

## REVIEW

# A systematic review and meta-analysis of nutritional and dietary interventions in randomized controlled trials for skin symptoms in children with atopic dermatitis and without food allergy: An EAACI task force report

Emilia Vassilopoulou<sup>1,2</sup>  | Anna Comotti<sup>3</sup> | Nikolaos Douladiris<sup>4</sup> | George N. Konstantinou<sup>5</sup>  | Torsten Zuberbier<sup>6,7</sup>  | Ilaria Alberti<sup>2</sup> | Carlo Agostoni<sup>2,8</sup> | Roberto Berni Canani<sup>9</sup> | Ioana Corina Bocsan<sup>10</sup> | Antonio Corsello<sup>8</sup> | Valentina De Cosmi<sup>8,11</sup> | Gavriela Feketea<sup>10,12</sup>  | Kirsi Laitinen<sup>13</sup> | Alessandra Mazzocchi<sup>8</sup> | Nicola A. Monzani<sup>8</sup> | Nikolaos G. Papadopoulos<sup>4</sup>  | Diego G. Peroni<sup>14</sup> | Constantinos Pitsios<sup>15</sup> | Franziska Roth-Walter<sup>16,17</sup>  | Isabel Skypala<sup>18,19</sup>  | Sophia Tsabouri<sup>20</sup>  | Abdoulie K. Baldeh<sup>21</sup> | Liam O'Mahony<sup>22</sup>  | Carina Venter<sup>23</sup>  | Gregorio Paolo Milani<sup>2,8</sup> 

## Correspondence

Emilia Vassilopoulou, Department of Nutritional Sciences and Dietetics, International Hellenic University, Thessaloniki 57400, Greece.  
Email: [vassilopoulouemilia@gmail.com](mailto:vassilopoulouemilia@gmail.com)

Carina Venter, Pediatric Allergy and Clinical Immunology, Children's Hospital Colorado/University of Colorado, Aurora, CO, USA.  
Email: [carina.venter@childrenscolorado.org](mailto:carina.venter@childrenscolorado.org)

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## Abstract

This systematic review and meta-analysis aimed to consolidate evidence on dietary interventions for atopic eczema/dermatitis (AD) skin symptoms in children without food allergies, following PRISMA 2020 guidelines. Systematic review updates were conducted in May 2022 and June 2023, focusing on randomized placebo-controlled trials (RCTs) involving children with AD but without food allergies. Specific diets or supplements, such as vitamins, minerals, probiotics, prebiotics, symbiotics, or postbiotics, were explored in these trials. Exclusions comprised descriptive studies, systematic reviews, meta-analyses, letters, case reports, studies involving elimination diets, and those reporting on food allergens in children and adolescents. Additionally, studies assessing exacerbation of AD due to food allergy/sensitization and those evaluating elimination diets' effects on AD were excluded. Nutritional supplementation studies were eligible regardless of sensitization profile. Evaluation of their impact on AD clinical expression was performed using SCORAD scores, and a meta-analysis of SCORAD outcomes was conducted using random-effect models (CRD42022328702). The review encompassed 27 RCTs examining prebiotics, Vitamin D, evening primrose oil, and substituting cow's milk formula with partially hydrolyzed whey milk formula. A meta-analysis of 20 RCTs assessing probiotics,

For affiliations refer to page 13.

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alone or combined with prebiotics, revealed a significant reduction in SCORAD scores, suggesting a consistent trend in alleviating AD symptoms in children without food allergies. Nonetheless, evidence for other dietary interventions remains limited, underscoring the necessity for well-designed intervention studies targeting multiple factors to understand etiological interactions and propose reliable manipulation strategies.

#### KEYWORDS

atopic dermatitis, childhood, diet, microbiome, nutrient, oils, postbiotics, prebiotics, probiotics, synbiotics, vitamin D

## 1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disorder characterized by skin dryness, intense pruritus.<sup>1,2</sup> The onset of AD is usually during childhood, and it affects 15%–30% of children.<sup>3,4</sup> About 5%–10% of adults suffer from AD, 25% of which are adult-onset cases.<sup>4,5</sup> Pathophysiology of AD is characterized by skin barrier impairment, due to defects in the stratum corneum (SC), an abnormal inflammatory immune response and skin microbial dysbiosis.<sup>6,7</sup>

The skin barrier impairment in AD applies to the thinner epidermis, with defective lipid and protein composition and function, leading to poor hydration, increased trans-epidermal water loss (TEWL) and increased permeability to microbes, irritants, and allergens.<sup>8</sup>

Non evidence-based food restriction practices, poor diet quality, and impaired growth are common in children with AD.<sup>9–11</sup> Disease severity is associated with poorer quality of life (QoL), affecting mental health.<sup>12–14</sup>

The management of AD focuses on: (a) minimization of the underlying inflammation, both locally and systemically, with corticosteroids, topical calcineurin inhibitors, and immunosuppressive and/or immunomodulating drugs in the most severe cases, in order to treat the AD and modify the impairment of the skin barrier, (b) restoration of the skin barrier, mainly through the use of moisturizers, and (c) identification of aggravating factors, and education of the patient and the family on how to avoid them, in order to alleviate the symptoms and improve the patient's QoL.<sup>15–17</sup>

Several studies have indicated that long-term “Western” dietary patterns rich in processed food, fat and sugar, lead to dysregulation of the Th1/Th2 balance, favoring the Th2 inflammatory pathway,<sup>18</sup> as confirmed by a recent meta-analysis by Li and colleagues.<sup>19</sup> Conversely, traditional dietary patterns, rich in natural products, such as the Mediterranean diet (MedDiet)<sup>20</sup> and the Korean diet,<sup>21</sup> are considered to be protective of AD, due to their high content of antioxidants, fibers and “good fat” sources, such as olive oil and fish oil, although the relevant research findings are inconsistent.<sup>22,23</sup>

In infants and young children, elimination diets have been suggested as a treatment of AD. These diets mainly involved the avoidance of common allergens, such as milk and egg.<sup>24,25</sup> Older children, adolescents and adults often follow exclusion diets, or attempt elimination diets, or use special health food preparations without the guidance of

a physician. In order to improve their eczema, they minimize (following an “exclusion diet”) or completely eliminate several foods or food groups.<sup>21</sup> Nosrati and colleagues reported in their survey that 68% of the AD patients excluded processed foods, 53.6% white flour products, 49% gluten and 35% nightshades, while they increased consumption of leafy vegetables (84%), fish (80%), and fruit (78%).<sup>26</sup>

Dietary interventions have been investigated in a wide range of studies, but the published results from randomized clinical trials (RCTs) of dietary interventions in patients with AD have not provided clear conclusions. To date, such trials have focused mainly on interventions with a wide range of dietary supplements, including fish oil, and vitamins D and E, but the interpretation of the results are limited due to low sample sizes and methodological issues.<sup>27–29</sup> Intervention studies with probiotics in some cases appeared promising.<sup>30</sup> The positive effect is probably linked to an improvement and rebalancing of the skin microbiota through the gut-skin axis.<sup>31,32</sup> However, the study population is often mixed, with some participants being food allergic or sensitized to several food allergens affecting food avoidance.

Due to the scarcity of comprehensive and reliable evidence for drafting a position or guideline paper on nutritional and dietary interventions for skin symptoms in children affected by AD without food allergy, we aimed to evaluate and summarize available data on this topic. To fulfill this task force's primary objective, a systematic review and meta-analysis was conducted.

## 2 | METHODS

This study was performed according to the Cochrane Handbook for Systematic Reviews Interventions and the statement by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group (PRISMA). The study was registered in the international prospective register of systematic reviews (PROSPERO) (code CRD42022328702).

### 2.1 | Literature search

A literature search was conducted on May 23, 2022 and updated on January 30, 2024, in PubMed, Embase and Web of Science

databases, using the following Medical Subject Heading (MeSH) terms and text words in the queries: "atopic eczema" OR "atopic dermatitis" AND "diet" OR "nutrition" OR "supplement" OR "probiotics" OR "prebiotics" OR "vitamin" OR "macronutrient" OR "micronutrient."

The complete search strategy of the three databases is included in the [Supporting Information](#). The reference lists of the retrieved articles and relevant articles were manually screened for further publications for inclusion.

A meta-analysis was performed when at least three studies assessed the same nutrient intervention (independent of the dose or duration of the intervention), and provided an improvement of the AD SCORAD severity score, where available.

## 2.2 | Inclusion criteria

The eligible studies were RCTs in children and adolescents with AD without food allergy, treated with: (a) a dietary modification; (b) a nutritional supplement (vitamins, mineral supplements, probiotics, prebiotics, symbiotics, and/or postbiotics); (c) at least one dietary intervention and at least one nutritional supplement. Furthermore, only trials evaluating the effects of interventions on skin clinical manifestations assessed by SCORAD or equivalent scores, regardless of the use of adjunctive topical anti-inflammatory treatment (e.g., corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors), were considered. Participants of any race were eligible for inclusion in the study.

## 2.3 | Exclusion criteria

Descriptive studies or systematic reviews and meta-analyses, letters, case reports, studies involving elimination diets and studies reported AD related to specific food allergens in children and adolescents were excluded. Studies evaluating the effect of elimination diets on the culprit food on the AD of food-allergic individuals were excluded. However, all nutritional supplementation studies were eligible independently of the sensitization profile of the examined subjects.

Studies on adults, animals (non-human) studies, ex vivo, and in vitro studies were also excluded.

## 2.4 | Screening and abstraction process

The Rayyan web tool was used to assist study selection,<sup>33</sup> and data extraction and risk of bias assessment were performed independently by two different reviewers (ND, GNK, TZ, IA, CA, RBC, CB, AC, VDC, GF, KL, AM, NAM, NGP, DP, CP, FRW, IS, ST, AKB, LOM, CV). Any title or abstract identified by either of the reviewers as potentially relevant was advanced to full-text review, and any discrepancies at full-text screening were resolved by discussion between

the two reviewers, and when necessary, by one of the main investigators (EV or GPM).

## 2.5 | Data extraction and management

Authors in pairs extracted independently the following data: (1) publication data: author, publication year, country of study; (2) study design: number of arms, blindness of the RCT, duration of follow-up, number of participating centers; (3) method used to diagnose AD; (4) participant characteristics for the intervention and control groups: number of recruited and randomized children, number of participants completing the study and included in the analyses, age and ethnicity, method of birth, co-morbidity, other relevant characteristics; (5) intervention and placebo ingredient(s): type, dose, duration of intervention, placebo intervention; (6) outcome indicators: SCORAD change (or equivalent), change in levels of antibodies/cytokines. In the case of dispute, the data included were decided by a third author (EV or GPM) after discussion.

## 2.6 | Statistical analysis

The outcome used in the meta-analysis was the change in SCORAD (or equivalent) score between pre-intervention and post-intervention values among the intervention and control group.

The mean difference (MD) and 95% confidence interval (95% CI) were used as summary statistics. When the mean and standard deviation ( $\pm$ SD) of the change were not reported in the original articles, these were calculated as described in the [Supporting Information](#).

Between-studies heterogeneity was quantified by statistics  $\tau^2$  and  $I^2$  and considered moderate if above 50% or substantial if above 75%. A fixed-effect model was used when no significant heterogeneity was detected among studies; otherwise, a random-effect model was used. Pooled results were displayed using a forest plot. To explore the cause of heterogeneity, we checked for outliers and influential cases. Studies were defined as outliers when their 95% CI is outside the 95% CI of the pooled effect, and influential cases as those studies with a large impact on the pooled effect or heterogeneity, regardless of how high or low the effect is.<sup>34</sup>

Other possible sources of heterogeneity (e.g., publication year and dose of supplementation) were assessed by meta-regression models. The funnel plot in combination with Egger's test was applied to investigate possible publication bias.

Sub-group analysis was applied to test the hypothesis that some studies have higher or lower true effect sizes than others, using a fixed-effects model, while studies within sub-groups were pooled using the random-effects model. Subsequently, a Q-test based on the overall sub-group results was used to determine significant difference between the groups.

Specifically, sub-group analysis was performed according to: (a) the duration of intervention (12 weeks or < or >12 weeks); (b)

probiotic strain (*Lactobacillus rhamnosus* vs. other probiotics, and *L. rhamnosus* vs. other *Lactobacillus* strains); (c) type of nutrient (probiotics vs. synbiotics i.e., probiotics with prebiotics, probiotics vs. postbiotics); (d) the overall dose ( $>1 \times 10^{10}$  CFU and  $\leq 1 \times 10^{10}$  CFU); (e) age of participants in various groups ( $\geq$  or  $<12$ ,  $<12$ ,  $12-24$ ,  $24-36$ ,  $>36$  or  $<12$ ,  $12-36$ ,  $<36$ ,  $\geq$  or  $<36$ ) and sub-analysed when appropriate number of studies ( $>3$ ) were available; (f) the race of the participants (Asian vs. Caucasian), and (g) the overall quality of the study.

The meta-analysis was conducted in R version 4.3.0 using meta and meta for packages.<sup>35</sup>

## 2.7 | Risk of bias assessment

The Cochrane Collaboration tool was used for assessment of the risk of bias (RoB) for the RCTs, which covered sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases.<sup>36</sup> Two reviewers for each article evaluated the bias of the literature independently, rated as "high risk," "low risk," or "unclear risk." The overall RoB was the least favorable assessment across the domains of bias.<sup>37</sup> The RoB was evaluated separately for the studies included in meta-analysis ( $N=19$ ) and included in the systematic review ( $N=7$ ), and presented graphically as summary barplots and traffic light plots.

## 3 | RESULTS

The PRISMA diagram for study search was used for article selection. The flow chart shown in Figure 1 depicts the process by which the relevant studies were retrieved from the databases, assessed, and selected, or excluded. In total, 27 studies met the criteria for inclusion in the review, 20 of which focused on probiotics/synbiotics, and 7 on other forms of supplementation.

Table 1 shows the seven studies included in the systematic review of dietary modifications or interventions with supplements other than probiotics. These RCTs included interventions with prebiotics, vitamin D, oils and special infant formulas.

### 3.1 | Vitamin D

Four RCTs have investigated supplementation with vitamin D (cholecalciferol) in infants and children with AD, at various dosages, ranging from 1000 to 5000 IU per day.<sup>39-42</sup> Three studies reported significant (daily dose: 1000 IU,<sup>39</sup> 5000 IU,<sup>41</sup> 1600 IU<sup>42</sup> vitD3 in a fat soluble drop) and one nonsignificant (1000 IU<sup>40</sup> vitD3 in a cellulose capsule) improvement in AD symptoms in children taking vitamin D, in comparison with those taking a placebo (Table 1).

### 3.2 | Primrose oil

One study supplemented evening primrose oil in children with AD at two different dosages, 320 mg and 160 mg, for 8 weeks. Significant improvement in symptoms was reported in the high-dose group.<sup>43</sup>

### 3.3 | Dietary modifications

In one study of infants with AD,<sup>44</sup> conventional cow's milk formula (CMF) was replaced by a partially hydrolyzed whey and casein formula (phCMF) in the intervention group. An improved SCORAD was reported in the group of infants receiving phCMF compared to the control group that received CMF (Table 1).

### 3.4 | Prebiotics

One study, which investigated the supplementation of fructooligosaccharides, such as kestose, in infants with AD for 12 weeks, reported a significant improvement in SCORAD scores compared to infants in a placebo group that received maltose<sup>45</sup> (Table 1).

Meta-analysis was not conducted on the data derived from the above seven studies. Although four of the studies pertained to Vitamin D, the variety of the outcome measures did not permit a meta-analysis.

### 3.5 | Probiotics/synbiotics/postbiotic

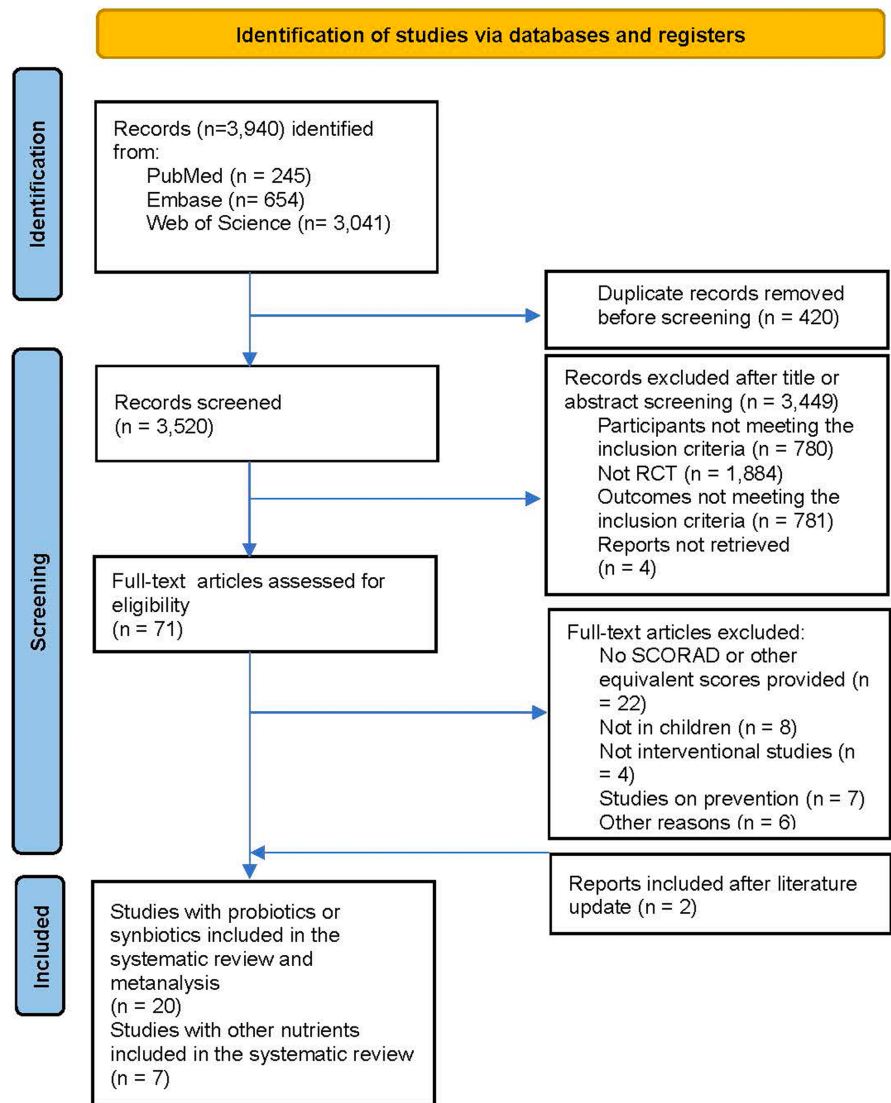
Twenty RCTs focusing on probiotics alone or in the form of synbiotics (probiotics with prebiotics) or postbiotics in a variety of combinations, have been included in the meta-analysis (Table 2). Seven of these were relevant to the use of *L. rhamnosus*, two of which reported a significant reduction in the SCORAD, compared to placebo,<sup>49,54</sup> three reported no effect, either when *L. rhamnosus* was used alone<sup>51</sup> or mixed with other *Lactobacillus* species<sup>50</sup> or with prebiotics.<sup>55,56,63</sup>

Six studies have used other *Lactobacillus* strains,<sup>46,53,57,58,61</sup> out of which five have reported a statistically significant benefit in comparison to the administration of placebo, while one<sup>64</sup> reported no difference.

A study used a mixture of various *Lactobacillus* strains, reporting a beneficial effect.<sup>60</sup> In three studies various *Lactobacillus* strains were combined with prebiotics (synbiotics),<sup>47,52,62</sup> and two of these studies demonstrated no effect, while one did.<sup>62</sup> Two studies used a mixture of *Lactobacillus* with other probiotics, with one study also including a prebiotic. Both reported benefit in comparison to the placebo.<sup>65,66</sup>

Two studies that used probiotics other than *Lactobacillus*, reported either no significant benefit<sup>59</sup> or only a borderline significant effect.<sup>48</sup>

**FIGURE 1** PRISMA flow diagram of selection of studies for systematic review on dietary intervention in children with atopic dermatitis. RCT, randomized controlled trial; SCORAD, scoring atopic Dermatitis.<sup>38</sup>



Three studies<sup>43,51,53</sup> utilized postbiotics, resulting in a significant reduction compared to the placebo. However, when compared to live cells,<sup>51,53</sup> no significant benefits were observed.

### 3.6 | Meta-analysis

Twenty studies on the use of probiotics/synbiotics/postbiotics, with a total of 1387 children, were included in the meta-analysis. The between-study heterogeneity variance was estimated at  $\tau^2=31.3$  (95% CI: 14.3–73.4), with an  $I^2$  value of 86% (95% CI: 80.4%–90.6%) and found to be significant ( $p<.001$ ).

The average estimated effect (mean difference, MD) on SCORAD score was 5.5 (95% CI: 2.8, 8.3), meaning that a significant positive effect, favoring the treatment groups, was demonstrated (assuming that higher change in scores represents better outcomes). The forest plot of the results is shown in Figure 2. The funnel plot (Figure 3) and the corresponding Egger's test ( $p<.001$ ) indicated publication bias.<sup>67</sup>

Three outlying studies were identified, assuming a random effects model.<sup>45,51,63</sup> On recalculation excluding these three outlying studies, the MD did not change significantly (MD=5.7, 95% CI: 3.7–7.6), but  $I^2$  heterogeneity was substantially reduced, from 86% to 51% ( $p=0.01$ , although the results of the Q-test remained significant), and  $\tau^2$  decreased to 8.2 (1.2, 39.3) ( $p<.001$ ). A forest plot of the meta-analysis without the outliers (their weights were set to zero) is depicted in Figure S1. The right side of Baujat plot (Figure S2) detected the same studies as influencing studies. One study<sup>50</sup> was particularly influential, since it had large impact on both the pooled effect (y-axis) and estimated heterogeneity (x-axis).

Sub-group analyses showed no statistically significant differences between sub-groups, as shown in Table 3. Although not significant, the effect size was lower (with 95% CI containing zero) for studies using *L. rhamnosus* than of those on other probiotics, and it was lower for studies using only probiotics than for those using synbiotics. In addition, there was a stronger effect for prolonged administration of probiotics and ages older than 36 months. The dose of the supplement did not exhibit a significant impact on the SCORAD change; it

**TABLE 1** Randomized controlled trials of the effect of nutrients, other than probiotics, on symptoms of atopic dermatitis (AD) in children, as measured by the Scoring Atopic Dermatitis (SCORAD) score or equivalent ( $N = 7$ ).

| Authors, year, country                                | Patients with AD: Intervention group (N) | Age (months) of participants in intervention group | Intervention                                                                 | Duration of intervention (weeks) | Patients with AD: control group (N) | Age (months) of participants in control group | Placebo                                                            | Change in SCORAD score                                                                                                                                                      |
|-------------------------------------------------------|------------------------------------------|----------------------------------------------------|------------------------------------------------------------------------------|----------------------------------|-------------------------------------|-----------------------------------------------|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Camargo et al., 2014, Mongolia <sup>39</sup>          | 47                                       | 108 ± 60                                           | Oral cholecalciferol (1000 IU/day)                                           | 4                                | 47                                  | 108 ± 60                                      | Identical placebo drop                                             | EASI adjusted mean change 6.5 in intervention vs. -3.3 in control group ( $p = .04$ )                                                                                       |
| Sanchez-Armendariz et al., 2018; Mexico <sup>40</sup> | 33                                       | 154.8 ± 127.2                                      | Vitamin D3 capsule (5000 IU/day)                                             | 12                               | 32                                  | 146.4 ± 25.8                                  | Identical cellulose capsule                                        | Patients with serum levels of 25 (OH)D of ≥20 ng/mL (20–29 ng/mL: 21.4 ± 11; 19.6 ± 11.6) had lower SCORAD than those with levels of <20 ng/mL (36.3 ± 13.8) ( $p < .001$ ) |
| Corrales et al., 2019, Canada <sup>41</sup>           | 21                                       | 97.2 ± 49.2                                        | Oral Vitamin D3 or cholecalciferol (2000 IU/day)                             | 12                               | 24                                  | 102 ± 61.2                                    | Identical placebo drop                                             | Decrease of 15.35 (9.71) in intervention vs. 15.13 (8.97) in control group ( $p = .7$ )                                                                                     |
| Mansour et al., 2020, Egypt <sup>42</sup>             | 44                                       | 144 ± 57                                           | Oral vitamin D3 1600 IU/day plus twice daily topical 1% hydrocortisone cream | 12                               | 42                                  | 132 ± 66                                      | Identical placebo plus twice daily topical 1% hydrocortisone cream | Mean EASI score 20.42 (14.6) in intervention vs. 27.47 (10.11) in placebo group ( $p = .035$ )                                                                              |
| Chung et al., 2018 <sup>43</sup>                      | 20                                       | 68.4 ± 70.8                                        | Evening primrose oil 320 mg/day                                              | 8                                | 20                                  | 64.8 ± 58.8                                   | Evening primrose oil 160 mg/day                                    | Mean EASI score in 320 mg group ( $p = .000$ ), but not in the 160 mg group ( $p = .55$ )                                                                                   |
| Jin et al., 2011, China <sup>44</sup>                 | 56                                       | 4.6 (range 1–6)                                    | Partially hydrolyzed whey and casein formula (pHCMF) <sup>a</sup>            | 12                               | 30                                  | 4.6 (range 1–6)                               | Conventional cow's milk formula (CMF)                              | Decrease pHCMF group: 13.00 (0–84) compared with CMF group: 28.00 (0–64) ( $p = .001$ )                                                                                     |
| Shibata et al., 2009, Japan <sup>45</sup>             | 15                                       | 17.0 ± 9.4                                         | Kestose                                                                      | 12                               | 14                                  | 17.4 ± 9.1                                    | Maltose                                                            | Kestose group: mean 19.5 (range 15.6–22.0); maltose group 37.5 (range 25.5–43.5), $p < .001$                                                                                |

Abbreviations: EASI, Eczema Area and Severity Index; pHCMF, partially hydrolyzed Cow's Milk Formula; SCORAD, SCORing Atopic Dermatitis.

<sup>a</sup>Morinaga, 5-Chome, Higashihara, Zama-city, Japan.

**TABLE 2** Randomized controlled trials of the effect of probiotics, synbiotics (light grey) or postbiotics (dark grey) on the symptoms of atopic dermatitis (AD) in children, as measured by the measured by the Scoring Atopic Dermatitis (SCORAD) score (N = 20).

| Authors, year, country                            | Patients with AD: intervention group (N) | Age (months)       | Intervention                                                                                                                                                       | Duration of intervention (weeks) | Patients with AD: control group (N) | Age (months)       | Placebo                          | Change in SCORAD score                                                                                              |
|---------------------------------------------------|------------------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|-------------------------------------|--------------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Ahn et al., 2019, South Korea <sup>46</sup>       | 41                                       | 57.6 ± 27.6        | <i>Lactobacillus pentosus</i> (10 <sup>10</sup> CFU)                                                                                                               | 12                               | 41                                  | 64.8 ± 36          | Identical placebo material       | Probiotic lower than placebo group in IgE sensitized AD (p = .019)                                                  |
| D'Auria et al., 2021, Italy <sup>47</sup>         | 26                                       | 12 (range 6–16)    | Heat-killed <i>Lactobacillus paracasei</i> CBA L74 with rice-dried powder                                                                                          | 12                               | 27                                  | 12 (range 8–23)    | Rice-dried powder                | No significant difference between groups                                                                            |
| Bodemer et al., 2017, France <sup>48</sup>        | 88                                       | 24                 | Capsules containing 3.5 mg bacterial lysate OM-85 (21 strains from 8 common respiratory pathogenic microorganisms) <sup>49</sup>                                   | 36                               | 82                                  | 24                 | Identical placebo capsule        | Borderline difference between OM-85 and placebo group (p = .05)                                                     |
| Carucci et al., Italy <sup>49</sup>               | 46                                       | 18.9 (8.6)         | <i>Lactocaseibacillus rhamnosus</i> GG (1 × 10 <sup>10</sup> CFU)                                                                                                  | 16                               | 45                                  | 16.4 (7.4)         | Identical placebo capsule        | Rate of patients achieving MCID <sup>50</sup> higher in intervention group (p < .05)                                |
| Chernyshov et al., 2009, Ukraine <sup>50</sup>    | 58                                       | 18.43–11.94 (2–46) | Lacidof I One capsule/day containing 95% <i>Lactobacillus rhamnosus</i> R0011 and 5% <i>Lactobacillus helveticus</i> R0052 (one capsule = 2 × 10 <sup>9</sup> CFU) | 4                                | 28                                  | 18.21–10.51 (2–44) | Identical placebo capsule        | No significant change in either group                                                                               |
| Folster-Holst et al., 2006, Germany <sup>51</sup> | 26                                       | 16.5 (range 1–53)  | <i>Lactobacillus rhamnosus</i> strain GG (5 × 10 <sup>9</sup> CFU twice/day)                                                                                       | 8                                | 27                                  | 21 (range 5–55)    | Identical to placebo material    | No significant difference between groups                                                                            |
| Gerasimov et al., 2010, Ukraine <sup>52</sup>     | 43                                       | 12–36              | <i>Lactobacillus acidophilus</i> DDS-1, <i>B. lactis</i> UABLA-12 with fructo-oligosaccharide (5 × 10 <sup>9</sup> CFU twice/daily)                                | 8                                | 47                                  | 12–36              | Pure powder of rice maltodextrin | Reduction of 33.7% in the probiotic and 19.4% in the placebo group (p = .001)                                       |
| Han et al., 2019, South Korea <sup>53</sup>       | 58                                       | 55.2 (±39.6)       | <i>Lactobacillus plantarum</i> C/JLP133 (0.5 × 10 <sup>10</sup> CFU twice/daily)                                                                                   | 12                               | 60                                  | 61.2 (±39.6)       | Identical placebo material       | Improvement (7.6 ± 12.0) in probiotic compared with placebo group (2.6 ± 10.1) (p = .041)                           |
| Jeong et al., 2019, South Korea <sup>54</sup>     | 50                                       | 68.04 (±39.6)      | Heat-killed bacteria <i>Lactobacillus rhamnosus</i> RHT3201 (10 <sup>10</sup> CFU/day)                                                                             | 12                               | 50                                  | 63.96 (±30.72)     | Identical placebo material       | Significantly greater reduction in postbiotic (–13.89 ± 10.05) than in the control group (–8.37 ± 9.95) (p = .0283) |

(Continues)

TABLE 2 (Continued)

| Authors, year, country                          | Patients with AD: intervention group (N) | Age (months)                                                   | Intervention                                                                                                                                                                        | Duration of intervention (weeks) | Patients with AD: control group (N) | Age (months)    | Placebo                                                                                                                     | Change in SCORAD score                                                                                                                                                                                                                        |
|-------------------------------------------------|------------------------------------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|-------------------------------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Navarro-López et al., 2018, Spain <sup>55</sup> | 26                                       | 112.2 (±42.96)                                                 | <i>Bifidobacterium lactis</i> CECT8145<br>Blongum CECT7347 (10 <sup>9</sup> CFUs)<br><i>Lactobacillus casei</i> CECT 9104<br>(1:1:1 ratio) freeze-dried powder with maltodextrin    | 12                               | 24                                  | 107.52 (±47.28) | Maltodextrin                                                                                                                | Significantly greater reduction in probiotic (−27.0) (−31.1 to −22.8) than in placebo group: −7.8 (−11.9 to −3.6) ( $p = .0376$ )                                                                                                             |
| Passeron et al., 2006, France <sup>56</sup>     | 17                                       | 5.38 (2–11)                                                    | <i>Lactobacillus rhamnosus</i> (Lcr35 1.2 × 10 <sup>9</sup> CFU) + prebiotic-specific preparation and metabolites secreted by the bacterium (synbiotic group)                       | 12                               | 22                                  | 6.33 (2–12)     | Skimmed milk powder (0.344 g—bovine protein 33%, lactose 52%, potato starch (0.759 g) and lactose (0.397 g) (control group) | Reduction in both groups. No significant difference between groups (synbiotic, $p = .07$ ; control, $p = .005$ )                                                                                                                              |
| Prakoeswa et al., 2022, Indonesia <sup>57</sup> | 12                                       | 68.4 (±55.2)                                                   | Capsule containing <i>Lactobacillus plantarum</i> IS-10506 (10 <sup>10</sup> cfu/day)                                                                                               | 12                               | 10                                  | 68.4 (±48.72)   | Identical placebo cellulose capsule                                                                                         | Decrease in probiotic (−22.04 ± 8.817) compared with placebo group (−18.533 ± 14.2) ( $p = .000$ )                                                                                                                                            |
| Rather, et al., 2021, South Korea <sup>58</sup> | 30 + 30                                  | Two sub-groups (a) 110.28 ± 59.64 (b) 110.16 ± 54.36           | Sachet 30 min after meal with (a) <i>Lactobacillus sakei</i> proBio65 (live) (b) ghost <i>L. sakei</i> proBio65 (dead cells)                                                        | 12                               | 30 + 30                             | 121.2 ± 53.88   | Identical placebo sachet                                                                                                    | Significant decrease in live cells ( $p = .0015$ ) and dead cells sub-groups ( $p = .0017$ ) but not in placebo group                                                                                                                         |
| Shafiei et al., 2011, Iran <sup>59</sup>        | 18                                       | 14.7 (±6)                                                      | Seven strains of probiotics 10mg of 1 × 10 <sup>9</sup> CFU plus prebiotic (990mg fructo-oligosaccharides)                                                                          | 8                                | 18                                  | 15.4 (±8.4)     | 1000 mg sucrose                                                                                                             | No statistical difference between groups                                                                                                                                                                                                      |
| Wang et al., 2015, Taiwan <sup>60</sup>         | 165                                      | 3 sub-groups (a) 94.32 ± 45.48 (b) 90.6 ± 54 (c) 100.08 ± 45.6 | (a) <i>Lacto bacillus paracasei</i> GMNL-133 (LP) (2 × CFU) (b) <i>Lactobacillus fermentum</i> GM090 (LF) (2 × 10 <sup>9</sup> CFU) (c) LP and LF mixture (4 × 10 <sup>9</sup> CFU) | 12                               | 55                                  | 96.48 (±47.64)  | Identical placebo capsule                                                                                                   | Significant improvement in all 3 probiotic sub-groups ( $p < .001$ ) 1 month after discontinuation of probiotics decrease in scores-difference from placebo group remained significant, after adjustment for age, gender, topical steroid use |

TABLE 2 (Continued)

| Authors, year, country                      | Patients with AD: intervention group (N) | Age (months)            | Intervention                                                                                                   | Duration of intervention (weeks) | Patients with AD: control group (N) | Age (months)          | Placebo                                                  | Change in SCORAD score                                                                                                                                                                                                                     |
|---------------------------------------------|------------------------------------------|-------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------|-------------------------------------|-----------------------|----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Woo et al., 2010, South Korea <sup>61</sup> | 41                                       | 75.6 (range 27.6–117.6) | <i>Lactobacillus sakei</i> KCTC 10755 BP ( $5 \times 10^9$ CFU)                                                | 12                               | 34                                  | 69.6 (range 24–116.4) | Matched-placebo                                          | Mean change of 13.1 points (95% CI 17.5 to 8.6) in probiotic group vs. 5.2 points (95% CI 8.8–1.5 points) in placebo group ( $p = .008$ )                                                                                                  |
| Wu et al., 2011, Taiwan <sup>62</sup>       | 27                                       | 93.6 ± 42               | Capsule containing <i>Lactobacillus salivarius</i> PM-A0006 ( $2 \times 10^9$ CFU) plus fructo-oligosaccharide |                                  | 27                                  | 82.8 (±40.8)          | Capsule containing prebiotic plus fructo-oligosaccharide | Probiotic group 27.4 ± 12.7 vs. placebo group 36.3 ± 14.9 ( $p = .022$ ) Significant decrease over time in both groups ( $p < .001$ ). Reduction rate of >50%: in placebo group ( $p = .006$ ) group and in probiotic group ( $p = .068$ ) |
| Wu et al., 2017, Taiwan <sup>63</sup>       | 33                                       | 18 ± 13.2               | ComProbi capsule containing 350mg <i>Lactobacillus rhamnosus</i> (MP108) plus maltodextrin                     | 8                                | 33                                  | 21.6 ± 13.2           | Identical capsule containing Maltodextrin                | No significant difference between groups                                                                                                                                                                                                   |
| Yan et al., 2019, Taiwan <sup>64</sup>      | 62                                       | 13.48 ± 7.72            | <i>Lactobacillus paracasei</i> ( $1 \times 1.010$ equivalent CFU)                                              | 16                               | 61                                  | 14.62 ± 7.88          | Maltodextrin                                             | No significant difference between groups                                                                                                                                                                                                   |
| Yesilova et al., 2012, Turkey <sup>65</sup> | 20                                       | 12–156                  | Four types of probiotic bacteria <sup>b</sup> ( $2 \times 10^9$ )                                              | 10                               | 20                                  | 12–156                | Skimmed milk powder and dextrose                         | Change from 35.4 ± 13.4 to 12.4 ± 7.2 in probiotic group, and from 28.1 ± 6.1 to 15.3 ± 5.1 in placebo group ( $p = .0015$ )                                                                                                               |

Abbreviation: CFU, colony-forming units.

<sup>a</sup>*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella ozaenae* and *pneumoniae*, *Staphylococcus aureus*, *Streptococcus viridans* and pyrogenes, *Neisseria catarrhalis*.<sup>b</sup>*Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius*.<sup>c</sup>MCID: Minimum Clinically Important Difference change for Atopic Dermatitis patients equal to a reduction of ≥8.7 points on the SCORAD index.

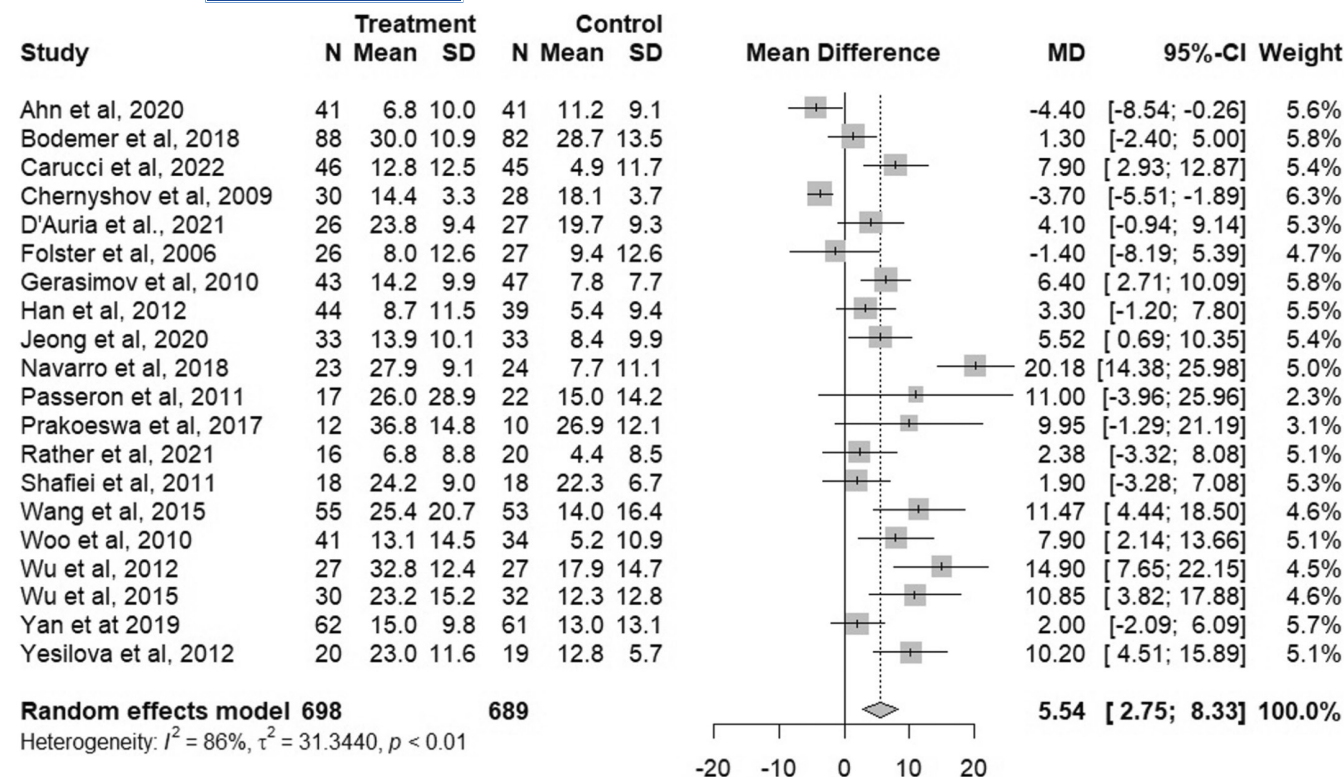


FIGURE 2 Forest plot of the meta-analysis of studies of the effect of probiotics on changes in the Scoring Atopic Dermatitis (SCORAD) scores in children with atopic dermatitis (20 studies, 1387 observations).

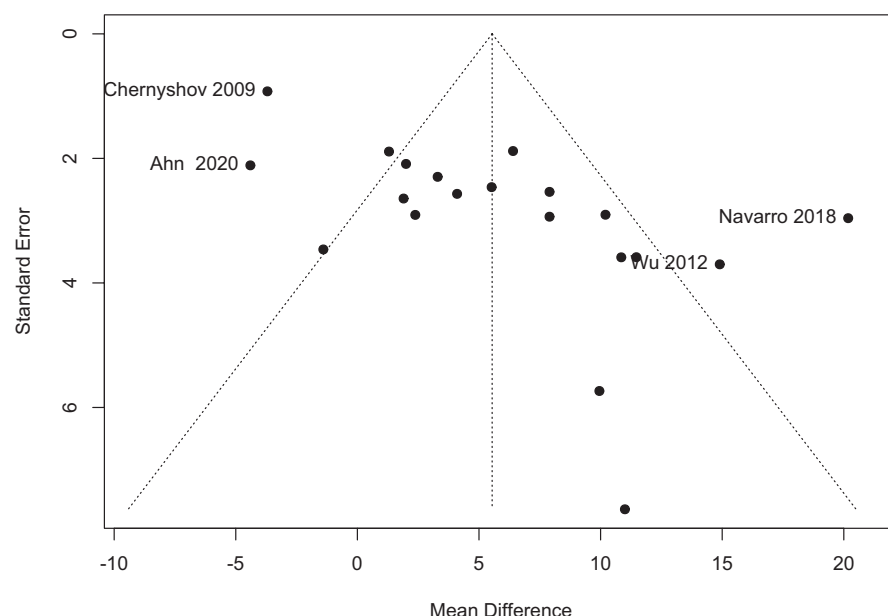


FIGURE 3 Funnel plot of the meta-analysis of studies of the effect of probiotics on changes in the Scoring Atopic Dermatitis (SCORAD) score in children with atopic dermatitis (20 studies, 1387 observations), representing publication bias. Studies outside the 95% confidence interval (CI) are labeled.

is noteworthy that lower doses were associated with a higher change, though this observation did not reach statistical significance ( $p=.15$ ). For studies with a high RoB the effect size was particularly high. Forest plots of all the sub-group analyses are shown in (Figures S3–S7). According to the meta-regression results, publication year was

not a significant effect size predictor ( $p=.8$ ). The bubble plot, which shows the estimated regression slope ( $\beta=0.04$ ,  $SD=0.3$ ) and the effect size of each study is reported in Figure S8.

RoB judgements for the studies are shown in Figures S9 and S10 (meta-analysis) and S11 and S12 (systematic review).

**TABLE 3** Randomized controlled trials of the effect of probiotics, postbiotics or synbiotics on the symptoms of atopic dermatitis (AD) in children, as measured by the measured by the Scoring Atopic Dermatitis (SCORAD) score: Sub-group analyses (20 studies).

| Sub-groups                     | Number of studies | MD (95% CI)        | I <sup>2</sup> | p-value |
|--------------------------------|-------------------|--------------------|----------------|---------|
| Type of nutrient               |                   |                    |                | p = .7  |
| Probiotic                      | 11                | 5.0 (0.8, 9.1)     | 90%            |         |
| Postbiotic                     | 3                 | 4.6 (1.0, 8.2)     | -              |         |
| Synbiotic                      | 6                 | 7.1 (2.9, 11.2)    | 62%            |         |
| Type of probiotics             |                   |                    |                | p = .5  |
| <i>Lactobacillus rhamnosus</i> | 6                 | 4.1 (-1.1, 9.2)    | 88%            |         |
| Other material                 | 14                | 6.1 (2.8, 9.5)     | 82%            |         |
| Duration of intervention       |                   |                    |                | p = .38 |
| <12 weeks                      | 7                 | 5.2 (0.1, 10.3)    | 91%            |         |
| 12 weeks                       | 9                 | 7.1 (2.1, 12.0)    | 85%            |         |
| >12 weeks                      | 4                 | 3.29 (0.7, 5.9)    | 37%            |         |
| Ethnicity                      |                   |                    |                | p = .9  |
| Asian                          | 11                | 5.3 (2.0, 8.6)     | 73%            |         |
| Caucasian                      | 9                 | 5.8 (0.9, 10.6)    | 92%            |         |
| Dose of supplement             |                   |                    |                | p = .15 |
| >1 × 10 <sup>10</sup> CFU      |                   | 3.53 (0.40; 6.66)  | 68%            |         |
| ≤1 × 10 <sup>10</sup> CFU      | 9                 | 8.65 (2.49; 14.81) | 94%            |         |
| Age of participants            |                   |                    |                | p = .18 |
| ≤36 months                     | 11                | 3.9 (0.9–6.9)      | 85%            |         |
| >36 months                     | 9                 | 7.8 (2.9–12.8)     | 85%            |         |
| Risk of bias                   |                   |                    |                | p = .2  |
| Low                            | 6                 | 6.1 (3.1, 9.1)     | 41%            |         |
| Moderate                       | 11                | 3.3 (-0.3, 6.9)    | 86%            |         |
| High                           | 4                 | 11.2 (3.3, 19.2)   | 85%            |         |

Abbreviations: MD, mean difference; 95% CI, 95% confidence interval; I<sup>2</sup>, I<sup>2</sup> heterogeneity.

## 4 | DISCUSSION

This systematic review, to the best of our knowledge, is the first to investigate the effect of dietary interventions, including dietary modifications and food supplements, in children with AD without food allergy. It included 27 RCTs of interventions that aimed to improve AD symptoms, as evaluated using the SCORAD score or another scoring system converted to SCORAD when possible. Gut microbiota modification, to date, appears to have attracted the major interest of researchers, with 20 RCTs involving intervention with probiotics and postbiotics alone or in combination with prebiotics.

Our meta-analysis of the 20 studies, including 1387 infants or children with AD, showed that supplementation with probiotics may benefit SCORAD outcomes, regardless of the race of the population under study.

Probiotics are live organisms, that when administered in sufficient amounts, modulate the intestinal microbiome and confer several health benefits on the host, including enhancing immune function by improving the integrity of the intestinal barrier.<sup>68,69</sup> Dysbiosis in AD has been thoroughly characterized<sup>70</sup> and various trials explored the effectiveness of pre and postbiotics in reducing the allergic phenomena and the severity of AD.<sup>17,71–73</sup>

In our meta-analysis, we observed a trend toward a higher effect when: (a) the intervention period is longer than 12 weeks, (b) the children are older than 36 months of age at inclusion to the study, (c) probiotics other than *L. rhamnosus* are used, and (d) probiotics are used in combination with prebiotics, in the form of synbiotics.

The age group of children with AD, for use of probiotic supplementation has gained the attention of several studies, but the results have been contradictory. A meta-analysis published in 2017 by Huang and colleagues on the efficacy of probiotics in 1070 children and adolescents with AD aged ≤18 years, concluded that the benefit was higher in children older than 12 months.<sup>74</sup> The lower efficacy of probiotics in infants aged under 1 year was further supported by the meta-analyses conducted by Jiang and colleagues<sup>75</sup> and Husein-El Ahmed and colleagues,<sup>76</sup> but the authors reported a high degree of diversity among the studies with participants aged <1 year. In contrast, Zhao and colleagues<sup>77</sup> supported that supplementation in infants under 1 year might be more effective. In our systematic review, we detected improved SCORAD scores as an effect of administration of probiotics throughout childhood, but with a more pronounced effect in children aged older than 36 months. Recent research describes the first 1000 days of life as the optimum window for preventive interventions impacting the microbial colonization.<sup>78</sup>

The trend toward a better therapeutic response, though, after the third year of life is possibly indicative of the slow transformation of the gut microbiota in infants from a “maternal-like,” taxonomically and functionally, state during the first 2 years of life<sup>79</sup> toward an adult-like state during the age period 3–5 years.<sup>80</sup> This more effective response might also be an indication of the parallel ongoing maturation of the skin<sup>81</sup> and the immune system.<sup>82</sup>

An important factor affecting the efficacy of the probiotics is the duration of treatment, but differences were observed among the studies. We observed that a period of administration of more than 12 weeks might benefit the SCORAD outcomes, but the differences in this outcome did not reach statistical significance. The data of Jiang and colleagues supported the theory that the benefit might increase after 8 weeks of supplementation, but, again, not to a significant degree.<sup>75</sup> Conversely, Zhao and colleagues in their meta-analysis including infants aged  $\leq 36$  months of age with moderate-to-severe AD symptoms, a supplementation of preparations containing *Lactobacillus* given for periods of  $< 8$  weeks is significantly more effective.<sup>77</sup> However, our study encompassed a wider age range, including older children. It is possible that a more extended period of probiotic administration may be required for enhanced effectiveness, but further investigation is necessary in the future.

Some studies concluded that the response to probiotic supplementation might be determined by the phylogenetic characteristics of the populations investigated,<sup>83</sup> as they observed a significant reduction in SCORAD scores in Asian, but no effect in European participants.<sup>74</sup> This observation was not supported by our meta-analysis, as no difference in effect was demonstrated between Asian and European participants.

Many researchers used *L. rhamnosus* for their interventions, but we determined no higher effectiveness in its capacity to reduce the SCORAD score in children with AD, in comparison to other probiotics or other *Lactobacillus* strains. On the contrary, we observed a nonsignificant trend towards greater effectiveness of other strains of *Lactobacillus* or other probiotics used in interventions to treat AD. Our findings are thus in accordance with Huang and colleagues, whose data supported that *L. rhamnosus* is not effective for improvement of SCORAD scores in children with AD, but that a significant benefit may be provided by *L. fermentum*, *L. salivarius*, and a mixture of different *Lactobacillus* strains.<sup>74</sup> Jiang and colleagues also reported an apparent but nonsignificant, beneficial effect on AD outcomes when mixed strains are administered in comparison to single-strain probiotics.<sup>75</sup>

Prebiotics are non-digestible food compounds that are fermented by intestinal microbiota to produce metabolites such as short-chain fatty acids and are potentially able to confer health benefits to the host.<sup>84</sup> To examine the theory that probiotics might function better when combined with prebiotics<sup>85,86</sup> we compared outcomes from studies using synbiotics and those using probiotics only. In line with the meta-analysis of Chang and colleagues that supported the greater effect of synbiotic supplementation, in comparison to the probiotics alone, after the first year of life, we identified a nonsignificant trend in favor of synbiotics. As such, the use

of prebiotics to enhance commensal bacterial growth, microbiome diversity, and the overall health of the host,<sup>87</sup> is still unclear due to the limited number of studies in infants and children,<sup>45</sup> thus no clear outcomes are permitted.

Postbiotics are defined as a preparation of inanimate microorganisms and/or their components that confer a health benefit on the host.<sup>88</sup> They refer to the metabolites or byproducts produced by probiotics as they carry out their actions in the gut, often through processes like fermentation.<sup>89</sup> Postbiotics present promising alternatives to probiotics, as they mitigate the risk associated with using live microbial strains.<sup>88</sup> In the case of AD it has been hypothesized that postbiotics influence the molecular composition of enterocytes, leading to the closure of the intestinal barrier and providing antibacterial activity.<sup>89</sup> The systematic review and meta-analysis of Carol et al. which included 9 RCTs with postbiotics in a total of 793 children with AD, concluded that there was low-certainty evidence regarding the therapeutic effectiveness of *Lactobacillus paracasei* GM080.<sup>69</sup> Similarly, we were unable to identify significant beneficial effects of postbiotics in our meta-analysis.

Furthermore, despite the substantial variation in the doses employed for gut microbiota manipulation, ranging from  $10^9$  to  $10^{10}$  CFU/day, no significant differences were observed in their effectiveness concerning SCORAD outcomes. This finding is consistent with a recent meta-analysis conducted by Xue et al., encompassing 1000 patients AD, which concluded that the probiotic's benefit persists irrespective of the quantity used.<sup>71</sup>

Vitamin D, which acts like a pleiotropic hormone, has been suggested to benefit skin immunity, barrier function, and inflammation due to its capacity to regulate the proliferation and differentiation of keratinocytes.<sup>90,91</sup> Furthermore, vitamin D demonstrates pluripotent effects on functions within the adaptive immune system, including the activation of T-cells and maturation of dendritic cells.<sup>92,93</sup> Vitamin D was used in four RCTs in infants and children and provided consistent benefit, regardless of the dose, when used in a fat-soluble matrix,<sup>39,41,42</sup> but not when used in a water-soluble (cellulose) capsule.<sup>40</sup> In addition, a meta-analysis conducted by Kim and colleagues supported vitamin D supplementation in the treatment of AD in adults.<sup>94</sup> Future research should take into consideration the baseline serum vitamin D levels of the population under study.<sup>95,96</sup>

Among the hypotheses on the pathogenesis of AD is a deficiency of essential fatty acids in the skin.<sup>29,97</sup> Fatty acid levels have a direct impact on the impairment or repair of the functioning of the epidermal barrier. Therefore it is considered important to maintain optimal levels of monounsaturated fatty acids (MUFA) and an equilibrium of omega-3 and omega-6 fatty acids for the synthesis of long-chain fatty acids, specifically C20 eicosanoic and C22 docosahexaenoic acids, as well as the subsequent formation of bioactive lipids like prostaglandins.<sup>97–99</sup> Evening primrose oil, extracted from the flowering plant *Oenothera biennis*, is rich (8%–10%) in gamma-linolenic acid (GLA), an  $\Omega$ -6 fatty acid, offering an anti-inflammatory action.<sup>100</sup> Supplementation of evening primrose oil in children was shown to improved SCORAD outcomes in a single RCT.<sup>43</sup> Fatty acids, and

especially omega-3 fatty acids, have been used for the prevention of AD in RCTs, but their use in the treatment of AD has been limited and applied in adults.<sup>20,101</sup>

Finally, information on the possible benefits of dietary modifications for the management of AD during infancy or childhood is scarce. Most relevant studies focused on food elimination and highlighted the fact that these should be considered carefully and applied under strict indications, as such dietary manipulation may increase the risk of both nutritional deficiencies and the future presentation of food allergy.<sup>24,25,102</sup> Only one study was identified in the current study: partially hydrolyzed cow's milk (pHMF) infant formula showed a favorable effect as compared to conventional cow's milk formula.<sup>44</sup>

Our systematic review and meta-analysis had certain limitations. First, the effect size on the minimal clinically important difference (MCID) of SCORAD was lower than 8.7, which indicates inadequate clinical responsiveness of the intervention.<sup>103</sup> Nevertheless, probiotics supplementation could be used as an add-on therapy to the maintenance therapy consisting of emollients and gentle skin care.

It may also be regarded as an adjunctive therapy to decrease the frequency of using anti-inflammatory topical agents, systemic anti-inflammatory or immunosuppressive treatments, and other biologicals, which are often effective but costly.<sup>104</sup> However, further exploration is needed to confirm this potential benefit. Second, although we attempted to minimize heterogeneity and publication bias in the meta-analysis, significant heterogeneity among the RCTs remained evident. We were able, however, to detect the most influential outliers, after the removal of which, heterogeneity became moderate with a stable effect size. Differences in intervention methods (single, or mixture of probiotic strains, or combined with prebiotics or postbiotics and dosage), duration of intervention, and study population (race, age), contributed to the heterogeneity. The low number of studies in the various sub-group analyses performed reduced the confidence associated with the data interpretation and increased the heterogeneity and publication bias. Finally, for the same reason, we could not draw robust conclusions as to which probiotic strain or strains, or which synbiotic should be given to children with AD, at which age, and for how long, in order to lower SCORAD score maximally. In the past, the different species used in the interventions were collectively categorized under the genus of *Lactobacillus*. However, recent advancements in nomenclature have led to their dispersion into new classifications.<sup>105</sup> Only one of the included studies adopted the updated nomenclature, while we retained the terminology originally employed in the original articles. Moreover, we could not conduct meta-analysis of the data from the relevant studies with vitamin D in children, because of the different, and non-comparable, ways of describing the outcomes. Another aspect which was not covered in the meta-analysis are studies where potential factors commonly omitted by patients were investigated by exposure studies. One example is the dietary avoidance of sugar based on the belief that it might provoke AD signs. Although the short-term effect of sugar was excluded in a DBPC trial,<sup>106</sup> the long-term effect on skin microbiome has not been studied yet, and

cannot be excluded as the sugar dose influences the gut microbiota synthesis.<sup>107</sup>

## 5 | CONCLUSIONS

The results of this systematic review and meta-analysis highlight the intensive efforts of the research community to find dietary means to alleviate the symptoms of AD in children without FA. To date, vitamin D, and probiotics have been more extensively examined, and both show promise in moderating skin symptoms as measured by SCORAD or an equivalent measurement.

From our meta-analysis on the use of probiotics, a consistent trend was revealed regarding the alleviation of AD symptoms in children without food allergy, the mechanisms likely being the manipulation of gut microbiota with probiotics, with subsequent eubiosis. Regarding the appropriate age for intervention and its optimal duration, it is apparent that adequately powered RCTs, involving stratified populations and specific interventions and using standardized measures will be needed to draw firm conclusions about the species of probiotics and the prebiotics to be combined, dosages, and treatment periods, and at which age of life the greatest efficacy will be achieved. Alternatively, with such a multifactorial disease and with such a multitargeted intervention, we might need to proceed by designing studies where we should use the "omics" (transcriptomics, proteomics, and metabolomics) in order to acquire knowledge of an etiological interaction and a significant outcome.

## AUTHOR CONTRIBUTIONS

EV conceptualized and supervised the study, interpreted the data, and wrote the first draft of the manuscript. ND, GNK, TZ, IA, CA, RBC, CB, AC, VDC, GF, KL, AM, NAM, NGP, DP, CP, FRW, IS, ST, AKB, LOM, and CV performed literature search, extracted data and performed quality assessment and gave a significant contribution to data interpretation. AC performed statistical analysis and gave a significant contribution to data interpretation. ND, GNK, IS, LOM, and CV gave a significant contribution in data interpretation and discussion in their field of expertise. GPM conceptualized and supervised the study, interpreted the data, and gave a significant contribution in his field of expertise. All authors critically reviewed the manuscript.

## AFFILIATIONS

<sup>1</sup>Department of Nutritional Sciences and Dietetics, International Hellenic University, Thessaloniki, Greece

<sup>2</sup>Pediatric Area, Fondazione IRCCS Ca' Granda—Ospedale Maggiore Policlinico, Milan, Italy

<sup>3</sup>Occupational Medicine Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

<sup>4</sup>Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece

<sup>5</sup>Department of Allergy and Clinical Immunology, 424 General Military Training Hospital, Thessaloniki, Greece

<sup>6</sup>Institute of Allergology, Charité - Universitätsmedizin Berlin, Berlin, Germany

<sup>7</sup>Allergy and Immunology, Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Berlin, Germany

<sup>8</sup>Department of Clinical Sciences and Community Health, University of Milan, Milano, Italy

<sup>9</sup>Department of Translational Medical Science, University of Naples "Federico II", Naples, Italy

<sup>10</sup>Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

<sup>11</sup>Department of Food Safety, Nutrition and Veterinary Public Health, Istituto Superiore di Sanità - Italian National Institute of Health, Rome, Italy

<sup>12</sup>Department of Pediatrics, "Karamandaneio" Children's Hospital of Patra, Patras, Greece

<sup>13</sup>Faculty of Medicine, Institute of Biomedicine, Research Centre for Integrative Physiology and Pharmacology and Nutrition and Food Research Center, University of Turku, Turku, Finland

<sup>14</sup>Department of Clinical and Experimental Medicine, Section of Pediatrics, University of Pisa, Pisa, Italy

<sup>15</sup>Medical School, University of Cyprus, Nicosia, Cyprus

<sup>16</sup>Department of Interdisciplinary Life Sciences, Messerli Research Institute, University of Veterinary Medicine, Vienna, Austria

<sup>17</sup>Institute of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria

<sup>18</sup>Royal Brompton & Harefield Hospitals, Part of Guys & St Thomas NHS Foundation Trust, London, UK

<sup>19</sup>Department of Inflammation & Repair, Imperial College of London, London, UK

<sup>20</sup>Child Health Department, University of Ioannina School of Medicine, Ioannina, Greece

<sup>21</sup>Department of Public Health and Community Medicine, Sahlgrenska Academy, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

<sup>22</sup>APC Microbiome Ireland, Department of Medicine, School of Microbiology, University College Cork, Cork, Ireland

<sup>23</sup>Pediatric Allergy and Clinical Immunology, Children's Hospital Colorado/University of Colorado, Aurora, Colorado, USA

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## CONFLICT OF INTEREST STATEMENT

George N. Konstantinou is or recently was a speaker and/or advisor for and/or has received research funding from AstraZeneca, Chiesi, GSK, Menarini, Novartis, Nutricia, Pfizer, Sanofi, Vianex. T. Zuberbier has received institutional funding for research and/or honoraria for lectures and/or consulting from Amgen, AstraZeneca, AbbVie, ALK, Almirall, Astellas, Bayer Health Care, Bencard, Berlin Chemie, FAES, HAL, Henkel, Kryolan, Leti, L'Oreal, Meda, Menarini, Merck, MSD, Novartis, Pfizer, Sanofi, Stallergenes, Takeda, Teva and UCB, Uriach. IC Bocsan has received honoraria for lectures from AstraZeneca,

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

Emilia Vassilopoulou  <https://orcid.org/0000-0002-2665-5908>

George N. Konstantinou  <https://orcid.org/0000-0003-1371-6764>

Torsten Zuberbier  <https://orcid.org/0000-0002-1466-8875>

Gavriela Feketea  <https://orcid.org/0000-0001-9026-2597>

Nikolaos G. Papadopoulos  <https://orcid.org/0000-0002-4448-3468>

Franziska Roth-Walter  <https://orcid.org/0000-0001-5005-9228>

Isabel Skypala  <https://orcid.org/0000-0003-3629-4293>

Sophia Tsabouri  <https://orcid.org/0000-0001-7584-5401>

Liam O'Mahony  <https://orcid.org/0000-0003-4705-3583>

Carina Venter  <https://orcid.org/0000-0002-7473-5355>

Gregorio Paolo Milani  <https://orcid.org/0000-0003-3829-4254>

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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