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Emollients in infancy to prevent atopic dermatitis: a systematic review and meta-analysis

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Data availability statement

The data used in the manuscript are extracted from the published articles (primary studies). All such primary studies are cited in the manuscript with complete reference provided in the reference list. The data extracted are summarized in the tables, figures and supporting information included in the manuscript.

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Author Contributions

Youjia Zhong - substantial contributions to design, acquisition and interpretation of data, drafting and revising the manuscript

Miny Samuel - substantial contributions to analysis and interpretation of data, revising the manuscript critically for important intellectual content

Hugo van Bever - substantial contributions to conception and design, revising the manuscript critically for important intellectual content

Elizabeth Huiwen Tham - substantial contributions to conception and design, acquisition and interpretation of data, revising the manuscript critically for important intellectual content

All have given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content. All authors have also agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Abstract

Background: Several studies have evaluated prophylactic emollients as a preventive strategy against atopic dermatitis (AD) and food allergy (FA). We aimed to synthesize the evidence on efficacy and safety of prophylactic emollients started during the first 6 weeks of infancy for prevention of AD and FA.

Methods: MEDLINE, Embase, CINAHL, BIOSIS and the Cochrane Library databases were searched systematically for randomized controlled trials published between January 2000 to July 2020, which assessed the effects of prophylactic emollients initiated within the first 6 weeks of life on the development of AD within 24 months of age, compared to no treatment. Risk of bias and certainty of evidence were assessed using the Cochrane Collaboration's tool and GRADE process respectively.

Results: Of the 1486 articles identified, 10 studies fulfilled inclusion criteria. In infants given emollients, there was no significant reduction on the development of AD (risk ratio (RR) 0.84, 95% confidence interval (CI) 0.64, 1.10) compared to the control group. However, there was significant benefit of prophylactic emollients (RR 0.75, 95% CI 0.62 – 1.11) in the high-risk population (n=8 studies). There was also significant benefit (RR 0.59, 95% CI 0.43,0.81) in studies (n=6) where emollients were used continuously to the point of AD assessment; but not when treatment was ceased for an interval before AD assessment. There were no protective effects on FA found.

Conclusion: The prophylactic application of emollients initiated in early infancy may prevent AD, especially in high-risk populations and when used continuously. We hypothesize that emollients may delay rather than prevent AD.

Key words

Atopic dermatitis, emollient, food allergy, moisturizer, prevention

Introduction

Atopic dermatitis / Eczema (AD) is a common chronic inflammatory skin condition, affecting up to 30% of children worldwide, and severe eczema often persists into adulthood.[1,2] There is a strong causal relationship between AD and food allergy (FA), and a large proportion of young children with moderate-to-severe AD are food-sensitised or clinically food-allergic.[3,4] In addition, the propensity for allergic rhinitis and asthma to develop in later childhood – the atopic march – occurs in approximately half of paediatric patients with AD.[5]

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The peak incidence of atopic dermatitis is between 3 to 6 months of life.[6,7] Increased trans-epidermal water loss (TEWL), a surrogate measure for skin barrier integrity, seems to predate the development of atopic dermatitis.[8] In fact, when measured in the neonatal period, TEWL has been shown to be associated with increased risk of atopic dermatitis in later childhood.[9,10] The dual-allergen exposure hypothesis postulates that the impaired skin barrier permits allergen penetrance which, in the presence of cytokine dysregulation promoting Th2 inflammation, eventually culminates in clinical FA.[11]

Accordingly, attention has been directed towards epithelial barrier therapy with emollients as a potential strategy for prevention of AD and FA. In 2014, two separate randomized controlled trials (RCTs), from USA/UK and Japan, showed encouraging results, albeit both were pilot studies and only enrolled high-risk infants.[12,13] A cost-effectiveness analysis concluded that usage of emollients as a preventative therapy for AD was attractive from both a medical and economic perspective, because side effect profile and cost-benefit analysis were both favourable.[14] However, early in 2020, two large randomised controlled trials conducted in Norway / Sweden (PreventADALL) and the United Kingdom (BEEP) did not show any effect of emollient application on prevention of AD; the BEEP study was done in high-risk infants while PreventADALL recruited the general population.[15,16]

The objective of this study was to perform a systematic review and meta-analysis of all randomised controlled trials that evaluated the efficacy and safety of prophylactic emollients introduced during the first 6 weeks of life to prevent the onset of AD in early childhood, with a secondary analysis of FA outcomes. A cut-off of 6 weeks was chosen for regular emollient therapy since most eczema starts after this period; and thus is the critical window for interventions for TEWL correction to be implemented. Age at AD assessment, whether the studies included high-risk populations or a general population, and whether there was a time interval between the period of emollient application and the AD assessment, were also assessed.

Methods

This systematic review used a pre-specified protocol for literature search and synthesis as recommended by the statement "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA).[17] The review protocol was finalized in August 2020, and registered in the PROSPERO International Prospective Register of Systematic Reviews, ID 230275.

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Search strategy for identification of studies

Electronic databases MEDLINE, Embase, CINAHL, BIOSIS and the Cochrane Library were searched for published articles (from 1 January 2000 to 31 July 2020). No language or geographical restrictions were placed on the searches. To achieve the maximum sensitivity of the search strategy, we used combinations of free text and medical subject heading terms. Search terms used included: "atopic dermatitis" / "eczema" / "atopic eczema", "moisturiser" / "emollient" / "skin intervention" / "barrier therapy" / "triple-lipid" / "ceramide", "infant" / "child" / "pediatrics" / "newborn". (Further details are provided in the Supporting Information Text – Tables A-1 to A-5)

Criteria for considering studies for this review

Screening criteria were defined *a priori*. All randomised, controlled and prospective clinical trials were included. The study population was infants up to 6 weeks of age, either from a general population or a high-risk population, who did not have AD at the point of recruitment. Intervention was an emollient only *versus* standard care, which could either be no treatment, or adjuvant skin interventions that were given to both the intervention and control groups. The primary outcome measure of interest was occurrence of AD assessed by validated criteria in children below 24 months of age. Where present in the included studies, sensitisation or clinical allergy to food, adherence to treatment, and adverse outcomes attributed to the treatment were also analysed.

If the intervention group was given adjuvant skin interventions such as bath products or skin care advice in addition to the emollient, but not the control group, these studies were included. However, studies which included a non-skin intervention such as prebiotics, probiotics or synbiotics for all arms of the trial; recruited infants older than 6 weeks of age; or had no validated criteria for AD assessment were excluded. For studies with more than 2 arms, the arms which included only skin emollients and the comparator group were analysed, while arms that included non-skin interventions were excluded.

Study selection process

Studies identified from the electronic databases and the internet searches were reviewed by two researchers (YZ and EHT), independently and in parallel, to determine eligibility. Any disagreement about study relevance was resolved in discussion with a third party (HVB).

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Data extraction

Data was extracted from the full text of articles by one study author using a standardized form, including trial characteristics, patient demographics, treatment information, study quality-assessment items, and data for development of AD, food sensitisation, food allergy, adherence to protocol in both arms, and adverse events. Data extraction was quality-checked by two other study authors.

Risk of bias assessment

Risk of bias was assessed using the PRISMA guidelines for the primary outcome, development of AD, using the Cochrane risk of bias 2.0 tool.[18]

Analysis methods

Where outcomes were reported as dichotomous data in trials, risk ratio (RR) and 95% confidence interval (CI) were calculated for meta-analysis. Study heterogeneity was assessed based on the Cochrane Handbook for Systematic Reviews of Interventions recommendations, in that I^2 values of 0% to 40% represent low heterogeneity; 40% to 75% may represent substantial heterogeneity, and 75% to 100% may represent considerable heterogeneity.[19] In addition to the I^2 value, the Chi^2 statistic and its P value were presented and considered as the direction and magnitude of the treatment effects.

Random-effects model or fixed-effect model meta-analyses were used to estimate the pooled treatment effect.[20,21] Review Manager 5.4.1 software was used for the analyses (RevMan 2020). Subgroups of interest for the analysis were by: infant age or treatment duration (eg 6 months, 12 months, 24 months), and interval versus no interval between emollient cessation and AD assessment.

To rate the certainty of evidence for primary outcomes - development of AD, 'Summary of findings' tables were created for outcomes using the GRADEpro Guideline Development Tool (GRADEpro GDT 2015).

Results

Results of the search

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A total of 1486 studies were identified from the electronic databases. Fifty-three were eligible for full text review. After exclusion for study type, population, outcome measures, duplication, and incomplete data, 10 studies were eventually included in the systematic review and meta-analysis.[12,13,15,16,22-27] (Figure 1) Key characteristics of the 10 included studies are presented in Table 1.

All 10 studies were RCTs, of which two had a factorial design. Only the study arms that were relevant to the study question were included for analysis. There were 2 pilot studies,[12,13] but as these were conducted as RCTs and patients were not duplicated in any other studies, they were included as individual studies. Blinding of subjects or parents was not possible in all trials due to the nature of the intervention, but all investigators and outcome assessors were blinded. Infants were recruited up to 6 completed weeks of life, and interventions lasted up to 6 to 12 months of age. The emollients used in the intervention arms were of varying types such as creams, oils, gels, balms, and emulsions, with varying recommended regimes in terms of body parts for application and frequency. Control arms were not prescribed any emollient regime, but skin care advice regarding bathing (that mirrored that of the interventional arm) was given to the control arms in 3 studies.

Two studies recruited subjects from the general population,[15,22] whereas the other 8 recruited subjects who were at high risk for AD, based on a strong family history of atopy.[12,13,16,23-27](Table 1) Three studies assessed the primary outcome of development of AD by 6 months of age;[13,23,24] 6 studies assessed this between 6 and 12 months of age;[12,15,22,25-27] and 1 study assessed this at 24 months of age[16](Table 1). All studies used validated diagnostic criteria such as the Hanifin and Rajka diagnostic criteria, or the UK working party criteria, or a refinement of this;[12,15,16,22,25,26] one study followed the AD guidelines by Eichenfield et al in 2014[6] (Table 1). Age of assessment of AD, risk of population recruited, and whether there was an interval between cessation of emollient application and AD assessment, formed the basis for our subsequent subgroup analyses.

Risk of bias in included studies

Figure 2[12,13,15,16,22-27] shows the risk of bias within all included RCTs for primary outcome, development of AD, as judged by two researchers. The main risk of bias was attributable to unequal adherence to treatment in the intervention group compared to adherence to avoidance in the control group (where adherence to avoidance in control group = (1 – contamination rate))

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(Table 2). Where these differed by more than 10%, the study was considered to have a high risk of bias. This directly led to 5 studies having high risk of bias or some concern for risk of bias.[16,22,24,25,27] Otherwise, the studies were well conducted and there was generally low risk of bias in other domains.

Effects of interventions

Development of atopic dermatitis

Data from 10 trials were included in this analysis, with 3507 randomized subjects (1746 in intervention group; 1671 in control group). Data was pooled using a random-effects model (Figures 3a-d).

When data was pooled overall from all 10 studies irrespective of age, the risk of development of AD was not significantly different when the emollient group was compared with the control group: risk ratio (RR) 0.84 (95% confidence interval (CI) 0.64 ,1.10, I^2 = 60%) (Grade of evidence ⊕⊕◯◯) (Figure 3a, 4). There was a significant amount of heterogeneity observed across the 10 trials. (I^2=64%). The test for subgroup difference was I^2 = 47.4%, suggesting that infant's age could be a factor that modifies the effect of emollients in comparison to the control group.

Studies were then stratified by age at AD assessment, and pooled evidence from 3 studies suggests that infants receiving active treatment had significantly lower risk of developing AD compared to the control group when development of AD was assessed at 6 months of age; RR 0.55 (95% CI 0.36, 0.85; I^2= 5%). Pooled evidence from 6 studies which assessed AD between 6 and 12 months of age showed no significant difference for development of AD; RR 0.92 (95% CI 0.61, 1.38; I^2 = 66%). Chalmers et al (the BEEP study)[16] assessed AD at 24 months and also showed no significant effect; RR 0.92 (95% CI 0.76, 1.11) (Figures 3a).

Of the 10 studies, 8 studies included high-risk infants.[12,13,16,23-27] When a meta-analysis was performed in only these high-risk infants, the risk of developing AD was significantly reduced in infants given emollients (RR 0.75 (95% CI 0.62, 0.91, I^2 = 10%) compared to placebo or no treatment. The trials that included all infants irrespective of their underlying risk did not seem to benefit within the 1-year period of application of emollients, compared to placebo (Figure 3b, 4).[15,22] (Grade of evidence ⊕⊕⊕◯) Stratifying by age of assessment of AD, the RR was significant both for those assessed up to 6 months of age, at 0.55 (95% CI 0.36, 0.84, I^2 = 0%) and those assessed between 6 and 12 months of age, at 0.62 (95% CI 0.44, 0.89, I^2= 0%) but not at 24

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months. In contrast, there was no significant effect of emollients on AD prevention, with a RR of 1.43 (95% CI 1.11, 1.85, I^2= 0%) in studies which recruited normal-risk infants (Figure S1, S2).

In order to determine whether the effects seen with the earlier age of assessment in the initial analysis could be attributed to the duration of emollient application, studies were then stratified by whether or not there was an interval between emollient treatment and AD assessment. For example, if emollient treatment was recommended until 6 months of age, but assessment of AD was only at 12 months of age, there was deemed to be an interval between emollient application and outcome assessment. The median time interval across 4 studies which had an interval was 7 months (range 4-12) months.[15,16,22,26] The studies which had no interval between emollient application and AD assessment showed a significant effect on reduction of AD development, with RR 0.59 (95% CI 0.43, 0.81, I^2 = 0%). In contrast, the studies which had an interval between emollient application and AD assessment had no significant reduction of AD risk, with RR 1.11 (95% CI 0.80, 1.54, I^2 = 68%). However, there was significant heterogeneity among these studies (Figure 3c).

Adherence, contamination, and per-protocol analysis

Adherence to the recommended emollient regimen was variable in the intervention groups, ranging from 27% to 93% (Table 2). Contamination was defined as the percentage of subjects in the control group who reported using emollients in a way that mirrored the intervention arm. This ranged from < 1% to 46% between studies. Where there were multiple measures of adherence reported, the definition which coincided with the definition for contamination was presented. Due to significantly low adherence and high contamination rates in some studies, a per-protocol analysis was also done (Figure S3, S4, S5), which supported the same findings as the intention-to-treat analysis (Figures 3a, b, c).

Food sensitisation and clinical allergy

Four studies assessed food sensitisation with skin prick tests or specific IgE to food allergens, and 2 studies assessed clinical food allergy (Table 2). Chalmers et al 2020 performed oral food challenges, while Dissanayake et al 2019 used a parent-reported questionnaire.[16,22] A pooled analysis showed that usage of emollients up to 12 months of age did not significantly change the rate of food sensitisation (specific IgE or skin prick tests) to any food in infants, compared to control groups (RR 1.10 (95% CI 0.83, 1.46, I^2 = 40%) (Figure 3d, 4) (Grade of evidence ⊕⊕⊕◯).

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Adverse events

There were 4 incidences of slippages in intervention groups in all the studies in the meta-analysis. However, none resulted in serious injury or hospitalisation. Skin infections were reported in 3 studies[13,16,25] and there was evidence of an increase in skin infections in the intervention group (RR 1.34, 95% CI 1.03, 1.75, $I^2 = 100\%$) (Figure S6), mainly contributed by Chalmers et al 2020[16] (Table 2).

Discussion

This meta-analysis has shown that the efficacy of prophylactic emollients for AD prevention is dependent on the study population's risk, age at outcome assessment and treatment duration. There was demonstrable reduction of AD development up to 6 months of age in all populations and it was efficacious up to 12 months of age in high-risk populations. Increased TEWL has been shown to predate the development of atopic dermatitis, and to be higher in early infancy for those who would go onto develop AD in later childhood.[8-10] As such, it is biologically plausible that prophylactic emollient therapy may only be indicated in high-risk infants who are already at genetic risk for AD[28], and who already demonstrate high TEWL in early infancy. In practice, selection of high-risk families for targeted intervention may also achieve better adherence. The study by Skjerven et al,[15] which recruited a large number (n = 1074) of infants from the general population, had a significantly low treatment adherence rate, suggesting that compliance to this intervention is difficult in an unselected population in real life.

Another key finding is the age and treatment duration-specific efficacy of prophylactic emollients. The intervention reduced AD risk up to 6 months of age in unselected populations and up to 12 months of age in high-risk populations. While the BEEP study, which was the only study to date which assessed AD at 24 months of age, showed no benefit against AD risk even in their high-risk population,[16] parents in this study were advised to stop emollient use after 1 year of age. This meta-analysis demonstrated that continuous use of emollients was protective compared to having an interval between treatment cessation and AD assessment, indicating that the effect of this intervention ceases soon after the treatment is withheld. Studies which included an interval between emollient cessation and assessment of AD had a median interval of 7 (range 4 to 12) months, so the effect is lost in less than a year.

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Further supporting evidence from our subgroup analysis demonstrated that the protective effect was only seen when the AD outcome was assessed while the child was still on regular emollients. This suggests that prophylactic emollients may merely *delay* the onset rather than completely prevent the development of AD. It could thus be postulated that while the prophylactic emollients may attenuate the deleterious effects of increased TEWL in early life, they do not modulate the other genetic and environmental factors responsible for AD pathogenesis, and thus only delay but not completely obviate the eventual clinical emergence of the disease. This hypothesis requires further mechanistic studies for validation.

There was significant heterogeneity across the studies included in the meta-analysis. Clinical studies differed widely in terms of type of emollient used, frequency and duration of emollient application (ranging from 4 times per week[15] to 3 times a day[22]), and the body parts where emollients were applied (ranging from face only[15], to full body[13,16,25-27]). Studies which reported significant benefit of prophylactic emollients tended to have recommended daily or more frequent applications of emollient to the majority of the skin surface, but this could not be quantified as some studies did not specify body part or frequency of application (Table 1).

One area of challenge across many studies was the low adherence in the intervention groups, and contamination in the control groups, whereby parents in the control group applied emollients in a way that mirrored the intervention group (contamination bias). This is unsurprising since blinding was not possible and study participation itself raises subjects' awareness of the potential hazards of dry infant skin and may reduce willingness to comply to product avoidance if randomized to this group. Furthermore, emollients are easily obtained over the counter for their own use.

Only two studies – Thitthiwong et al 2020[27] and Lowe et al (the PEBBLES pilot)[26] – attempted to quantify the amount of emollient applied to the skin surface for subjects. It is thus recommended that future studies incorporate better efforts to quantify both adherence in the intervention group and contamination in the control group with greater precision, to facilitate both per-protocol and intention-to-treat analyses that could be more biologically meaningful. A feasible way to do this would be to weigh used emollient bottles from parents at each study visit to quantify adherence.

An individual participant data (IPD) Cochrane meta-analysis was recently performed on all skin care interventions in infants for the AD and food allergy prevention over the same time period, and published during the preparation of our manuscript. The Cochrane group found no difference in the risk of AD by 1-3 years of age, including in high-risk individuals.[29] The main reason for the differences reported is that the Cochrane meta-analysis asked a broader question of whether all

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skin interventions – including bathing products only– used in all stages of infancy prevented AD. They thus included a greater number of studies (n=17); among which were Abraham et al 2018 which studied the effectiveness of chlorhexidine baths and saline baths, and Sankaranarayanan et al, which studied oil massages; this could dilute the effect of emollients as a targeted intervention for AD prevention.[30,31] The AD outcome was also less strictly defined in the Cochrane study, including studies such as Yonezawa et al 2018[32], which used the Neonatal Skin Condition Score to assess for the presence of any skin problems in general rather than strictly AD. The Cochrane meta-analysis also used an IPD approach, and thus five studies (Simpson et al 2014, Horimukai et al 2014, Bellemere et al 2018, Kataoka et al 2020 and Thitthiwong et al 2019)[12,13,23,24,27] which showed a beneficial effect of emollients were not included in the meta-analysis as they only provided aggregate data. As a result, no beneficial effect was found for high-risk populations in the Cochrane study when IPD data from 3 studies were pooled, but in this study a benefit was found in the high-risk population when aggregate data from 8 eligible studies were pooled. Another crucial difference is that the Cochrane meta-analysis included all studies which used skin care interventions on infants less than 12 months who did not have pre-existing AD; this study specifically only included emollient usage started in very early infancy (6 weeks of life), the critical window between birth and AD inception when preventive interventions such as TEWL correction may be most useful.

Emollients were generally safe, with a total of 4 incidences of slippages in the intervention groups and 2 in the control groups across all 10 studies. Pooled evidence from three studies suggest an increased risk of skin infections with emollients compared to the control arm. These events were mainly contributed by Chalmers et al 2020;[16] however this was a parent-reported outcome with no objective ascertainment, and included all bacterial, fungal and viral infections, which made it difficult to draw a specific pathological association with emollient application. However, by using IPD data and by including more studies in the analysis, the Cochrane study found that skin care interventions likely increase the risk of infection. This possible association between emollients and skin infections should be rigorously studied in the form of pathogen-specific physician-diagnosed infections in future clinical trials on this topic.

One limitation in our study is the small number of studies that could be included, as we intentionally restricted the intervention to emollients alone to elucidate its specific role in AD and food allergy prevention. It is encouraging that larger trials such as PEBBLES (NCT03409367), CASCADE (NCT03409367) and PACI (UMIN-CTR-UMIN000028043) are underway, but data

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are still unavailable at this time for inclusion into this meta-analysis. In addition, the types of emollients used in different studies is a major source of heterogeneity; the number of studies we could include was not large enough to be able to stratify them by type of emollients used. Another limitation is that food sensitisation and food allergy outcomes are equivocal because of insufficient long-term data. As such, it is still unclear if the reduction of AD at 1 year of age will translate to protection against food sensitisation or other atopic outcomes in high-risk groups. However, our findings provide insights for interpretation and future research directions for clinical trials aimed at answering these important clinical questions.

In conclusion, the prophylactic and continuous application of emollients on infant skin may prevent AD in high-risk populations and when used continuously. However, we hypothesize that the prophylactic emollients may be delaying the onset, rather than fully preventing the manifestations of AD. This study thus supports recommendations for targeted prevention approaches, instead of the general population, while monitoring for a possible increase in skin infections and having a low threshold to treat these. A common challenge for randomised trials in this field is variable adherence in the intervention group, as well as usage of emollients in the control group, which dilutes any observed effect. Future studies should focus on recruiting those with a strong family history of atopic disease, assessing AD at sequential time points for subjects with and without cessation of therapy, and quantifying adherence in both intervention and control groups in terms of amount of emollient used for each subject, to inform mechanisms through which this intervention exerts its protective effects.

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Table 1: Characteristics of included randomised controlled trials

Study, year, country (study name if any)	Trial design Number per arm Study period	Time period of emollient application	Intervention emollient used	Emollient areas and frequency	Other skin care advice	Source of recruitment of mothers	Inclusion criteria for infants	Age of AD assessment	Criteria for ascertainment of AD	Time points for ascertainment
Bellemere et al 2018, France[23] †	RCT Total number of infants = 120; Intervention = 60, Control = 60‡	2-3 weeks to 6 months	Balm; not specified	Twice a day Part of body not specified	For interventional arm only: Cleansing cream and bath oil twice a week from same brand	Not mentioned	2 atopic first degree relatives	6 months	Not specified	Birth, 30 days, 90 days, 4 months, 6 months

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Chalmers et al 2020, United Kingdom (BEEP) [16]	RCT Investigator-blinded Total number of infants = 1394; Intervention = 693, Control = 701 Study period: Nov 2014 - Nov 2016	< 3 weeks / median age 11 days (7-17) - 1 year of age	DoubleBase Gel (Dermal Laboratories) or Diprobase cream (Bayer)	At least once to whole body daily excluding scalp and also after every bath	For both arms: Mild cleanser / shampoos. Avoid soap, bubble bath, baby wipes	Antenatal / postnatal services, invitation by GP, posters in hospitals and community	First degree relative with allergic rhinitis / asthma / atopy	24 months	UK working party refinement of Hanifin and Rajka diagnostic criteria	3, 6, 12, 18, 24 months

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Dissanayake et al 2019, Japan[22]	RCT 2 x 2 factorial design (only 2 of 4 arms used for analysis) Investigator blinded Total number of infants = 275; Intervention = 138, control = 120 Study period: Oct 2012 to Mar 2014	Birth to 6 months	REPAIR cream (Daiichi Sankyo) which contains ceramide, cholesterol and free fatty acids	2-3x/day particularly on cheeks and peri-oral area; apply to other parts of body at discretion	NA	Maternity wards, recruitment letters, advertisement	Term infants	12 months	Criteria of Japanese Dermatological Association at 1, 6, 9 months, 1 year (questionnaires) and UK working party's diagnostic criteria (questionnaire) at 1 year	1, 6, 9, 12 months

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Horimukai et al 2014, Japan[12]	RCT Investigator blinded Total number of infants = 118; Intervention = 59, control = 59 Study period Nov 2010 - Nov 2013	< 1 week to ~ 8 months (32 weeks)	Emulsion-type emollient (2e Douhet) emulsion	Daily Part of body unspecified	For both arms: Petroleum jelly prescribed	Women with family history of AD at antenatal clinic	First degree relative with physician-diagnosed AD	~ 8 months (32 weeks)	Modified Hanifin-Rajka criteria	4, 12, 24, 32 weeks
Kataoka et al 2010, Japan[24]	RCT Total number of infants = 71 Intervent	Starting age not specified Stopped at 6 months	Not specified	More than once a day	For interventional arm only: Not to wash their face with	Not mentioned	Family history of AD within the second degree of	6 months	Not specified	1 week, 1 month, 4 months, 6 months

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	ion = 36, Control = 35‡				any detergent		kinship			
Lowe et al, 2017, Australia (PEBBLES pilot)[26]	RCT Investigator-blinded Total number of infants = 80; Intervention = 41, Control = 39 Study period: May 2013 - July 2014	< 4 weeks to 6 months	Ceramide-dominant EpiCeram (PuraCap Pharmaceutical LLC)	6g EpiCeram emollient to full skin surface of child twice a day	NA	Maternity wards	Parents or older sibling with allergic disease (asthma, AD, allergic rhinitis / conjunctivitis, food allergy)	12 months	UK working party criteria	6 weeks, 6 months, 12 months

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McClanahan et al 2019, United States[25] †	RCT Investigator-blinded Total number of infants = 100; Intervention = 54, Control = 46 Study period: June 2011 - Jan 2014	< 3 weeks to 12 months	Cetaphil Restoraderm (Galderma)	All body surfaces excluding scalp and diaper area Frequency unspecified	NA	Maternity wards, recruitment letters, advertisement	First degree relative with allergic rhinitis / asthma / AD	12 months	UK working party refinement of Hanifin and Rajka diagnostic criteria	2, 6, 12 months

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Simpson et al 2014, United Kingdom / United States[13]	RCT Investigator-blinded Total number of infants = 124; Intervention = 64, Control = 60 Study period May 2010 - May 2011	< 3 weeks to 6 months	Choice of 3: UK - sunflower seed oil (William Hodgson and Co), doublebase gel (Dermal Laboratories), liquid paraffin 50% in white soft paraffin US - sunflower seed oil (William Hodgson and Co), Cetaphil cream (Galderma	Entire body surface except scalp Frequency unspecified	For both arms: Avoid soap and bubble bath Use mild-fragrance free sunthetic cleanser for babies Avoid bath oils and additives Use mild, fragrant free shampoo for babies Avoid washing suds of shampoo over body Avoid using baby	UK: during pregnancy and by advertisement US: postnatal wards	First degree relative with allergic rhinitis / asthma / atopy	6 months	As determined a blinded investigator - dermatologist or dermatology specialist nurse	10 day, 6 weeks, 12 weeks, 18 weeks, 24 weeks

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			Laboratories), Aquaphor Healing Ointment (Beiersdorf)		wipes					
Skjerven et al 2020, Norway / Sweden (Prevent ADALL)	RCT 2 x 2 factorial design (only 2 of 4 arms used for	< 2 weeks to 8 months	Ceridal (GlaxoSmithKline Consumer Healthcare)	Entire face 4 days per week	For interventional arm only: 1. Baths for 5-10 min with added	All women attending 18-week antenatal ultrasound visit at study sites	Gestational age > 35 weeks	12 months	Either UK Working Party diagnostic criteria at 3, 6,	3, 6, 12 months

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[15]	analysis) Investigator blinded Total number of infants = 1074; Intervention = 575, control = 596 Study period: Dec 2014 - Oct 2016				emulsified oil (0.5 dL of bath oil per 8 L of water) 2. Discouraged use of soap				12 months OR Hanifin and Rajka diagnostic criteria at 12 months	

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Thitthiwong et al 2020, Thailand [27]	RCT Investigator-blinded Total number of infants = 53; Intervention = 526 Control = 25 Study period: Jan 2016-Apr 2017	< 7 weeks to 9 months	"Cold Cream" formulated by hospital, containing white petrolatum, stearyl alcohol, propylene glycol and glycerin	all over the body except periorbital and perioral areas at least once daily	NA	Paediatric outpatient department of hospital	Parents or siblings had history of allergic disease such as AD, asthma, allergic rhinitis, allergic conjunctivitis, food allergy	9 months	Atopic Dermatitis guidelines by Eichenfield et al in 2014	2, 4, 6, 9 months

†: these studies were funded by pharmaceutical companies

‡: information was only available for total number of participants and authors were not contactable; thus an equal number was assigned to each treatment arm for analysis

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Table 2: Adherence, adverse events and outcomes for food sensitisation and food allergy

Study, year, country (study name if any)	Number per arm (per-protocol numbers = pp in brackets)	Adherence criteria	Adherence percentage in interventional arm / Contamination percentage in control arm†	Adverse events in intervention and control groups	Method used to measure food sensitisation	Food sensitisation outcomes in intervention and control groups	Food allergy outcomes reported	Food allergy outcomes intervention and control groups
Bellemere et al 2018, France[23]	Total number of infants = 120 Intervention = 60, Control = 60§	Not assessed	Not reported	Not reported	NA	NA	NA	NA

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Chalmers et al 2020, United Kingdom (BEEP)[16]	Total number of infants = 1394; Intervention = 693 (pp = 598), Control = 701 (pp = 612) Study period: Nov 2014 - Nov 2016	Emollients were applied at least 3-4 times per week to most of the child's body (at least two of face and neck, arms and legs, or trunk)	Adherence for intervention = 74% Contamination for control = 15%	Slippages: Intervention = 3, control = 2 None resulted in serious injury or hospital admission. Skin infections: Intervention = 15%, control = 11%	SPT to milk, egg and peanut at 2 years	Egg, milk, or peanut: Intervention = 12%, control = 9% Egg: Intervention = 9%, control = 7%	Oral food challenge to milk, egg and peanut at 2 years	Egg, milk or peanut: Intervention = 7%, control = 5% Egg: Intervention = 6%, control = 4%
Dissanayake et al 2019, Japan[22]	Total number of infants = 275; Intervention = 138 (pp = 120), control = 120 (pp = 117) Study	Applied emollient at least twice a day	Adherence for intervention = 80% Contamination for control not reported	Not reported	sIgE to egg white, milk and ovomucoid at 9 months	Egg or milk: Intervention = 60.5%, control = 46.1%	Parent-returned questionnaire at 9 months	Egg or milk: Intervention = 11%, control = 13%

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	period: Oct 2012 to Mar 2014							
Horimukai et al 2014, Japan[12]	Total number of infants = 118; Intervention = 59 (pp = 50), control = 59 (pp = 49) Study period Nov 2010 - Nov 2013	Not assessed	Not reported	Not reported	sIgE to egg white and ovomucoid at 32 weeks	Egg white: Intervention = 42%, control = 45% Ovomucoid: Intervention = 19%, control = 6.8%	NA	NA
Kataoka et al 2010, Japan[24]	Total number of infants = 71 Intervention = 36, Control = 35§	Not assessed	Not reported	Not reported	NA	NA	NA	NA

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Lowe et al, 2017, Australia (PEBBLES pilot)[26]	Total number of infants = 80; Intervention = 41 (pp = 37), Control = 39 (pp = 36) Study period: May 2013 - July 2014	At least 3 days per week	Adherence for intervention = 93% Contamination for control = 39%	None	SPT to egg, milk, peanut at 6months and 12months	Egg, milk or peanut at 6 months: Intervention = 12.8%, control = 22.9% Egg, milk or peanut at 12months: Intervention = 8.8%, control = 19.4% Egg at 6 months: Intervention = 10.3%, control = 17.1% Egg at 12 months: Intervention = 5.9%, control = 16.7%	NA	NA

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McClanahan et al 2019, United States[25]	Total number of infants = 100; Intervention = 54 (pp = 41), Control = 46 (pp = 36) Study period: June 2011 - Jan 2014	Applying intervention or control emollient 5 or more days per week	Adherence for interventional = 66.7% Contamination for control = 45.5%	Bacterial skin infection 4/54 (7.4%) in intervention group, 3/46 (6.5%) in control group	NA	NA	NA	NA
Simpson et al 2014, United Kingdom / United States[13]	Total number of infants = 124; Intervention = 64 (pp = 55), Control = 60 (pp = 33) Study period May 2010 - May 2011	At least 5 days per week	Adherence for intervention = 85% Contamination for control = 13.3%	Superficial skin infections: 3/64 (4.7%) in intervention group, 3/60 (5.0%) in control group	NA	NA	NA	NA

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Skjerven et al 2020, Norway / Sweden (Prevent ADALL) [15]	Total number of infants = 1074; Intervention = 575 (pp = 499), control = 596 (pp = 572)	Application of face cream for average of at least 3-5 days per week for at least 16 weeks of the full 25 weeks	Adherence in intervention = 27% Contamination in control <1%	1 in intervention group (slippage)	NA	NA	NA‡	NA
Thitthiwong et al 2020, Thailand [27]	Total number of infants = 53; Intervention = 26 (pp = 25) Control = 27 (pp = 27) Study period: Jan 2016- Apr 2017	Not assessed	Not reported	None	NA	NA	NA	NA

†contamination = percentage in control arm who reported using emollients in a way that mirrored the interventional arm

‡ planned but not published yet

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§information was only available for total number of participants and authors were not contactable; thus an equal number was assigned to each treatment arm for analysis

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Figure legends:

Figure 1: PRISMA flow chart of included studies

Figure 2: Risk of bias summary

Abbreviations: D1, D2, D3, D4, D5 = domains 1 to 5 of the Cochrane risk of bias 2.0 tool.

Figure 3: (a) Effect of prophylactic emollients for prevention of atopic dermatitis (based on ITT analysis best case scenario) – all populations **(b)** Effect of prophylactic emollients for prevention of atopic dermatitis (based on ITT analysis best case scenario) - high risk populations only **(c)** Effect of prophylactic emollients for prevention of atopic dermatitis (based on ITT analysis best case scenario) – based on interval between duration of emollient application and assessment **(d)** Effect of prophylactic emollients for prevention of food sensitization to any food (egg, milk, peanut)

Abbreviations: ITT = intention to treat

Figure 4: GradePro table summarising grades of evidence

Figure 5

Prophylactic emollients applied from the first 6 weeks of infancy reduces the development of atopic dermatitis (AD) in populations at high risk of AD but not in the general population. There was significant benefit where prophylactic emollients were used continuously to the point of AD assessment, but not when treatment was ceased for an interval. Prophylactic emollients used in infancy may delay the manifestations of AD rather than prevent its development

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Supporting Information

*Abbreviations***:** ITT = intention to treat

Supporting Information Text: Literature Search Strategy

Supporting Information Figures

Figure S1: Effect of prophylactic emollients for prevention of atopic dermatitis (based on ITT analysis best case scenario) – normal risk populations only

Figure S2: Effect of prophylactic emollients for prevention of atopic dermatitis (per-protocol analysis) – normal risk populations only

Figure S3: Effect of prophylactic emollients for prevention of atopic dermatitis (per-protocol analysis) – all populations

Figure S4: Effect of prophylactic emollients for prevention of atopic dermatitis (per-protocol analysis) – high risk populations only

Figure S5: Effect of prophylactic emollients for prevention of atopic dermatitis (based on per-protocol analysis) – based on interval between duration of emollient application and assessment

Figure S6: Effect of prophylactic emollients on Skin infections (based on ITT analysis)

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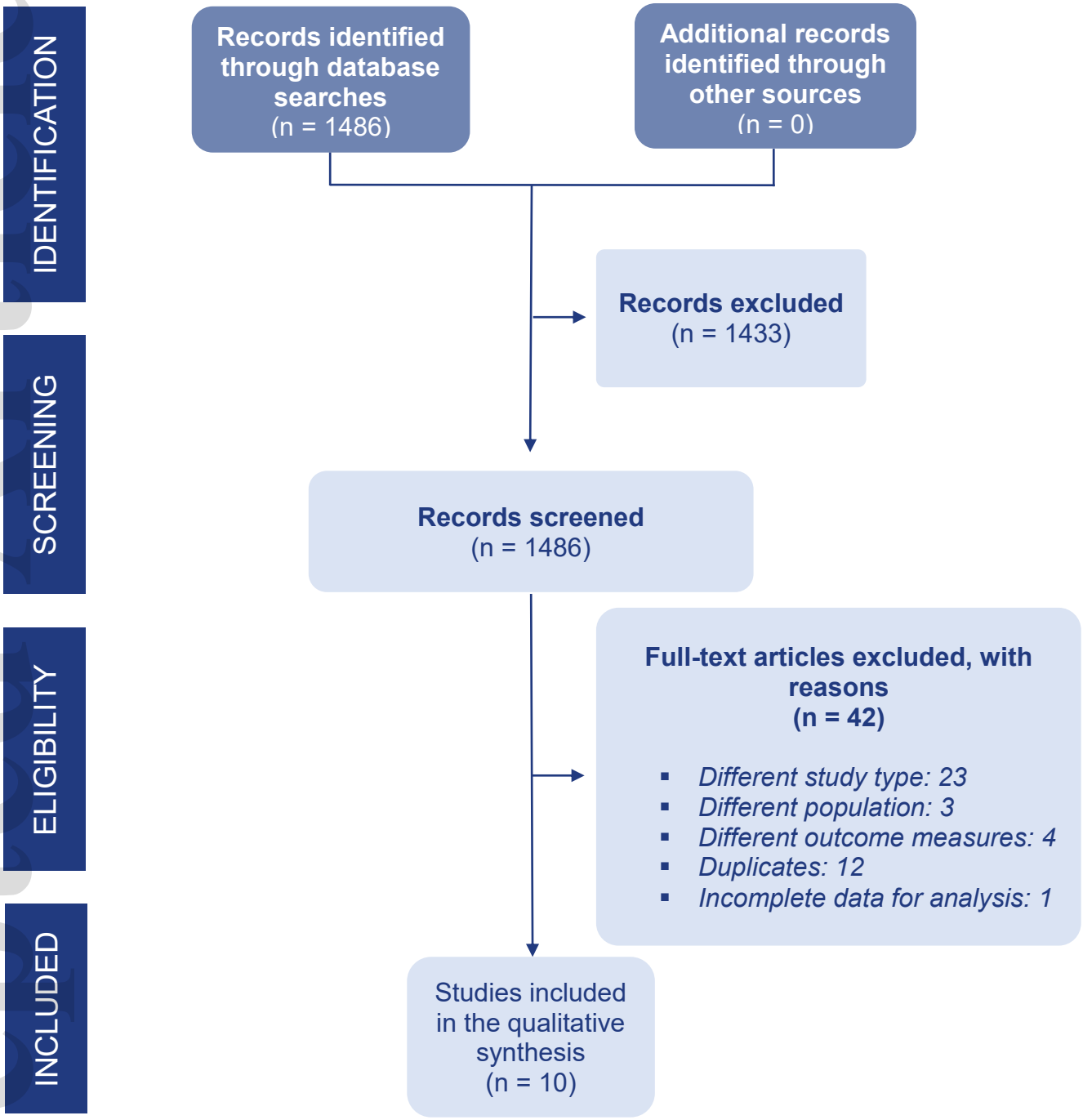


Figure 1_Zhong et al.

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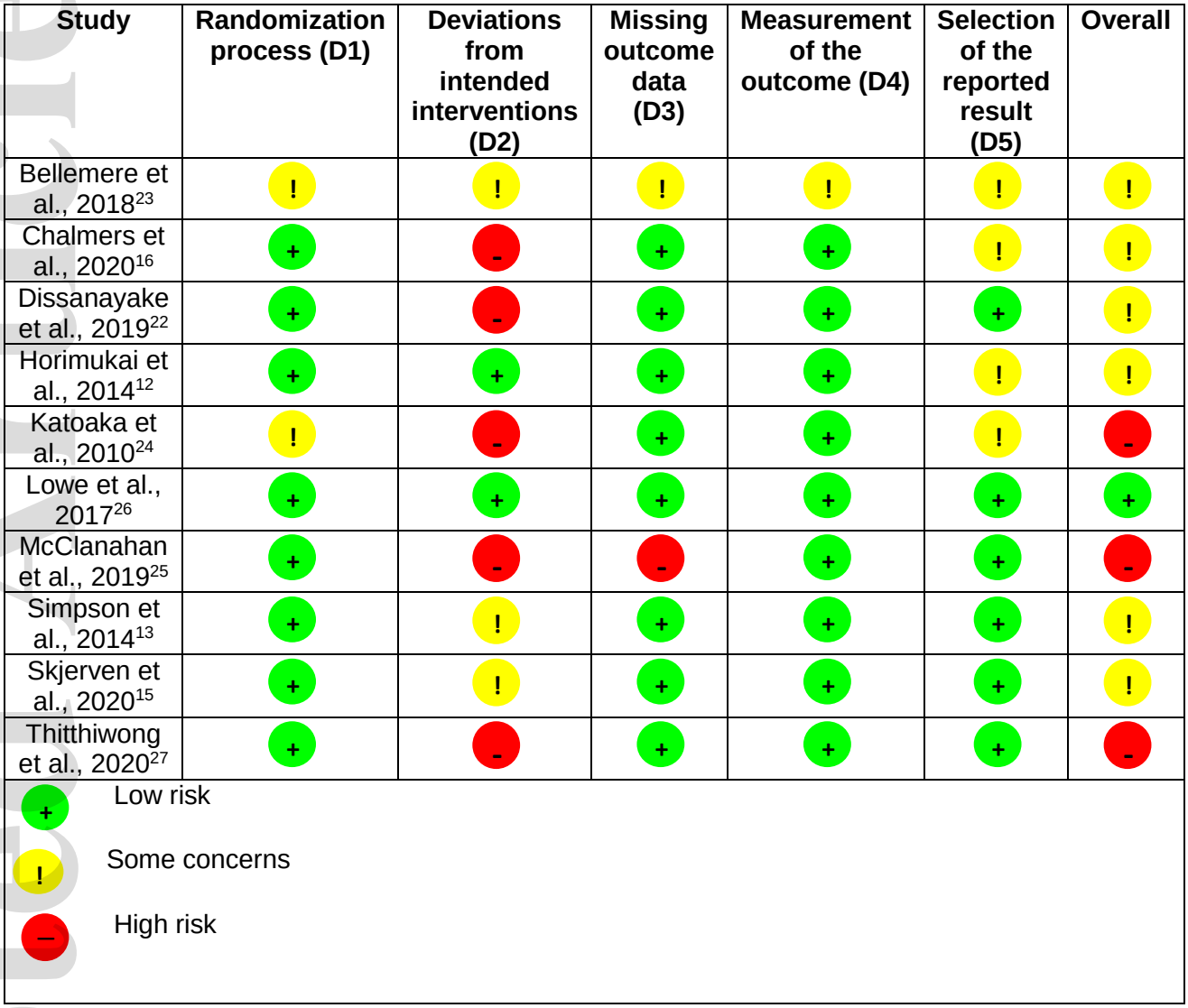
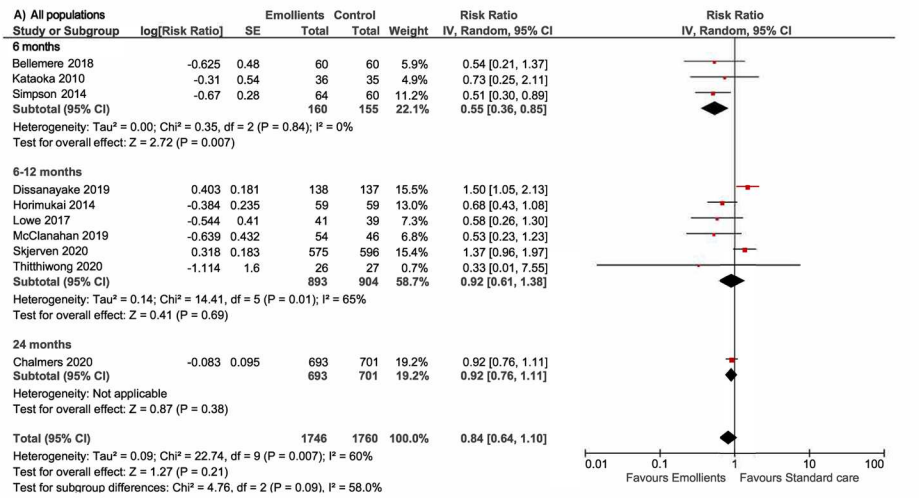
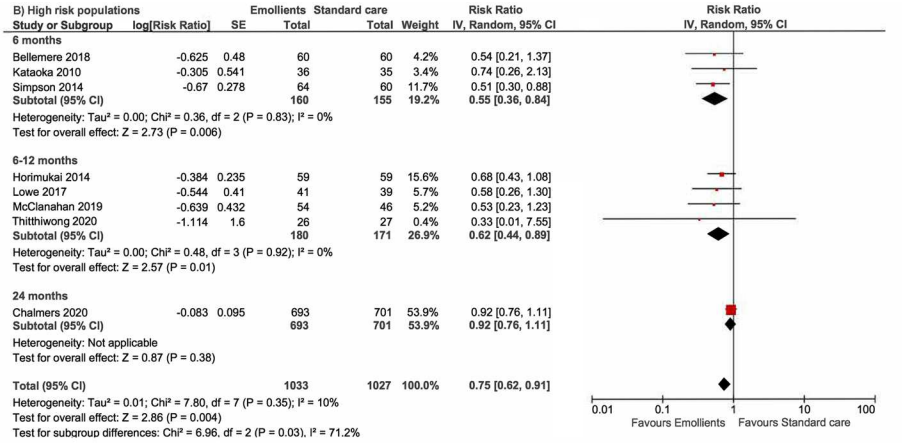
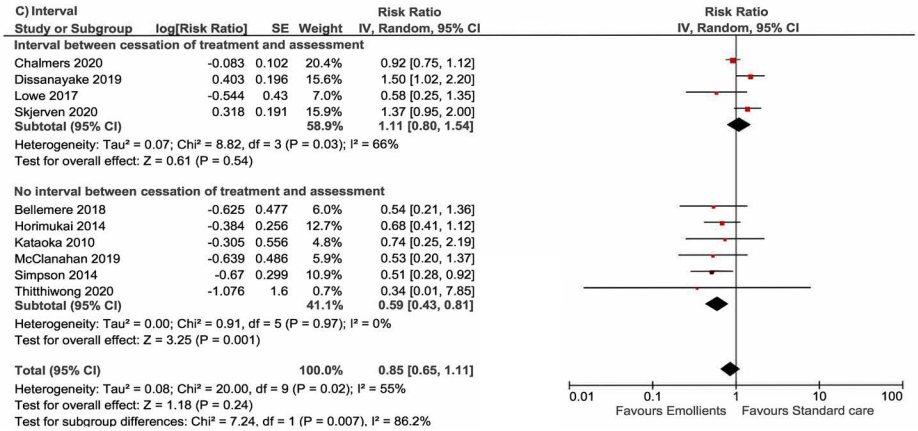


Figure 2_Zhong et al.

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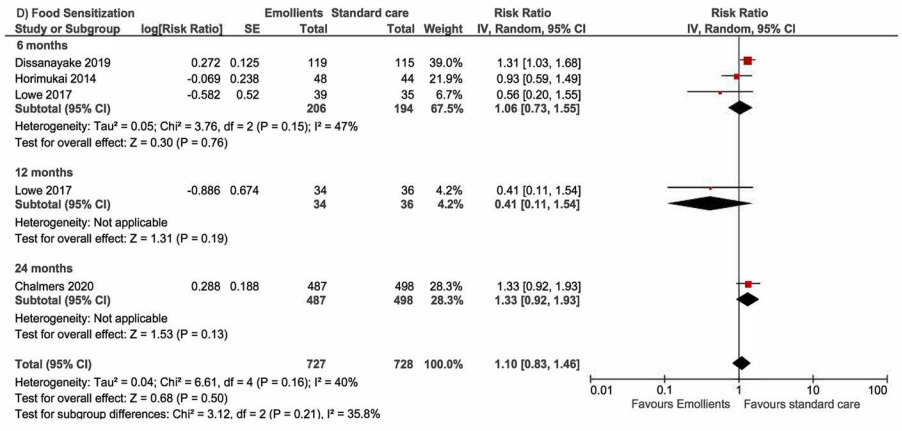


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Patient or population: prevention of atopic dermatitis in infants
Intervention: prophylactic emollients
Comparison: standard skin care

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Development of atopic dermatitis (AD)	3505 (10 RCTs)	⊕⊕◯◯ LOW[a,b]	**RR 0.84** (0.64 to 1.10)
Development of atopic dermatitis in high risk subjects (AD high risk)	2059 (8 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.75** (0.62 to 0.91)
Development of food sensitisation (Sensitisation)	1455 (5 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.85** (0.65 to 1.11)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

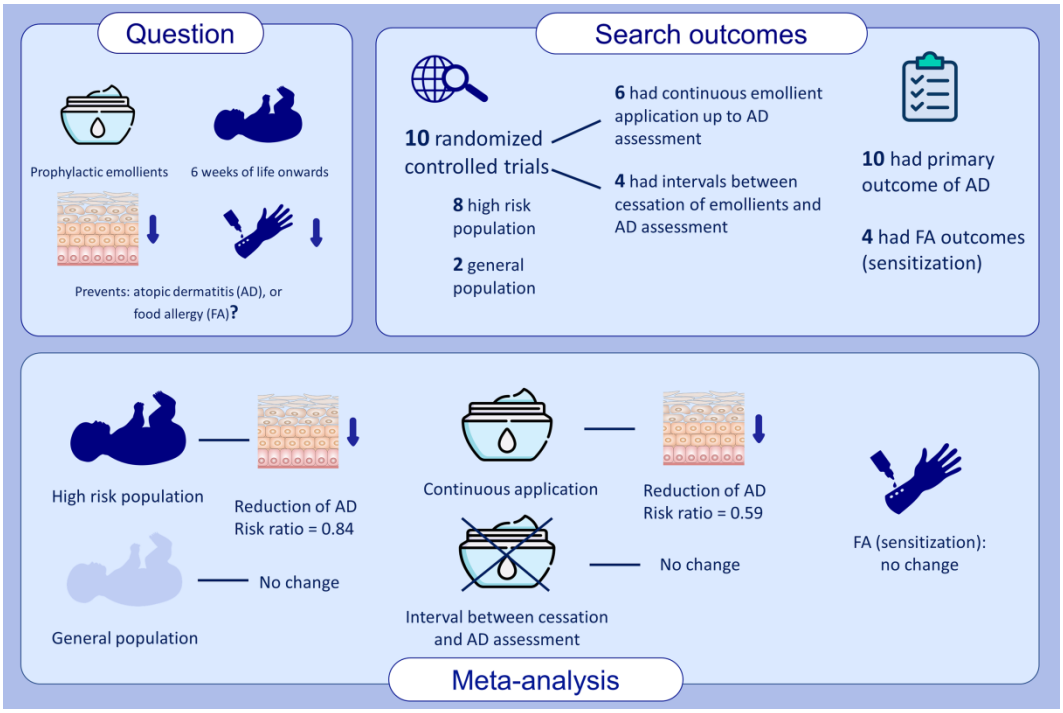
Explanations
a. There was low adherence in intervention groups, and a significant rate of contamination (where control groups used emollients in a way that mirrored the intervention group) in many of the studies
b. 2 studies out of 10 showed possible increase in atopic dermatitis in intervention groups

Figure 4_Zhong et al.

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Supporting Information

Abbreviations: ITT = intention to treat

I. Supporting Information Text:

- Literature Search Strategy

II. Supporting Information Figures

- **Figure S1**: Effect of prophylactic emollients for prevention of atopic dermatitis (based on ITT analysis best case scenario) – normal risk populations only

- **Figure S2**: Effect of prophylactic emollients for prevention of atopic dermatitis (per-protocol analysis) – normal risk populations only

- **Figure S3**: Effect of prophylactic emollients for prevention of atopic dermatitis (per-protocol analysis) – all populations

- **Figure S4**: Effect of prophylactic emollients for prevention of atopic dermatitis (per-protocol analysis) – high risk populations only

- **Figure S5**: Effect of prophylactic emollients for prevention of atopic dermatitis (based on per-protocol analysis) – based on interval between duration of emollient application and assessment

- **Figure S6**: Effect of prophylactic emollients on Skin infections (based on ITT analysis)

I. Supporting Information Text:

- Literature Search Strategy

1.1 Search Strategy for Identification of Studies

A systematic literature review will be performed. Searches will encompass electronic medical databases and clinical trial registers. In addition, the bibliographies of key articles will be reviewed to identify other relevant articles that may be appropriate for inclusion.

The search results will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart, and the reasons for inclusion and exclusion of each identified study will be clearly explained (Moher et al., 2009).

1.1.1 Electronic Databases

We will perform literature searches of the following electronic databases:

- MEDLINE and MEDLINE In-Process (using PubMed platform)
- Embase (using Elsevier Platform)
- CINAHL (using EBSCO publishing)
- BIOSIS
- The Cochrane Library, including the following:
    - The Cochrane Central Register of Controlled Trials
    - The Cochrane Database of Systematic Reviews
    - Database of Abstracts of Reviews of Effectiveness

1.1.2 Internet Websites and Other Resources

. The following websites will be searched to identify ongoing trials:

ClinicalTrials.gov: http://clinicaltrials.gov/

International Clinical Trials Registry Platform: http://www.who.int/ictrp/en/

Reference lists of any relevant studies, recent systematic reviews, and meta-analyses will be searched for further studies of interest because these are typically good sources of additional material that can supplement the articles retrieved from the standard medical databases.

1.1.3 Time Horizon and Language Search Limits

For this systematic review, the electronic database searches will be performed for the period January 2000 to July 2020.

There will be no limit on language, or geographical perspective. We will use external resources to extract relevant information from the included non–English-language articles. If

such resources are not available we will contact external translation services to extract relevant information from and/or acquire translations of source documents.

1.1.4 Search Terms

The following sets of search terms will be used:

Search terms relating to the health condition of interest (e.g., terms for Disease [Medical Subject Heading (MeSH)]):

- atopic dermatitis, eczema, atopic eczema

Search terms relating to interventions

- Moisturizer, emollient, skin intervention, barrier therapy, triple-lipid, ceramide

Study type(s): terms for “Randomized Controlled Trial”[Publication Type] or “Controlled Clinical Trial”[Publication Type]

Errore. L'origine riferimento non è stata trovata. Table A-1 in Appendix A provide a full listing of planned search terms.

Appendix A

Search Strategies

Table A-1. PubMed Search Strategy

Term Group, Search Number		Search Terms	Hits
Population	#1	"Dermatitis, Atopic/prevention and control"[MAJR] OR ((("dermatitis, atopic"[MeSH Terms] OR ("dermatitis"[All Fields] AND "atopic"[All Fields])) OR "atopic dermatitis"[All Fields]) OR ("atopic"[All Fields] AND "eczema"[All Fields]) OR "atopic eczema"[All Fields]) OR "eczema"[MeSH Terms] OR "eczema"[All Fields] OR "eczemas"[All Fields]	44,097
Intervention	#2	"moisture"[All Fields] OR "moistures"[All Fields] OR "moisturisation"[All Fields] OR "moisturiser"[All Fields] OR "moisturisers"[All Fields] OR "moisturising"[All Fields] OR "moisturization"[All Fields] OR "moisturize"[All Fields] OR "moisturized"[All Fields] OR "moisturizer"[All Fields] OR "moisturizers"[All Fields] OR "moisturizes"[All Fields] OR "moisturizing"[All Fields] OR "emollients"[Pharmacological Action] OR "emollients"[MeSH Terms] OR "emollients"[All Fields] OR "emollient"[All Fields] OR "ceramide s"[All Fields] OR "ceramides"[MeSH Terms] OR "ceramides"[All Fields] OR "ceramide"[All Fields] OR "Emulsions"[Mesh]	79,771
Population	#3	Infant[MeSH] OR infant[tiab] OR infants[tiab] OR infancy[tiab] OR newborn[tiab] OR baby[tiab] OR babies[tiab] OR neonate[tiab] OR neonates[tiab] OR neonatal[tiab] OR Child[MeSH] OR child[tiab] OR toddler[tiab] OR toddlers[tiab] OR Pediatrics[MeSH] OR paediatric[tiab] OR paediatrics[tiab] OR pediatric[tiab] OR pediatrics[tiab]	2,932,644
All studies	#4	#1 AND #2 AND #3	605
Exclusion terms	#5	“Animals”[MeSH] NOT “Humans”[MeSH]	4,724,962
	#6	“Comment”[Publication Type] OR “Letter”[Publication Type] OR “Editorial”[Publication Type] OR “Case Reports”[Publication Type] OR “Clinical Trial, Phase I”[Publication Type] OR “case study”[Title] OR “case studies”[Title] OR “case report”[Title] OR “case reports”[Title] OR “case series”[Title]	3,879,958
All studies	#7	#4 NOT (#5 OR #6)	**540**

MeSH = Medical Subject Heading.

Table A-2. Embase Search Strategy

Term Group, Search Number		Search Terms	Hits
Population	#1	'atopic dermatitis'/exp OR ("dermatitis" AND "atopic") OR "atopic dermatitis" OR ("atopic" AND "eczema") OR ("atopic eczema") OR 'eczema'/exp OR "eczema" OR "eczemas"	84,330
Intervention	#2	"moisture" OR "moistures" OR "moisturisation" OR "moisturiser" OR "moisturisers" OR "moisturising" OR "moisturization" OR "moisturize" OR "moisturized" OR "moisturizer" OR "moisturizers" OR "moisturizes" OR "moisturizing" OR 'emollient agent'/exp OR "emollients" OR "emollient" OR "ceramide s" OR 'ceramide'/exp OR "ceramides" OR "ceramide" OR 'emulsion'/exp	115,459
Population	#3	'infant'/exp OR infant:ti,ab OR infants:ti,ab OR infancy:ti,ab OR newborn:ti,ab OR newborn:ti,ab OR baby:ti,ab OR babies:ti,ab OR neonate:ti,ab OR neonates:ti,ab OR neonatal:ti,ab OR 'Child'/exp OR child:ti,ab OR toddler:ti,ab OR toddlers:ti,ab OR 'pediatrics'/exp OR paediatric:ti,ab OR paediatrics:ti,ab OR pediatric:ti,ab OR pediatrics:ti,ab	3,458,810
All studies	#4	#1 AND #2 AND #3	1,286
Exclusion terms	#5	'Animals'/exp NOT 'Humans'/exp	5,476,306
	#6	Comment*:ti OR 'Editorial'/it OR 'Letter'/it OR 'case report'/exp OR case report* OR 'phase 1 clinical trial'/exp OR 'case study':ti OR 'case studies':ti OR 'case report':ti OR 'case reports':ti	3,121,001
All studies	#7	#4 NOT (#5 OR #6)	1,038
	#8	#7 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	**455**

MeSH = Medical Subject Heading.

Table A-3. Cochrane Library Search Strategy

Term Group, Search Number		Search Terms	Hits
Population	#1	MeSH descriptor: [Dermatitis, Atopic] explode all trees	1766
	#2	MeSH descriptor: [Eczema] explode all trees	1042
	#3	#1 OR #2 OR ("dermatitis" AND "atopic") OR "atopic dermatitis" OR ("atopic" AND "eczema") OR ("atopic eczema") OR "eczema" OR "eczemas"	6532
Intervention	#4	MeSH descriptor: [Emollients] explode all trees	419
	#5	MeSH descriptor: [Ceramides] explode all trees	80
	#6	MeSH descriptor: [Emulsions] explode all trees	998
	#7	#4 OR #5 OR #6 OR "moisture" OR "moistures" OR "moisturisation" OR "moisturiser" OR "moisturisers" OR "moisturising" OR "moisturization" OR "moisturize" OR "moisturized" OR "moisturizer" OR "moisturizers" OR "moisturizes" OR "moisturizing" OR "emollients" OR "emollient" OR "ceramide s" OR "ceramides" OR "ceramide"	**4336**
Population	#8	MeSH descriptor: [Infant] explode all trees	**31588**
	#9	MeSH descriptor: [Child] explode all trees	**55053**
	#10	MeSH descriptor: [Pediatrics] explode all trees	**666**
	#11	#8 OR #9 OR #10 OR infant:ti,ab OR infants:ti,ab OR infancy:ti,ab OR newborn:ti,ab OR newborn:ti,ab OR baby:ti,ab OR babies:ti,ab OR neonate:ti,ab OR neonates:ti,ab OR neonatal:ti,ab OR child:ti,ab OR toddler:ti,ab OR toddlers:ti,ab OR paediatric:ti,ab OR paediatrics:ti,ab OR pediatric:ti,ab OR pediatrics:ti,ab	**180023**
All studies	#12	**#3 AND #7 AND #11** Cochrane review =22 Trials = 328 Protocol = 1	**351**

Table A-4. BIOSIS Search Strategy

Term Group, Search Number		Search Terms	Hits
Population/Intervention	#1	Topic= "dermatitis, atopic"[MeSH Terms] OR ("dermatitis" AND "atopic") OR "atopic dermatitis" OR ("atopic" AND "eczema") OR ("atopic eczema") OR "eczema"[MeSH Terms] OR "eczema" OR "eczemas"	27,662
	#2	TOPIC= "moisture" OR "moistures" OR "moisturisation" OR "moisturiser" OR "moisturisers" OR "moisturising" OR "moisturization" OR "moisturize" OR "moisturized" OR "moisturizer" OR "moisturizers" OR "moisturizes" OR "moisturizing" OR "emollients"[MeSH Terms] OR "emollients" OR "emollient" OR "ceramide s" OR "ceramides"[MeSH Terms] OR "ceramides" OR "ceramide" OR "Emulsions"[Mesh]	114,115
	#3	Topic= Infant[MeSH] OR infant OR infants OR infancy OR newborn OR baby OR babies OR neonate OR neonates OR neonatal OR Child[MeSH] OR child OR toddler OR toddlers OR Pediatrics[MeSH] OR paediatric OR paediatrics OR pediatric OR pediatrics	1,626,506
All studies	#4	#1 AND #2 AND #3	228
Exclusion terms	#5	“Animals” [MeSH] NOT “Humans” [MeSH]	964,109
	#6	Ti=“Comment” OR “Letter OR “Editorial”	22,880
All studies	#7	#4 NOT (#5 OR #6)	**226**

Table A-5. CINAHL Search Strategy

Term Group, Search Number		Search Terms	Hits
Population/Intervention	S1	"dermatitis, atopic"[MeSH Terms] OR ("dermatitis" AND "atopic") OR "atopic dermatitis" OR ("atopic" AND "eczema") OR ("atopic eczema") OR "eczema"[MeSH Terms] OR "eczema" OR "eczemas"	7,654
All studies	S2	"moisture" OR "moistures" OR "moisturisation" OR "moisturiser" OR "moisturisers" OR "moisturising" OR "moisturization" OR "moisturize" OR "moisturized" OR "moisturizer" OR "moisturizers" OR "moisturizes" OR "moisturizing" OR "emollients"[MeSH Terms] OR "emollients" OR "emollient" OR "ceramide s" OR "ceramides"[MeSH Terms] OR "ceramides" OR "ceramide" OR "Emulsions"[Mesh]	5,201
	S3	Infant[MeSH] OR infant OR infants OR infancy OR newborn OR baby OR babies OR neonate OR neonates OR neonatal OR Child[MeSH] OR child OR toddler OR toddlers OR Pediatrics[MeSH] OR paediatric OR paediatrics OR pediatric OR pediatrics	941,628
	S4	#1 AND #2 AND #3	302
	S5	“Animals” NOT “Humans”	108,646
	S6	“Comment” OR “Letter” OR “Editorial”	111,224
	S7	S4 NOT (S5 OR S6)	**297**

II. Supporting Information Figures

Figure S1: Effect of prophylactic emollients for prevention of atopic dermatitis (based on ITT analysis best case scenario) – normal risk populations only

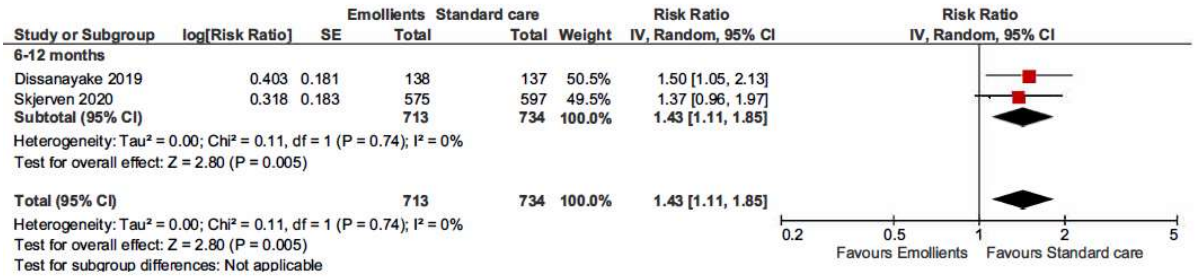


Figure S2: Effect of prophylactic emollients for prevention of atopic dermatitis (per-protocol analysis) – normal risk populations only

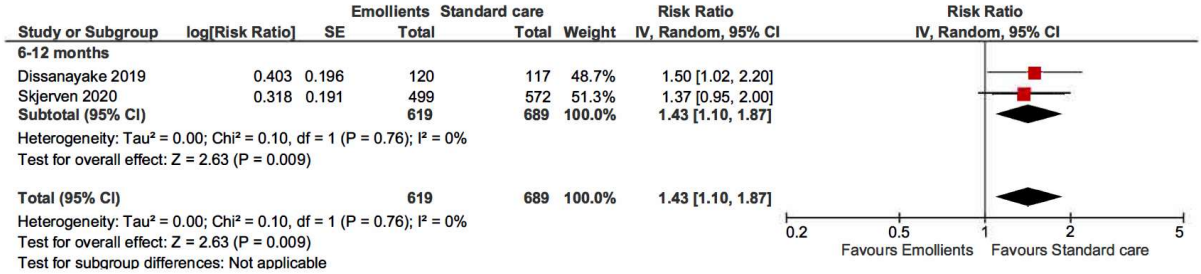


Figure S3: Effect of prophylactic emollients for prevention of atopic dermatitis (per-protocol analysis) – all populations

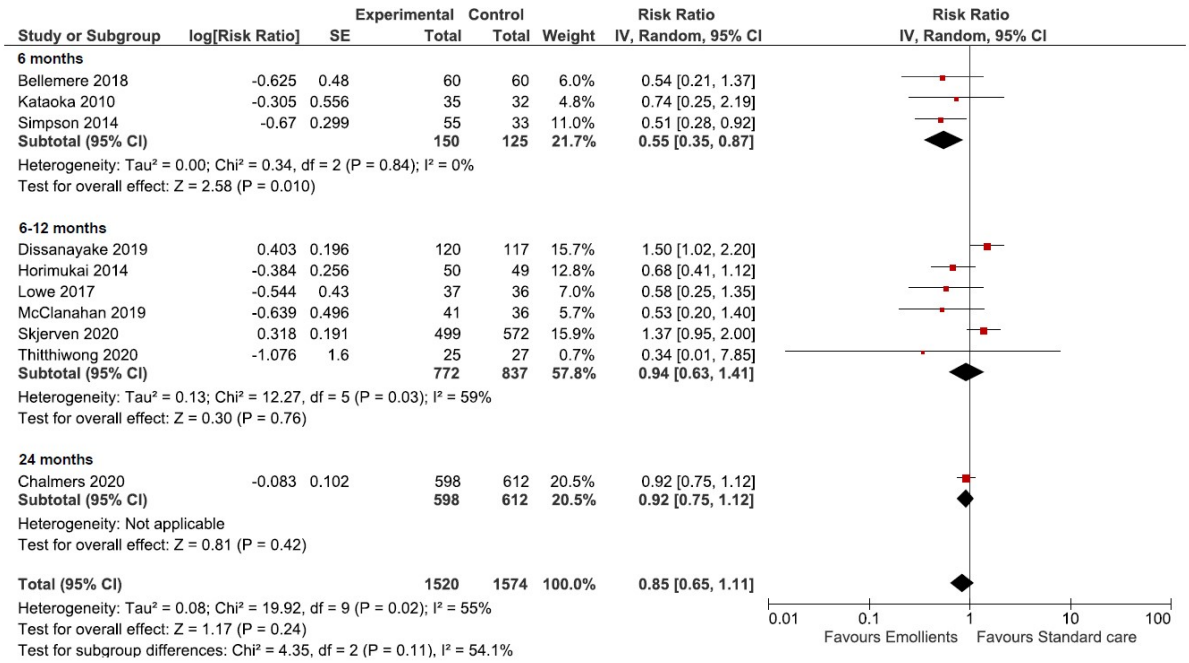


Figure S4: Effect of prophylactic emollients for prevention of atopic dermatitis (per-protocol analysis) – high risk populations only

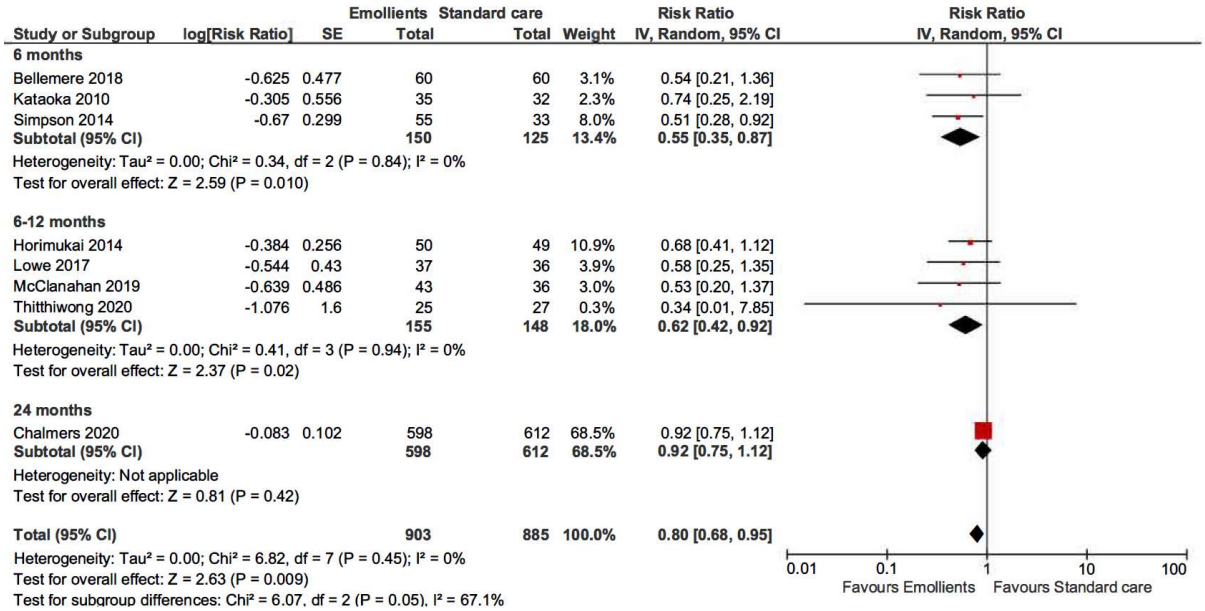


Figure S5: Effect of prophylactic emollients for prevention of atopic dermatitis (based on per-protocol analysis) – based on interval between duration of emollient application and assessment

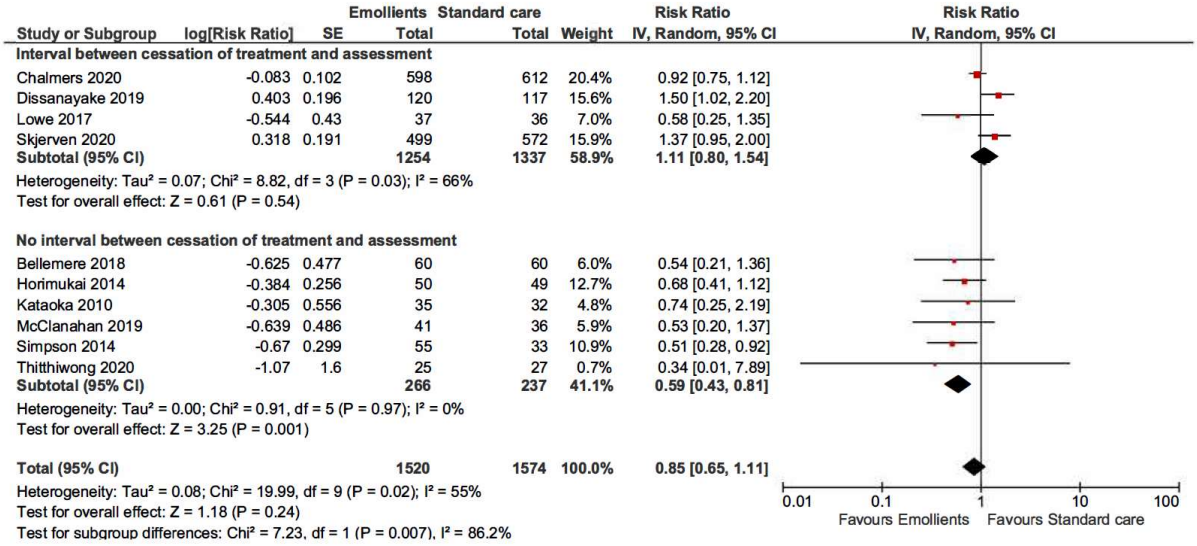


Figure S6: Effect of prophylactic emollients on Skin infections (based on ITT analysis)

