Systematic Reviews and Meta-analysis

Efficacy of moisturizers in paediatric atopic dermatitis: A systematic review and meta-analysis of randomised controlled trials

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Abstract

Background: Topical moisturizer is recommended for atopic dermatitis.

Aims: The aim of the study was to investigate the knowledge gap regarding the efficacy of moisturizer in young patients.

Methods: A systematic review and meta-analysis were conducted on randomised controlled trials comparing participant's ≤15 years with atopic dermatitis, receiving either topical moisturizer or no moisturizer treatment. Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.

Results: Six trials were included (intervention *n*= 436; control *n*= 312). Moisturizer use extended time to flare by 13.52 days (95% confidence interval 0.05–26.99, I^2 88%). Greater reduction in risk of relapse was observed during the first month of latency (pooled risk ratio 0.47, 95% confidence interval 0.31–0.72, I^2 28%) compared to the second and third months (pooled risk ratio 0.65, 95% confidence interval 0.47–0.91, I^2 35% and pooled risk ratio 0.63, 95% confidence interval 0.47–0.83, I^2 33%, respectively).Treated patients were 2.68 times more likely to experience a three–six months remission (95% confidence interval1.18–6.09, I^2 56%). Moisturizer minimally improved disease severity and quality of life.

Limitations: There is a dire need to conduct randomised controlled trials with more robust and standardised designs.

Conclusion: Moisturizer benefits young patients with atopic dermatitis. However, more research is needed to better estimate its efficacy.

Keywords: Emollient, moisturizer, children, atopic dermatitis

Plain Language Summary

Atopic dermatitis is an inflammatory skin disease with skin dryness, itching and recurring flares that impacts patient's quality of life. Moisturizer is a widely recommended treatment and while its benefit has been explored in adult, we are uncertain how well they work in children less than 15 years. To meet this end, we searched the literature for trials comparing results in children given moisturizer versus ones without treatment to conduct a systematic review and meta-analysis. Through combining data from six studies, we found that regular users have a longer flare-free period (by two weeks) and are 2.7 times more likely to remain flare-free for three–six months compared to non-users. Moisturizer relieves personal symptoms, namely, itching and sleep loss, but not physician-assessed signs, such as skin dryness, redness, swelling and crusting. Its use marginally boosts quality of life. However, the shortcoming of our research is that there is lack of well-designed trials included for analysis, thus diminishing the certainty of evidence. Nevertheless, moisturizers appear to be beneficial for treating atopic dermatitis in children.

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Introduction

Atopic dermatitis is a chronic relapsing inflammatory condition.[1-4] Its hallmark manifestations are baseline xerosis with acute remitting flares of pruritic eczema followed by periods of temporary remission.[1,3] With over 90% of cases occurring within five years of age, atopic dermatitis notably affects the well-being of young patients and caregivers. Poor sleep, lowered self-esteem and missed school days are common indicators of its impact on patients' lives.[1,3,5] Therefore, preventing flare-ups and alleviation of disease severity while in remission is crucial to ensure good quality of life.[1,6]

During disease maintenance, recommendations advocate three practices: daily moisturizer application after warm bath/shower with non-soap cleansers, antiseptic control with diluted bleach bath at least twice weekly and avoidance of known allergens, irritants, or extreme temperatures.[7-10] Monotherapy moisturizer may be sufficient for primary treatment of acute exacerbations in mild disease.[9,10] For moderate to severe cases, topical corticosteroid and topical calcineurin inhibitor may be added in a stepwise manner to the baseline moisturizer regimen, along with adjunctive use of wet wrap therapy.[9,10] Therefore, moisturizer plays an integral role in both maintenance and preventing of exacerbation, regardless of severity.[11]

Moisturizers are a collective group of products that hydrates the skin, which ultimately relieves pruritus and xerosis.[12,13] Their active ingredients include humectants that aid water retention in stratum corneum, occlusives that prevent water loss and emollients that smoothen the skins surface.[14] Different formulations, such as soap substitutes and bath moisturizers, are available for convenient usage in multiple contexts, which this review will focus on. The topical formulations are among the cornerstones for atopic dermatitis management.[9]

Pooled data from all ages have shown that daily application of moisturizers alleviated disease severity, prolonged clinical latency and improved quality of life.[11] However, in clinical practice children are often less tolerant to this time-consuming therapy compared to adults, possibly due to irritation of the skin, an unpleasant smell, or a greasy sensation.[11] The rationale of this study emerged from these limitations in compliance, in which results from adult may not completely translate to children. Since paediatric care poses unique challenges, we identified the need to investigate efficacy of moisturizers in prolongation of clinical latency, alleviation of disease severity and improvement in quality of life, compared to no treatment in atopic dermatitis of children under 15 years through pooling of randomised controlled trial results.

Methods

The systematic review and meta-analysis were conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline.[15] The protocol was registered in PROSPERO (CRD42020188379).

Search strategy

We searched Ovid Embase, Ovid Medline, Web of Science, Cochrane Database of Controlled Trials (CENTRAL), CINAHL, GREAT and DARE for relevant randomised controlled trials from inception to July 31, 2020. A cross-reference check was attempted to identify additional studies.

Eligibility criteria

Selected studies had to meet the following inclusion criteria: (1) participants age ≤15 years old with atopic dermatitis, diagnosed by a physician using U.K. Working Party's diagnostic criteria for atopic dermatitis or Hanifin and Rajka criteria, who have received prior treatment and are flare-free at study initiation;[16,17] (2) intervention of any type of topical moisturizer, applied daily at any amount or duration and (3) a control group of no moisturizer treatment. Cointervention such as cleansing gel, bodywash, topical corticosteroid, topical calcineurin inhibitor, antibiotics or antihistamine were allowed if both groups were administered the same agent; (4) studies that investigated our pre-specified outcomes and (5) experimental studies that were either a randomised controlled trial or controlled clinical trial published in English.

The required exclusion criteria: (1) Any other forms of moisturizer apart from cream or lotion; (2) studies that compared moisturizer with active ingredient versus standard moisturizer without such ingredient and (3) studies that investigated adjunctive effect of moisturizer with another agent (such as topical corticosteroid, topical calcineurin inhibitor, antibiotics and antihistamines) compared to moisturizer alone.

Data collection

The titles and abstracts were independently reviewed by two authors against the criteria. Full texts were evaluated, when necessary, especially when abstracts did not clarify the participants' age or presence of a no moisturizer control. Two researchers collected data independently using a data extraction form. Details of participants (age and gender, inclusion and exclusion criteria, baseline data, number randomised and number of dropouts), method (study design, blinding, randomisation, study duration, investigators and outcome assessors), intervention groups (details of treatment regimen, dosage, frequency, location of application and duration), results (types of outcomes collected and timing of assessment), funding source and declarations of interest were collected. Contact with the research authors was attempted when essential information was unclear. Bias was evaluated independently by two authors using the Cochrane 'Risk of bias' tool, in which the risk in each bias domain was graded as either 'high,' 'unclear,' or 'low.'[18] We also intended to assess publication bias using funnel plot analysis, given the known

limitations of the method. Any disagreements between the authors were adjudicated by a third reviewer.

Synthesis of results

Our primary outcomes were extension of time to flare in days after the disease has been controlled with moisturizer therapy. The secondary outcomes were risk of relapse after each month of latency and rate of remission (defined as flare-free period of greater or equal to three months), alleviation of global disease severity, individual signs and symptoms and improvement in quality of life. Two authors analysed the data using the random-effects model in RevMan 5.3.[18] To analyse dichotomous data, the risk ratio and the corresponding 95% confidence interval were pooled. For continuous data, the mean difference and its standard deviation were used when studies employed the same measurement to quantify an outcome, while standardised mean difference and standard deviation were pooled if different measurements were applied. Time-to-events was calculated as a hazard ratio, which the log hazard ratio and its standard error were utilised to perform meta-analysis through the generic inverse variance method. When studies had a 'flare rescue' treatment after the initial maintenance duration, only data pertaining to the maintenance phase were included for our outcome measures. If any data was found to be missing, we would attempt to contact the research authors for relevant details. When necessary, we approximated means or time-to-events from figures reported in the articles.

Finally, the certainty of evidence was assessed by two researchers using the Grading of Recommendations, Assessment, Development and Evaluation framework.[19] Starting from a 'high' quality level, each comparison was downgraded one level for serious (or two levels if very serious) risk of bias, inconsistency, indirectness, or imprecision.

Results

Study selection

The initial search retrieved a total of 3590 publications [Figure 1]. After de-duplication, we assessed the titles and abstracts of 1988 studies.We then screened the full text of 94 articles and found six that satisfied the inclusion criteria. Common reasons for exclusion of articles were the use of vehicle/placebo instead of a no treatment control,[20-24] and wrong comparisons of topical corticosteroids versus moisturizers.[25-28]

Study characteristics

Table 1 illustrates the characteristics of included publications.[29-34] They were published between 2006 and 2017, were mostly multi-center and conducted in Europe.

Table 1:Characteristics of studies included for quantitative analyses

Author and year	Study design	Study duration (months)	Number (intervention, control)	Baseline characteristics		Treatment Arms				Conflict of interest
				Age (mean years)	Gender, M (%)	Intervention		Placebo/ vehicle	Cointervention in both groups	
						Description	Regimen			
Giordano-Labadie *et al*., 2006. France	Multicentre, open label,	2	37, 39	3.92	NR	Exomega milk®	Twice daily over whole body	None	Cleansing bar (A-Derma®)	None declared
Grimalt *et al*., 2007. France	Multicentre, open label,	1.5	91, 82	5.96	50.3	Exomega milk®	Twice daily over whole body	None	Hygiene product (not specified)	Pierre Fabre
Weber *et al*., 2015. Germany	Single centre, open label,	6	21,24	3.55	53.3	Eucerin® Eczema Relief Body Crème	Once daily over whole body	None	Hypoallergenic Cleanser (by Beiersdorf Inc. Wilton, CT)	None declared
Bianchi *et al*., 2016. Italy	Multicentre, open label,	1	28, 27	2.5	NR	Avène Xeracalm balm	Twice daily over whole body	None	Hygeine product (Trixera)	Pierre Fabre
Ma *et al*., 2017. China	Single centre, single blinded,	3	32, 32	5.4	42.1	Cetaphil® Restoraderm ® moisturizer	Twice daily over whole body	None	Cetaphil® Restoraderm® body wash	Galderma R&D
Tiplica *et al*., 2017. Romania	Multicentre, Open label, Three arms	3	Arm 1:111, Arm 2: 116, Control:108	4.10	48.1	Arm 1: Dexeryl® Arm 2: Atopiclair®	Arm 1: Twice daily over whole body Arm 2: Three times daily on affected or previous affected skin	None	None	Pierre Fabre

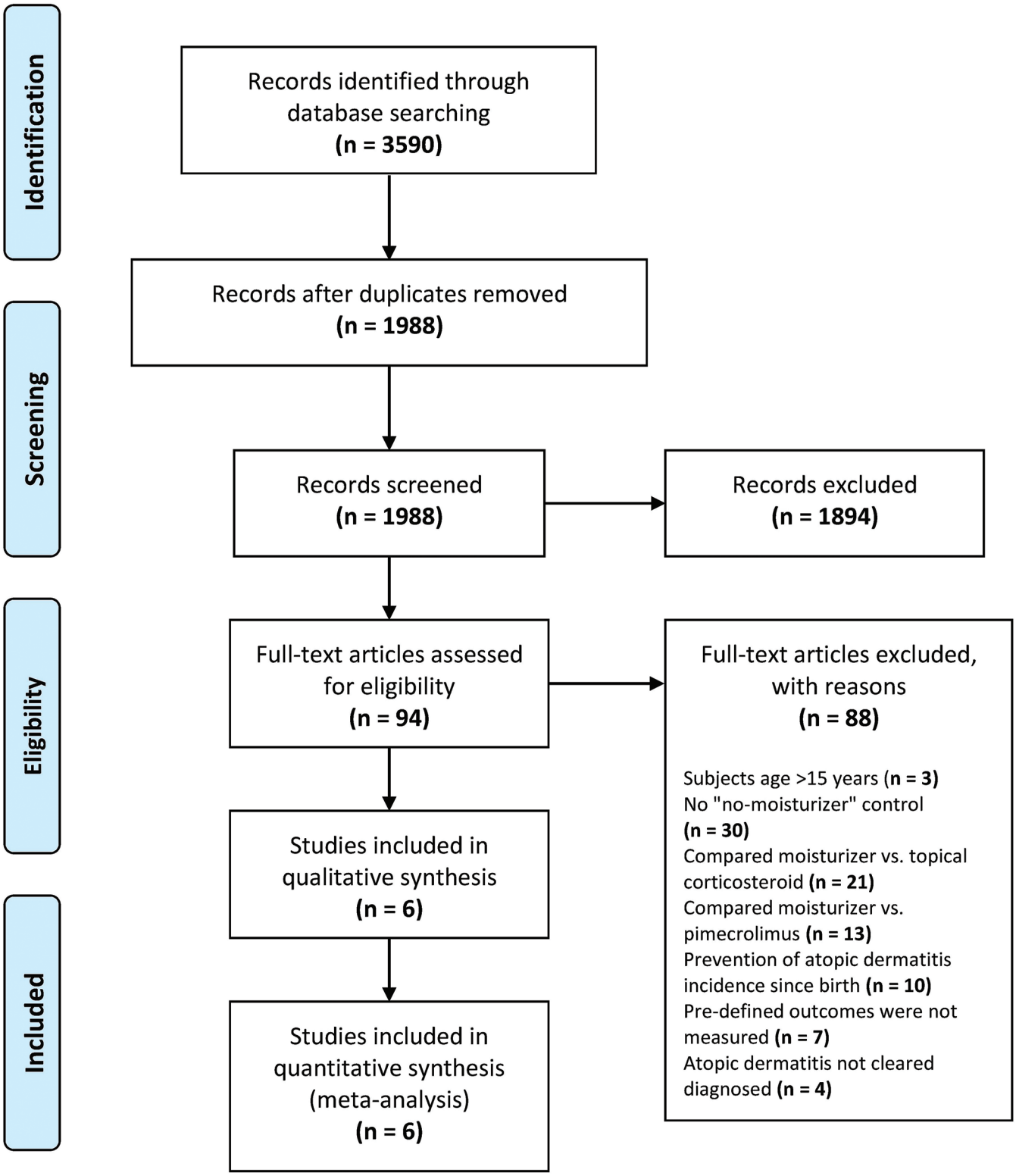

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram showing the methodology in selecting articles for final analyses

Patients had mild to moderate severity (Scoring Atopic Dermatitis (SCORAD) of 5 to 35 or Investigator Global Assessment of 2 to 3), except for Grimalt *et al.* were done on moderate to severe disease (SCORAD 20–70).[31] The number of participants ranged from 45 to 335 in each study, with a total of 748 subjects (intervention 436, control 312). Participants' age varied from one month to 12 years. The study durations ranged from one to six months, with a mean length of 2.4 months.

Tiplica *et al*. had a three-arm design in which the moisturizer of interest, Dexeryl® (Pierre Fabre) and reference emollient,

Atopiclair® (Sinclair Pharma) were compared against no treatment.[33] Other moisturizers were investigated included Exomega Milk® (Pierre Fabre).[30,31] Avène Xeracalm Balm®(Pierre Fabre),[29] Eucerin® Eczema Relief Body Crème (Beiersdorf)[34] and Cetaphil Restoraderm® (Galderma).[32] While Tiplica *et al*. did not administer any cointervention, the other five studies gave a standardised cleanser or hygiene product to research arms.

Four separate publications have declared their source of funding as the pharmaceutical industry of the studied product.[29,31-33] Giordano-Labadie *et al*. and Weber *et al*. did not report their sponsorship, but the intervention was manufactured by the company that employed their researchers, making these parties the likely funding sources.[30,34]

Risk of bias within studies

As summarised in Figure 2, all trials incorporated randomisation and allocation concealment, which limited selection bias. However and most strikingly, investigators and outcome assessments were not blinded in all of the studies.[29-34] Two of six publications had an unclear risk for attrition bias due to high dropout rates in the control or had missing data from questionnaires.[31,33] Bianchi *et al*.[29] and Tiplica *et al*.[33] demonstrate high risk for publication bias because they did not report results on individual signs and symptoms, although the data were collected as part of their Scoring atopic dermatitis assessments. Taken together, we appraised all included studies as showing a high overall risk for bias. We did not evaluate funnel plot symmetry to assess publication bias due to insufficient number of trials.

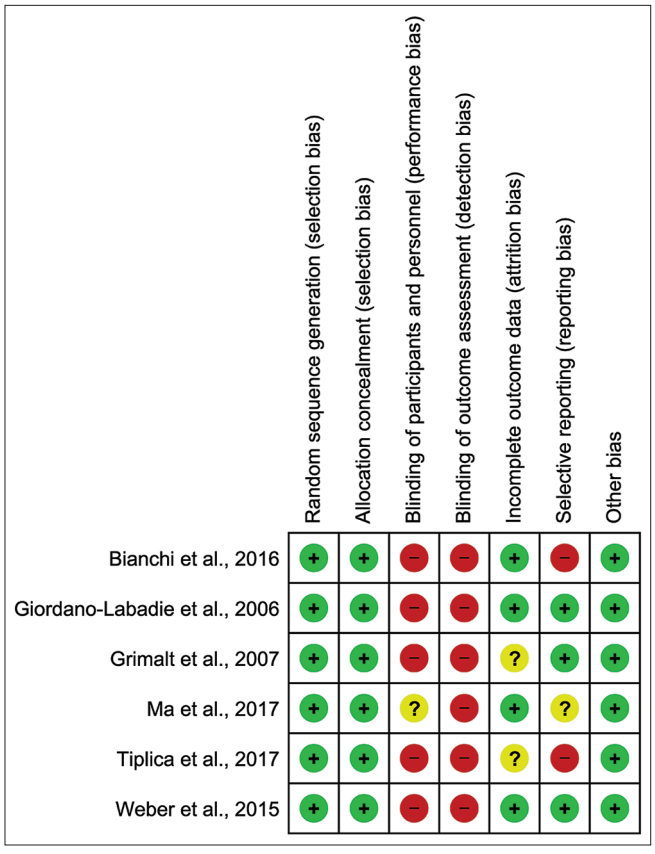

Figure 2: Risk of bias summary: review authors' judgments about each risk of bias item for each included study

Effect of moisturizer on outcomes

Extension of time to flare

Moisturizer treated participants experienced an extension of 13.52 days in time to flare compared to control [Figure 3a; 3 studies, *n*=231;95% confidence interval 0.05–26.99, I^2 88%].[32-34] Apart from the wide confidence interval and limited sample size, the quality of evidence was downgraded to 'very low' due to risk of bias, indirectness and inconsistency [Table 2].[33,34]

Risk of relapse after each month of latency

Results from three randomised controlled trials (*n*=441) show that those who applied moisturizer experienced a lower risk of flare-up compared to control after the first month of latency [Figure 3b, pooled risk ratio 0.47, 95% confidence interval 0.31–0.72, I^2 28%].[32-34] The protective effect was present throughout the second and third month but with smaller magnitudes of effect [Figure 3c, pooled risk ratio 0.65, 95% confidence interval 0.47–0.91, I^2 35%; Figure 3d, pooled risk ratio 0.63, 95% confidence interval 0.47–0.83, I^2 33%, respectively]. We regarded the certainty of evidence for these outcomes as 'low' because of lack of investigator, participant and outcome assessment blinding and indirectness of comparison [Table 2].

Rate of remission

Pooled result from Tiplica *et al*. and Weber *et al*., with durations of three and six months, accordingly, demonstrated that moisturizer-treated patients were 2.68 times more likely to experience a remission [Figure 3e; *n*=378;95% confidence interval 1.18–6.09, I^2 56%]. Although our finding demonstrates a marked difference, Weber *et al*. has individually shown a rate of flare that is more than double of Tiplica *et al*. (Weber *et al*. 45 participants, hazard ratio 4.95, 95% confidence interval 1.62–15.1; Tiplica *et al*. 335 participants, hazard ratio 2.01 and 95% confidence interval 1.44–2.81, respectively).[33,34] Along with serious heterogeneity, risk of bias, indirectness and imprecision, the certainty of evidence was ranked as 'very low'[Table 2].

Changes in global disease severity and individual signs and symptoms

When considering global changes in severity, the moisturizer group shows greater improvement in disease status, evidently from a –3.46 points difference in SCORAD from the control [Figure 3f; 4 randomised controlled trials, *n*=638; 95% confidence interval:6.05—0.87, I^2 89%].[29-31,33] The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) certainty was 'very low' quality due to glaring risk of bias, inconsistency, indirectness and imprecision [Table 2].

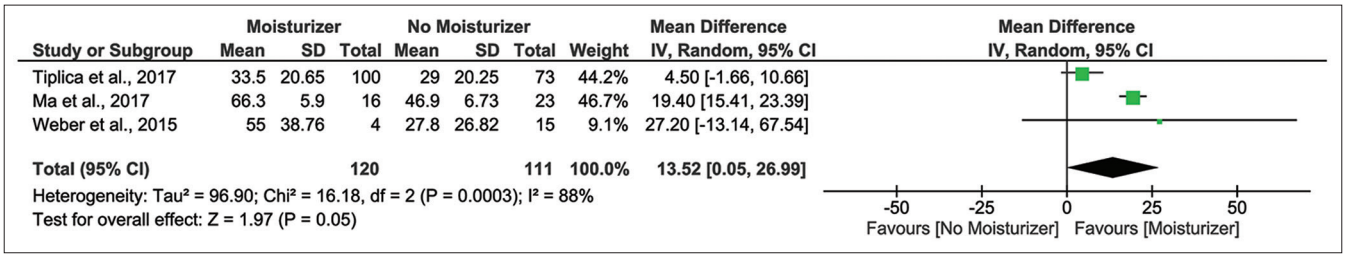

Figure 3a: Forest plot for differences in time to flare (days) in moisturizer user versus non-user

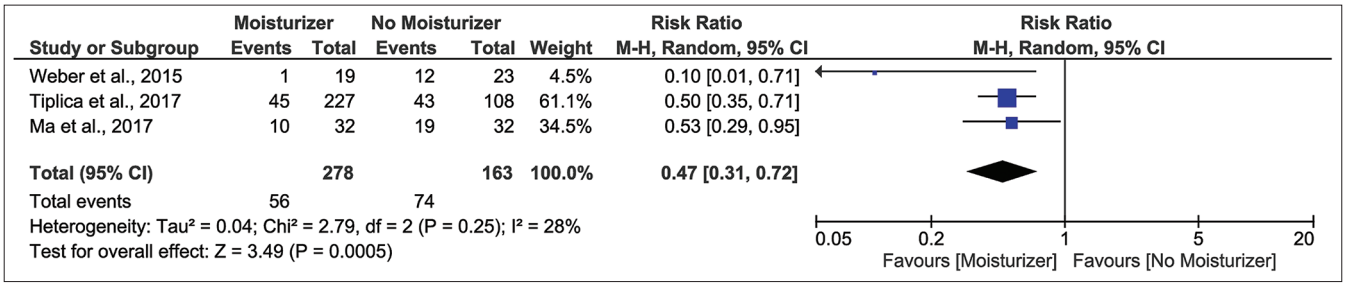

Figure 3b: Forest plot for risk of relapse at one month of latency in moisturizer user versus non-user

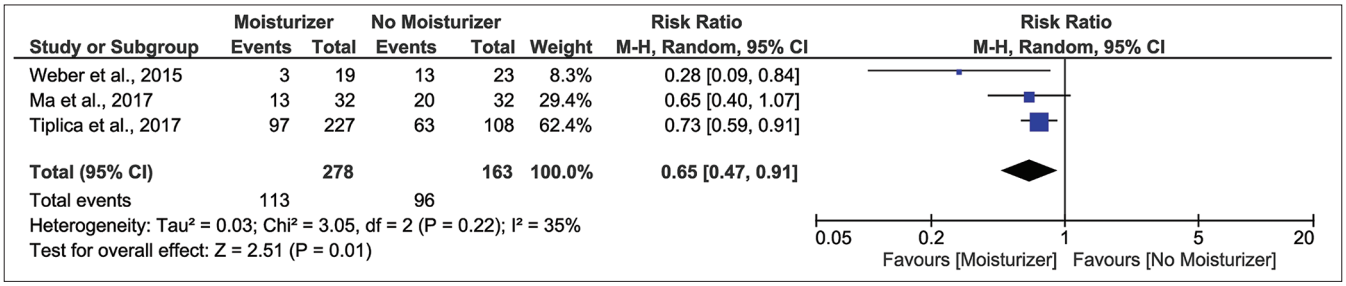

Figure 3c: Forest plot for risk of relapse at two month of latency in moisturizer user versus non-user

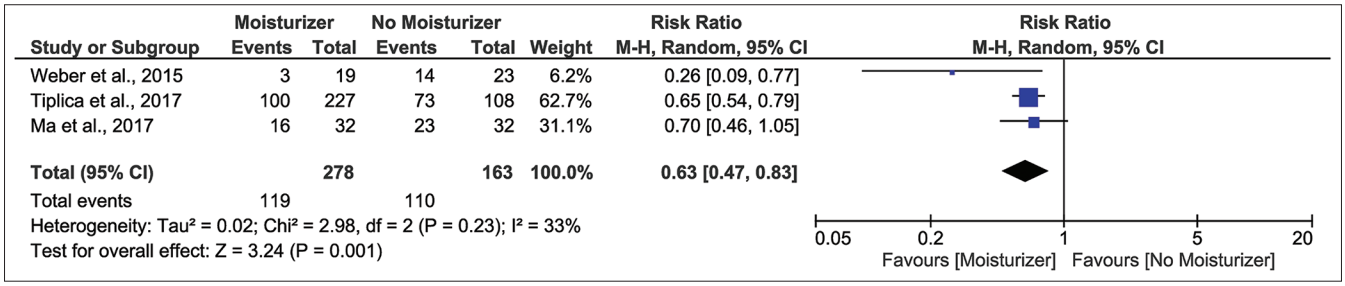

Figure 3d: Forest plot for risk of relapse at three month of latency in moisturizer user versus non-user

Investigator-assessed signs showed no improvements. Pooled analysis reveals a non-significant reduction in risk of xerosis after product use [Figure 3g;3 randomised controlled trials, n=235; pooled risk ratio 0.72 and 95% confidence interval 0.50–1.04, I^2 42%].[29,31,32] Grimalt *et al*. and Giordano-Labadie *et al*. have described negligible improvements in redness, swelling, oozing/crusting, scratch marks and lichenification, although numerical data were not reported.[29-31,33] These outcomes showed 'very low' and 'low' certainty of evidence, respectively [Table 2].

Moisturizer appeared to alleviate participant-assessed symptoms of pruritus and sleep loss. In Bianchi *et al*., the moisturizer group demonstrated greater pruritus score changes than the control (–74.6% and –35.9%, respectively), while in Tiplica *et al*., treatment resulted in lower post-study scores (Dexeryl® 0.42 ± 0.08, $P<0.001$; Atopiclair® 0.56 ± 0.08, $P<0.001$; no moisturizer 1.09 ± 0.08). Similarly, for sleep loss, the post-treatment scores were lower in patients and caregivers in Tiplica *et al*. and Grimalt *et al*., respectively (Tiplica *et al*.: Dexeryl® 0.27 ± 0.06, $P=0.013$; Atopiclair® 0.27 ± 0.06, $P=0.014$; no moisturizer 0.47 ± 0.06; Grimalt *et al*. 0.26 ± 0.48 vs. 0.53 ± 0.77, $P=0.006$).[31,33] The GRADE certainty for both outcomes were 'low' due to lack of investigator, participant and outcome assessment, blinding and indirectness of comparison, which prevented pooling of results [Table 2].

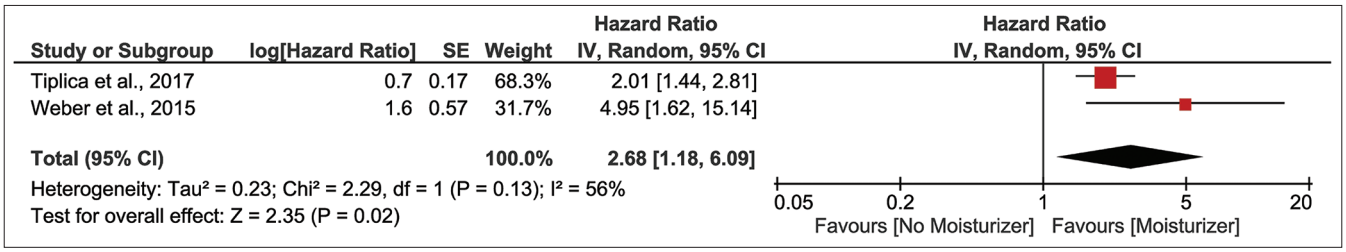

Figure 3e: Forest plot for rate of remission in moisturizer user versus non-user

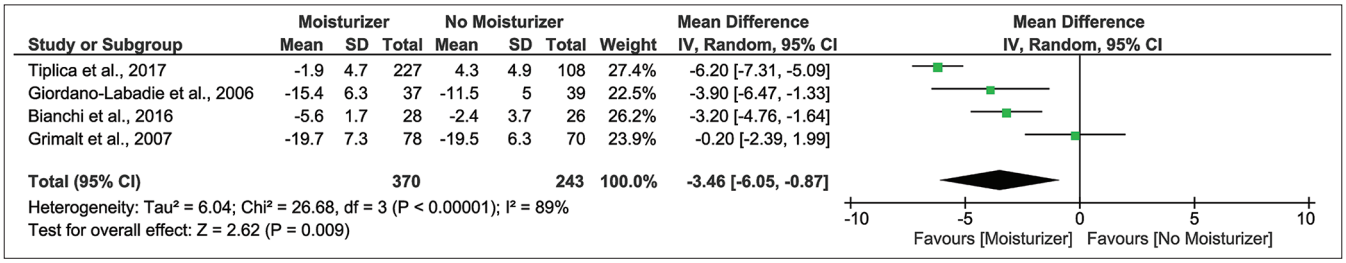

Figure 3f: Forest plot for differences in SCORing Atopic Dermatitis (SCORAD) index in moisturizer user versus non-user

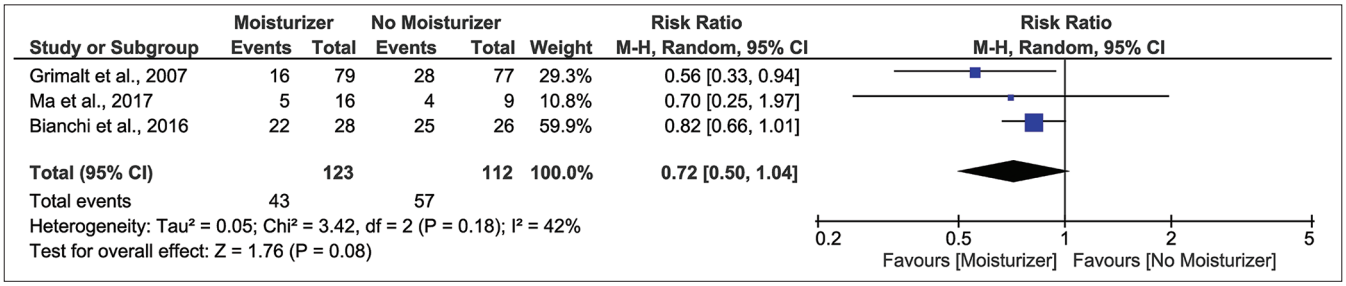

Figure 3g: Forest plot for risk of xerosis in moisturizer user versus non-user

Taken together, our findings suggest moisturizer marginally improves atopic dermatitis severity by relieving patient's subjective illness rather than the objective signs.

Quality of life

Giordano-Labadie *et al*. and Tiplica *et al*. have shown that moisturizer users experienced greater, but marginal, score changes in children's dermatology life quality index and patient-oriented eczema measure compared to control (Giordano-Labadie *et al*.: –0.8 ± 0.4; *P*=0.001 and –0.4 ± 1.5; *P*=0.172, accordingly; and Tiplica *et al*.: Dexeryl® -3.23 ± 0.10; Atopiclair® -2.00 ± 0.10; no moisturizer 0.72 ± 0.11).[30,33] On the other hand, Grimalt *et al*. have shown no significant differences in Infant's Dermatitis Quality of Life Index scores between treated and control groups (*P*=0.131).[31] Similar to other outcomes, we assessed the GRADE quality as 'very low' due to high risk of bias, conflicting individual results and differences in scoring system used [Table 2].

Discussion

Although moisturizers are widely recommended in paediatric atopic dermatitis, most studies that illustrate their efficacy utilize designs where moisturizers of interest were compared to a placebo/vehicle, as opposed to a no moisturizer control, which reflects the indirectness of comparison.[7,9,10,20-24] Therefore, we aimed to evaluate moisturizer against a no treatment group to clearly assess its efficacy in the young.[11]

Our primary outcome shows that moisturizer grants an additional two-week extension of flare-free period in children. The protective effect during the first month of latency is greatest compared to subsequent months, with a remaining 47% risk reduction by the third month. Our findings reveal a lower moisturizer efficacy compared to that of van Zuuren *et al*., in which their pooled result from all ages showed a 60% risk reduction (2 randomised controlled trials, *n*=87, pooled risk ratio 0.4 and 95% confidence interval 0.23–0.7, I^2 0%) at six months of latency.[11] Similarly, we have shown that children were 2.7 times more likely to experience a three to six months remission, but van Zuuren *et al*. has demonstrated a magnitude of 3.74 times from pooling 2 randomised controlled trials with duration of six months (*n*=87, 95% confidence interval 1.86 to 7.5, I^2 0%).[11] While the previous results included fewer studies and smaller sample sizes, age-related variation could also explain the lower magnitudes of efficacy in our study. This is because children may inherently

Table 2: Summary of findings with assessment of evidence quality according to the Grading of Recommendations, Assessment, Development and Evaluation framework

Outcome	Number of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Moisturizer	Risk difference with Moisturizer
Extension of time to flare (days)	231(3 randomized controlled trials)	⨁◯◯◯VERY LOW[a,b,c,d]	-	The mean extension was 0 days	MD 13.52 higher(0.05 higher to 26.99 higher)
Risk of relapse after one month of latency	441(3 randomized controlled trials)	⨁⨁◯◯LOW[a,c]	RR 0.47(0.31–0.72)	454 per 1,000	241 fewer per 1,000(313 fewer to 127 fewer)
Risk of relapse after two months of latency	441(3 randomized controlled trials)	⨁⨁◯◯LOW[a,c]	RR 0.65(0.47–0.91)	589 per 1,000	206 fewer per 1,000(312 fewer to 53 fewer)
Risk of relapse after three months of latency	441(3 randomized controlled trials)	⨁⨁◯◯LOW[a,c]	RR 0.63(0.47–0.83)	675 per 1,000	250 fewer per 1,000(358 fewer to 115 fewer)
Rate of remission	377(2 randomized controlled trials)	⨁◯◯◯VERY LOW[a,b,c,d,e]	HR 2.68(1.18–6.09)	672 per 1,000	278 more per 1,000(60 more to 327 more)
Reduction in SCORing Atopic Dermatitis (Scoring atopic dermatitis) score	613(4 randomized controlled trials)	⨁◯◯◯VERY LOW[a,b,d,f]	-	The mean reduction in Scoring atopic dermatitis was 0	MD 3.46 lower(6.05 lower to 0.87 lower)
Reduction in xerosis	235(3 randomized controlled trials)	⨁◯◯◯VERY LOW[a,e,g]	RR 0.72(0.50–1.04)	509 per 1,000	143 fewer per 1,000(254 fewer to 20 more)
Reduction in redness, swelling, oozing/crusting, scratch marks and lichenification	224(2 randomized controlled trials)	⨁⨁◯◯LOW[a,e]	-	Not pooled	Not pooled
Reduction in pruritus score	389(2 randomized controlled trials)	⨁⨁◯◯LOW[a,h]	-	Not pooled	Not pooled
Reduction in sleep loss score	483(2 randomized controlled trials)	⨁⨁◯◯LOW[a,i]	-	Not pooled	Not pooled
Improvement in quality of life	559(3 randomized controlled trials)	⨁◯◯◯VERY LOW[a,k,l]	-	Not pooled	Not pooled

*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, MD: Mean difference, RR: Risk ratio, HR: Hazard ratio

Grading of Recommendations, Assessment, Development and Evaluation 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: Downgraded one level for performance, detection and publication bias
b: Downgraded one level for inconsistency (serious heterogeneity: I^2> 50%)
c: Downgraded one level for indirectness (Tiplica *et al*. allowed the use of topical corticosteroid during remission)[32]
d: Downgraded one level for imprecision (wide confidence interval)
e: Downgraded one level for imprecision (limited sample size)
f: Downgraded one level for indirectness (Giordano-Labadie *et al*., Grimalt *et al*., and Tiplica *et al*., allowed the use of topical corticosteroid during remission)[29-30, 32]
g: Downgraded one level for indirectness (the proportion of patients with xerosis were compared instead of xerosis scores)
h: Downgraded one level for indirectness (Bianchi *et al*. reported changes from baseline score, while Tiplica *et al*. reported post-study scores between groups)[31,32]
i: Downgraded one level for indirectness (Tiplica *et al*. reported post-treatment scores for patients, while Grimalt *et al*. reported scores for caregivers)[29,32]
j: Downgraded two levels for inconsistency (Giordano-Labadie *et al*. and Tiplica et al. reflected improvement in quality of life, while Grimalt *et al*. did not) [29-30, 32]
k: Downgraded one level for indirectness (each included studies utilized different scoring system to assess quality of life)

have a more active disease progression compared to adults, thus ultimately reflecting diminished effect of moisturizers in this age group.[11] In addition, moisturizer relieved pruritus and xerosis, but not objective signs. This is consistent with previous studies suggesting its primary role in relieving subjective symptoms.[11,13,35] However, their benefits may be too marginal to confer clinical significance, as pooled SCORAD change (3.46 points) did not meet the reported minimal clinically important difference of 8.7, a finding comparable to a 2.42 points reduction from the previous meta-analysis.[11,36] Due to conflicting results and lack of a fixed scoring system, it is difficult to conclude that moisturizers improve quality of life. Based on our findings, its benefits may be minimal in practice, considering the score changes in Giordano-Labadie *et al*. and Tiplica *et al*., which do not meet the corresponding minimal clinically important differences for CDLQI and patient-oriented eczema measure (2.5 and 3.4, respectively).[30,33,36,37] This is in line with results from van Zuuren *et al*. that also demonstrated no significant improvement in quality of life scores (2 randomised controlled trials, n=177, standardised mean difference: 0.15, 95% confidence interval: 0.55–0.24, I^2=42.19%).[11]

The efficacy of moisturizer remains inconclusive as evident from the GRADE certainty assessment. Included studies demonstrated serious risk for bias due to lack of participant, researcher and outcome assessment blinding, which could have affected investigators' judgment in confirming new flares: the main determinant of result validity. Publication bias was likely to be present as only a limited number of small-scale randomised controlled trials on this topic were published. Negative results from long-term follow-ups may not proceed to publication, which accounted for the presence of mostly short duration trials. Therefore, with only 2-4 studies contributing to the major findings, our result lacks generalization. Indirectness was due to differences in study design, especially in Giordano-Labadie *et al*., Grimalt *et al*. and Tiplica *et al*., which allowed the use of topical corticosteroid.[30,31,33] Thus, the efficacy of moisturizer may be overestimated in these studies.[26,28] Imprecision was mainly due to limited sample sizes and wide confidence intervals. Similar to limitations faced by the previous meta-analysis, our findings must be interpreted with great caution due to little confidence in the effect estimates.[11]

Limitations

There is a dire need to conduct randomised controlled trials with more robust and standardised designs. We propose that future trials must: (1) include blinding of participant, investigator and outcome assessments; (2) recruit larger sample sizes with longer follow-up periods beyond six months because moisturizers are safe;[11](3) provide details on the level of care (i.e. community clinic and secondary care) and time of the year/season in which participants were recruited, as these crucial factors impact how moisturizers are prescribed and used, to ensure improved result generalizability;[38,39] (4) control the strength of topical corticosteroid used between trials or avoid them entirely if the main goal is to assess moisturizer efficacy; (5) utilize a universal scoring system for each outcome to ensure directness and allow inter-trial comparison and quantitative synthesis and (6) further assess minimal clinically important differences for each scoring system, as these values determines the applicability of the product in real-life practices. Not until high quality randomised controlled trials are available could we conclude the efficacy of moisturizer in paediatric atopic dermatitis.

Conclusion

Moisturizers are effective at prolonging remission and reducing risk of relapse but may have limited efficacy in improving disease severity and quality of life in paediatric atopic dermatitis. Despite our findings, high quality randomised controlled trials with standardised designs are warranted to confirm the effectiveness of moisturizers in the young.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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