RESEARCH PAPER

EFFECTIVENESS OF DIFFERENT EMOLLIENT FORMULATIONS FOR THE PRIMARY PREVENTION OF ATOPIC DERMATITIS IN INFANTS AND CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS AND PRIMARY COMPARATIVE STUDIES

[1] Fitriana I ; [2] Ismail N. I ; [3] Jamil A
[1,2,3] Department of Dermatology and Venereology, Faculty of Medicine, Universiti Kebangsaan Malaysia
Corresponding Email : ilmafitri@yahoo.com

ABSTRACT

Background: *Atopic dermatitis (AD) is the most burdensome inflammatory skin disease of childhood, and epidermal barrier dysfunction detectable in the first weeks of life precedes clinical disease. Prophylactic emollient therapy is biologically plausible, but randomized controlled trials (RCTs) have yielded discordant results, and whether the formulation of the emollient determines efficacy remains unresolved.* ***Objective:*** *To synthesise RCTs and primary comparative studies published in the last 15 years on the effectiveness and safety of emollients, and of different emollient formulation categories, for the primary prevention of AD in infants and children.* ***Methods:*** *This review followed PRISMA 2020. PubMed/MEDLINE, Europe PMC and ClinicalTrials.gov were searched from 1 January 2011 to 15 October 2026, supplemented by Consensus semantic searching and citation chasing. Eligible designs were RCTs, comparative (non-randomized controlled) studies, cohort studies and case series in infants without AD at baseline. Emollients were classified a priori as ceramide/physiological-lipid–enriched, paraffin/petrolatum-based (basic occlusive), emulsion/emollient-plus, or mixed/participant-selected/bundled regimens. Risk of bias was assessed with RoB 2 and ROBINS-I. Risk ratios (RR) were pooled with restricted maximum likelihood random-effects models and Hartung–Knapp–Sidik–Jonkman confidence intervals; certainty was graded with GRADE.* ***Results:*** *Twenty-two studies (18 RCTs; four non-randomized studies) were included; 16 RCTs (5,229 infants) contributed to the primary meta-analysis. Emollient application did not significantly reduce the cumulative incidence of AD overall (RR 0.88, 95% CI 0.69–1.13; I^2 = 63%; 95% prediction interval 0.42–1.86; low certainty). No formulation category was clearly superior (test for subgroup differences P = 0.23); point estimates favoured emulsion/emollient-plus products (RR 0.77, 0.51–1.18) and mixed regimens (RR 0.68), whereas ceramide-enriched (RR 1.12) and basic paraffin/petrolatum products (RR 1.08) showed no benefit. Protection was apparent when emollients were still being applied at outcome assessment (RR 0.71, 0.51–0.99) but not after cessation (RR 1.11; interaction P = 0.026), during early infancy (≤6 months: RR 0.46, 0.29–0.73) but not at ≥24 months (RR 0.98, 0.73–1.32), and in high-risk infants (RR 0.76, 0.57–1.01) rather than unselected populations (RR 1.17; interaction P = 0.038). Baseline (control-arm) AD risk explained 78% of between-trial heterogeneity. Emollients did not significantly alter skin infection (RR 1.14, 0.69–1.88), food allergy (RR 1.10, 0.60–2.03) or food sensitisation (RR 1.23, 0.64–2.37), all at low to very low certainty. Observational cohorts linked frequent emollient bathing and moisturisation with higher odds of AD and food allergy.* ***Conclusion:*** *Routine prophylactic emollients do not produce a durable reduction in AD across unselected infant populations, and current evidence does not establish the superiority of any single formulation category. Continuous application of well-formulated, non-paraffin-bath emulsions in high-risk infants may delay disease onset during early infancy. Adequately powered head-to-head trials stratified by baseline risk, filaggrin genotype and climate are required.*

Keywords: *Atopic Dermatitis, Emollients, Primary Prevention, Infant, Skin Barrier, Meta-Analysis*
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INTRODUCTION

Atopic dermatitis (AD) is the leading cause of skin-related disability worldwide. Modelling studies estimate that approximately 102.8 million children are affected globally, with an overall paediatric prevalence of 4.0% and markedly higher estimates in high-income regions, and the Global Burden of Disease 2021 analysis projects that the absolute number of affected individuals will continue to rise until 2050 driven by population growth. Pooled point prevalence in children and adolescents reaches 11.1% when standardised definitions are applied, and onset is concentrated in the first year of life, so that infancy represents the critical window for any preventive strategy.[1–3]

Because impairment of the epidermal barrier precedes the clinical onset of AD, regular application of emollients from birth has been proposed as a simple, inexpensive and safe primary-prevention strategy. Randomised controlled trials (RCTs), however, have produced discordant results, ranging from a halving of AD incidence in early proof-of-concept trials to no benefit, or possible harm, in large pragmatic trials. Emollients also differ fundamentally in composition, from basic paraffin and petrolatum occlusives to ceramide-dominant barrier-repair creams and emollient-plus formulations, and whether the type of emollient determines preventive efficacy has not been resolved.[4–8]

Clinicians and caregivers therefore face an unresolved practical question: if emollients are to be used for prevention, which type should be chosen, when should application start, for how long, and in which infants? The 2026 American Academy of Dermatology guideline issued only a conditional recommendation for moisturising skin care to reduce AD occurrence, explicitly citing uncertainty about formulation and target population. We therefore conducted an updated systematic review and meta-analysis restricted to the last 15 years, explicitly comparing emollient formulation categories and integrating RCTs with primary comparative and cohort studies.[9–12]

A. Objectives of the Study

The general objective was to evaluate the effectiveness and safety of emollients for the primary prevention of AD in infants and children by synthesising RCTs and primary comparative studies published in the last 15 years. The specific objectives were (1) to estimate the pooled effect of emollient application on the cumulative incidence of AD; (2) to compare emollient formulation categories (ceramide/physiological-lipid–enriched, paraffin/petrolatum-based, emulsion/emollient-plus, and mixed or participant-selected regimens) indirectly and, where available, directly; (3) to explore effect modification by baseline atopic risk, continuity of application, duration, frequency, region and risk of bias; and (4) to quantify secondary outcomes, including AD at ≤6 and ≥24 months, skin infection, food allergy and food sensitisation.[13]

B. Research Question and Hypothesis

Primary question (PICO): In infants and children without AD at baseline (P), does regular application of emollients, and do specific emollient formulation categories (I), compared with no routine emollient, standard skin-care advice or an alternative emollient (C), reduce the cumulative incidence of clinically diagnosed AD (O)? Secondary objectives were to (i) compare formulation categories indirectly and, where available, directly; (ii) examine effect modification by baseline atopic risk, continuity of application at outcome assessment, intervention duration, application frequency, geographic region and risk of bias; (iii) evaluate durability of effect beyond 24 months; and (iv) quantify safety and allergic outcomes, including skin infection, food allergy and food sensitisation.[13]

The research hypothesis (H_1) was that regular emollient application reduces the cumulative incidence of AD compared with no routine emollient and that the magnitude of protection differs between formulation categories; the null hypothesis (H_0) stated that emollients do not alter AD incidence and that no formulation category is superior.

C. Significance of the Study

Theoretically, this review updates and extends the evidence base by incorporating six trials published since the last major syntheses, classifying products a priori by formulation, and integrating non-randomised evidence on exposure patterns such as emollient bathing. Clinically, it provides paediatricians, dermatologists, family physicians and caregivers with evidence-based guidance on whether, which, when and in whom emollients should be used for prevention, which is particularly relevant to tropical, resource-constrained settings such as Indonesia where product choice and cost strongly influence adherence.[9,14]

LITERATURE REVIEW

A. Atopic Dermatitis in Infancy: Burden and Barrier Pathophysiology

The pathogenesis of AD reflects reciprocal interactions between epidermal barrier dysfunction, type 2-skewed immune activation, microbial dysbiosis dominated by Staphylococcus aureus and environmental exposures. Structural deficits in filaggrin, intercellular lipids (ceramides, cholesterol and free fatty acids) and natural moisturising factor increase transepidermal water loss (TEWL), raise surface pH and facilitate penetration of irritants, allergens and microbes, which in turn trigger keratinocyte alarmins (thymic stromal lymphopoietin, interleukin-33) and Th2 cytokines that further down-regulate barrier proteins, perpetuating an itch–scratch cycle. This "outside-in" model has framed the epidermis not only as a target of treatment but as a modifiable gateway to the atopic march.[15–18]

Prospective cohorts support a causal role for early barrier impairment. Elevated forehead TEWL during the first week of life predicted subsequent AD irrespective of filaggrin (FLG) genotype, dry skin at 3 months predicted AD at 6 months, and FLG loss-of-function mutations conferred an approximately three-fold increase in early eczema in the population-based PreventADALL cohort. Impaired barrier function at 3 months was further associated with allergic sensitisation by 6 months, suggesting that the skin may be a portal for transcutaneous sensitisation to food allergens.[19–22]

B. Emollients: Classification, Formulation and Mechanisms of Action

Emollients are the cornerstone of AD management and are strongly recommended for established disease by the European (EuroGuiDerm), American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology, and American Academy of Dermatology guidelines. These products act through occlusion (petrolatum, paraffin, mineral oils), humectancy (glycerol, urea, sodium pyrrolidone carboxylic acid) and lipid replenishment (ceramides, cholesterol, free fatty acids), and modern "emollient-plus" formulations incorporate non-medicated actives such as colloidal oat, niacinamide or bacterial lysates. Formulations nevertheless differ substantially in their effects on the stratum corneum: some plant oils and frequent oil bathing can impair lamellar lipid organisation and increase TEWL, whereas physiological-lipid mixtures are designed to restore barrier architecture.[8,23–27]

From a formulation perspective, emollients can be grouped by their dominant mode of action and vehicle. Occlusive agents such as white soft paraffin, liquid paraffin and petrolatum form a hydrophobic film that reduces TEWL; humectants such as glycerol, urea and sodium pyrrolidone carboxylic acid draw water into the stratum corneum; and physiological lipids (ceramides, cholesterol and free fatty acids, ideally at an equimolar or ceramide-dominant ratio) integrate into the intercellular lamellae and support barrier recovery. Vehicles range from ointments and anhydrous balms to creams, lotions, gels, oils and bath additives, differing in occlusivity, cosmetic

acceptability, the amount applied and the likelihood of irritant or allergenic excipients. Emulsifiers, preservatives, fragrances and food-derived ingredients may themselves perturb the immature infant barrier or provide a route for epicutaneous sensitisation, so products marketed under the common label 'emollient' are pharmacologically heterogeneous.[8,12,16,28]

C. Previous Studies

Two proof-of-concept RCTs published in 2014 reported 32–50% relative reductions in AD among high-risk neonates who received daily emollients, but the subsequent large pragmatic BEEP and PreventADALL trials found no benefit and signalled possible increases in skin infection and food allergy. Since then, smaller trials using specialised formulations, very early initiation or short intervention windows (for example, STOP-AD) have again reported protection, and the decentralised CASCADE trial (2025) observed a 16% relative risk reduction in an unselected primary-care population.[4–7,29–31]

Previous evidence syntheses have reached divergent conclusions. The Cochrane individual participant data (IPD) review concluded that skin-care interventions probably do not change eczema risk and probably increase skin infections, whereas aggregate-data meta-analyses suggested benefit in high-risk infants and when emollients were applied continuously; a network meta-analysis ranked emulsion-type moisturisers highest. These reviews pre-date several recent trials (Kottner, STOP-AD, Harder, Inuzuka, Hachai and CASCADE), frequently pooled heterogeneous products as a single intervention, and seldom integrated non-randomised comparative and cohort evidence on exposure patterns such as emollient bathing.[32–39]

D. Research Gap

Several gaps persist. First, previous syntheses largely pooled heterogeneous products as a single intervention, so the comparative effectiveness of formulation categories remains uncertain. Second, the most recent trials, including Kottner (2023), STOP-AD (2023), Harder (2023), the PAF head-to-head trial (2023), Hachai (2024) and the decentralised CASCADE trial (2025), have not been synthesised together with earlier evidence. Third, non-randomised comparative and cohort studies addressing emollient bathing and frequency of moisturisation have not been integrated with randomised evidence. Finally, data from tropical and Southeast Asian settings remain scarce despite plausible effect modification by climate.[30,31,40–45]

E. Novelty

The novelty of this review lies in its formulation-centred approach: products were classified a priori into four categories on the basis of ingredient lists and vehicle, enabling formulation-specific subgroup analyses alongside the only available head-to-head trial. The review restricts evidence to the last 15 years, applies REML random-effects models with Hartung–Knapp–Sidik–Jonkman inference and prediction intervals, explicitly separates outcomes measured during and after emollient application, models baseline risk as an effect modifier, and integrates RoB 2-appraised RCTs with ROBINS-I-appraised comparative and cohort studies.[46–48]

METHODS

A. Research Design and Registration

The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Eligibility criteria, outcome hierarchy, emollient classification and subgroup hypotheses were specified before data extraction. Registration: [insert PROSPERO identifier if registered; otherwise state that the protocol was not prospectively registered and is available from the corresponding author].[13]

B. Eligibility Criteria

Eligibility followed the PICOS framework summarised in Table 1. In accordance with the review question, RCTs (individually or cluster-randomised, including factorial designs), non-randomised comparative (controlled) studies, prospective or retrospective cohort studies and case series were eligible. Systematic reviews and meta-analyses were not eligible as primary evidence and were not entered into the characteristics tables, but they were used for citation chasing and are compared with our findings in the Discussion. Studies of children with established AD (treatment or maintenance trials) were excluded because they address a different clinical question.[47,48]

Table 1. Eligibility criteria according to the PICOS framework

Domain	Inclusion criteria	Exclusion criteria
Population	Term or near-term neonates, infants and children (0–18 years; in practice enrolment ≤10 weeks of age) without AD at baseline; general-population or high-risk (family history of atopy) samples	Pre-existing AD or other inflammatory dermatosis; preterm neonatal intensive-care populations studied for sepsis or mortality
Intervention	Regular application of any emollient/moisturiser (cream, ointment, lotion, gel, balm, oil or oil bath additive) to the whole body or large body areas, alone or within a skin-care regimen	Topical anti-inflammatory drugs (corticosteroids, calcineurin inhibitors); emollients combined with an active systemic co-intervention whose effect cannot be separated (e.g., synbiotics without factorial separation)
Comparator	No routine emollient, standard skin-care advice, as-needed emollient, or a different emollient formulation (head-to-head)	No comparator for analytic designs (case series analysed descriptively only)

Domain	Inclusion criteria	Exclusion criteria
Outcomes	Primary: cumulative incidence of AD diagnosed by clinician (UK Working Party, Hanifin–Rajka or equivalent) or physician diagnosis in records. Secondary: AD ≤6 months and ≥24 months, skin infection, food allergy, food sensitisation, cutaneous adverse events, adherence	Studies reporting only skin biophysics (TEWL, hydration, pH), microbiome or biomarkers without a clinical outcome
Study design	RCTs; non-randomised comparative studies; cohort studies; case series	Narrative or systematic reviews, meta-analyses, editorials, protocols without results, conference abstracts without full report, animal or in vitro studies
Time/language	Published 1 January 2011–15 October 2026 (≤15 years); any language with an English abstract	Published before 2011

C. Information Sources and Search Strategy

PubMed/MEDLINE, Europe PMC (including preprints and PubMed Central full texts) and the ClinicalTrials.gov registry were searched from 1 January 2011 to 15 October 2026; searches were executed on 18 October 2026. The Consensus academic search engine (semantic retrieval across >200 million peer-reviewed records) was used with five targeted natural-language queries to identify additional trials and cohorts, and reference lists of included studies and of previous systematic reviews (Cochrane 2021/2022, Zhong 2022, Xu 2022, Liang 2023, Priyadarshi 2022, Grześk-Kaczyńska 2024) were screened. The complete reproducible strategies are presented in Table 2.[32,33,35–39]

Table 2. Electronic search strategies (executed 18 October 2026)

Source	Search string / query	Records
PubMed/MEDLINE	(("Dermatitis, Atopic"[MeSH] OR "atopic dermatitis"[tiab] OR eczema[tiab]) AND (emollient*[tiab] OR moisturi*[tiab] OR "skin care"[tiab] OR skincare[tiab] OR petrolatum[tiab] OR ceramide*[tiab] OR "Emollients"[MeSH] OR "skin barrier"[tiab]) AND (infant*[tiab] OR newborn*[tiab] OR neonat*[tiab] OR "Infant"[MeSH] OR child*[tiab]) AND (prevent*[tiab] OR incidence[tiab] OR "Primary Prevention"[MeSH] OR onset[tiab])) AND ("2011/01/01"[dp] : "2026/10/15"[dp])	395
Europe PMC	(TITLE_ABS:("atopic dermatitis" OR eczema)) AND (TITLE_ABS:(emollient* OR moisturi* OR "skin care" OR skincare OR ceramide* OR petrolatum)) AND (TITLE_ABS:(infant* OR newborn* OR neonat*)) AND (TITLE_ABS:(prevent* OR incidence OR onset)) AND (PUB_YEAR:[2011 TO 2026])	142 (8 unique)
ClinicalTrials.gov (API v2)	Condition: atopic dermatitis; Intervention: emollient OR moisturizer; Other terms: prevention AND (infant OR newborn)	19
Consensus (semantic)	(1) emollient from birth prevention of atopic dermatitis infants RCT; (2) ceramide-dominant emollient prevention PEBBLES; (3) moisturizer to neonates prevents AD; (4) moisturizer use early infancy and AD/food allergy cohort; (5) emollient prophylaxis high-risk infants RCT — top 20 records each	100
Citation searching	Backward/forward citation chasing of included reports and six previous SR/MA	9

D. Study Selection

Records were de-duplicated by PubMed identifier and DOI. Publication-type metadata were used as an automation filter to

remove reviews, editorials, comments, case reports, guidelines, consensus statements and protocols that were not themselves trials. The remaining titles and abstracts were screened independently by two reviewers against Table 1, followed by full-text assessment; disagreements were resolved by consensus or adjudication by a third reviewer. Companion publications (protocols, long-term follow-up, secondary analyses and economic evaluations) were collated under the parent study, and the most complete report was used for each outcome.[13]

E. Data Extraction, Variables and Operational Definitions

Two reviewers extracted data using a piloted form: bibliographic details, country and climate, design and setting, population risk definition, sample size randomised and analysed, emollient product, ingredients and vehicle, regimen (start age, frequency, body area, duration), comparator, contamination and adherence, outcome definitions, assessor blinding, time points, and effect estimates. Operational definitions of the extracted variables are summarised in Table 3. Intention-to-treat denominators were preferred. When arm-level event counts were not reported, counts were back-calculated from reported proportions and analysed denominators (rounded to the nearest integer); these trials are flagged and were removed in a dedicated sensitivity analysis. For 2×2 factorial trials, the emollient-only arm was compared with the no-intervention arm in the primary analysis (avoiding interaction with the co-intervention), and margins (all skin-intervention versus all non-skin arms) were used in sensitivity analysis.[7,49]

Table 3. Operational definitions of extracted variables

Variable	Operational definition; scale	Ascertainment
Emollient use	Regular (≥4 days/week, usually ≥once daily) application of a topical moisturiser (cream, ointment, lotion, gel, balm, oil) or emollient bath additive intended to hydrate and protect the skin barrier. Scale: Dichotomous (yes/no).	Intervention arm as randomised/allocated
Emollient formulation category	A: ceramide/physiological-lipid–enriched (ceramide-dominant or ceramide-containing barrier-repair creams); B: paraffin/petrolatum-based basic occlusive products (including cold cream and oil-bath additives); C: emulsion/emollient-plus (glycerol-rich oil-in-water emulsions, colloidal oat, niacinamide or other non-medicated actives, standardised lipid-rich creams); D: mixed, participant-selected (choice among products) or bundled regimens (moisturiser plus modified bathing). Scale: Nominal (A–D).	Product name and ingredient list in the trial report or manufacturer data
AD incidence (primary)	New AD during follow-up fulfilling UK Working Party/Hanifin–Rajka criteria, investigator-diagnosed eczematous dermatitis, or physician diagnosis in medical records; time point closest to 12 months, otherwise the trial's primary time point. Scale: Dichotomous.	Blinded investigator, research nurse or chart abstraction
Continuity at assessment	Emollient still being applied (ongoing) versus stopped before the outcome time point (ceased). Scale: Dichotomous.	Intervention duration versus assessment age
Baseline atopic risk	High-risk: ≥1 first-degree relative with AD, asthma or allergic rhinitis; unselected: general population. Scale: Dichotomous.	Trial inclusion criteria
Skin infection	Any parent-reported or clinician-diagnosed bacterial/viral skin infection during the intervention period. Scale: Dichotomous or rate ratio.	Safety reports

Variable	Operational definition; scale	Ascertainment
Food allergy	Clinician- or challenge-confirmed IgE-mediated food allergy or, where only available, parent-reported immediate reaction. Scale: Dichotomous.	Oral food challenge, algorithm or questionnaire
Food sensitisation	Positive skin prick test (wheal ≥3 mm) or specific IgE ≥0.35 kU/L to ≥1 food allergen. Scale: Dichotomous.	Laboratory/SPT
Adherence	Proportion of intervention-arm caregivers applying emollient as prescribed (≥5 days/week or daily). Scale: Percentage.	Diaries, questionnaires

F. Risk-of-Bias Assessment

Risk of bias for the primary outcome of each RCT was assessed with the revised Cochrane tool (RoB 2) across five domains (randomisation process, deviations from intended interventions [effect of assignment], missing outcome data, measurement of the outcome, and selection of the reported result) with an overall judgement of low risk, some concerns or high risk; the cluster-randomised variant was applied to PreventADALL. Non-randomised studies were assessed with ROBINS-I across seven domains. Assessments were performed independently by two reviewers with consensus.[47,48,50]

G. Statistical Analysis

Risk ratios (RR) with 95% confidence intervals (CI) were the effect measure for dichotomous outcomes; a 0.5 continuity correction was applied to all cells of trials with zero events in one arm. Log RRs were pooled using inverse-variance random-effects models with the restricted maximum likelihood (REML) estimator of between-study variance (τ^2) and the Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustment, using the modified variant that prevents intervals narrower than the conventional Wald interval; for subgroups with fewer than three studies, Wald-type intervals were reported because HKSJ with very few studies is over-conservative. DerSimonian–Laird random-effects and Mantel–Haenszel fixed-effect models were fitted as sensitivity analyses. Approximate 95% prediction intervals were calculated for analyses with ≥3 studies. For outcomes where some trials reported only ratio estimates (for example, an incidence rate ratio for skin infections in BEEP and reported RRs in CASCADE), generic inverse-variance pooling of log ratios was used. Observational adjusted odds ratios were displayed but not pooled because exposure definitions were non-commensurable. Analyses were performed in Python (NumPy/SciPy) with custom code validated against standard formulae and RevMan conventions.[46,51]

Statistical heterogeneity was quantified with Cochran's Q, I^2 (25%, 50% and 75% indicating low, moderate and high heterogeneity) and τ^2. Pre-specified subgroup analyses examined: emollient formulation category (A–D); baseline atopic risk; continuity of application at outcome assessment; intervention duration (≤6 versus >6 months); prescribed frequency; geographic region; overall risk of bias; and trial size (<200 versus ≥200, as a probe for small-study effects). Differences between subgroups were tested with a χ^2 test of interaction. Univariable random-effects meta-regression (method-of-moments τ^2) explored control-arm AD incidence (baseline risk), intervention duration, publication year and log-transformed sample size, with the proportion of τ^2 explained reported as R^2.[52]

Robustness was examined by (i) alternative estimators; (ii) excluding high risk-of-bias trials and restricting to low risk-of-bias trials; (iii) excluding trials with back-calculated counts; (iv) excluding trials with <100 participants; (v) excluding the trial with an as-needed petrolatum comparator and the trial using a bundled bathing–moisturiser regimen; (vi) analysing factorial trials by their margins; (vii) adding the PEBBLES pilot with approximate counts; (viii) substituting the 5-year BEEP outcome; and (ix) leave-one-out and cumulative meta-analysis. Influence and outliers were explored with Galbraith (radial), Baujat and L'Abbé plots. Small-study effects were assessed visually with contour funnel plots, Egger's regression test, Begg's rank correlation and Duval–Tweedie trim-and-fill (L0 estimator), recognising the limited power of these tests with 16 studies.[53,54]

H. Certainty of Evidence

Certainty for each outcome was rated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (high, moderate, low, very low), considering risk of bias, inconsistency, indirectness, imprecision (optimal information size and whether the 95% CI crossed thresholds of appreciable benefit or harm, RR 0.75 and 1.25) and publication bias. Evidence from non-randomised studies entered at low certainty following ROBINS-I-informed guidance. Absolute effects were calculated by applying pooled RRs to the pooled control-arm risk.[52,55,56]

I. Ethical Considerations

Ethical approval was not required because this study synthesised published, de-identified aggregate data. All included studies reported approval by their respective research ethics committees and informed parental consent.

RESULTS

A. Study Selection

The database and registry searches identified 556 records (PubMed 395, Europe PMC 142, ClinicalTrials.gov 19). After removal of 134 duplicates, 193 records excluded by publication-type automation and five records without retrievable metadata, 224 records were screened, of which 181 were excluded on title/abstract. Forty-three reports were assessed in full; 11 were excluded (six registry records without peer-reviewed results, two with ineligible outcomes, one single-arm phase I safety study, one without an extractable comparative estimate and one economic model). Other methods (Consensus and citation chasing) yielded seven further reports, of which three were excluded (an established-

AD treatment trial, a trial with a synbiotic co-intervention and a conference abstract). Overall, 22 studies reported in 36 publications were included: 18 RCTs and four non-randomised studies (one clinic-allocated controlled study, two cohorts and one historically controlled comparative study). Sixteen RCTs comprising 5,229 analysed infants contributed to the primary meta-analysis (Figure 1).[13,57]

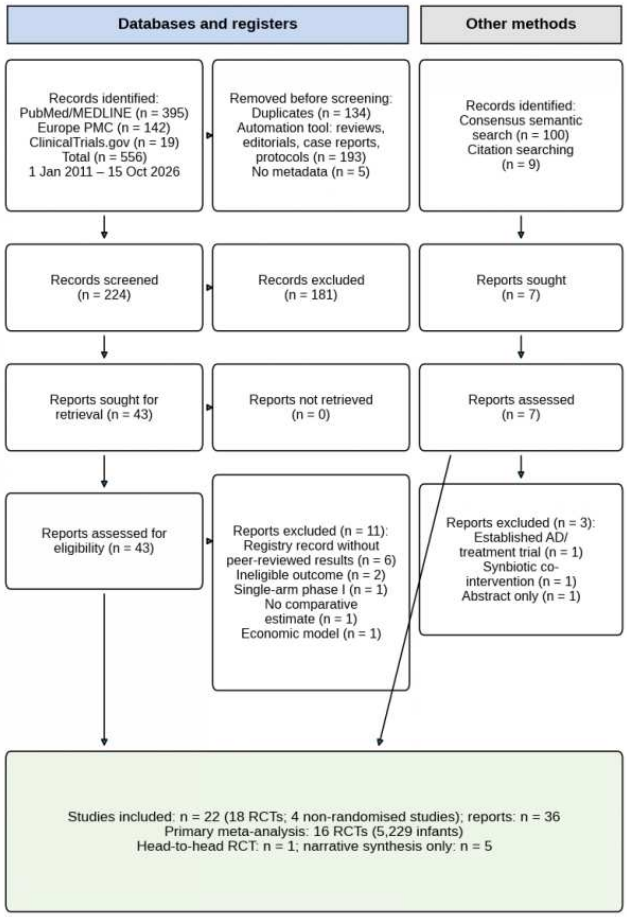


Figure 1: PRISMA 2020 flow diagram of study identification, screening and inclusion. RCT, randomised controlled trial; SR/MA, systematic review/meta-analysis.

B. Characteristics of Included Randomised Trials

The 18 RCTs were published between 2014 and 2025 and were conducted in Japan (n = 4), Thailand (n = 3), Germany (n = 2), the USA (n = 3, plus one joint US–UK trial), the UK, Ireland, Norway/Sweden, Singapore and Australia (Table 4). Thirteen enrolled infants at high risk of atopy by family history and four enrolled unselected general-population infants; one compared two moisturisers head-to-head. Interventions started within the first 4 days to 9 weeks of life and lasted from 2 to 24 months. Products spanned ceramide-dominant barrier-repair creams (EpiCeram, Locobase Repair, Cetaphil Restoraderm), paraffin/petrolatum-based creams, gels, cold cream and oil-bath additives (Diprobase, Doublebase, PreventADALL bath oil and facial cream), glycerol-rich emulsions and emollient-plus balms (2e, colloidal-oat Aveeno Dermexa, Lipikar), and participant-selected products. The primary outcome was assessed between 6 and 24 months, by blinded investigators in most trials.[4–7,14,30,31,40–43,49,58–63]

Table 4. Characteristics of the included randomised controlled trials (n = 18)

Study; country; design	Population (N randomised/analysed); intervention (category); comparator	AD outcome; main finding
Simpson 2014 [4] USA/UK; multicentre RCT	Population: High-risk neonates; 124 (108) Intervention: Parental choice of 3 products per country incl. sunflower seed oil and paraffin/petrolatum creams/gels (D); ≥1×/day from ≤3 weeks for 6 mo Comparator: No emollient	Outcome: Investigator-assessed AD; 6 mo Finding: 12/55 vs 23/53; RR 0.50 (0.28–0.90)
Horimukai 2014 [5] Japan; RCT	Population: High-risk (parent/sibling AD); 118 (118) Intervention: Emulsion-type moisturiser 2e (C); daily from week 1 to 32 weeks Comparator: Petroleum jelly as needed on dry areas	Outcome: AD/eczema (modified Hanifin–Rajka, dermatologist); 32 wk Finding: 19/59 vs 28/59; ~32% fewer (log-rank P = 0.012)
Glatz 2018 [58] USA; RCT (mechanistic)	Population: High-risk; 23 (23) Intervention: Cetaphil Moisturizing Cream (B); 1×/day from ≤3 weeks for 6 mo Comparator: No routine emollient	Outcome: Clinical AD; 6 mo Finding: 1/11 vs 3/12; lower skin pH, ↑ bacterial richness
Lowe 2018 [59] Australia; pilot RCT	Population: High-risk; 80 (≈74) Intervention: EpiCeram ceramide-dominant triple-lipid cream (A); 2×/day birth–6 mo Comparator: Standard care	Outcome: AD (UK WP); 6 and 12 mo Finding: Trend to less AD; food sensitisation 3/34 vs 7/36 (narrative only)
McClanahan 2019 [60] USA; single-centre RCT	Population: High-risk; 100 (≈70) Intervention: Cetaphil Restoraderm: pseudoceramide, arginine, sodium PCA, shea (A); 1×/day from ≤3 weeks, 12 mo Comparator: Emollient of choice as needed	Outcome: Blinded investigator AD; 12 and 24 mo Finding: 13.2% vs 25.0% (P = 0.20); 28% loss to follow-up

Study; country; design	Population (N randomised/analysed); intervention (category); comparator	AD outcome; main finding
Dissanayake 2019 [49] Japan; 2×2 factorial RCT	Population: General population; 549 (459) Intervention: Locobase Repair (ceramide, cholesterol, FFA in petrolatum/paraffin base) (A); 2–3×/day birth–6 mo Comparator: No intervention (synbiotic arms separated)	Outcome: Questionnaire + paediatrician; 12 mo Finding: Skin-care only 46/120 vs none 30/117; no protection
Yonezawa 2019 [61] Japan; RCT with 2-year follow-up	Population: General population; (155 followed) Intervention: Moisturiser ≥1×/day + bathing every 2 days (D); 0–3 mo Comparator: Daily bathing, no moisturiser	Outcome: Parent-reported AD/eczema; 24 mo Finding: 14/67 vs 14/88; no difference
Chalmers 2020 (BEEP) [6,64,65] UK; pragmatic multicentre RCT	Population: High-risk; 1394 (1210) Intervention: Diprobase cream or Doublebase gel (B); daily to 12 mo (median start day 11) Comparator: Standard skin-care advice	Outcome: UK WP eczema, blinded nurses; 24 mo (follow-up to 5 y) Finding: 139/598 vs 150/612; aRR 0.95 (0.78–1.16); skin infections IRR 1.55
Skjerven 2020 (PreventADALL) [7,27,66] Norway/Sweden; cluster-randomised 2×2 factorial	Population: General population; 2397 infants Intervention: Paraffin-based bath additive + facial cream (B); ≥4 days/week, 2 weeks–<9 mo Comparator: No intervention (food arms separated)	Outcome: UK WP/Hanifin–Rajka, masked investigators; 12 mo Finding: Skin-only 64/575 vs none 48/596; RD +3.1%
Thitthiwong 2020 [62] Thailand; RCT	Population: High-risk <10 weeks; 52 (52) Intervention: Basic emollient cream (B); ≥1×/day + skin-care advice, to 9 mo Comparator: Skin-care advice only	Outcome: Clinical AD; 9 mo Finding: 0/25 vs 4/27 (P < 0.05)
Ng 2021 [63] Singapore; pragmatic RCT	Population: ≥2 first-degree atopic relatives; 200 (ITT 200) Intervention: Cetaphil Restoraderm ceramide/filaggrin-product moisturiser (A); from ≤2 weeks, 12 mo Comparator: No moisturiser	Outcome: AD and SCORAD; 12 mo Finding: 37/100 vs 35/100; moderate–severe 4% vs 6%; food sensitisation ↑
Techasatian 2022 [14] Thailand (tropical); RCT	Population: High-risk; 154 (≈144) Intervention: One of five emollients (four 'therapeutic', one petrolatum) (D); 1×/day from ≤3 weeks to 6 mo Comparator: Skin-care advice	Outcome: Clinical AD; 6 mo Finding: RR 0.39 (0.24–0.64); miliaria/impetigo more frequent
Kottner 2023 [40] Germany; pragmatic RCT	Population: High-risk; 160 (150 FAS) Intervention: Standardised regimen with lipid-rich (21%) leave-on product (C); 1×/day, 12 mo Comparator: Parent-preferred skin care	Outcome: Blinded investigator AD; 12 and 24 mo Finding: 24 mo: 19.5% vs 15.1% (MI); AD more severe in controls
Ní Chaoimh 2023 (STOP-AD) [30,67] Ireland; investigator-blinded RCT	Population: High-risk; 321 (257) Intervention: Aveeno Dermexa Fast & Long-Lasting Balm, colloidal oat (C); 2×/day from ≤4 days to 8 weeks Comparator: Routine skin care	Outcome: Clinical AD/UK WP; 6 and 12 mo Finding: 39/119 vs 64/138; RR 0.71 (0.52–0.97)
Harder 2023 [41] Germany; pilot RCT	Population: High-risk; 50 (50) Intervention: Lipikar emollient-plus balm (C); ≥1×/day to 12 mo Comparator: Skin-care advice	Outcome: Clinical AD; 12–24 mo Finding: 28% vs 24%; aRR 1.19; earlier microbiome diversification
Inuzuka 2023 (PAF) [42] Japan; assessor-blinded 3-arm phase II RCT	Population: High-risk; 60 (60) Intervention: Fam's Baby 2×/day (A) or 1×/day (B) vs 2e 1×/day (C); to 32 weeks Comparator: Active comparator (2e)	Outcome: AD onset; 32 wk Finding: 11/20, 5/20 and 10/20; HR B vs C 0.36 (0.12–1.06)

Study; country; design	Population (N randomised/analysed); intervention (category); comparator	AD outcome; main finding
Hachai 2024 [43] Thailand; RCT	Population: High-risk ≤10 weeks; 60 (56) Intervention: In-house cold cream (B); with routine education, to 12 mo Comparator: Routine skin-care education	Outcome: Clinical AD; 12 mo Finding: 7/29 vs 4/27 (P = 0.38)
Simpson 2025 (CASCADE) [31] USA; decentralised pragmatic RCT, 25 primary-care clinics	Population: Unselected; 1247 (1228) Intervention: Choice of 5 bland emollients incl. ceramide lotion/ointment and petrolatum-based products (D); 1×/day from ≤9 weeks to 24 mo Comparator: Refrain from routine emollient	Outcome: Physician-diagnosed AD in records; 24 mo Finding: 36.1% vs 43.0%; RR 0.84 (0.73–0.97)

A–D, emollient categories (see Table 3). AD, atopic dermatitis; aRR, adjusted risk ratio; FAS, full analysis set; FFA, free fatty acids; HR, hazard ratio; IRR, incidence rate ratio; ITT, intention to treat; MI, multiple imputation; mo, months; PCA, pyrrolidone carboxylic acid; RD, risk difference; UK WP, UK Working Party criteria; wk, weeks. Systematic reviews and meta-analyses are deliberately not included in this table.

C. Emollient Formulations and Adherence

Table 5 details the composition and physicochemical rationale of each product grouped by category, together with reported adherence and control-arm contamination. Adherence was high in short or small trials (STOP-AD ≥86% daily during 8 weeks; Harder ≥88%) but declined over longer pragmatic interventions (BEEP 88% at 3 months to 74% at 12 months; full protocol adherence only 27% in PreventADALL). Contamination, i.e. regular emollient use in control arms, ranged from <20% (BEEP, STOP-AD) to 39–45% (PEBBLES pilot, McClanahan), which biases intention-to-treat estimates towards the null.[6,28–30,41]

Table 5. Emollient formulation categories, products, key ingredients and implementation characteristics

Category; trials	Products and key ingredients	Mechanism; adherence/ contamination
A. Ceramide/physiological-lipid–enriched Lowe 2018; McClanahan 2019; Dissanayake 2019; Ng 2021	EpiCeram (ceramide-dominant 3:1:1 ceramide–cholesterol–FFA, pH ~5); Cetaphil Restoraderm (hydroxypalmitoyl sphinganine/ceramide NP, arginine, sodium PCA, shea, sunflower oil, niacinamide); Locobase Repair (ceramide 3, cholesterol, oleic/palmitic acid in petrolatum–paraffin base)	Lamellar lipid replenishment ± NMF components Adherence/contamination: 76% ≥5 d/wk (Lowe); 87%→67% (McClanahan); ~80% ≥2×/day (Dissanayake); 36% drop-out (Ng); contamination 39–45%
B. Paraffin/petrolatum-based (basic occlusive) Glatz 2018; Chalmers 2020; Skjerven 2020; Thitthiwong 2020; Hachai 2024	Diprobase cream (liquid/white soft paraffin); Doublebase gel (isopropyl myristate, liquid paraffin, glycerol); paraffin-based bath oil + fatty facial cream; Cetaphil Moisturizing Cream (petrolatum/glycerol); in-house cold cream	Occlusion; bath additives deposit mineral oil Adherence/contamination: 88%→74% (BEEP); 27% full adherence (PreventADALL)

Category; trials	Products and key ingredients	Mechanism; adherence/ contamination
C. Emulsion/emollient-plus Horimukai 2014; Kottner 2023; Ní Chaoimh 2023; Harder 2023; (Inuzuka 2023)	2e (Shiseido) glycerol-rich oil-in-water emulsion; standardised leave-on cream (21% lipid); Aveeno Dermexa balm (colloidal oat, glycerol, ceramide-precursor lipids); Lipikar AP+ (shea, niacinamide, Aqua Posae filiformis lysate); Fam's Baby	Humectancy + light occlusion ± anti-inflammatory or microbiome-modulating actives Adherence/contamination: ≥86% daily (STOP-AD); ≥88% (Harder); 7.9 g/day (Horimukai)
D. Mixed, participant-selected or bundled Simpson 2014; Yonezawa 2019; Techasatian 2022; Simpson 2025	Choice among sunflower seed oil, paraffin gels/creams and petrolatum (Simpson 2014); five emollients incl. petrolatum (Techasatian); five bland emollients incl. CeraVe ceramide lotion/ointment, Cetaphil and Vanicream lotions (CASCADE); moisturiser + reduced bathing (Yonezawa)	Heterogeneous Adherence/contamination: 85% ≥5×/wk at 6 mo (Simpson 2014); 67–77% (CASCADE)

FFA, free fatty acids; NMF, natural moisturising factor; PCA, pyrrolidone carboxylic acid; d/wk, days per week. Ingredient information was taken from trial reports and published formulation analyses.

D. Characteristics of Non-Randomised Studies

Four non-randomised studies comprising 3,136 infants addressed emollient exposures (Table 6). In a Norwegian controlled pilot, infants with xerosis attending a single intervention clinic who received frequent oil baths and facial fat cream more often had normal skin at 6 months (75% vs 37.5%) and less often probable AD (4.0% vs 19.0%, not significant) than infants attending five observation clinics. Within the Enquiring About Tolerance (EAT) cohort, each additional weekly moisturisation at 3 months was associated with higher odds of food allergy (aOR 1.20, 1.13–1.27), and in the Irish BASELINE birth cohort emollient bathing at 2 months was associated with AD by 2 years (aOR 2.41, 1.56–3.72). A Japanese historically controlled study of less invasive washing plus moisturising found no overall difference in AD at 12 months, but lower prevalence among infants born in the dry, cold season (2.9% vs 21.2%).[44,45,68,69]

Table 6. Characteristics of included non-randomised comparative and cohort studies (n = 4)

Study; design; population	Exposure; outcome	Main result; ROBINS-I
Kvenshagen 2014 [68] Norway; clinic-allocated controlled pilot 6-week-old infants with xerosis, no AD (56)	Exposure: Frequent oil bath (0.5 dL) + facial fat cream (1 clinic) vs observation (5 clinics) Outcome: Skin quality score; probable AD at 6 mo	Normal skin 75% vs 37.5% (P < 0.001); probable AD 4.0% vs 19.0% (NS) ROBINS-I: Serious
Perkin 2021 (EAT) [45] England & Wales; cohort nested in RCT Exclusively breastfed 3-month-olds (1303)	Exposure: Parent-reported moisturisation frequency at 3 mo Outcome: Food allergy; sensitisation at 36 mo	aOR 1.20 (1.13–1.27) per additional weekly moisturisation ROBINS-I: Serious
O'Connor 2023 (BASELINE) [44] Ireland; unselected birth cohort 1505 analysed of 2183	Exposure: Emollient bathing ± frequent emollient application at 2 mo Outcome: AD at 6, 12, 24 mo	aOR 2.41 (1.56–3.72) for bathing; combined exposure aOR 1.74–2.59 ROBINS-I: Serious
Yuguchi 2024 [69] Japan; historically controlled comparative study Infants born 2019 (132) vs 2020 (140)	Exposure: Less invasive washing + moisturising vs traditional skin care Outcome: Questionnaire-reported AD at 6 and 12 mo	No overall difference; Jan–Mar births 2.9% vs 21.2% (P = 0.025) ROBINS-I: Serious

aOR, adjusted odds ratio; NS, not significant. Overall ROBINS-I judgements were driven by confounding (exposure by indication/season), self-reported exposure and unblinded outcome ascertainment.

E. Risk of Bias

Among the 18 RCTs, three (BEEP, PreventADALL and the PAF head-to-head trial) were at low overall risk of bias, 12 raised some concerns, and three were at high risk (Figures 2 and 3; Table 7). Some concerns arose predominantly in domain 2 because blinding of caregivers is impossible for a topical intervention and control-arm contamination was common, and in domain 4 where outcome assessors were not explicitly blinded or AD was parent-reported. High risk was driven by substantial or differential attrition (McClanahan 28%; Ng 36%) and by parent-reported outcomes in an unblinded trial (Yonezawa). All non-randomised studies were judged at serious overall risk, principally owing to confounding (Figure 28).[47,60,61,63]

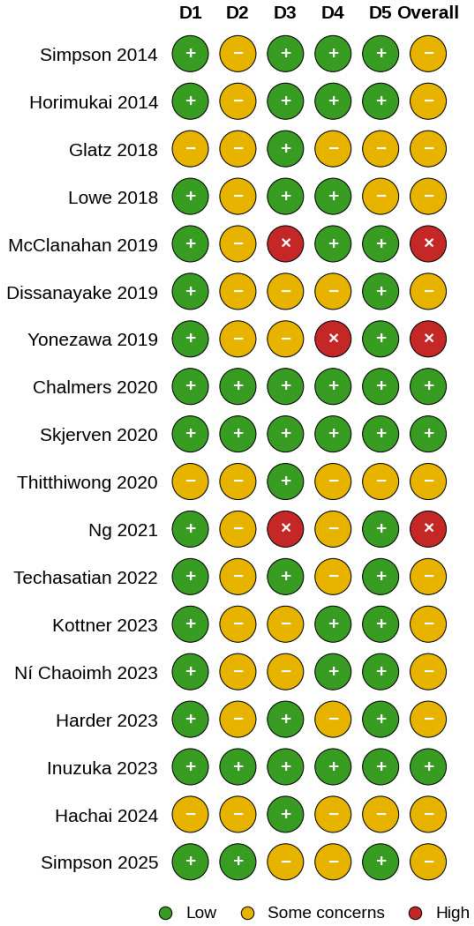


Figure 2: Risk-of-bias traffic-light plot (RoB 2) for the 18 included RCTs. D1, randomisation process; D2, deviations from intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result. Green (+), low risk; yellow (−), some concerns; red (×), high risk.

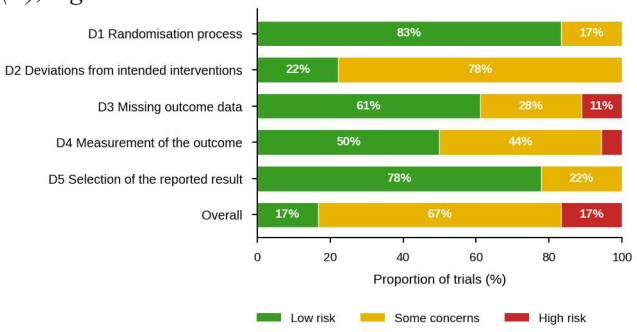


Figure 3: Risk-of-bias summary plot: proportion of RCTs at low risk, some concerns and high risk for each RoB 2 domain and overall.

Table 7. Principal justifications for RoB 2 judgements (primary outcome)

Trial	Key concerns (domain)	Overall
Chalmers 2020 (BEEP); Skjerven 2020 (PreventADALL)	Computer-generated (cluster) randomisation; blinded outcome assessors; ITT with <15% missing data; prespecified outcomes	Low
Inuzuka 2023 (PAF)	Central randomisation; assessor-blinded; complete follow-up	Low
Simpson 2014; Horimukai 2014; Techasatian 2022; Harder 2023	Unblinded caregivers with some control contamination (D2); assessor blinding not fully described in some (D4)	Some concerns
Dissanayake 2019; Kottner 2023; Ní Chaoimh 2023	Post-randomisation exclusions or differential withdrawal (D3; STOP-AD 25% vs 13%); questionnaire-based diagnosis (Dissanayake, D4)	Some concerns
Glatz 2018; Thitthiwong 2020; Hachai 2024; Lowe 2018	Small pilots with limited reporting of allocation concealment (D1), assessor blinding (D4) and analysis plans (D5)	Some concerns
Simpson 2025 (CASCADE)	Physician diagnosis abstracted from records influenced by unblinded families (D4); <20% missing primary outcome (D3)	Some concerns
McClanahan 2019; Ng 2021	Attrition 28% and 36%, under-enrolment (D3)	High
Yonezawa 2019	Parent-reported AD/eczema by unblinded families (D4); follow-up of a subset (D3)	High

F. Primary Outcome: Cumulative Incidence of Atopic Dermatitis

Across 16 RCTs (2,566 infants in emollient arms and 2,663 in control arms), AD developed in 637 (24.8%) emollient-treated and 737 (27.7%) control infants. The pooled random-effects estimate showed no statistically significant reduction (RR 0.88, 95% CI 0.69–1.13; P = 0.29), with substantial heterogeneity (I^2 = 63%, τ^2 = 0.107, Q = 40.4, P < 0.001) and a 95% prediction interval of 0.42–1.86, indicating that a future trial could plausibly observe anything from a 58% reduction to an 86% increase (Figure 4). Individual trials ranged from marked protection (Techasatian 2022, RR 0.38, 0.23–0.63; Simpson 2014, RR 0.50, 0.28–0.90) to a significant increase (Dissanayake 2019, RR 1.50, 1.02–2.19). The DerSimonian–Laird model gave a similar estimate (RR 0.89, 0.74–1.07), whereas the Mantel–Haenszel fixed-effect estimate, which is dominated by the two largest pragmatic trials, reached nominal significance (RR 0.90, 0.82–0.98); given the clinical and statistical heterogeneity, the random-effects result is considered primary.[4,14,46,49]

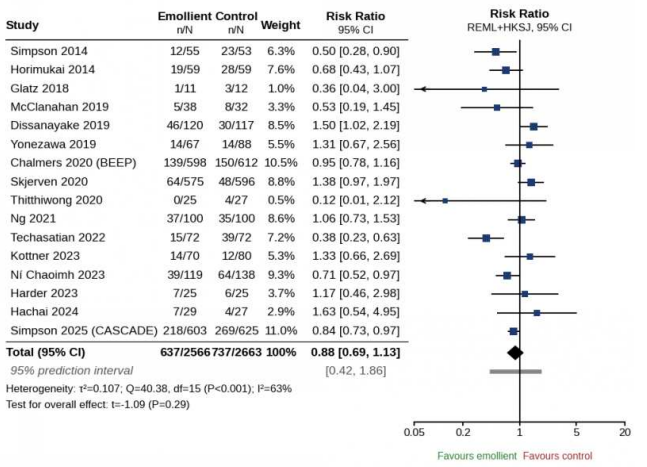


Figure 4: Forest plot of emollient versus no routine emollient for the cumulative incidence of atopic dermatitis (16 RCTs). Squares, trial RRs sized by random-effects weight; horizontal lines, 95% CI; diamond, pooled REML–HKSJ estimate; grey bar, 95% prediction interval.

Narrative synthesis of individual trials. Statistically significant protection was observed in four trials, all of which applied emollients during the outcome window or started within the first days of life: the 2014 US/UK feasibility trial, the Japanese 2e emulsion trial (by log-rank analysis), the tropical Thai trial and STOP-AD, in which an 8-week colloidal-oat balm regimen begun within 4 days of birth reduced cumulative AD at 12 months. CASCADE, the largest trial in an unselected population, showed a modest but significant reduction while daily application continued to 24 months. Conversely, the two largest European trials (BEEP and PreventADALL), which used paraffin-based products or oil-bath additives started at a median of 11 days or 2 weeks, found no benefit, and the Locobase Repair arm of the Japanese factorial trial showed a significant increase. Small pilots (Glatz, Thitthiwong, Harder, Hachai) were too imprecise to be informative individually.[4–7,14,30,31,41,43,49,58,62]

G. Subgroup Analyses by Emollient Formulation and Effect Modifiers

Emollient formulation category (Figure 5). No category was statistically superior (test for subgroup differences $\chi^2 = 4.34$, df = 3, P = 0.23). Ceramide/physiological-lipid–enriched products (three trials) showed no protective effect (RR 1.12, 95% CI 0.41–3.09), nor did paraffin/petrolatum-based basic occlusives (five trials; RR 1.08, 95% CI 0.66–1.77). Emulsion/emollient-plus products showed the most favourable and most homogeneous estimate (four trials; RR 0.77, 95% CI 0.51–1.18; $I^2 = 19\%$), driven by the glycerol-rich 2e emulsion and the colloidal-oat balm used in STOP-AD. Mixed or participant-selected regimens yielded a similar point estimate with very high heterogeneity (RR 0.68, 95% CI 0.29–1.55; $I^2 = 77\%$).[5,30,37]

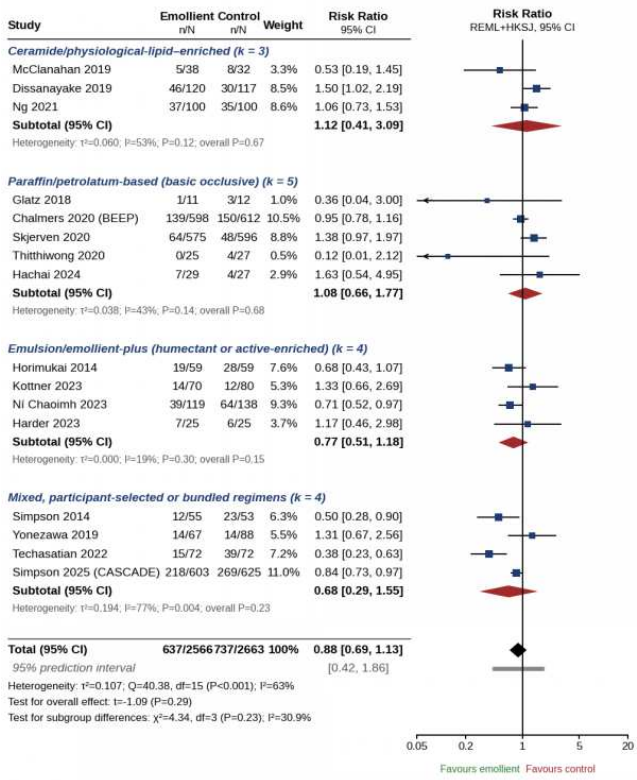


Figure 5: Subgroup forest plot by emollient formulation category: ceramide/physiological-lipid–enriched; paraffin/petrolatum-based basic occlusive; emulsion/emollient-plus; and mixed, participant-selected or bundled regimens.

Baseline atopic risk (Figure 6). In high-risk infants (12 trials) emollients reduced AD by about one quarter with borderline precision (RR 0.76, 95% CI 0.57–1.01), whereas no benefit was seen in unselected populations (four trials; RR 1.17, 95% CI 0.70–1.98); the interaction was significant (P = 0.038). The unselected stratum was, however, internally inconsistent: CASCADE showed protection, whereas PreventADALL and Dissanayake showed point estimates above 1.[7,31,49]

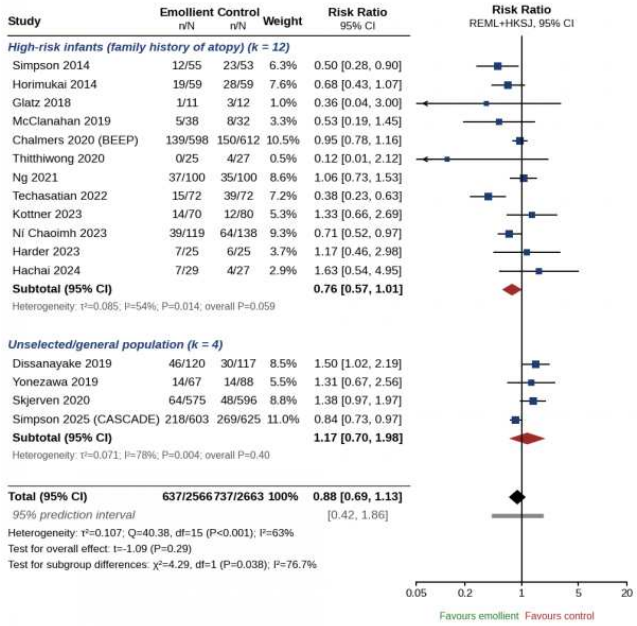


Figure 6: Subgroup forest plot by baseline atopic risk (high-risk infants with a family history of atopy versus unselected general-population infants).

Continuity of application (Figure 7). When emollients were still being applied at the time of outcome assessment (10 trials), AD incidence was reduced by 29% (RR 0.71, 95% CI 0.51–0.99); when application had ceased before assessment (six trials), no effect remained (RR 1.11, 95% CI 0.78–1.56; interaction P = 0.026). This pattern is consistent with a delay, rather than a prevention, of disease onset.[35]

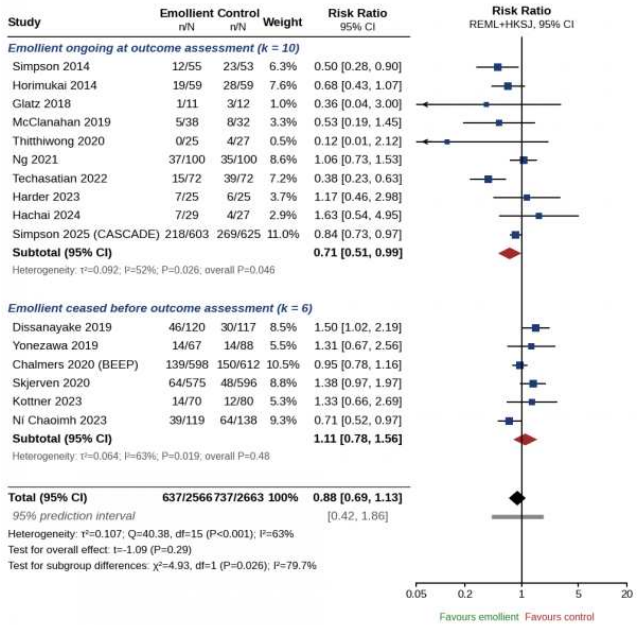


Figure 7: Subgroup forest plot by emollient status at outcome assessment (ongoing versus ceased before assessment).

Intervention duration, frequency, region, risk of bias and trial size (Figures 8–12). Interventions of ≤6 months (RR 0.74, 95% CI 0.39–1.42) and >6 months (RR 0.96, 95% CI 0.78–1.17) did not differ significantly (P = 0.34). Trials prescribing once-daily application showed a borderline benefit (RR 0.76, 95% CI 0.56–1.03), whereas twice-daily (RR 1.02, 95% CI 0.49–2.12) and less-than-daily or unclear regimens (RR 1.23, 95% CI 0.71–2.13) did not (P = 0.034); this observation is confounded by product and population and is hypothesis-generating only. No significant differences were found by region (Asia RR 0.90, 95% CI 0.50–1.60; Europe RR 1.01, 95% CI 0.68–1.51; North America RR 0.67, 95% CI 0.35–1.28; P = 0.26), by overall risk of bias (P = 0.32) or by trial size (<200: RR 0.74, 95% CI 0.48–1.13; ≥200: RR 1.01, 95% CI 0.75–1.35; P = 0.16). All subgroup results are summarised in Table 8.[55]

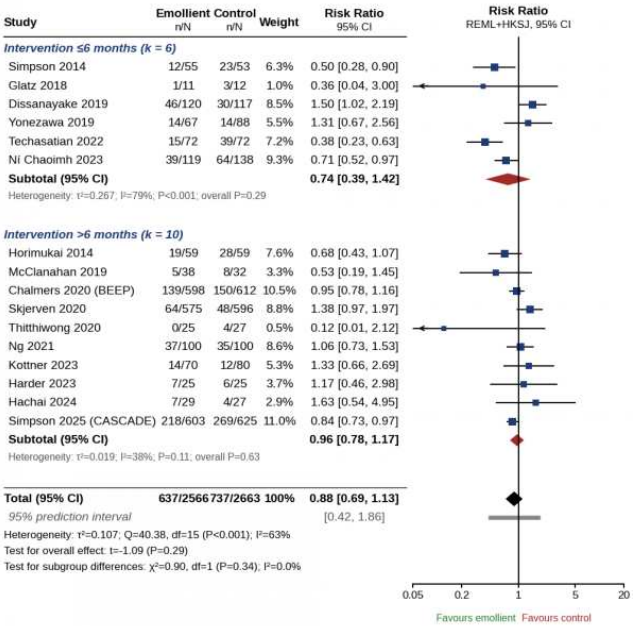


Figure 8: Subgroup forest plot by duration of emollient intervention (≤6 months versus >6 months).

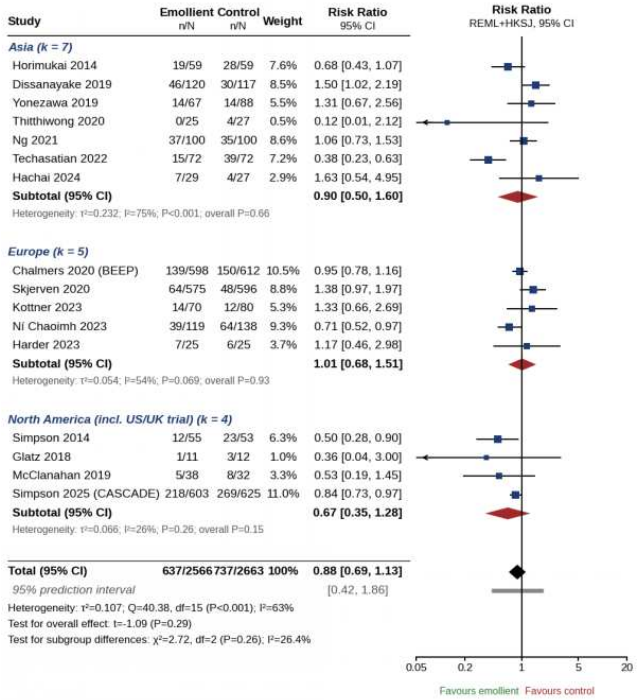


Figure 9: Subgroup forest plot by geographic region (Asia, Europe, North America).

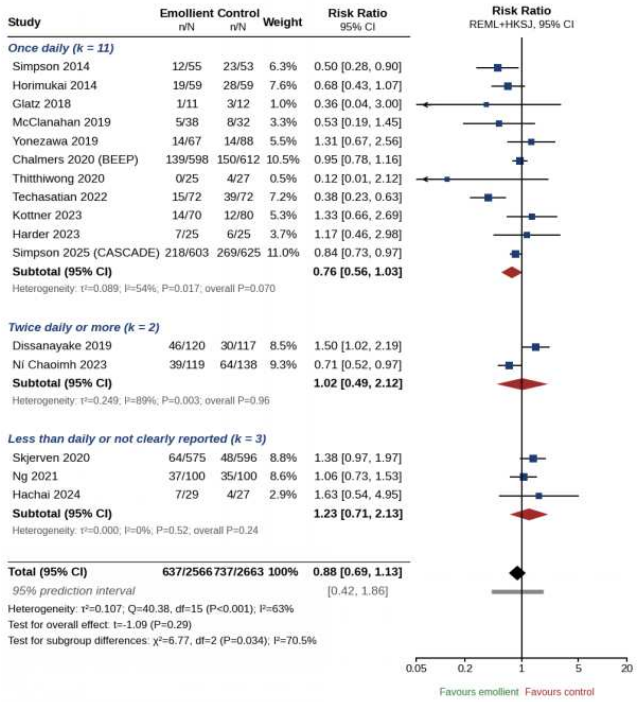


Figure 10: Subgroup forest plot by prescribed application frequency.

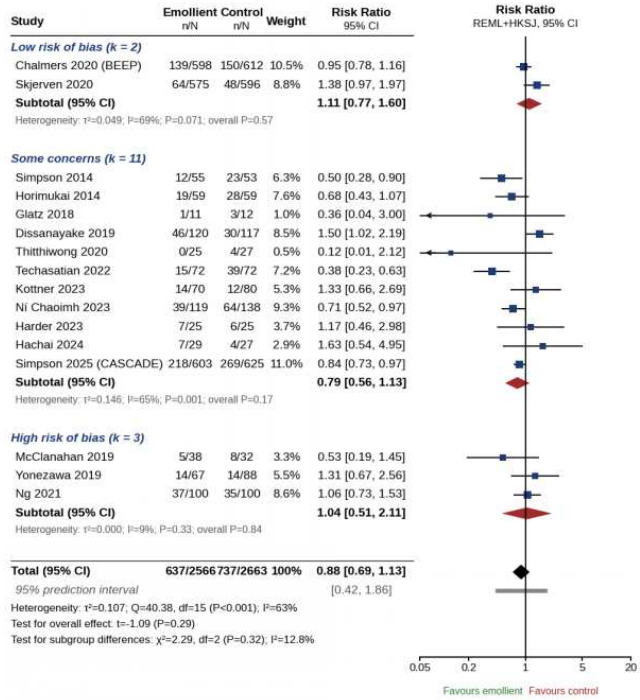


Figure 11: Subgroup forest plot by overall RoB 2 judgement.

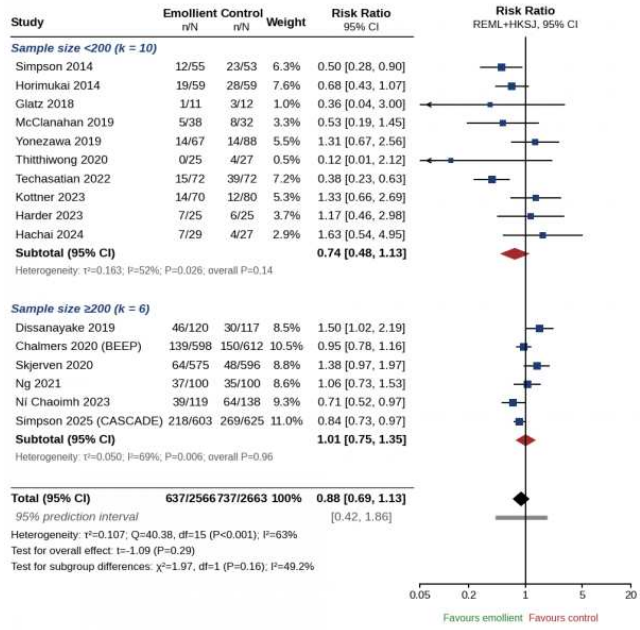


Figure 12: Subgroup forest plot by trial size (<200 versus ≥200 participants) as a probe for small-study effects.

Table 8. Summary of subgroup analyses for the primary outcome (REML random effects; HKSJ CI where k ≥ 3)

Factor / subgroup	k	RR (95% CI)	I² (%)
Emollient category (P interaction = 0.227)			
Ceramide/physiological-lipid–enriched	3	1.12 (0.41–3.09)	53
Paraffin/petrolatum-based (basic occlusive)	5	1.08 (0.66–1.77)	43
Emulsion/emollient-plus (humectant or active-enriched)	4	0.77 (0.51–1.18)	19

Factor / subgroup	k	RR (95% CI)	I² (%)
Mixed, participant-selected or bundled regimens	4	0.68 (0.29–1.55)	77
Baseline atopic risk (P interaction = 0.038)			
High-risk infants (family history of atopy)	12	0.76 (0.57–1.01)	54
Unselected/general population	4	1.17 (0.70–1.98)	78
Status at assessment (P interaction = 0.026)			
Emollient ongoing at outcome assessment	10	0.71 (0.51–0.99)	52
Emollient ceased before outcome assessment	6	1.11 (0.78–1.56)	63
Intervention duration (P interaction = 0.344)			
Intervention ≤6 months	6	0.74 (0.39–1.42)	79
Intervention >6 months	10	0.96 (0.78–1.17)	38
Application frequency (P interaction = 0.034)			
Once daily	11	0.76 (0.56–1.03)	54
Twice daily or more	2	1.02 (0.49–2.12)	89
Less than daily or not clearly reported	3	1.23 (0.71–2.13)	0
Region (P interaction = 0.257)			
Asia	7	0.90 (0.50–1.60)	75
Europe	5	1.01 (0.68–1.51)	54
North America (incl. US/UK trial)	4	0.67 (0.35–1.28)	26
Overall risk of bias (P interaction = 0.318)			
Low risk of bias	2	1.11 (0.77–1.60)	69
Some concerns	11	0.79 (0.56–1.13)	65
High risk of bias	3	1.04 (0.51–2.11)	9
Trial size (P interaction = 0.161)			
Sample size <200	10	0.74 (0.48–1.13)	52
Sample size ≥200	6	1.01 (0.75–1.35)	69

H. Sensitivity Analyses and Influence Diagnostics

The null overall result was robust (Table 9). Excluding high risk-of-bias trials (RR 0.86, 0.64–1.15), restricting to low risk-of-bias trials (RR 1.11, 0.77–1.60), removing trials with back-calculated counts (RR 0.96, 0.74–1.25; Figure 13), excluding trials with <100 participants, analysing factorial trials by their margins (RR 0.85, 0.69–1.04), adding the PEBBLES pilot, or substituting the 5-year BEEP outcome did not materially change the estimate. Leave-one-out estimates ranged from 0.84 to 0.95, all with confidence intervals including 1 (Figure 14). The cumulative meta-analysis showed that an early signal of benefit after the 2014 proof-of-concept trials was progressively attenuated as larger trials accrued (Figure 15).[6,7,64]

Table 9. Sensitivity analyses for the primary outcome

Analysis	k	RR (95% CI)	I² (%)
Primary analysis (REML + HKSJ)	16	0.88 (0.69–1.13)	63
DerSimonian–Laird random effects (Wald CI)	16	0.89 (0.74–1.07)	63
Mantel–Haenszel fixed effect	16	0.90 (0.82–0.98)	63
Excluding high risk-of-bias trials	13	0.86 (0.64–1.15)	68
Low risk-of-bias trials only	2	1.11 (0.77–1.60)	69
Excluding trials with back-calculated event counts	12	0.96 (0.74–1.25)	55
Excluding trials with <100 participants	11	0.89 (0.67–1.18)	72
Excluding Horimukai 2014 (petrolatum-as-needed comparator)	15	0.90 (0.70–1.17)	64
Excluding Yonezawa 2019 (bundled bathing–moisturiser regimen)	15	0.86 (0.67–1.11)	64
Factorial trials analysed by margins (all skin vs no-skin arms)	16	0.85 (0.69–1.04)	54
Adding Lowe 2018 (approximate counts from reported percentages)	17	0.88 (0.69–1.10)	61
BEEP 5-year outcome substituted for 2-year outcome	16	0.90 (0.70–1.15)	67

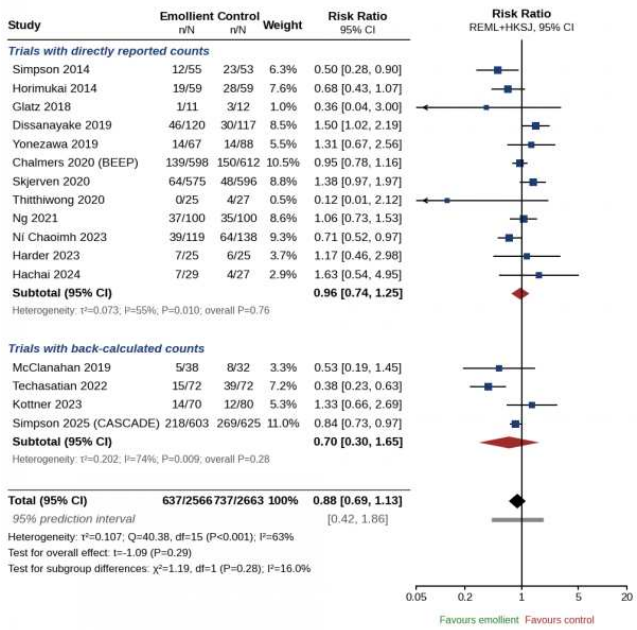


Figure 13: Sensitivity forest plot separating trials with directly reported arm-level counts from those with counts back-calculated from reported percentages.

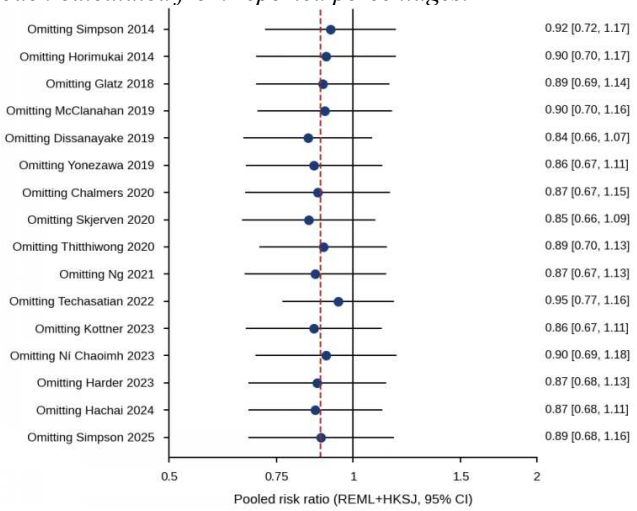


Figure 14: Leave-one-out sensitivity analysis: pooled RR (REML–HKSJ) after omitting each trial in turn.

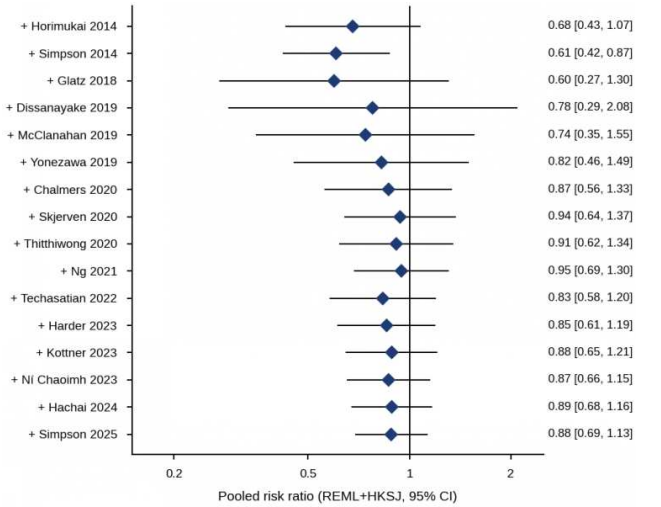


Figure 15: Cumulative meta-analysis ordered by year of publication.

I. Small-Study Effects and Meta-Regression

The contour funnel plot was visually symmetrical (Figure 16); Egger's test (intercept -0.20, SE 0.70; P = 0.78) and Begg's test (Kendall τ = -0.08; P = 0.69) gave no evidence of small-study effects, and trim-and-fill imputed 0 studies. The Galbraith plot identified Techasatian 2022 (more protective than expected) and Dissanayake 2019 and PreventADALL (less protective) as lying outside the ±2 band, and the Baujat plot confirmed that Techasatian 2022, Dissanayake 2019, Skjerven 2020 (PreventADALL) contributed most to heterogeneity and influence (Figures 17 and 18). The L'Abbé plot showed that benefit clustered in trials with high control-arm incidence (Figure 19).[53,54]

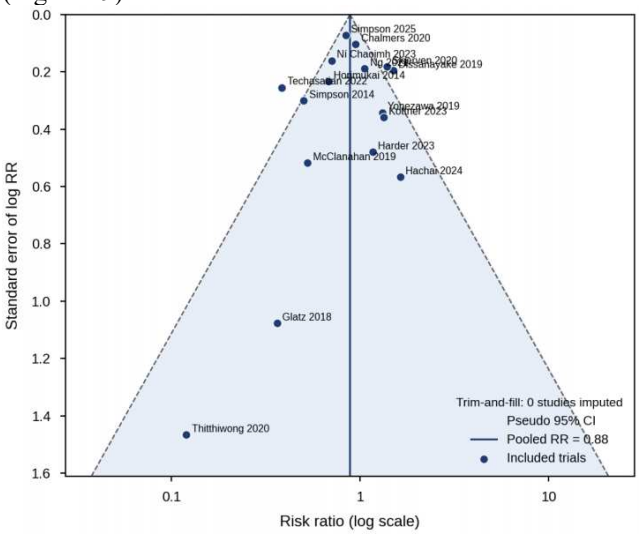


Figure 16: Contour-enhanced funnel plot with trim-and-fill for the primary outcome (no studies imputed).

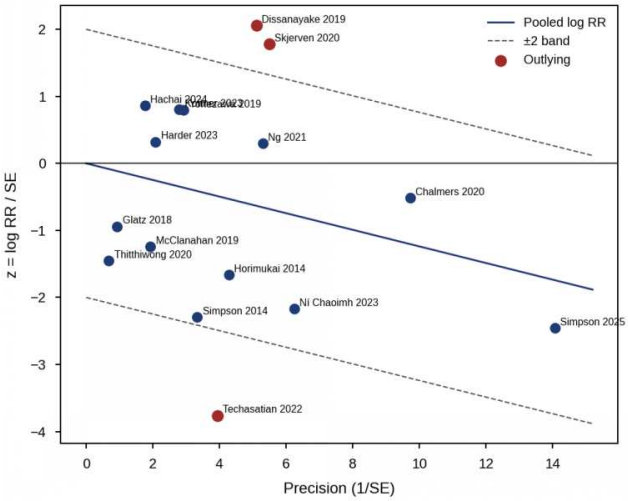


Figure 17: Galbraith (radial) plot of standardised log RR against precision; points outside the ±2 band indicate outlying trials.

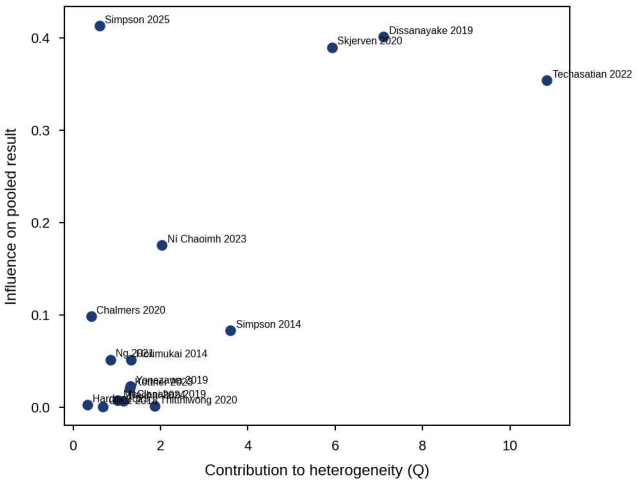


Figure 18: Baujat plot of each trial's contribution to overall heterogeneity (x-axis) versus influence on the pooled estimate (y-axis).

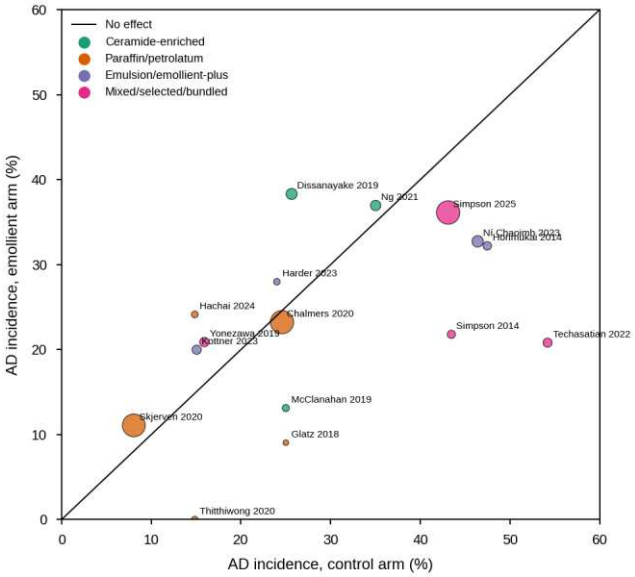


Figure 19: L'Abbé plot of AD incidence in emollient versus control arms, coloured by emollient category; bubble area proportional to sample size.

In meta-regression (Table 10; Figure 20), control-arm AD incidence was a strong modifier: each 10-percentage-point higher baseline incidence was associated with a 18% greater relative reduction (β = -0.020 per percentage point, P < 0.001), explaining 78% of between-trial variance. Intervention duration (P = 0.69), publication year (P = 0.45) and log sample size (P = 0.24) were not associated with effect size. Because control-arm risk is a component of the RR itself, this association is susceptible to regression-to-the-mean and ecological bias and should be interpreted cautiously.[34]

Table 10. Univariable random-effects meta-regression of log RR (primary outcome, k = 16)

Covariate	β (SE)	P	R^2 (%)
Control-arm AD incidence (per 1 percentage point) residual $\tau^2 = 0.014$	-0.020 (0.005)	<0.001	78
Intervention duration (per month) residual $\tau^2 = 0.099$	0.007 (0.018)	0.69	0
Publication year (per year) residual $\tau^2 = 0.090$	0.025 (0.033)	0.45	0
ln(total sample size) residual $\tau^2 = 0.078$	0.109 (0.093)	0.24	0

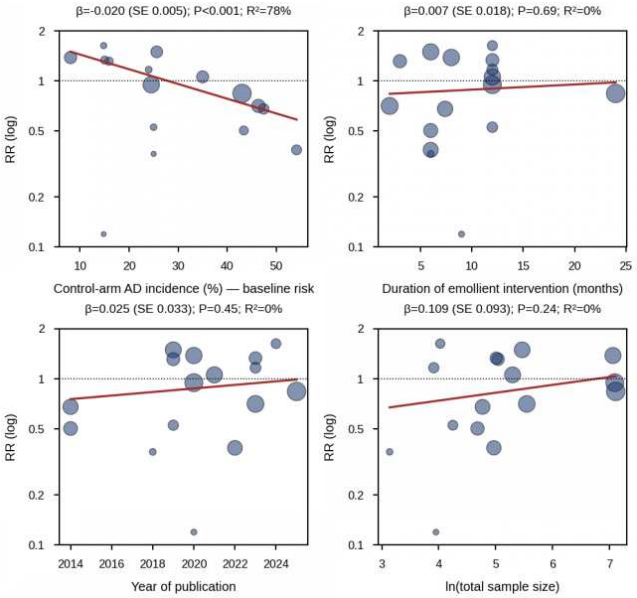


Figure 20: Bubble plots of random-effects meta-regression of the RR on control-arm AD incidence, intervention duration, publication year and ln(sample size); bubble size proportional to weight; red line, fitted regression.

J. Secondary Outcomes

Early-infancy and durable AD outcomes. In four trials reporting AD at ≤6 months, emollients more than halved incidence (RR 0.46, 95% CI 0.29–0.73; I^2 = 0%; Figure 25). In contrast, at or beyond 24 months (five trials, including BEEP follow-up to 5 years) no effect was observed (RR 0.98, 95% CI 0.73–1.32; I^2 = 52%; Figure 24), reinforcing the delay-not-prevention interpretation.[14,30,60,64]

Skin infection. Pooling five trials (generic inverse variance, including the BEEP incidence rate ratio) gave a non-significant increase (RR 1.14, 95% CI 0.69–1.88; I^2 = 41%; Figure 21). The largest single signal came from BEEP (IRR 1.55, 1.15–2.09), whereas STOP-AD and CASCADE showed no excess; Techasatian reported more miliaria and suspected impetigo in a tropical climate without arm-level counts.[6,14,30,31]

Food allergy and food sensitisation. Emollients did not significantly change food allergy (RR 1.10, 95% CI 0.60–2.03; four trials; Figure 22) or food sensitisation (RR 1.23, 95% CI 0.64–2.37; five trials; Figure 23); estimates were imprecise and directionally inconsistent, ranging from a possible increase in BEEP (aRR 1.47) and Ng 2021 to reductions in the PEBBLES pilot and CASCADE (parent-reported). These findings are summarised in Table 11.[6,31,59,63,66]

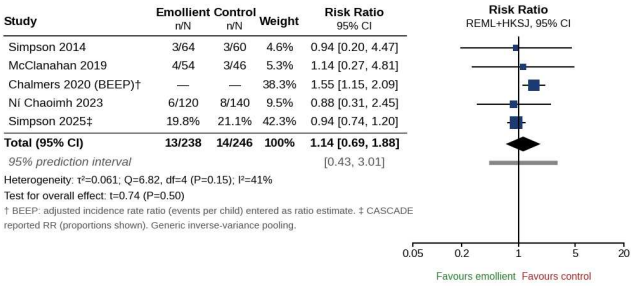


Figure 21: Forest plot of skin infection during the intervention period (generic inverse-variance pooling).

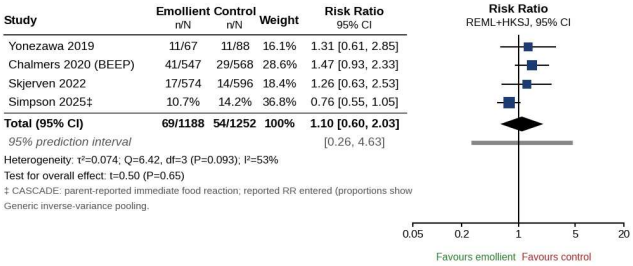


Figure 22: Forest plot of food allergy by 2–3 years.

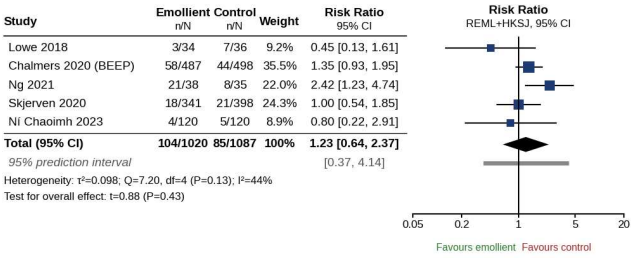


Figure 23: Forest plot of food allergen sensitisation.

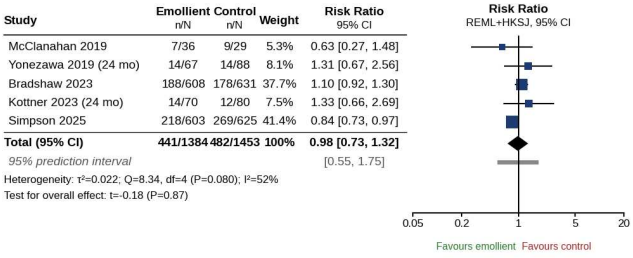


Figure 24: Forest plot of AD at or beyond 24 months of age (durability of effect).

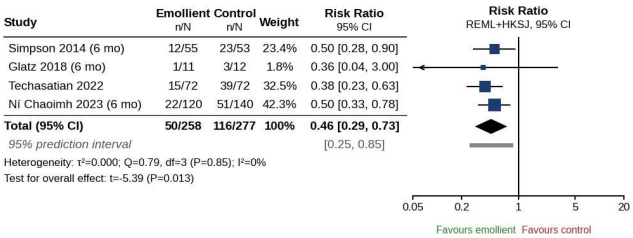


Figure 25: Forest plot of AD in early infancy (≤6 months).

Table 11. Summary of secondary outcome meta-analyses

Outcome (k; participants)	RR (95% CI); P	I^2 (%)	95% PI
AD ≤6 months (4; 535)	0.46 (0.29–0.73); P = 0.013	0	0.25–0.85
AD ≥24 months (5; 2,837)	0.98 (0.73–1.32); P = 0.87	52	0.55–1.75

Outcome (k; participants)	RR (95% CI); P	I^2 (%)	95% PI
Skin infection (5; ≈3,100)	1.14 (0.69–1.88); P = 0.50	41	0.43–3.01
Food allergy (4; ≈3,700)	1.10 (0.60–2.03); P = 0.65	53	0.26–4.63
Food sensitisation (5; 2,107)	1.23 (0.64–2.37); P = 0.43	44	0.37–4.14

PI, prediction interval. Participant numbers marked ≈ include trials contributing ratio estimates without exact denominators.

K. Head-to-Head Comparison of Emollient Formulations

Only one RCT directly compared formulations. In the assessor-blinded PAF trial, once-daily Fam's Baby was associated with a numerically lower AD incidence than once-daily 2e (5/20 vs 10/20; RR 0.50, 0.21–1.20; hazard ratio 0.36, 0.12–1.06), whereas twice-daily Fam's Baby was not (11/20 vs 10/20; RR 1.10, 0.61–1.99), suggesting that over-application in infants bathed daily may be counter-productive (Figure 26). Within BEEP, two paraffin-based products were offered but not randomised against each other, and CASCADE allowed switching among five products, precluding valid within-trial formulation comparisons.[6,11,31,42]

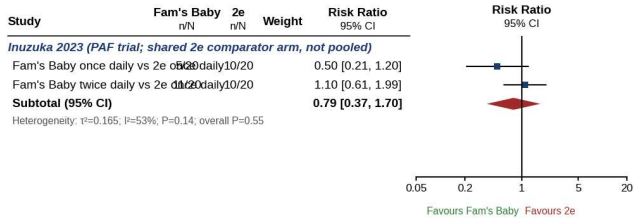


Figure 26: Head-to-head comparison of moisturiser formulations within the PAF trial (Fam's Baby versus 2e). The two comparisons share the 2e arm and are therefore not pooled.

L. Observational Evidence on Emollient Exposure Patterns

The two cohorts that quantified emollient exposure consistently associated frequent emollient use in early infancy with adverse atopic outcomes (Figure 27): emollient bathing and combined bathing plus frequent application at 2 months were associated with higher odds of AD at 6, 12 and 24 months in BASELINE, and moisturisation frequency at 3 months showed a dose–response association with food allergy and with food and aeroallergen sensitisation in EAT. Both studies were judged at serious risk of confounding by indication (parents of infants with dry or reactive skin moisturise more), so causal inference is limited; nevertheless, they align with the randomised finding that frequent mineral-oil baths increased TEWL at 3 months in PreventADALL.[27,44,45,56]

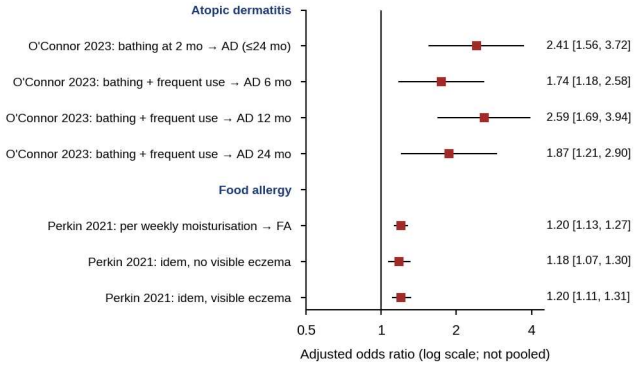


Figure 27: Descriptive forest plot of adjusted odds ratios from cohort studies relating early emollient exposure to AD and food allergy (estimates not pooled).

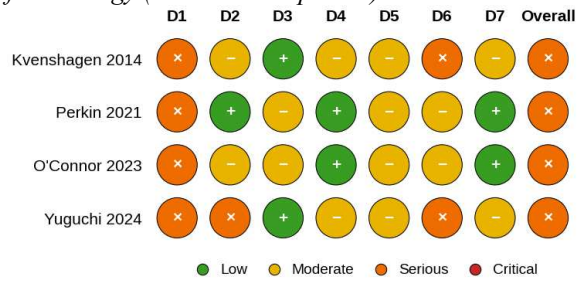


Figure 28: ROBINS-I traffic-light plot for the non-randomised studies. D1, confounding; D2, selection of participants; D3, classification of interventions; D4, deviations from intended interventions; D5, missing data; D6, measurement of outcomes; D7, selection of the reported result.

M. Certainty of Evidence

Using GRADE, certainty was low for the overall effect of emollients on AD incidence (downgraded for inconsistency and imprecision), low for benefit in high-risk infants, with continuous application, in early infancy and for absence of effect at ≥24 months, low for skin infection, and very low for food allergy and food sensitisation (Table 12). Evidence on the comparative effectiveness of formulation categories was very low certainty because comparisons were predominantly indirect (between trials) and confounded by population, timing and climate.[52,55]

Table 12. GRADE summary of findings: emollients versus no routine emollient for primary prevention of AD in infants

Outcome (k; N)	Risk per 1000: control → emollient (95% CI)	RR (95% CI)	Certainty; reasons
AD, overall (16; 5,229)	277 → 244 (192–312)	0.88 (0.69–1.13)	⨁⨁◯◯ Low Inconsistency (I^2 63%, PI 0.42–1.86); imprecision
AD, high-risk infants (12; 2,438)	304 → 231 (174–308)	0.76 (0.57–1.01)	⨁⨁◯◯ Low Inconsistency; CI includes no effect

Outcome (k; N)	Risk per 1000: control → emollient (95% CI)	RR (95% CI)	Certainty; reasons
AD, emollient ongoing at assessment (10; 2,049)	406 → 289 (207–403)	0.71 (0.51–0.99)	⊕⊕◯◯ Low Risk of bias (small trials, some concerns); inconsistency
AD ≤6 months (4; 535)	419 → 192 (121–304)	0.46 (0.29–0.73)	⊕⊕◯◯ Low Risk of bias; small information size
AD ≥24 months (5; 2,837)	332 → 326 (243–437)	0.98 (0.73–1.32)	⊕⊕◯◯ Low Inconsistency; imprecision; parent-reported outcomes in some
Skin infection (5; ≈3,100)	168 → 192 (117–315)	1.14 (0.69–1.88)	⊕⊕◯◯ Low Imprecision; indirectness (rate ratio in BEEP)
Food allergy (4; ≈3,700)	76 → 84 (45–154)	1.10 (0.60–2.03)	⊕◯◯◯ Very low Risk of bias (parent report); inconsistency; imprecision
Food sensitisation (5; 2,107)	78 → 96 (50–185)	1.23 (0.64–2.37)	⊕◯◯◯ Very low Risk of bias; inconsistency; serious imprecision
Comparative effect of formulation categories	— → —	Subgroup P = 0.23	⊕◯◯◯ Very low Indirect between-trial comparisons; one small head-to-head RCT

Assumed control risk = pooled control-arm risk of contributing trials. GRADE: ⊕⊕⊕⊕ high; ⊕⊕⊕◯ moderate; ⊕⊕◯◯ low; ⊕◯◯◯ very low.

DISCUSSION

This updated systematic review of 22 studies, including 16 RCTs with 5,229 infants in the primary meta-analysis, found that prophylactic emollient application does not produce a statistically significant or durable reduction in the cumulative incidence of AD across all populations (RR 0.88, 95% CI 0.69–1.13), with substantial heterogeneity and a prediction interval spanning important benefit and harm. Three consistent effect modifiers emerged: emollients were associated with fewer AD cases while they were still being applied, during early infancy, and in infants at high familial risk, whereas the effect disappeared after cessation and by 24 months. No formulation category was demonstrably superior, although emulsion/emollient-plus products showed the most favourable and least heterogeneous estimate, and neither ceramide-enriched nor basic paraffin/petrolatum products showed benefit. Safety and allergic outcomes were imprecise, and observational data suggested that frequent emollient bathing and moisturisation may be associated with harm.[33,35]

The hypothesis that physiological-lipid replacement would outperform simple occlusion is mechanistically attractive because AD skin and pre-AD infant skin show reduced long-chain ceramides and altered lamellar organisation. However, the three ceramide-enriched trials in our synthesis yielded discordant results: McClanahan observed a non-significant halving of AD, Ng reported no difference with higher food sensitisation, and the Locobase Repair arm of Dissanayake showed a higher AD incidence than the untreated arm. These products differ substantially from one another (pseudoceramide versus ceramide 3 versus ceramide NP, presence of paraffin bases, sunflower oil or niacinamide), so 'ceramide-containing' is not a homogeneous pharmacological class. A 2025 review of lipid-based barrier-repair therapy similarly concluded that preventive evidence remains limited to non-significant trends, and the outcome of the definitive PEBBLES trial of a ceramide-dominant cream is awaited.[28,49,60,63,70]

Basic paraffin/petrolatum-based products, the most widely recommended and cheapest category, did not prevent AD. Notably, the two largest null trials both relied predominantly on paraffin-based products and, in PreventADALL, on mineral-oil bath additives. A randomised substudy of PreventADALL showed that frequent oil baths increased TEWL at 3 months despite reducing visible dryness, and an observational cohort associated emollient bathing at 2 months with more than double the odds of AD. Paraffin-rich bath additives may therefore act as surfactant-like delivery systems that perturb the developing stratum corneum, and this should not be extrapolated to leave-on petrolatum, whose occlusive efficacy and cost-effectiveness are well established.[6,7,27,44,71]

Emulsion/emollient-plus products, comprising the glycerol-rich 2e emulsion, a colloidal-oat balm, a standardised lipid cream and a niacinamide/bacterial-lysate balm, yielded a 23% non-significant reduction with low heterogeneity. This is consistent with the network meta-analysis by Liang and colleagues, which ranked emulsion-type emollients highest (SUCRA 82.6%), and with mechanistic data from STOP-AD showing early microbiome shifts and biomarker (S100A8/9) differences associated with reduced AD. Editorials have argued that the success of STOP-AD and Horimukai reflected refined emulsion vehicles and very early initiation, compared with the paraffin formulations and later starts (median day 11 or 2 weeks) of the null trials. Our data support this hypothesis but cannot disentangle formulation from timing, because the emollient-plus trials also started earliest.[5,10,11,30,37,67,72]

Plant oils deserve specific comment. Sunflower seed oil was one option in the 2014 US/UK trial, but olive oil damages stratum corneum integrity, both oils delayed lipid-lamellae maturation compared with no oil in neonates, and sunflower seed oil increased TEWL in preterm infants. These data, together with the null results for oil baths, argue against recommending culinary or massage oils for AD prevention.[4,26,73,74]

The strongest and most consistent signal in our analysis concerned continuity: emollients reduced AD by 29% while application continued, and by more than half when outcomes were measured at ≤6 months, but showed no effect after cessation or at ≥24 months. This replicates the observation by Zhong and colleagues and is compatible with three non-exclusive mechanisms: temporary masking of xerosis-driven early eczema, true delay of disease onset with later catch-up, or attrition of a genuine effect as adherence wanes. Long-term follow-up of BEEP to 5 years showed no reduction (aRR 1.10), whereas STOP-AD demonstrated persistence of a 29% reduction 10 months after an 8-week intervention, possibly reflecting initiation within 4 days of birth, during the window of rising TEWL. Whether earlier or longer application can convert delay into prevention remains the central unanswered question.[19,30,35,64]

Several included trials provide mechanistic insight. In the US mechanistic trial, six months of a petrolatum/glycerol cream lowered skin pH and increased bacterial richness, with a higher proportion of Streptococcus salivarius, a commensal inversely associated with AD severity. The German pilot observed earlier diversification of the skin microbiome and reduced Streptococcus and Staphylococcus abundance at one month, and STOP-AD sub-studies linked short-term emollient use to microbiome shifts at 2 months that were associated with reduced AD at 12 months, while elevated antecubital S100A8/9 at 8 weeks predicted AD in FLG wild-type infants. These data suggest that emollients may influence the early cutaneous ecosystem and innate inflammatory tone independently of TEWL, which was largely unchanged across trials. Formulations that acidify the skin surface, provide physiological lipids without disrupting lamellar order, and avoid surfactant-like emulsifiers are therefore theoretically preferable, but the clinical relevance of these surrogate changes remains to be proven.[15,18,41,58,67,72]

Adherence and contamination are central to interpreting pragmatic prevention trials. In BEEP, adherence fell from 88% to 74% over the first year, and only 27% of PreventADALL families adhered fully to the skin intervention, whereas small explanatory trials reported adherence above 85%. Simultaneously, 13–45% of control families used emollients regularly. Both phenomena dilute intention-to-treat contrasts and may partly explain why efficacy signals in small, closely supervised trials did not translate into large pragmatic effectiveness trials. Paradoxically, Techasatian found less AD with low ('as needed') than with moderate adherence in a hot, humid climate, implying that more is not always better; the PAF trial similarly found once-daily superior to twice-daily application of the same moisturiser. The optimal dose of emollient for infant skin is unknown and may depend on climate and bathing frequency.[4,6,14,29,42]

Benefit was confined to high-risk infants (RR 0.76) and, in meta-regression, increased with control-arm AD incidence, which explained most of the between-trial variance. Higher baseline incidence may identify populations with greater barrier vulnerability (for example, FLG loss-of-function carriers, in whom STOP-AD observed a larger relative effect), or populations in which clinical assessment captures milder, emollient-responsive eczema. Paradoxically, CASCADE found greater benefit in infants without a family history of atopy, and the presence of a dog modified the effect, underscoring that family history is a crude proxy for barrier risk. Future trials should stratify by objective markers such as neonatal TEWL, FLG genotype or skin biomarkers.[21,30,31,67]

No significant regional interaction was found, but climate plausibly modifies both efficacy and tolerability. In tropical Thailand, Techasatian observed the largest protective effect yet reported, alongside more miliaria and suspected impetigo, and found that low (as-needed) adherence was associated with less AD than moderate adherence. A Japanese study suggested that moisturising benefited only infants born in the dry, cold season. These observations, relevant to Southeast Asian settings such as Indonesia, argue for climate-adapted regimens (lighter emulsions, as-needed application during humid seasons) rather than uniform daily occlusion.[14,43,62,69]

Our pooled skin-infection estimate (RR 1.14) was imprecise and lower than the Cochrane IPD estimate (RR 1.33, 1.01–1.75), largely because CASCADE, the newest and largest trial, showed no excess. The BEEP signal (IRR 1.55) may relate to occlusion, transfer of microbes from fingers or containers, or contamination of tubs; pump dispensers and hand hygiene are prudent. For food allergy, randomised evidence remains very uncertain, with point estimates ranging from harm (BEEP, aRR 1.47) to benefit (parent-reported, CASCADE). The dual-allergen exposure hypothesis predicts that applying emollients with food-derived ingredients or with food-contaminated hands could promote transcutaneous sensitisation, consistent with the dose–response association between moisturisation frequency and food allergy in EAT. Emollients for neonatal use should therefore be free of food proteins, fragrances and common contact allergens, and applied with clean hands.[6,8,31,33,45,75]

Table 13 contrasts our findings with previous syntheses. Consistent with the Cochrane IPD analysis, we found no overall protective effect, but by adding six recent trials and analysing formulation and continuity explicitly, we reproduced the subgroup signals reported by Zhong and Priyadarshi and the formulation ranking of Liang. Unlike earlier reviews, we integrated non-randomised cohort evidence that raises concern about emollient bathing and high-frequency moisturisation, and we quantified the role of baseline risk. The persisting disagreement among reviews reflects differing eligibility (emollients alone versus all skin-care interventions), outcome time points (closest to 2 years versus any time point) and analytic choices, all of which interact with the time-dependent nature of the effect.[33–39]

Table 13. Comparison with previous systematic reviews and meta-analyses (discussion only; not part of the included-study set)

Review; scope; search date	Trials (participants); pooled AD result	Key additional findings
Kelleher 2021/2022, Cochrane IPD [32–34] All skin-care interventions, healthy term infants; Sept 2021	33 identified; 7 in primary eczema MA (3,075) RR 1.03 (0.81–1.31) at 1–3 years; moderate certainty	Skin infection RR 1.33 (1.01–1.75); food allergy RR 2.53 (0.99–6.49, 1 trial)
Zhong 2022 [35] Emollients started ≤6 weeks; July 2020	10 RCTs RR 0.84 (0.64–1.10)	Benefit in high-risk infants and with continuous use (RR 0.59, 0.43–0.81)
Xu 2022 [36] Early emollients in infants	9 RCTs OR 0.70 (0.48–1.01)	No publication bias by Egger's test
Liang 2023, NMA [37] Different emollient types; Feb 2022	11 RCTs High-risk: RR 0.64 (0.47–0.88)	Emulsion ranked best (SUCRA 82.6%); more adverse events with emollients
Priyadarshi 2022 [38] Term healthy and at-risk newborns; Nov 2021	16 RCTs (5,643) At-risk: RR 0.74 (0.63–0.86); healthy: RR 1.29 (0.96–1.72)	Effects on food allergy uncertain
Grześk-Kaczyńska 2024 [39] RCTs from last 5 years; Sept 2023	11 RCTs Narrative/mixed	Six of 11 trials showed no preventive effect
Present review Emollients; RCTs + comparative/cohort studies; Oct 2026	16 RCTs in primary MA (5,229); 22 studies overall RR 0.88 (0.69–1.13); low certainty	Formulation not decisive; benefit only while applied, ≤6 months and in high-risk infants; baseline risk explains heterogeneity

For general-population infants, routine prophylactic emollients cannot be recommended on the basis of current evidence. For infants at high familial risk, particularly where parents value a possible delay in onset of eczema during infancy, a shared decision to apply a fragrance-free, food-protein-free emulsion or emollient-plus product once daily from the first days of life, continued throughout infancy, is reasonable, provided caregivers are informed about uncertain long-term benefit and a possible small increase in skin infection. Mineral-oil bath additives and culinary oils should be avoided. These suggestions align with the conditional recommendation of the 2026 American Academy of Dermatology prevention guideline and with health-economic analyses showing that the cost-effectiveness of prevention depends on product price and effect size.[9,24,71,76]

LIMITATIONS AND FUTURE WORK

Strengths include a reproducible multi-source search restricted to the last 15 years with exact record counts, inclusion of the most recent trials (including CASCADE 2025), a priori formulation classification, use of REML with HKSJ inference and prediction intervals, extensive sensitivity and influence diagnostics, separate handling of factorial designs, explicit flagging of back-calculated data, integration of non-randomised evidence assessed with ROBINS-I, and GRADE appraisal. Limitations must also be acknowledged. Embase, CENTRAL, Web of Science and Scopus were not searched directly, although citation chasing of Cochrane and other reviews mitigates this. Arm-level counts were back-calculated for four trials and approximated for the PEBBLES pilot, although excluding these did not change conclusions. Formulation comparisons were largely indirect and confounded by timing of initiation, population risk, climate and adherence, and the 'mixed' category is inherently heterogeneous. Outcome definitions and time points varied (6–24 months; clinician, record-based or parent-reported), and contamination in control arms biased intention-to-treat estimates towards the null. Tests for small-study effects have low power with 16 trials, and subgroup findings, including the frequency analysis, are hypothesis-generating.[53–55]

Future trials should (i) randomise directly between well-characterised formulations (ceramide-dominant cream, glycerol-rich emulsion, petrolatum) rather than against no treatment; (ii) start within the first days of life and pre-specify outcomes during and after the intervention to distinguish delay from prevention; (iii) enrich or stratify by objective barrier risk (neonatal TEWL, FLG genotype, S100A8/9) and by climate; (iv) avoid oil-bath additives and standardise bathing practices; (v) measure adherence objectively and limit control-arm contamination; and (vi) include oral food challenge-confirmed food allergy and harmonised core outcomes. The ongoing PEBBLES and SEAL trials will provide important evidence on ceramide-dominant products and on combined skin-care and food-allergy prevention.[8,67,70]

CONCLUSION AND RECOMMENDATIONS

Conclusion

Prophylactic emollient therapy in infancy does not durably reduce AD across unselected populations, and current evidence does not establish that any single emollient formulation category is superior. Benefit appears confined to the period of active application, to early infancy and to high-risk infants, and is greatest where baseline incidence is high, supporting a delay-rather-than-prevention model. Emulsion/emollient-plus products initiated within the first days of life are the most promising candidates, whereas mineral-oil bath additives and culinary oils should be avoided. Rigorous head-to-head trials stratified by barrier risk and climate are needed before formulation-specific recommendations can be made.[9,33]

Recommendations

1. Routine prophylactic emollient application should not be recommended for unselected general-population infants solely to prevent AD.

2. For infants at high familial risk, a shared decision may be made to apply a fragrance-free, food-protein-free emulsion or emollient-plus product once daily from the first days of life throughout infancy, with counselling that benefit appears limited to the period of use and that a small increase in skin infection cannot be excluded; mineral-oil bath additives and culinary or massage oils should be avoided.
3. In tropical climates such as Indonesia, lighter emulsions applied according to skin dryness, together with gentle bathing practices and hand hygiene, are preferable to uniform heavy occlusion.
4. Future research should prioritise adequately powered head-to-head RCTs of well-characterised formulations, initiated within the first days of life, stratified by objective barrier risk (neonatal TEWL, FLG genotype) and climate, with outcomes measured both during and after the intervention and with challenge-confirmed food allergy.

DECLARATIONS

Ethics approval: Not applicable; this study synthesised published aggregate data.
Registration: [Insert PROSPERO identifier if registered; otherwise state that the protocol was not prospectively registered.]
Author contributions: [Initials]: conceptualisation, search, screening, data extraction and drafting; [Initials]: risk-of-bias assessment, statistical analysis and critical revision; [Initials]: supervision, clinical interpretation and critical revision. All authors approved the final manuscript.
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Data availability: Extracted arm-level data are reported in Tables 4, 6 and S1; analysis code and search outputs are available from the corresponding author on reasonable request.
Use of AI-assisted tools: Artificial-intelligence-assisted semantic search (Consensus) was used only to identify candidate records; all screening, extraction, analysis and interpretation were performed and verified by the authors.

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SUPPLEMENTARY MATERIAL

Table S1. Arm-level data for the primary outcome

Trial	Emollient vs control (n/N)	RR (95% CI); weight	Data handling
Simpson 2014	12/55 vs 23/53	0.50 (0.28–0.90) Weight 6.3%	Reported
Horimukai 2014	19/59 vs 28/59	0.68 (0.43–1.07) Weight 7.6%	Reported
Glatz 2018	1/11 vs 3/12	0.36 (0.04–3.00) Weight 1.0%	Reported
McClanahan 2019	5/38 vs 8/32	0.53 (0.19–1.45) Weight 3.3%	Back-calculated from reported % and analysed denominators
Dissanayake 2019	46/120 vs 30/117	1.50 (1.02–2.19) Weight 8.5%	Emollient-only vs no-intervention arms (factorial)
Yonezawa 2019	14/67 vs 14/88	1.31 (0.67–2.56) Weight 5.5%	Reported
Chalmers 2020 (BEEP)	139/598 vs 150/612	0.95 (0.78–1.16) Weight 10.5%	Reported
Skjerven 2020 (PreventADALL)	64/575 vs 48/596	1.38 (0.97–1.97) Weight 8.8%	Skin-only vs no-intervention arms (cluster factorial)
Thitthiwong 2020	0/25 vs 4/27	0.12 (0.01–2.12) Weight 0.5%	Zero cell: 0.5 continuity correction
Ng 2021	37/100 vs 35/100	1.06 (0.73–1.53) Weight 8.6%	Reported
Techasatian 2022	15/72 vs 39/72	0.38 (0.23–0.63) Weight 7.2%	Back-calculated from reported % and analysed denominators
Kottner 2023	14/70 vs 12/80	1.33 (0.66–2.69) Weight 5.3%	24-month multiple-imputation proportions applied to FAS arms (back-calculated)
Ní Chaoimh 2023 (STOP-AD)	39/119 vs 64/138	0.71 (0.52–0.97) Weight 9.3%	Reported
Harder 2023	7/25 vs 6/25	1.17 (0.46–2.98) Weight 3.7%	Reported
Hachai 2024	7/29 vs 4/27	1.63 (0.54–4.95) Weight 2.9%	Reported
Simpson 2025 (CASCADE)	218/603 vs 269/625	0.84 (0.73–0.97) Weight 11.0%	Back-calculated from reported % and analysed denominators