Abramson M, Thien FC. Reported adverse food reactions overestimate true food allergy in the community. *European Journal Of Clinical Nutrition* 2002;**56**(1):31-6.

Yosipovitch 2000

Yosipovitch G, Maayan-Metzger A, Merlob P, Sirota L. Skin barrier properties in different body areas in neonates. *Pediatrics* 2000;**106**(1):105-8.

ADDITIONAL TABLES

Table 1. Glossary of Terms

Term	Definition
Adolescence	A period in development, roughly between ages 10 and 19 years, between the onset of puberty and the acceptability of adult identity and behaviour
Allergic (atopic) march	The typical pattern of onset of allergic disease from eczema, to food allergy, to asthma and allergic rhinitis

Table 1. Glossary of Terms *(Continued)*

Allergic rhinitis	Rhinitis is a group of symptoms affecting the nose, typically sneezing, itching or congestion. Allergic rhinitis is 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	An 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	A genetic predisposition to develop allergic diseases such as eczema food allergy, asthma and allergic rhinitis, often associated with the production of IgE antibodies
Ceramides	Lipid (fatty) molecules found in the lipid bilayer of the intercellular matrix
Eczema	A 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	An 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)	A 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	An allergen that typically enters the immune system via the respiratory tract and is airborne, such as house dust mite or pollen
Mast cells	A 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
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 individual's perception 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)	A non-invasive measurement of water loss across the epidermis used as a measure of skin barrier function

Table 1. Glossary of Terms *(Continued)*

Urticaria	Rash which is a transient erythematous itchy swelling of skin

APPENDICES

Appendix 1. Draft 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) (Lefebvre 2019)]

Appendix 2. Draft 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 3. Draft 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 4. 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 their 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 allergies 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

(Continued)

20. Pre-existing health state in the infant, such as very preterm birth (less than 32 weeks' gestation) or congenital skin condition
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 or 2 or more)
46. Number of first degree relatives with food allergy (0, 1 or 2 or more)
47. Number of first degree relatives with asthma (0, 1 or 2 or more)
48. Number of first degree relatives with rhinitis/hay fever (0,1 or 2 or more)

Compliance data

(Continued)

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

CONTRIBUTIONS OF AUTHORS

MK was the contact person with the editorial base.
MK co-ordinated the contributions from the co-authors and wrote the final draft of the protocol.
SC, EA, VC, developed the methods sections.
MK drafted the clinical sections of the background and responded to the clinical comments of the referees.
SC responded to the methodology and statistics comments of the referees.
AL is the principal investigator of ACTRN12613000472774 and contributed significantly to the data synthesis and statistical analysis plan.
LT reviewed the draft of the protocol and will screen titles.
NS and ED are the investigators on JPRN-UMIN000010838 and contributed to discussions on protocol and analysis plan.
KY is principal investigator of JPRN-UMIN000013260 and contributed to discussion on protocol and analysis plan.
YO, KYH, KM are investigators JPRN-UMIN000004544 and contributed to discussion on protocol and analysis plans.
HW, JC are investigators on the BEEP study (Chalmers 2017), and contributed ideology to the initial review proposal, reviewed protocol drafts and provided feedback and comments.
HS, KC, ER are investigators on the PreventADALL trial (Lødrup 2018), and reviewed initial protocol drafts and provided feedback and comments.
CS provided expertise on skincare products.
LA and LD provided assistance and advice on individual participant data set up and protocol development.
RJB wrote the first draft of the protocol, contributed to development of methods and is the guarantor of the final review.

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