Title: Skin care interventions in infants for preventing eczema and food allergy: a Cochrane systematic review and individual participant data meta-analysis

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Conflict of interest statement

The authors declare the following interests. MK; I have received honoraria for speaking at educational conferences organised by Nutricia, which does not manufacture/market any of the interventions or potential comparators in this review. SC none known. VC none known. EA none known. KCL : my institution received money from multiple sources: The Regional Health Board South East, the Norwegian Research Council, Oslo University Hospital, the University of Oslo, Health and Rehabilitation Norway, Østfold Hospital Trust, Norwegian Association of Asthma and Allergy, the Kloster Foundation, Norwegian society of Dermatology and Venerology, Arne Ingel's scholarship, First Medical Laboratory, the Foundation for Healthcare and Allergy Research in Sweden, the Vårdal Foundation, Swedish Asthma and Allergy Association's Research Foundation, Swedish Research Council, the Initiative for Clinical Therapy Research, the Swedish Heart-Lung Foundation, SFO-V Karolinska Institutet, Hesselman Research Foundation, and Thermo-Fisher, Uppsala, Sweden. My institution received an honorarium and travel expenses from Thermo Fischer, Uppsala, Sweden for a lecture at the European Academy of Allergy and Clinical Immunology (EAACI) Congress 2018. HOS; My institution received money for the PreventADALL study (Lødrup 2018) from the two largest governmental grant agencies in Norway, The South-Eastern Norway Regional Health Authority and the Norwegian Research Council, which are not commercial sponsors. EMR; declares no real or perceived conflict of interest for the present review, however I have received honoraria for presentations on atopic dermatitis and psoriasis from Sanofi Genzyme, Perrigo, MEDA, Novartis and Norwegian patient organizations for atopic dermatitis and psoriasis in the last 36 months. AL; has received grant funding from the National Health and Medical Research Council to undertake a skin barrier intervention study. He also declares that Primus Pharmaceuticals have donated EpiCeram (a skin barrier treatment) for the use in these studies, free of charge. ED: none known. NS none known. KY My institution has received grants from the Mitsubishi Foundation and Mishima Kaiun Memorial Foundation that supported the

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Author contribution statement:

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

Data sharing statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request. This article is based on a Cochrane Review published in the Cochrane Database of Systematic Reviews 2021 Issue 2 doi:10.1002/14651858.CD013534.pub2. Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

Abstract

Objective: Eczema and food allergy start in infancy and have shared genetic risk factors that affect skin barrier. We aimed to evaluate whether skincare interventions can prevent eczema or food allergy.

Design: A prospectively-planned individual participant data meta-analysis was carried out within a Cochrane systematic review to determine whether skincare interventions in term infants prevent eczema or food allergy

Data sources: Cochrane Skin Specialised Register, CENTRAL, MEDLINE, Embase and trial registries to July 2020.

Eligibility criteria for selected studies: Included studies were randomised control trials of infants < 1 year with healthy skin comparing a skin intervention to a control, for prevention of eczema and food allergy outcomes between 1 – 3 years.

Results: Of the 33 identified trials, 17 trials (5823 participants) had relevant outcome data and 10 (5154 participants) contributed to IPD meta-analysis. Three of seven trials contributing to primary eczema analysis were at low risk of bias and the single trial contributing to primary food allergy analysis was at high risk of bias. Interventions were mainly emollients, applied for the first 3-12 months. Skin care interventions probably don't change risk of eczema by age 1-3 years (RR 1.03, 95% CI 0.81, 1.31; I^2=41%; moderate certainty; 3075 participants, 7 trials). Sensitivity analysis found heterogeneity was explained by increased eczema in a trial of daily bathing as part of the intervention. It is unclear whether skin care interventions increase risk of food allergy by age 1-3 years (RR 2.53, 95% CI 0.99 to 6.47; very low certainty; 996 participants,1 trial), but they probably increase risk of local skin

infections (RR 1.34, 95% CI 1.02, 1.77; I^2=0% moderate certainty; 2728 participants, 6 trials).

Conclusion: Regular emollients during infancy probably do not prevent eczema and probably increase local skin infections.

Introduction

Allergic diseases such as eczema and food allergy are some of the most common long term conditions in young people [1, 2]. Eczema and food allergy often coexist, and are both associated with genetic variations that cause an impaired skin barrier [3, 4]. Early-onset eczema is a risk factor for IgE-mediated food allergy, leading some to propose that eczema causes food allergy [5, 6]. There have been many attempts to identify an effective intervention for primary prevention of eczema or food allergy. Systematic reviews found some evidence that probiotics in late pregnancy may decrease eczema risk, and that early introduction of allergenic foods may decrease risk of allergy to the same foods [7, 8]. However the probiotic literature may suffer from issues of selective reporting and early introduction of multiple allergenic foods has proved to be a challenging recommendation to comply with [9]. Thus, simple, achievable, safe and effective ways of preventing eczema or food allergy are still needed.

Emollients are the mainstay of treatment for those with established eczema and can increase the time between eczema exacerbations [10]. Emollients increase stratum corneum hydration, improve comfort, and reduce itch when used on skin that already has active eczema. In some studies emollients have led to a decrease in transepidermal water loss (TEWL) across the skin, suggesting an effect on skin barrier function [11, 12]. If emollients can improve skin barrier function or skin hydration, they may be able to prevent the onset of eczema and potentially food allergies [13]. In this prospectively planned systematic review with individual participant data (IPD) meta-analysis we evaluated whether skincare interventions during infancy can change risk of developing eczema and food allergy, in general populations or in those at high hereditary risk for these outcomes.

Materials and methods

This systematic review and individual patient data meta-analysis was conducted using standard Cochrane methodology, and according to its own pre-published protocol and statistical analysis plan [14, 15]. The study was approved by the Imperial College London Research Ethics Committee on 18th May 2018 (reference 18IC4563).

In brief, we included parallel-group or factorial randomised controlled trials (RCTs), including both individual and cluster-randomised trials. Eligible trials evaluated healthy term infants (<12 months of age) without pre-existing health or skin conditions and any skin care intervention that could potentially enhance skin barrier function, reduce dryness or reduce subclinical inflammation. Eligible interventions included moisturisers/emollients, bathing products, advice regarding reducing soap exposure and bathing frequency and use of water softeners. Comparison was to routine skin care, however that was classified in the study setting. Outcome measures are summarised below:

Primary outcomes

1. Eczema, defined where available by the Hanifin and Rajka criteria in their original form or the UK Working Party refinement of them [16], other modifications of the Hanifin and Rajka criteria, doctor diagnosis of eczema or of none of these were available then by patient / parent report.

2. Food allergy, defined where available as confirmed IgE-mediated food allergy diagnosis using oral food challenge (OFC). If OFC not available, food allergy diagnosed by investigator assessment using a combination of clinical history and

allergy skin prick or specific IgE testing was used. Primary foods of interest were milk, egg and peanut, the commonest food allergens in children aged 1 to 3 years.

Secondary outcomes

1. Adverse events during intervention period, including skin infection, stinging or allergic reactions to moisturisers, slippage accidents around the time of bathing or application of emollient and severe adverse events.

2. Eczema severity assessed by investigators using Eczema Area and Severity Index or similar validated method [17].

3. Parent-reported eczema severity using Patient Oriented Eczema Measure or similar validated patient-reported measure [18]

4. Time to onset of eczema.

5. Parent report of immediate (less than two hours after ingestion) reaction to a known food allergen, namely milk, soya, wheat, fish, seafood, peanut, tree nut, egg or a local common food allergen.

6. Allergic sensitisation to foods and inhalants, evaluated by skin prick test wheal ≥ 3mm or if not available, via serum-specific IgE >0.35kUa/L.

Search strategy

We searched the Cochrane Skin Specialised Register, CENTRAL, MEDLINE, Embase, the World Health Organization clinical trial meta-registry and clinicaltrials.gov up to July 2020. The full search strategy is shown in the systematic review protocol in supporting information.

Data collection and analysis

This was a prospectively planned individual patient data meta-analysis, registered on Prospero in February 2017 [19]. This review was undertaken according to the methods

of Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 [20]. Prospectively acquired data are those data that were not known to their trial investigators prior to PROSPERO registration on 8th February 2017. Analysis was conducted following a statistical analysis plan with sensitivity analysis and sub group analysis for both individual and trial factors which was finalised before undertaking data analysis. It was a two stage IPD analysis process, with individual trial investigator review of the stage 1 analysis findings before proceeding to stage 2. Treatment effects were calculated following the intention-to-treat principle using regression models. Derived effects were combined across trials using random effects inverse variance models. Heterogeneity was assessed using the I^2 statistic and visual examination of forest plots. The risk of bias of included studies was assessed by MK, RJB and SC using the Cochrane risk of bias 2 tool, where risk of bias is evaluated separately for each outcome within included trials. The certainty of the body of evidence was assessed using the GRADE approach by MK, SC and RJB. For trials providing compliance data we estimated the complier average causal effect using instrumental variable methods [21]. Sensitivity analysis explored the impact of risk of bias and heterogeneity. Trial sequential analysis was used to identify when the optimum information size or futility boundaries for pre-defined effect sizes in relation to the two co-primary outcomes had been reached. Additional methods are shown in the statistical analysis plan in the supplementary material.

Results

Search results are summarised in Figure 1. Of thirty-three eligible studies only 17 trials, randomising 5823 participants, had outcome data relevant to eczema, food allergy or the adverse events of interest reported. The trials with no relevant outcome data generally had a follow-up of less than four weeks and had short term physiological skin outcomes or no skin outcomes (See Table 1. Characteristics of included studies). Ten studies, randomising 5154 participants, contributed to IPD meta-analysis with one of these studies having data on adverse events only. Overall the majority of evidence included in this review was at low risk of bias or there were some concerns but not high risk of bias. For the primary outcome of eczema three of seven studies included in IPD meta-analysis had low risk of bias, with missing outcome data the main concern in the other trials, leading to instability of study estimates under different assumptions related to the missing data. For the primary outcome of food allergy, only one study was included. While the overall study was low risk of bias, the measurement of primary food allergy outcome was classified as high risk of bias due to missing outcome data leading to instability of the effect estimate, and evidence that missingness depended on the outcome [22].

The characteristics of included studies are summarised in Table 1. All 10 trials contributing to the meta-analysis were based in well-resourced settings (UK, US, Norway, Sweden, Australia, Japan). Six enrolled participants with an increased eczema risk based on a family history of allergic conditions. Interventions were single interventions such as emollients in most trials, and two studies were factorial trials. In trials using emollients; various different types of emollients were used, including ceramide-based emollient. Instructions for emollient use ranged from all over body twice daily, to face only, to emulsified in bath. All trials that contributed

data to primary outcome meta-analysis used an emollient alone or as part of a combined intervention. Emollients were initiated in the first three weeks of life and used for three to 12 months at a frequency of once to twice daily. In studies evaluating emollient use, up to 30% of control group participants reported using emollient regularly (Supplementary table 2).

The effects of interventions are summarised in the Summary of Findings Table, including GRADE certainty of evidence ratings (Table 2). For eczema at 1 to 3 years, pooled individual patient data from 3075 participants in seven emollient studies found these probably do not influence eczema risk (RR 1.03, 95% CI 0.81 to 1.31, I^2=41%; Figure 2A). Sensitivity analysis identified the trial of Skjerven 2020 (PreventADALL trial), which used an emollient emulsified in a bath as the intervention, as the main source of statistical heterogeneity (Figure 2B). The interaction effect between treatment and FLG mutation was estimated for just one study and did not show a significant treatment interaction (RR 1.22, 95% CI 0.71 to 2.11 for individuals with at least one FLG mutation). The interaction effect between treatment and family history of allergic disease on eczema by 1 to 3 years could be estimated for three trials with 3172 participants, of whom 1663 were included in analysis – there was no significant interaction (RR 0.95, 95% CI 0.35 to 2.61, I^2=0%; Figure 2C). The secondary outcomes for eczema were evaluated using parent report of eczema severity; (RR 1.17, 95% CI 0.82 to 1.67; 1171 participants in 1 trial) and time to onset of eczema (HR 0.86, 95% CI 0.65, 1.14; I^2=53%; moderate certainty evidence; 3349 participants in 9 trials and clinician observed eczema severity (SMD -0.02, 95% CI -0.17 to 0.12, 1228 participants in 3 trials). No significant effects were observed for any secondary eczema outcomes.

For food allergy, diagnosis from 1 to 3 years using oral food challenge was available for 996 participants in one study and favoured standard care (RR 2.53, 95% CI 0.99 to 6.47; Figure 2D). In pre-planned sensitivity analysis for IgE mediated food allergy confirmed by oral food challenge or via an investigator assessment based on clinical history and/or skin prick tests, data was available for 1115 participants from one study (Chalmers 2020) and again favoured standard care, with reduced effect size (RR 1.46, 95% CI 0.91 to 2.34; Figure 2E). Allergic sensitisation to a food allergen at age 1 to 3 years was similar in intervention and control groups (RR 0.86, 95% CI 0.28 to 2.69; I^2=70%; very low certainty evidence; 1055 participants in 2 trials; Figure 2F) and parent report of immediate reaction to food allergen was increased in the intervention group (RR 1.27, 95% CI 1.00, 1.61; low certainty evidence; 1171 participants in 1 trial).

For adverse events: skin infections were reported in pooled individual participant data from 2728 participants in three studies, showing increased skin infection in the intervention arm (RR 1.34, 95% CI 1.02 to 1.77; I^2=0%; Figure 2G). Risk of infant slippages was also increased in the intervention arms (RR 1.42, 95% CI 0.67, 2.99; I^2=0%; low certainty evidence; 2538 participants in 4 trials; Figure 2H) as were stinging reactions to moisturisers (RR 2.24, 95% 0.67, 7.43; I^2=0%; low certainty evidence; 343 participants in 4 trials) and severe adverse events (RR 1.80 95% CI 0.45, 7.18; I^2 1367 participants in 3 trials; Figure 2I).

We conducted complier average causal effect (CACE) analysis to evaluate the effect of adherence to the intervention. These analyses are summarised in Table S3 in the supplementary material and show a pooled CACE for eczema by 1-3 years, where a complier as defined as a user of emollient 3 or more days a week over the intervention period, of RR 0.65 [0.29, 1.45]; I^2=0%; 1440 participants in 3 trials.

Finally, in the trial sequential analysis (TSA) to evaluate whether further trials of eczema prevention are worthwhile we found that further trials of similar emollients are unlikely to change the conclusion that emollients don't reduce eczema risk by ≥30% (Figure 3A). However, there was insufficient information to establish whether emollients reduce eczema risk by ≥20% (Figure 3B).

Discussion

In this Cochrane systematic review with prospectively planned individual participant data meta-analysis, we found that emollients during infancy probably do not influence risk of eczema development, and probably promote local skin infections. We did, however, identify some evidence that early skincare practices might be relevant to eczema development, with emollient applied as part of a daily bath promoting increased risk of eczema in one trial. We did not identify completed trials of other types of skincare interventions with eczema as an outcome measure. We therefore cannot exclude the possibility that novel emollient formulations might be able to influence eczema development. We were also unable to conclude whether or not emollients influence risk of food allergy development.

This review was also designed to examine predefined individual factors that may influence the effect of the intervention, most importantly risk factors for allergic disease namely, family history and FLG mutation. There was less statistical power for subgroup analyses than for the overall meta-analyses, but our subgroup analyses did not suggest a likelihood of differential effects in infants at higher risk of allergic disease. Overall compliance with daily emollient, where reported, was modest, but CACE analysis did not suggest the interventions were any more effective when adherence to interventions was high.

For most trials the main intervention was an emollient, of various constitution and typically 3 to 12 months duration. One trial, Skjerven 2020, showed an increase in eczema in the intervention group in our analysis, leading to some statistical heterogeneity in the main eczema analysis (I^2=41%), which was reduced (to I^2 = 0%) when this trial was removed (Figure 2B) [23]. This was a factorial randomised trial, with

skin care interventions and early food introduction. Due to a significant interaction between the interventions only the skin care and control arms of the trial could be utilised in our primary analysis, however in sensitivity analysis including all four arms findings were similar. (Table 1 in supplemental tables). The skin intervention was a combination of daily facial emollient and daily baths with paraffin-based bath oil. In our analysis of data from this trial, there was an increased risk of eczema in the intervention group. Given the absence of an effect on eczema seen in the other emollient trials, this finding raises the possibility that daily baths could potentially have an adverse effect on skin barrier function and increase risk of eczema development. This hypothesis is supported by recent findings from the EAT study showing an association between increased bathing frequency in the first months and increased eczema prevalence [24]. Further work is needed to identify whether skincare interventions based on the nature or frequency of bathing during the first months of life might be a valid approach for eczema prevention.

For our co-primary outcome of food allergy, we were unable to ascertain whether skin care interventions influence development of IgE mediated food allergy when compared with standard care, as only one study diagnosed food allergy by oral food challenge which was judged at high risk of bias due to potential differential loss to follow up between arms [25]. Further work from PreventADALL will give us more information about emollient/bathing effects on food allergy development in 2021. If the evidence for increased food sensitisation in the skin barrier intervention group holds in future studies, it would give further support to the possibility that food sensitisation occurs through the skin.

Although we identified 33 studies to fit our inclusion and exclusion criteria, the majority of studies did not contribute to the meta-analysis as they did not have

eczema or food allergy outcomes, therefore we cannot tell whether these shorter term and often multiple interventions would impact on prevention of eczema or food allergy. There is no standard classification system for emollients. The term emollient is used in many languages both colloquially and in a medical or pharmaceutical context. There is no single, comprehensive definition of the term. Our overall analysis grouped all emollients together, and we also conducted pre-planned subgroup analysis on “simple” and more “complex” emollients (data not shown). We acknowledge the wide diversity in emollient products, and that other researchers may classify them in a different way. Two trials included in the IPD classified as “complex emollients” used a ceramide base emollient. We await the results of two further ongoing trials of “complex" ceramide-dominant emollients which should report later next year [26, 27].

The evidence for food allergy prevention is sparse, with only one study reporting this outcome mainly because there is significant difficulty in measuring food allergy outcomes in prevention studies. Oral food challenges, necessary to firmly document food allergy, are costly and time consuming, and may not be acceptable to parents [25, 28]. Finally, all of these trials were in developed settings, with an overall unwanted effect of increased skin infections related to emollient use. Previous trials in low income settings, and of premature infants, reported a decrease in invasive infections in infants following topical oil massage, however a Cochrane review reported less conclusive findings [29]. It is thus important to remember that our findings related to skincare interventions in term infants in developed settings where eczema is common.

In conclusion, we found that emollients during infancy probably do not prevent eczema from developing, and they probably increase the risk of local skin infections.

Further trials should evaluate other skincare interventions, including advice to reduce potentially harmful skincare practices, and should fully assess effects on food allergy as well as eczema. These may require basic mechanistic studies initially to determine if there any potential negative effect on infant skin over the first year of life.

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References

1. Van Cleave J, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. Jama. 2010;303(7):623-30.
2. Bai G, Herten MH-v, 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-e.
3. 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.
4. 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.
5. 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 & Experimental Allergy. 2015;45(1):255-64.
6. Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol. 2016;137(4):1071-8.
7. Garcia-Larsen V, Ierodiakonou D, Jarrold K, Cunha S, Chivinge J, Robinson Z, et al. Diet during pregnancy and infancy and risk of allergic or autoimmune disease: A systematic review and meta-analysis. PLOS Medicine. 2018;15(2):e1002507.
8. de Silva D, Halken S, Singh C, Muraro A, Angier E, Arasi S, et al. Preventing food allergy in infancy and childhood: Systematic review of randomised controlled trials. Pediatric Allergy and Immunology 2020;31(7):813-826. doi: 10.1111/pai.13273.
9. Voorheis P, Bell S, Cornelsen L, Quaife M, Logan K, Marrs T, et al. Challenges experienced with early introduction and sustained consumption of allergenic foods in the Enquiring About Tolerance (EAT) study: A qualitative analysis. Journal of Allergy and Clinical Immunology. 2019;144(6):1615-23.
10. van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BWM. Emollients and moisturisers for eczema. The Cochrane database of systematic reviews. 2017;2(2):Cd012119.
11. Lodén M. Effect of moisturizers on epidermal barrier function. Clinics in Dermatology. 2012;30(3):286-96.
12. Rawlings AV, Canestrari DA, Dobkowski B. Moisturizer technology versus clinical performance. Dermatol Ther. 2004;17 Suppl 1:49-56.
13. Allen KJ, Koplin JJ. Prospects for Prevention of Food Allergy. The Journal of Allergy and Clinical Immunology: In Practice. 2016;4(2):215-20.
14. Kelleher MM, Cro S, Cornelius V, Axon E, Lodrup Carlsen KC, Skjerven HO, et al. Skincare interventions in infants for preventing eczema and food allergy. Cochrane Database of Systematic Reviews. 2020;2:CD013534. doi: 10.1002/14651858.CD013534.
15. Cro S BR, 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. 2020 zenodo.org/record/3610604#.XiGKU8j7SUk doi: 10.5281/zenodo.3610604
16. Williams HC, Jburney PG, Hay RJ, Archer CB, Shipley MJ, Ahunter JJ, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. British Journal of Dermatology. 1994;131(3):383-96.
17. 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.

18. 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.
19. Boyle RJ WH, Askie L, Lodrup-Carlsen K, Montgomery A, Chalmers J, Shimojo N, Kelleher MM, Mead E. Prospectively planned meta-analysis of skin barrier studies for the prevention of eczema and associated health conditions. PROSPERO. 2017; CRD42017056965.
20. Tierney JF SL, Clarke M. Chapter 26, Individual patient data. In: Higgins JP GS, editor. Cochrane Handbook for Systematic Reviews of Interventions Version 6 Cochrane; 2019.

21. 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.
22. Kelleher MM, Cro S et al. Skincare interventions in infants for preventing eczema and food allergy. Cochrane Database of Systematic Reviews. 2021;2:CD013534 doi:10.1002/14651858.CD013534.pub2.
23. Skjerven HO, Rehbinder EM, Vettukattil R, LeBlanc M, Granum B, Haugen G, et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. Lancet (London, England). 2020;395(10228):951-61.
24. Marrs T, Perkin MR, Logan K, Craven J, Radulovic S, McLean WHI, et al. Bathing frequency is associated with skin barrier dysfunction and atopic dermatitis at three months of age. J Allergy Clin Immunol Pract. 2020;8(8):2820-2.
25. Kelleher MM, Jay N, Perkin MR, Haines RH, Batt R, Bradshaw LE, et al. An algorithm for diagnosing IgE-mediated food allergy in study participants who do not undergo food challenge. Clin Exp Allergy 2020;50(3):334-42. doi: 10.1111/cea.13577.
26. Eichner B, Michaels LAC, Branca K, Ramsey K, Mitchell J, Morris CD, et al. A Community-based Assessment of Skin Care, Allergies, and Eczema (CASCADE): an atopic dermatitis primary prevention study using emollients-protocol for a randomized controlled trial. Trials. 2020;21(1):243.
27. Lowe A, Su J, Tang M, Lodge CJ, Matheson M, Allen KJ, et al. PEBBLES study protocol: a randomised controlled trial to prevent atopic dermatitis, food allergy and sensitisation in infants with a family history of allergic disease using a skin barrier improvement strategy. BMJ Open. 2019;9(3):e024594.
28. Hsu E, Soller L, Abrams EM, Protudjer JLP, Mill C, Chan ES. Oral Food Challenge Implementation: The First Mixed-Methods Study Exploring Barriers and Solutions. J Allergy Clin Immunol Pract. 2020;8(1):149-56.e1.
29. Cleminson J, McGuire W. Topical emollient for preventing infection in preterm infants. Cochrane Database of Systematic Reviews. 2016;1:CD001150. doi: 10.1002/14651858.CD001150.pub3.

Tables

Table 1. Characteristics of included studies

Table 2. Summary of Findings including GRADE certainty of evidence assessment

Figure legends

Figure 1. PRISMA flow diagram.

Figure 2. Effects of emollients on risk of eczema overall (A), without the PreventADALL bathing study (B) and test for interaction with filaggrin gene mutation status (C); effects on risk of food allergy by oral food challenge (D), food allergy by physician assessment including allergy testing and where available oral food challenge (E) and allergic sensitisation to food (F); and risk of skin infection (G), slippages (H) and serious adverse events (I) with emollients. All data were analysed using 2-stage IPD meta-analysis and a random effects model.

Figure 3. Trial sequential analysis of emollient trials, showing the heterogeneity-adjusted optimal information size for detecting a reduction of ≥30% (A) or ≥20% (B) in risk of developing eczema. There were insufficient data for food allergy to conduct meaningful TSA. The vertical red line is the optimal information size i.e. the cumulative sample size required to establish with 95% 2-sided confidence whether the intervention reduces risk of eczema by ≥30% (n=5534) or ≥20% (n=13,072). Horizontal brown lines are z scores of +1.96 or -1.96, equal to two-sided P=0.05. The cumulative Z-statistic (blue line) approaches, but does not cross the futility boundary for ≥30% risk reduction (Figure 3A), indicating that further studies of similar interventions are unlikely to change the conclusion that emollients don't reduce eczema risk by ≥30%. The Z-statistic does not approach either the futility boundary or the trial sequential monitoring boundary (curved red line) for ≥20% risk reduction (Figure 3B), indicating insufficient information to determine whether or not emollients reduce eczema risk by ≥20%.

Supporting Information

Supplementary Tables and Figure

Table S1. Sensitivity analysis for eczema 1- 3years

Table S2. Compliance data by trial

Table S3. CACE estimates for eczema for 1-3 years

Table S4. Prisma 2009 reporting checklist