Patient Education Programs in Pediatric Atopic Dermatitis: A Systematic Review of Randomized Controlled Trials and Meta-Analysis

Mutong Zhao · Yuan Liang · Chunping Shen · Ying Wang · Lin Ma · Xiuhua Ma

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ABSTRACT

Introduction: Patient education is crucial for improving disease outcomes in atopic dermatitis (AD). This review aims to summarize evidence about the effectiveness of educational programs for parents of pediatric AD patients.

Methods: PubMed and Embase (inception to Feb 2020) were searched and randomized controlled trials (RCTs) in English were included. Risk of bias was assessed using Cochrane risk of bias tools and quality of evidence was assessed by Grading of Recommendations Assessment, Development and Evaluation (GRADE). Pooled standardized mean difference (SMD) and 95% confidence intervals (CIs) were calculated for the disease severity instrument (Scoring of Atopic Dermatitis, SCORAD) and quality of life (QoL) instruments using the random-effects model.

Results: A total of 13 RCTs were included in the systematic review. The meta-analysis of SCORAD contained seven studies with a total of 1853 patients. The reduction in disease severity (SCORAD) was larger in the treatment group (SMD = -8.22, 95% CI = -11.29, -5.15; P < 0.001; I² = 78.6%). Subgroup analyses revealed that the association was modified by the frequency of sessions (P for Cochran Q < 0.01) and the duration of follow-up (P for Cochran Q < 0.01). No significant effect-modification was observed for disease severity and borderline significance was observed for session delivery (individual vs group session). The pooled effect sizes for QoL measures including Dermatitis Family Index (SMD = -0.65, 95% CI = -1.49, 0.18), Children’s Dermatology Life Quality Index (SMD = -1.61, 95% CI = -3.76, 0.55; I² = 89.0%) and Infants’ Dermatology Quality of Life Index (SMD = 0.30, 95% CI = -1.04, 1.63; I² = 63.1%) were not significant.

Conclusions: Structured patient education is beneficial and should be implemented for the management of AD patients. However, an optimal delivery mode needs to be determined.
Keywords: Atopic dermatitis; Education; Meta-analysis; Parental education; Pediatric; Systematic review

Key Summary Points

Atopic dermatitis parental education of pediatric patients is associated with a significant reduction in disease severity and thus should be implemented into daily clinical practice.

Atopic dermatitis educational programs are encouraged to incorporate the following areas of focus: skincare, diet, psychological managements, and topical steroid usage.

Follow-up duration modifies the effect with longer follow-up showing inferior results, indicating that iterations of implementation might be promising in providing long-standing benefits.

The existing body of evidence was rate as very low to moderate for certainty due to risk for performance and detection bias.

Contamination was likely due to the single center design of the studies included, suggesting that the true effect might be even larger.

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing disease that affects an increasing population [1]. A significant health burden is inflicted by severe pruritus and the prolonged disease course. Studies have shown that patients with AD have compromised quality of live (QoL), a higher likelihood of anxiety and depression, and increased use of healthcare resources [2–4].

Since 1998, therapeutic patient education (TPE) has been recognized as beneficial in both health and financial terms [5]. It plays a crucial role in the management of chronic diseases including cardiovascular diseases and cancer [6–10]. Recent guidelines on AD also recommended that patient education be provided [11–13]. However, no consensus has been reached on the optimal scope, frequency, and tailoring of delivery. Meanwhile, the initiatives of incorporating digital tools as new ways of education delivery including educational video and on-line resources, have shown promising results [14, 15]. Synthesizing the current literature to better understand the role of TPE is important for decision-making by both clinical practitioners and policy-makers. The present study thus aimed to systematically review the impact of various TPE programs on the disease severity and QoL improvements in the population of pediatric AD patients.

METHODS

This review was registered on PROSPERO (CRD42019129832). This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Search Strategy

The MEDLINE and Embase databases were searched from inception to Feb 2020 using the following inquiry terms “atopic dermatitis” or “eczema” and “patient education” and “randomized controlled trials” and “pediatric” (Supplementary Table E1). The inquiry was restricted to human subjects in English. A manual review of references cited in existing reviews and meta-analyses was conducted to identify additional studies. Two researchers (Mutong Zhao and Yuan Liang) evaluated the retrieved articles independently using the inclusion criteria described in the subsequent section. Disagreements were resolved by a third reviewer (Chunping Shen).

Eligible Criteria

All published randomized clinical trials (RCTs) that evaluated the effects of parental education...
on pediatric AD patients were included. Studies published in English were included. An article was excluded when only hand eczema was evaluated as a subject of disease. Interventions that were entirely psychologic without evaluation of AD disease severity changes were excluded from the current analysis and were discussed in a previous review [18]. Studies that evaluated the educational effect of written action plans alone without a concomitant comprehensive educational program were excluded to maintain treatment homogeneity, as action plans were found to have been written at an inappropriately high reading level [19] which might induce heterogeneous interpretations without instruction. Case reports, observational studies, letters to editors and quasi-experimental studies were also excluded. Furthermore, duplicate data were excluded while the study reporting the largest number of participants was retained. Studies that only presented data in graphic form without reporting a numerical value were included in the qualitative but excluded from the quantitative analysis.

Data Extraction

Two researchers independently extracted data on the first author, year, study design, sample sizes, intervention and control treatments, outcome measures, and potential confounders including disease severity, session delivery matrices, and follow-up duration.

Quality Assessment

The risk of bias in individual studies was assessed according to the Cochrane risk of bias guidelines, which included random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach was used to evaluate the quality of evidence, which has four levels of evidence: high, moderate, low, or very low.

Quantitative Synthesis

The effects were pooled using Stata version 12.0 (StataCorp, College Station, TX, USA). The primary outcome was the Scoring of Atopic Dermatitis (SCORAD) index at the end of the follow-up. The QoL instruments, such as Infants’ Dermatitis Quality of Life Index (IDQOL), Children’s Dermatology Life Quality Index (CDLQI) and Dermatitis Family Impact (DFI) were pooled as the secondary outcome measures. The estimates for standardized mean differences (SMDs) were pooled using the random-effects models. Heterogeneity was assessed using the $I^2$ and the Cochran’s $Q$ statistics and an $I^2$ of $>50\%$ or a $P$ for Cochran’s $Q$ of $<0.1$ were regarded as significant. Subgroup analyses were conducted based on curriculum frequency, follow-up duration, disease severity, and delivery methods (i.e., individual vs group sessions). For sensitivity analysis, the objective measure of SCORAD was pooled. Publication bias was assessed by the visual inspection of the funnel plots. All statistical tests were two-sided, and statistical significance was defined as $P < 0.05$. The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Search Results

Our search generated 524 citations (Fig. 1). A total of 393 articles were excluded by title or abstract. Nineteen studies were assessed for full text and thirteen RCTs were included in the final systematic review [20–30], which involved 2632 subjects.

Characteristics of Studies

Table 1 outlines the characteristics of the included studies. Pre-intervention disease severity varied across studies, e.g., five and one study exclusively included moderate to severe and mild to moderate AD patients, respectively, and four others recruited participants with unlimited
disease severity. Follow-up ranged from 1 week to 24 months post-intervention. The delivery of sessions included individual consultations \((n = 2)\) [23, 26], videotape \((n = 2)\) [31, 32], daily text messages \((n = 1)\) [29], and group sessions \((n = 8)\) [20–22, 24, 25, 27, 28, 30]. Programs focused on the medical delineation of the disease, allergic components, lifestyle recommendations, stress management, and practical instructions on skin care and topical drugs. The outcome assessments were divided into five elements: disease severity \((n = 10)\); QoL \((n = 10)\); psychological burden \((n = 3)\); knowledge, including topical steroid phobia \((n = 2)\); and moisturizer consumption \((n = 1)\). Disease severity was measured using the SCORAD \((n = 8)\) [20, 21, 23–28] and Eczema Area and Severity Index \((EASI)\) \((n = 3)\) [29, 31, 32]. Both patient-oriented [21–24, 27, 28, 30] and family [20–22, 24, 25, 28, 30] QoL were delineated.

**Qualitative Assessment of Studies**

Supplementary Figure S1 displays the risk of bias summary. Overall, the risk for performance bias and detection bias was high. The quality of evidence was rated as moderate for SCORAD and DFI, and very low for IDQOL and CDLQI by GRADE (Supplementary Table E2). The funnel plot for publication bias of studies included in the quantitative analyses of SCORAD, DFI, IDQOL, and CDLQI was largely symmetric, Supplementary Figure S2.
| References | Year | Age (years) | Follow-up | Treatment / control no. | Control Disease severity | Content | Disease severity | Treatment / control no. | Outcome measures |
|------------|------|-------------|-----------|-------------------------|-------------------------|---------|-----------------|-------------------------|------------------|
| Singer [29] | 2018 | 0.3–3.8 | Daily | 14/16 | Unclear | Disease burden; precipitators; skin care | Disease severity | Treatment / control no. | Outcome measures |
| Liang [27] | 2018 | 4–14 | 6 months | 293/249 | Four weekly lectures | Unclear | Moderate to severe | Long-term management, food allergy, psychological assessment, skin care | Disease burden; precipitators; skincare | (1) SCORAD; (2) IDQOL; (3) CDLQI; (4) Knowledge assessment questionnaire |
| Pustisek [25] | 2016 | 0.25–12 | 2 months | 64/64 | One-time lecture with written material | Unclear | Moderate to severe | Basic medical information, psychological management, food allergy and diet, skin care | Disease burden; precipitators; skincare | (1) SCORAD; (2) FDLQI; (3) STAI and PPS |
| Staab [20] | 2006 | 0.25–7 | 12 months | 274/244 | Six weekly group sessions | Unclear | Moderate to severe | Basic medical information, psychological management, food allergy and diet, skin care | Disease burden; precipitators; skincare | (1) SCORAD and P.O. |
| References  | Year | Age (years) | Follow-up | Treatment/ control, no. | Treatment | Control | Disease severity | Contents | Outcome measures |
|-------------|------|-------------|-----------|------------------------|----------|---------|----------------|----------|----------------|
| Futamura [21] | 2013 | 0.5–6       | 6 months  | 29/30                  | Two continuous days of group meeting with information booklet | Standard care and information booklet | Moderate to severe | Basic medical information, treatments and adverse effects, allergen and avoidance, skin care | (1) SCORAD and POSCORAD; (2) Questionnaire on scores for pruritus, sleeplessness and corticosteroid anxiety; (3) DFI |
| Grillo [28] | 2006 | 0–16        | 12 weeks  | 32/29                  | One-time workshop | Standard care | Unlimited | Basic medical information, precipitators, skin care, practical session | (1) Objective SCORAD; (2) DFI, CDLQI, and IDQOL |
| Shaw [23] | 2008 | 0–18        | The 1 or 3 month follow-up appointment determined by severity | 51/55 | One-time individualized education | Unclear | Unlimited | Medical treatment, skin care, allergen avoidance, pruritus reliefs, lifestyle managements | (1) SCORAD; (2) CDLQI, and IDQOL |
| Chinn [30] | 2002 | 0.5–4       | 12 weeks  | 55/42                  | One-time session | Unclear | Unclear | Basic medical information; treatment application; skin care | (1) CDLQI or IDQOL and DFI |
|             |      | 4–16        |           | 50/50                  |           |         |                 |          | |
| Weber [22] | 2008 | 2–16        | 24 months | 16/16                  | Fortnightly support group for 6 months | Unclear | Moderate to severe | Overview of the disease and treatment followed by discussion | (1) CDLQI and DFI; (2) McGill pain questionnaire for pruritus assessment |
Table 1 continued

| References | Year  | Age  | Follow-up | Treatment/control, no. | Treatment | Control | Disease severity | Contents                                                                 | Outcome measures                          |
|------------|-------|------|-----------|------------------------|-----------|---------|-----------------|------------------------------------------------------------------------|-------------------------------------------|
| Moore [26] | 2009  | <16  | 4 weeks   | 49/50                  | One-time  | Standard care | Unlimited | Basic medical information, precipitator avoidance, treatments and information booklet | (1) SCORAD                                |
|            |       |      |           |                        | individual consultation with information booklets |         |                  |                                                                                                                                  |                                           |
| Schuttelaar [24] | 2010   | <4   | 12 months | 37/34                  | One-time | Standard care | Unlimited | Basic medical information, allergies, skin care, practical session and written action plan | (1) SCORAD and objective SCORAD; (2) CDLQI or IDQOL and DFI; (3) Program satisfaction |
|            |       |      | 4–16      | 35/35                  | group     |         |                  |                                                                                                                                  |                                           |
|            |       |      |           |                        | session or education during individual follow-up visits |         |                  |                                                                                                                                  |                                           |
| Saritha [31] | 2018   | 0–16 | 6 weeks   | 5/5                    | Video on AD | Video on a placebo tape | Unclear | Unclear | (1) Topical steroid phobia and adherence; (2) EASI                                                                 |                                           |
| Park [32]  | 2017  | 0.3–4.3 | 1 week | 10/11                  | One-time video tape with tailored leaflet | Same video tape without tailored leaflet | Mild to moderate | Skin care and tailored ideal amount of moisturizer | (1) Moisturizer usage; (2) EASI                                                 |                                           |

EASI eczema area and severity index, SCORAD Scoring of Atopic Dermatitis, CDLQI Children’s Dermatology Life Quality Index, IDQOL Infants’ Dermatology Quality of Life Index, DLQI Dermatitis Life Quality Index, PO-SCORAD Patient Oriented SCORAD; FDLQI Family Dermatitis Life Quality Index, STAI State Trait Anxiety Inventory, PPS Perceived Stress Scale, DLQI Dermatitis Life Quality Index, QoLIAD Quality of Life Index for Atopic Dermatitis, BDI Beck Depression Inventory, EQ-SD EuroQol 5-Dimension, POEM patient-oriented eczema measure, HADS-D Hospital Anxiety and Depression Score, DFI Dermatitis Family Impact, RCT randomized control trial, JUCKKI/JUCKJU Itching cognitions questionnaires
### a

| Author     | Effect (95% CI) | Weight |
|------------|----------------|--------|
| Futamura M (2013) | -12.40 (-17.15, -7.65) | 11.17 |
| Grillo M (2006) | -16.89 (-20.60, -3.18) | 7.74 |
| Liang Y (2018) | -2.46 (-4.88, -0.04) | 13.94 |
| Moore EJ (2009) | -9.93 (-14.57, -5.29) | 11.31 |
| Pustisek N (2016) | -13.36 (-18.72, -8.00) | 10.40 |
| Schutte Laar ML (2010) | -3.10 (-6.89, 0.69) | 12.38 |
| Staab D (2006) | -6.80 (-11.74, -1.86) | 10.93 |
| Staab D (2006) | -11.80 (-16.94, -6.66) | 10.67 |
| Staab D (2006) | -4.70 (-7.56, -1.84) | 13.46 |
| Overall (I-squared = 78.6%) | -8.22 (-11.20, -5.15) | 100.00 |

**NOTE:** Weights are from random-effects model, effects are standardized mean differences.

### b

| Author     | Effect (95% CI) | Weight |
|------------|----------------|--------|
| Futamura M (2013) | -1.20 (-3.38, 0.98) | 14.62 |
| Schutte Laar ML (2010) | -1.10 (-2.78, 0.58) | 24.58 |
| Grillo M (2006) | -0.32 (-1.35, 1.61) | 8.14 |
| Chinn DJ (2002) | -0.94 (-1.50, 0.60) | 52.66 |
| Overall (I-squared = 0.0%) | -0.65 (-1.45, 0.16) | 100.00 |

**NOTE:** Weights are from random-effects model, effects are standardized mean differences.

### c

| Author     | Effect (95% CI) | Weight |
|------------|----------------|--------|
| Liang Y (2018) | -0.85 (-1.51, -0.19) | 37.58 |
| Grillo M (2008) | 1.58 (-0.47, 3.63) | 20.96 |
| Schutte Laar ML (2010) | 0.10 (-2.11, 2.31) | 19.45 |
| Chinn DJ (2006) | 1.20 (-0.80, 3.10) | 22.01 |
| Overall (I-squared = 63.1%) | 0.30 (-1.04, 1.63) | 100.00 |

**NOTE:** Weights are from random-effects model, effects are standardized mean differences.

### d

| Author     | Effect (95% CI) | Weight |
|------------|----------------|--------|
| Liang Y (2018) | -0.72 (-1.45, 0.01) | 27.74 |
| Grillo M (2008) | -5.33 (-7.02, -3.64) | 24.34 |
| Schutte Laar ML (2010) | -0.70 (-2.51, 1.11) | 23.82 |
| Chinn DJ (2006) | 0.24 (-1.50, 2.00) | 24.10 |
| Overall (I-squared = 89.9%) | -1.81 (-3.78, 0.05) | 100.00 |

**NOTE:** Weights are from random-effects model, effects are standardized mean difference.
Quantitative Analyses of SCORAD

A trial that failed to adequately randomize baseline characteristics, and a trial that compared two different deliveries of intervention [23, 32] were excluded to reduce heterogeneity (the reasons for exclusion in meta-analysis are summarized in Supplementary Table E3). Effect sizes for parental educational programs were pooled using SCORAD as the majority of the studies used this matrix. The final meta-analysis of SCORAD comprised seven studies and a total of 1853 patients [20, 21, 24–28]. Overall, participants in the group that received therapeutic education had a significantly greater reduction in SCORAD at the end of the follow-up (SMD \(-8.22, 95\% \text{ CI } = -11.29, -5.15; P < 0.001; \text{ Fig. 2a} \)). The heterogeneity was high and statistically significant (\(P\) for Cochran \(Q\) \(< 0.001, I^2 = 78.6\%\)). Sensitivity analysis revealed that the result was robust to the objective measure of SCORAD (SMD \(-7.38, 95\% \text{ CI } = -10.37, -4.39; P < 0.001\) [20, 21, 24, 28]). The subgroup analyses (Table 2) revealed that follow-up duration and session frequency were sources of heterogeneity (\(P\) for Cochran \(Q \) < 0.01). The strata of studies with shorter follow-up duration and a single session delivery had greater improvement in SCORAD (\(P\) for Cochran

Table 2 Subgroup analyses of RCTs included in the meta-analyses of SCORAD

| Parameters                      | Studies, no. | Treatment/ control, no. | SMD (95% CI)          | \(P\) value | \(I^2\), \% |
|---------------------------------|--------------|-------------------------|-----------------------|-------------|-------------|
| Frequency*                      |              |                         |                       |             |             |
| One single session [14, 17, 18, 21] | 4            | 174/173                 | \(-12.11 (−14.83, −9.39)\) | \(< 0.01\) | 0.0         |
| Cumulative sessions [13, 19]    | 2            | 739/626                 | \(-5.88 (−9.36, −2.40)\) |             | 73.5        |
| Follow-up duration, months*     |              |                         |                       |             |             |
| \(< 6 \) [17, 18, 21]           | 3            | 840/725                 | \(-11.97 (−15.28, −8.65)\) |             | 0.0         |
| \(\geq 6 \) [13, 14, 16, 19]   | 4            | 145/143                 | \(-6.45 (−9.63, −3.27)\) |             | 77.0        |
| Disease severity                |              |                         |                       | 0.71        |             |
| Moderate to severe AD [13, 14, 17, 19] | 4         | 832/720                 | \(-8.19 (−11.99, −4.38)\) |             | 82.3        |
| Unlimited [16, 18, 21]          | 3            | 153/148                 | \(-8.74 (−15.55, −1.94)\) |             | 78.0        |
| Delivery                        |              |                         |                       | 0.1         |             |
| Tailored individual session [18] | 1            | 49/50                   | \(-9.93 (−14.57, −5.29)\) |             | –           |
| Group session [13, 14, 16, 17, 19, 21] | 6          | 936/818                 | \(-8.03 (−11.35, −4.70)\) |             | 79.8        |

Based on total SCORAD
AD atopic dermatitis, SMD standardized mean difference, CI confidence interval, SCORAD Scoring of Atopic Dermatitis
*Between subgroup \(Q\) statistics significant (\(P\) < 0.1)
Tailored sessions (for Cochran $Q = 0.10$) showed borderline significance when compared with group sessions. Additionally, the improvements did not seem to be significantly modified by the baseline disease severity (for Cochran $Q < 0.01$).

Quantitative Assessment of QoL Measures

The instruments for QoL varied among studies. We were able to pool effects of Dermatitis Family Index (DFI) [21, 22, 24, 28, 30], Children’s Dermatology Life Quality Index (CDLQI) [22–24, 27, 28, 30] and Infants’ Dermatology Quality of Life Index (IDQOL) [23, 24, 27, 28, 30]. For other measures including Family Dermatology Life Quality Index (FDLQI), Dermatology Life Quality Index (DLQI), and pruritus questionnaires, the pooling of data was impractical due to the limited number of studies. Four studies that randomized 462 participants were included in the pooling of DFI and the result was not significant (SMD = $-0.65$, 95% CI $-1.49$ to $0.18$, $P = 0.126$, Fig. 2b). There was low heterogeneity among the trials ($I^2 = 0.0\%$, $P = 0.838$). Similarly, for IDQOL that randomized 558 participants, therapeutic patient education did not appear to result in a statistically significant improvement (SMD = $0.30$, 95% CI $-1.04$ to $1.63$; $P = 0.665$; $I^2 = 63.1\%$; Fig. 2c). Additionally, CDLQI did not significantly change with TPE (SMD = $-1.61$, 95% CI $-3.76$ to $0.55$; $P = 0.144$; $I^2 = 89.0\%$; Fig. 2d). The heterogeneity was significant for both measures.

DISCUSSION

The present study reviewed recent literature on disease severity improvements from parental educational interventions. Compared to the most recent systematic review done in 2014 [9], our study added 2 and 6 more to the synthesis of quantitative and qualitative analysis, respectively. Additionally, we conducted subgroup analyses to explore sources of heterogeneity and examined the impact on QoL matrices. Sensitivity analysis using the objective measure of SCORAD was conducted to examine the potential impact of performance bias.

The current review found that the scope of educational interventions varied among studies. First, skin care was an area that was universally covered by all programs, highlighting the importance of using moisturizers to address the defective barrier [11, 33, 34]. In the meantime, it’s also important to clear up misunderstandings about “natural skin products” containing food allergens (e.g., goat’s milk, cow’s milk, peanut oil, almond oil, and oatmeal), as skin sensitization could incur serious consequences, including anaphylaxis [35]. There was also coverage of psychological burdens and management both by studies included in the current review [20, 25, 27] and by two additional adult studies [36, 37]. The psychological consequences of AD include a higher risk of depression and suicidal ideations [38]. While it has been well acknowledged that asthma and allergic rhinitis are important comorbidities arising from atopic march, other consequences including psychological comorbidities and impaired QoL for both the children and care givers should not be overlooked [20, 22, 25, 27, 39]. In realizing the psychological burdens of AD and its management, more could be done to improve the QoL of both. Food allergy and its link with AD have been extensively studied. Although an avoidance diet may lead to an improvement of the AD symptoms, this could also lead to nutritional and possible immune consequences (the development of immediate-type reactions) [40]. Thus, food avoidance should be initiated with discretion, especially when oral immunotherapy is available. Unfortunately, in a study that explored parents’ attitudes toward food elimination in the general population, 23% intentionally avoided giving at least one food to their children [41]. Guidance on this topic should be offered to reduce consequences of unnecessary food avoidance. Lastly, steroid phobia should be addressed adequately in these programs. Topical steroids are regarded as the mainstay in treating AD. Steroid phobia constitutes one of the major reasons for non-adherence and disease flares [42], affecting up to 60–73% of patients, which indicated that clarifications are needed in a
standard patient visit. As studies into this area have mostly been cross sectional, educational trials with an extended follow-up could be more informative in illustrating the learning curve of patients’ Knowledge, Attitudes and Practice (KAP) of topical steroids throughout the post-intervention periods. In conclusion, future TPE programs are encouraged to encompass four areas of focus: skin care, diet, psychological issues, and topical steroid usage. Only three studies in the present review addressed all four areas [20, 23, 27].

In the present study, a significant reduction in SCORAD was found, which supports the role of patient education. In the subgroup analyses, a greater reduction in SCORAD in studies with shorter follow-up durations was observed ($P$ for Cochran $Q < 0.01$). This was probably influenced by the parents’ knowledge-guided practice returning to their pre-interventional states after a longer washout period in studies with extended post-intervention follow-ups. Interestingly, a greater effect was found in the group of participants who were educated “once and for all”, when compared with those receiving a cumulative curriculum regime ($P$ for Cochran $Q < 0.01$). This was probably confounded by the shorter follow-up duration of single-session programs when compared with participants who received multiple sessions at intervals, i.e., parents that received a single session of education were universally followed for less than 6 months whereas those that were cumulatively educated were followed for longer periods. For long-term benefits to be achieved, it’s probably recommended to assess the learning curve of parents and to determine whether education should be delivered at iterations of small sessions rather than at serial comprehensive sessions. A borderline ($P$ for Cochran $Q = 0.1$) significant difference was identified between those who received tailored sessions versus those who were educated as a group; however, as there was only one study in the tailored delivery subgroup, this finding should be viewed with discretion and future studies are required to determine the optimal delivery. Initiatives examining education in digital settings (i.e., daily text messages and videotapes) have yielded inconclusive results. Singer et al. [29] reported a null result for EASI with the intervention of daily text messages while Saritha [31] reported a statistically significant reduction in EASI with videotape. As these studies were all pilot studies with a limited sample size ($n = 30$ and $10$, respectively), future studies with larger sample sizes are required to confirm the findings. Furthermore, patients with different disease severities appeared to benefit alike from educational programs ($P = 0.71$), indicating that TPE may be implicated regardless of disease severity.

The literature was inconsistent about the correlation of disease severity and QoL [42–45]. One explanation was that severity correlated better with QoL when disease activity was less severe [44], and as the disease proceeded into the moderate to severe spectrum, the association may gradually grow out of linearity. Meanwhile, as previous studies have indicated, a drastic change in disease activity (SCORAD change of 10 points) was only associated with a small improvement in QoL (CDLQI and DLQI of 0.12 and 0.13, respectively) [44, 46], indicating that other factors might be predictors of quality of life for AD patients. One such factor might be the affected body surface area [44, 47]. Another factor is the psychological burden, which has been shown to correlate with the Dermatology Life Quality Index but not EASI [48]. Taken together, these QoL instruments and disease severity instruments offer distinct information and should be separately assessed in efficacy trials of AD. In the present study, the pooled SMDs of QoL measures failed to reveal a significant difference, although the pooled SMD of SCORAD did. One reason might be that all but one study [27] included for the synthesis of QoL measures incorporated psychological management as a part of the program intervention, limiting its capacity to deal with QoL impairments. In the three studies with adequate randomization on baseline QoL that did touch on psychological issues, QoLs were significantly improved by the program [20, 25, 27]. Another attributing factor might be treatment compliance, which requires more time and participation in the treatment group [28], resulting in higher expectations and a lower rating of QoL. Although most studies have investigated
improvements in the QoL of patients, less is known about disease burden on family members (n = 6 reported [21, 22, 24, 25, 28, 30]). These matrices should be incorporated, because sleep disturbances and time spent in attending patients were problematic not only for the patients themselves, but also for their family members, particularly in pediatric patients [3]. Validated disease-specific family QoL questionnaires have been developed [49, 50], aiding in the scaling of this matter. In the present study, although we failed to identify a statistically significant difference in the comparison of family QoL, a clear trend favoring the treatment group was observed.

Health economics matrices were under-reported. Educational interventions have the benefit of being low-cost to implement; however, to maintain sustainable effects, long-lived changes in behavior should be achieved. Our study also suggested that that people’s behavior tends to approach baseline when they were followed for longer periods, indicating that TPE programs delivered at iterations across various intervals might be the most effective. On the other hand, this means that an increment in the cost is to be expected. Bosteon et al. reported a comparable medical consumption between the control and intervention groups in adult patients [36]. However, if program implementation and moisturizer consumption were to be calculated as program inputs, an increase in cost in the intervention group might be expected. No such study has been conducted in the pediatric population. Future studies comparing the cost-effectiveness of different methods and frequencies of delivery in pediatric AD patients are warranted. Compared with face-to-face training, web-based training has the benefit of being more cost-effective [51, 52]. One study on adult patients that compared two different deliveries of TPE, i.e., web-based video vs written pamphlets, found that there was a significantly greater reduction in disease severity in the former [53]. It is tempting to suggest that online settings could at least play a complementary role in future TPE programs.

One study [27] in the present review and two others in adult patients [53, 54] used knowledge questionnaires as the outcome of interest, although the instruments were not validated. Participants’ KAP could be quantitatively measured using KAP questionnaires, as was the case for asthma [55], cancer [56] and other chronic diseases [57]. To the best of our knowledge, the only validated questionnaire of such for AD was the TOPICOP questionnaire that measured topical corticosteroid phobia [58], and this has been translated into 15 languages. As was reported by Gonzales et al., a high level of TOPICOP score was associated with poor adherence [59], indicating that KAP instruments could serve as a useful surrogate for the evaluation of treatment adherence. More comprehensive KAP instruments should be developed, validated and incorporated in TPE programs of pediatric AD to facilitate the assessment of patient knowledge and for the development of more targeted education.

The present study was limited by a very low to moderate quality of evidence rated by GRADE (Supplementary Table E2) due to risk in performance and detection bias, i.e., blinding of participants and researchers was impractical and blinding of outcome assessors was not carried out by all studies. One approach to minimize performance bias in the absence of blinding is to use objective investigator-led instruments as the outcome of interest [60], which was the main reason for choosing objective SCORAD over pruritus SCORAD in the sensitivity analysis of the present study.

Furthermore, a trial with non-medication intervention is, by nature, susceptible to intra-group contamination, i.e., participant allocation may get contaminated due to the close proximity of patients and the provision of care by the same team [61, 62]. Intra-group contamination reduces the point estimate of an intervention’s effectiveness which may thereby lead to a type II error [63]. This means that the actual effect size is likely to be even larger than the observed. Compared with individual randomization, cluster randomization offers the privilege of minimizing contamination. Future studies might consider using a cluster-randomized design to obtain more valid results.

In terms of the scope of the present systematic review, the reason for including only educational programs and excluding action plans...
was to reduce heterogeneity, and it was acknowledged that this might affect the generalizability of our study. Future studies and reviews that focus on AD action plans might offer new perspectives on this topic. Meanwhile, since adult participants were not included, the present review is applicable to only pediatric studies with parental educational interventions.

CONCLUSIONS

In summary, present structured education programs benefit pediatric AD patients in terms of disease severity but do not appear to significantly improve quality of life. Future TPE programs were recommended to offer guidance on skin care, diet, psychological issues, and topical steroid usage. Efforts are needed to optimize the frequency, delivery, and cost-effectiveness of program implementation.

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Data Availability. All data generated or analyzed during this study are included in this published article as supplementary information files.

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