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Effects of probiotics for the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials

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ABSTRACT

Background: The effects of probiotics on the treatment of atopic dermatitis (AD) are inconclusive.

Objective: To determine the clinical effect of probiotics in the management of AD overall and in different age groups.

Methods: A comprehensive search of databases through December 2013 was performed. For this meta-analysis, randomized controlled trials measuring the treatment effects of probiotics or synbiotics in patients diagnosed with AD were included. The primary outcome was a difference in Scoring of Atopic Dermatitis (SCORAD) values between the treatment and placebo groups overall and in different age populations.

Results: Twenty-five randomized controlled trials ($n = 1,599$) were available for this meta-analysis. Significant differences in SCORAD values favoring probiotics over the control were observed overall (mean -4.51 , 95% confidence interval -6.78 to -2.24), in children 1 to 18 years old (-5.74 , 95% confidence interval -7.27 to -4.20), and in adults (-8.26 , 95% confidence interval -13.28 to -3.25). However, the effectiveness of probiotics in infants (<1 year old) with AD was not proved. The effect of synbiotic use was not significantly different from that of probiotic use. Treatment with a mixture of different bacterial species or of *Lactobacillus* species showed greater benefit than did treatment with *Bifidobacterium* species alone.

Conclusion: The overall result of this meta-analysis suggests that probiotics could be an option for the treatment of AD, especially for moderate to severe AD in children and adults. However, no evidence was found supporting the beneficial role of probiotics in infants.

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that can affect people of any age, but is most common in infants and children. It is characterized by intense pruritus and a repeated course of exacerbations and remissions that can cause sleep disruptions and irritability, which can impair the quality of life of the affected patients and their family members.¹ AD is certainly a chronic disease for which the importance of management should not be underestimated.

The cause of AD is unknown, but several hypotheses, including environmental, genetic, and immunologic factors, have been formulated to attempt to explain the possible causes. One of these

hypotheses involves the immunologic mechanisms in which the dysregulation of cellular immunity leads to allergic conditions owing to an imbalance of T-helper cell type (T_H) 1 to T_H 2. Relative lack of exposure to microorganisms during infancy or early childhood can lead to a predominant T_H 2 response.^{2–4} Gut microorganisms, also called *microbiota*, are actively involved in the immune system, and gut microbiota disruptions can contribute to the development of certain diseases.⁵ Slow development of *Bifidobacterium* species and *Lactobacilli* species has been seen in the gut microflora of allergic children.⁶

Topical steroids and emollients are often used to treat AD. In addition, immunomodulators, such as cyclosporine A, tacrolimus, or pimecrolimus ointment, are used for the management of AD, together with systemic corticosteroids for severe acute flare-ups. However, parents often fear possible side effects of these medications, leading to nonadherence.⁷

Owing to the limitations in the treatment of AD, other complementary and alternative therapies have been tried in

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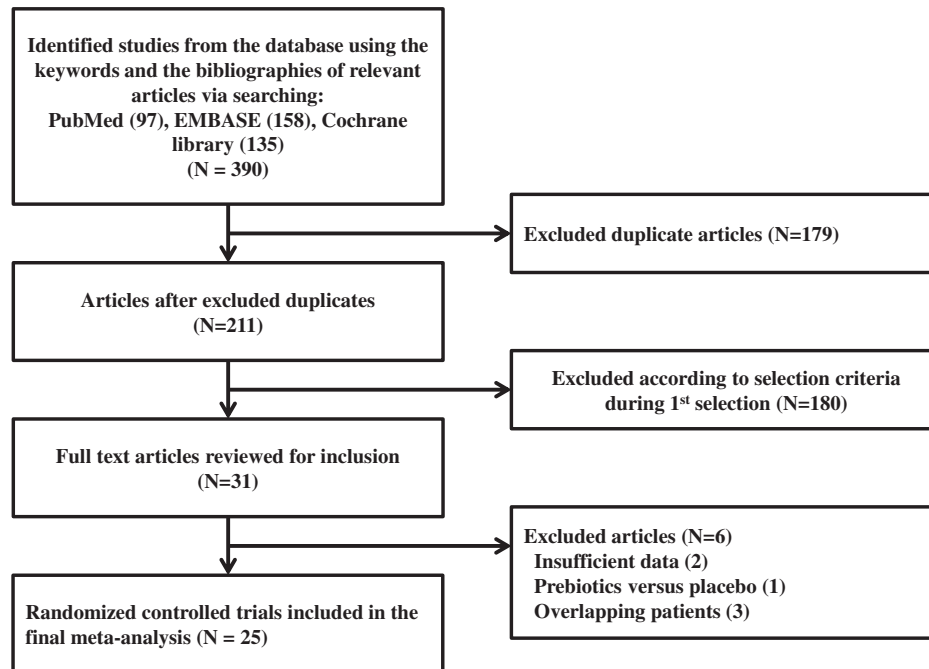


Figure 1. Flow diagram of the process of selecting relevant trials.

the management of the disease. Probiotics, defined as “live micro-organisms which, when administered in adequate amounts, confer a beneficial health effect on the host,”⁸ have been explored as alternative therapeutic and preventive options for the management of AD in many studies. Consumption of probiotics helps stimulate intestinal microbiota and suppress the T_H2 response, leading to improvements in the balance between T_H1 and T_H2 .⁹ Prebiotics, nondigestible oligosaccharides such as trans-galacto-oligosaccharide, fructo-oligosaccharide, and lactulose, have been used in recent studies to stimulate the growth of probiotics in the digestive system and to enhance the absorption of probiotics to maximize their effects.^{10,11} The term *synbiotics* refers to the simultaneous use of prebiotics and probiotics.¹² Recent studies using synbiotics have shown conflicting results, bringing about the need for more evaluations on the use of synbiotics.^{13–15}

A Cochrane systematic review by Boyle et al.¹⁶ included the results of 12 randomized controlled trials (RCTs) up to April 2008 and concluded that probiotics were not an effective treatment for eczema. One meta-analysis that included 6 prevention RCTs and 4 treatment RCTs up to May 2007 suggested potential preventive effects but concluded that the evidence of a therapeutic value for established AD was equivocal.¹⁷ Another meta-analysis included 10 RCTs up to January 2008 and showed a modest treatment effect in only pediatric AD.¹⁸ Overall, these reviews lack clinical evidence owing to the small numbers of subjects and have limited implications on only preventive effects. Fifteen eligible RCTs evaluating the treatment effect of probiotics have been published since. Recently published RCTs have assessed the use of prebiotics added to probiotics and have used adult populations, and there is a strong need to conduct a new meta-analysis that includes these recently published RCTs to summarize the treatment effect of probiotics and synbiotics overall and in different age groups.

Hence, the primary objective of this meta-analysis was to determine the clinical effects of probiotics in the management of AD overall and in different age groups. The secondary objective was to explore the key features affecting treatment efficacy based on the available evidence.

Methods

MEDLINE, Embase, and Cochrane Controlled Trials Register were searched through December 2013. The search strategy included using a validated filter for identifying RCTs, combined with searching with the following keywords: (*probiotics* OR *prebiotics* OR *synbiotics* OR *lactobacillus* OR *lactobacilli* OR *bifidobacteria* OR *bifidobacterium*) AND (*dermatitis*, *atopic* OR *eczema* OR *atopy*). Bibliographies of relevant articles were searched manually to identify additional studies.

Included were RCTs that measured the treatment effects of at least 1 probiotic using the Scoring of Atopic Dermatitis (SCORAD) in subjects diagnosed with AD. Studies were excluded if preventive effects were measured and if the severity of AD was not measured with SCORAD values. Two independent reviewers (S.O.K. and Y.M.A.) evaluated all the studies retrieved from the databases and the bibliographies. Disagreements between the reviewers were resolved by discussion with other co-authors. The quality of each RCT was measured using the Jadad score¹⁹ and by assessing the adequacy of the following components proposed by Juni et al.²⁰: generation of allocation, concealment of allocation, blinding, and use of the intention-to-treat method for statistical analysis when reported.

The following data were extracted by the 2 authors: study name, year of publication, country, intervention period, number of people included in the analysis, type of probiotics used, and SCORAD mean and SD.

The primary outcome was the change in the total SCORAD value from baseline to after treatment. To combine the studies' mean differences from baseline to after treatment and the SD of each, mean values were used. Investigators were contacted by e-mail to obtain raw or missing data. The response rate was low, with a rate of 25%^{15,21–24}; thus, the rest of the data were obtained from the studies and the meta-analysis report published in 2008 by Michail et al.¹⁸ When the SD was not available, the *P* value was used to calculate the mean differences. When more than 1 active treatment group was investigated, the active treatment groups were merged together into 1 active treatment group to compare with the 1 control group.

The overall effect was estimated singly based on the weighted mean difference (WMD) of SCORAD values from the baseline to the final intervention period for the probiotic and control groups in all trials. Also, the primary outcomes were evaluated after stratifying the trials by age groups: infants (<1 year old), children (1–18 years old), and adults (>18 years old). The value of the WMD with the 95% confidence interval (CI) was estimated based on the fixed-effects model (inverse variance method) and random-effects model (DerSimonian-Laird method).²⁵ Cochran Q and Higgins I^2 statistics were used to identify heterogeneity across selected studies. An I^2 value above 50% was considered to show substantial heterogeneity. Reporting bias was assessed using the funnel plot and the Egger test.²⁶ Sensitivity analyses also were conducted by excluding studies of lower quality.

The following subgroup analyses were planned in advance and performed: (1) use of synbiotics, (2) type of probiotic strains used, (3) treatment duration, (4) severity of AD at baseline, and (5) effect of IgE sensitization.

For all outcomes, a P value less than .05 was considered statistically significant. Data analysis was performed using Review Manager 5.2 (RevMan; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

In total, 390 articles were identified from the 3 databases in addition to relevant bibliographies (Fig 1). Twenty five RCTs were included in the meta-analysis,^{13–15,21–24,27–44} which had a total of 1,599 randomly allocated subjects: 896 subjects in the probiotics intervention group and 703 subjects in the control group. Four trials compared 2 intervention groups with 1 control group,^{24,29,32,36} so they were merged into 1 intervention group for accurate observation. Characteristics of all studies are presented in Table 1.

Although all trials were randomized, doubly blinded, and placebo controlled, each study varied in study quality. Table 2 presents the study qualities of each RCT. Publication bias was shown visually in the funnel plot and the Egger test suggested that small studies with negative results were lacking in the present meta-analysis (Egger regression intercept -2.64 , 95% CI -5.49 to 0.20 , $P = .034$; Fig 2).

Overall Clinical Effects

A random-effects model meta-analysis of all 25 trials showed a significant decrease in the mean difference of SCORAD values within the probiotics group compared with the control group (WMD -4.51 , 95% CI -6.78 to -2.24 , $P < .001$). However, significant heterogeneity among studies was observed ($I^2 = 87\%$; Fig 3).

Clinical Effect by Age Group

The age range of the randomized subjects was evaluated and the studies were categorized into 3 groups: infants (<1 year old), children (1–18 years old), and adults (>18 years old; Fig 4). The infant group included 6 studies (total 626 subjects), the children group included 8 studies (total 517 subjects), and the adult group included 4 studies (total 120 subjects). Seven studies were excluded in this analysis because they included more than 1 age group.^{14,21,27,30,35,37} The effects of probiotics were found to be significant in children (WMD -5.74 , 95% CI -7.27 to -4.20 , $P < .001$, $I^2 = 28\%$) and in adults (WMD -8.26 , 95% CI -13.28 to -3.25 , $P = .001$, $I^2 = 57\%$) by the fixed- and random-effects models, respectively. However, the WMD in SCORAD value between probiotics and placebo was not significant in the infant population (WMD 0.52 , 95% CI -1.59 to 2.63 , $P = .63$, $I^2 = 48\%$, random-effects model). A test for interactions showed statistically significant age group-related heterogeneity ($P < .001$, $I^2 = 91.9\%$).

Subgroup Analysis by Use of Synbiotics

Five studies (3 studies of children, 1 study of infants, and 1 for an uncategorized age group) used synbiotics for the treatment of AD. A subgroup analysis including these 5 studies showed extreme levels of heterogeneity (90%). Therefore, the subgroup analysis by use of synbiotics was performed only for the children population (WMD -7.02 , 95% CI -10.33 to -3.71 , $P < .001$, $I^2 = 32\%$) and showed a greater effect in decreasing the SCORAD value than probiotic treatment (WMD -5.56 , 95% CI -7.29 to -3.83 , $P < .001$, $I^2 = 26\%$). The test for interactions indicated statistically nonsignificant synbiotic use-related heterogeneity ($P = .40$, $I^2 = 0\%$).

Subgroup Analysis by Type of Probiotic Bacterial Species

The probiotic bacterial strains used in the trials were categorized into 3 groups: *Lactobacillus* species only, *Bifidobacterium* species only, and a mixture of these bacterial species. Three trials studied using different types of bacterial strain probiotics on either of the subjects' arms.^{24,29,36} The different types of probiotic strain groups were analyzed separately in this subgroup analysis. The mixture of different bacterial species showed the greatest effect on decreasing the SCORAD value (WMD -6.60 , 95% CI -10.42 to -2.79 , $P < .001$). Treatment with *Lactobacillus* species also showed significant positive effects (WMD -3.81 , 95% CI -6.42 to -1.21 , $P = .004$), but treatment with *Bifidobacterium* species showed negative results (WMD 1.75 , 95% CI 1.10 to 2.40 ; Table 3). A test for interactions showed statistically significant heterogeneity related to the type of probiotic bacterial species ($P < .001$, $I^2 = 93.9\%$).

Subgroup Analysis by Treatment Duration

Studies were categorized into 2 groups. The first group included trials having a treatment duration shorter than 8 weeks, and the second group included trials of at least 8 weeks. One study was excluded because its intervention period was applied to the 2 arms.²⁸ Probiotic treatment longer than 8 weeks showed statistically significant improvements in AD (WMD -4.98 , 95% CI -7.69 to -2.27 , $P < .001$), and treatment durations shorter than 8 weeks showed nonsignificant effects ($P = .34$). The test for interactions indicated statistically nonsignificant treatment duration-related heterogeneity ($P = .30$, $I^2 = 5.7\%$).

Subgroup Analysis by Baseline Severity of AD

Severity of AD was categorized into 3 groups based on baseline mean SCORAD value: mild (SCORAD value <25), moderate (SCORAD value $25-50$), and severe (SCORAD value >50).⁴⁵ One trial was excluded because no baseline SCORAD value was indicated.¹⁴

Probiotics were effective in treating subjects with moderate to severe AD (WMD -4.66 , 95% CI -7.33 to -1.99 , $P < .001$), although their effect was not greater than placebo in subjects with mild disease (WMD -0.81 , 95% CI -4.21 to 2.60 , $P = .25$). The test for interactions indicated statistically nonsignificant treatment duration-related heterogeneity ($P = .08$, $I^2 = 67.1\%$).

Effect of IgE Sensitization

Ten RCTs included IgE-sensitized subjects.^{15,21–24,29,33,35,37,40} However, these data were not available for subgroup analysis because the results were not applicable to the nonsensitized subjects, not to mention that there were not enough data to be used for statistical analysis. Two of the studies did not report SCORAD changes in the IgE-positive subjects.^{24,35} Gore et al²⁴ reported on changes in the IgE-positive subject ratio and found it was not affected by probiotic use. Eight studies reported the change in SCORAD values.^{15,21–23,29,33,37,40} Fölster-Holst et al²¹ and Gruber et al³³ did not find a significant benefit in SCORAD value change in

Table 1
General characteristics of randomized controlled trials included in the meta-analysis

Study, year (country)	Participants		Baseline AD severity/baseline SCORAD, treatment vs control	Probiotic treatment		Outcome summary
	Age	Treatment/control, n		Bacterial species (strain)/synbiotics; dose	Duration (wk)	
Children (1–18 y)						
Rosenfeldt et al, 2003 ²² (Denmark) ^a	1–13 y	23/20	moderate/40 (18–66) vs 35 (15–66) ^b	<i>Lactobacillus</i> (LR + LR2)/—; 1×10^{10} cfu of each strain twice daily	6	positive effect of probiotics was seen only in allergic subjects ($P = .04$)
Passeron et al, 2006 ³¹ (France)	2–12 y	17/22	moderate/39 (31.9–46.4) vs 39 (34.7–43.9) ^c	<i>Lactobacillus</i> (LR)/synbiotics; 1.2×10^9 cfu 3 times a day	12	no significant difference between synbiotics and placebo
Sistek et al, 2006 ²³ (New Zealand)	1.1–10.9 y	29/30	moderate/26 (21.9–30.8) vs 35.1 (28.9–42.8) ^d	mixture (LR + BL)/—; 2×10^{10} cfu/g/d	12	positive effect of probiotics was seen only in food-sensitized children ($P = .047$)
Gerasimov et al, 2010 ¹³ (Ukraine)	1–3 y	43/47	moderate/42.1 (12.6) vs 40.2 (10.5) ^e	mixture (LA + BL)/synbiotics; 5×10^9 cfu twice daily	8	greater SCORAD decrease in probiotic group than placebo group ($P = .001$)
Woo et al, 2010 ³⁸ (Korea)	2–10 y	41/34	moderate/42.6 (26.4–75.4) vs 40.0 (27.2–76.5) ^c	<i>Lactobacillus</i> (LS)/—; 5×10^9 cfu twice daily	12	decrease in SCORAD score was greater in probiotic group than in placebo group ($P = .008$)
Wu et al, 2011 ⁴⁰ (Taiwan)	2–14 y	27/27	severe/60.2 (12) vs 54.2 (14.5) ^e	<i>Lactobacillus</i> (LS2)/synbiotics; 2×10^9 cfu twice daily	8	significantly lower SCORAD value at 8 wk of treatment in synbiotic group than in placebo group ($P = .022$)
Yesilova et al, 2012 ⁴¹ (Turkey)	1–13 y	20/19	moderate/35.4 (13.4) vs 28.1 (6.1) ^e	mixture (BB2, LA, LC, LS2)/—; 4×10^9 cfu daily	8	greater SCORAD decrease in probiotic group than in placebo group ($P = .0015$)
Han et al, 2012 ⁴⁴ (Korea)	1–13 y	44/39	moderate/27.6 (10.0) vs 25.6 (9.0) ^e	<i>Lactobacillus</i> (LP2)/—; 5×10^9 cfu twice daily	12	greater SCORAD decrease in probiotic group than in placebo group ($P = .004$)
Infants (<1 y)						
Kirjavainen et al, 2003 ²⁸ (Finland) ^f	3.5–6.8 mo ^g	14/8	mild/19 (4–47) vs 13 (4–29) ^c	<i>Lactobacillus</i> (viable LGG)/—; 3×10^{10} cfu/kg (BW)/d	7.5	greater SCORAD decrease in probiotic group than in placebo group ($P = .02$)
Viljanen et al, 2005 ²⁹ (Finland)	1.4–11.9 mo	156/74	moderate/34.3 (17.2), 33.3 (15) vs 29.9 (12.2) ^e	<i>Lactobacillus</i> (LGG) or mixture ^h /—; 5×10^9 cfu or mixture twice daily	4	positive effect of probiotics was seen only in IgE-sensitized infants ($P = .036$)
Brouwer et al, 2006 ³² (Netherlands)	2.3–6.6 mo	33/17	mild/14.2 (3.7–41.1), 19.4 (3.5–59.1) vs 22.5 (9.0–39.2) ^b	<i>Lactobacillus</i> (LR or LGG)/—; 3×10^8 cfu/g	12	no significant difference between probiotics and placebo
Gruber et al, 2007 ³³ (Germany)	3–12 mo	54/48	mild/24.6 (8.8) vs 23.6 (7.8) ^e	<i>Lactobacillus</i> (LGG)/—; $>5 \times 10^9$ cfu twice daily	12	no significant difference between probiotics and placebo
van der Aa et al, 2010 ¹⁵ (Netherlands)	0–7 mo	42/43	moderate/35.6 (10.6) vs 34.7 (12.6) ^e	<i>Bifidobacterium</i> (BB)/synbiotics 1.3×10^9 cfu/100 mL	12	positive effect of synbiotics was seen only in IgE-sensitized infants ($P = .04$)
Gore et al, 2012 ²⁴ (UK)	3–6 mo	87/46	moderate/25.4 (22.1–29), 25.9 (22.8–29.2) vs 26.9 (23.4–30.6) ⁱ	<i>Lactobacillus</i> (LP) or <i>Bifidobacterium</i> (BL)/—; 1×10^{10} cfu	12	no significant difference between probiotics and placebo
Adults (>18 y)						
Roessler et al, 2008 ³⁴ (Germany)	23 y ^k	8/7	mild/24 (20.6–26.7) vs 24.9 (20.7–28.9) ^d	mixture (LP + LA + BL)/—; $3.9 \times 10^8 + 2.9 \times 10^4 + 5.9 \times 10^4$ cfu/g twice daily	8	no significant effects of probiotics
Yoshida et al, 2010 ³⁹ (Japan)	20–65 y	16/8	moderate/41.0 (18) vs 25.7 (6.6) ^e	<i>Bifidobacterium</i> (BB)/—; 1×10^{10} cfu twice daily	8	objective SCORAD decrease was significant in probiotic group ($P = .034$); placebo group showed no change

Iemoli et al, 2012 ⁴³ (Italy)	NA	31/15	moderate/46.3 (3.7) vs 45.0 (2.6) ^j	mixture (LS2 +BB)/—; 1 × 10 ⁹ cfu twice daily	12	greater SCORAD decrease in probiotic group than in placebo group (<i>P</i> < .001)
Drago et al, 2012 ⁴² (Italy)	18–46 y	19/19	moderate/27.6 (3.4) vs 24.3 (3.5) ^j	<i>Lactobacillus</i> (LS2)/—; 1 × 10 ⁹ cfu twice daily	16	SCORAD decrease significant in probiotic group (<i>P</i> < .001); placebo group showed no change
Age group not classified						
Majamaa and Isolauri, 1997 ²⁷ (Finland)	2.5–15.7 mo	13/14	moderate/26 (17–38) vs 21 (14–31) ^c	<i>Lactobacillus</i> (LGG)/—; 5 × 10 ⁸ cfu/g formula (500–1,000 mL)	4	SCORAD score improvement in LGG group (<i>P</i> = .008) but not in placebo group (<i>P</i> = .89)
Weston et al, 2005 ³⁰ (Australia)	6–18 mo	26/27	moderate/40.8 (6.8) vs 44.0 (10.4) ^e	<i>Lactobacillus</i> (LF)/—; 1 × 10 ⁹ cfu twice daily	8	greater SCORAD decrease in probiotic group than in placebo group (<i>P</i> = .03)
Fölster-Holst et al, 2006 ²¹ (Germany)	1–55 mo	26/27	moderate/43.3 (2.4) vs 41.4 (2.7) ^j	<i>Lactobacillus</i> (LGG)/—; 5 × 10 ⁹ cfu twice daily	8	no significant difference between probiotics and placebo
Chernyshov, 2009 ³⁵ (Ukraine)	2–48 mo	30/28	moderate/34.2 (3.8) vs 36.9 (4.0) ^e	<i>Lactobacillus</i> (LR 95%, LH 5%)/—; 2 × 10 ⁹ cfu/d	4.3	significant decrease of SCORAD in subjects who did not use topical steroids was shown only in probiotic group (<i>P</i> < .01)
Cukrowska et al, 2010 ³⁷ (Poland)	2.5–20 mo	27/28	moderate/35.4 (24.1) vs 33.5 (18.1) ^e	<i>Lactobacillus</i> (LC + LP)/—; 1 × 10 ⁹ cfu/d	12	induced clinical improvement mainly in children with IgE-dependent atopic eczema
Gobel et al, 2010 ³⁶ (Denmark)	18 mo ^k	34/16	mild/20.6 (13.1), 22.5 (11.0) vs 20.2 (8.3) ^e	<i>Lactobacillus</i> (LA) or <i>Bifidobacterium</i> (BL)/—; 1 × 10 ¹⁰ cfu/d	8	no overall beneficial effects of probiotics
Farid et al, 2011 ¹⁴ (Iran)	3–72 mo	19/21	NA	mixture ⁱ /synbiotics; 10 ⁹ cfu twice daily	8	greater SCORAD decrease in synbiotic group than in placebo group (<i>P</i> = .001)

Abbreviations: AD, atopic dermatitis; BB, *Bifidobacteria breve*; BB2, *Bifidobacterium bifidum*; BL, *Bifidobacteria lactis*; BW, body weight; cfu, colony-forming units; LA, *Lactobacillus acidophilus*; LC, *Lactobacillus casei*; LF, *Lactobacillus fermentum*; LGG, *Lactobacillus rhamnosus* strain GG or *Lactobacillus GG*; LH, *Lactobacillus helveticus*; LP, *Lactobacillus paracasei*; LP2, *Lactobacillus plantarum*; LR, *Lactobacillus rhamnosus*; LR2, *Lactobacillus reuteri*; LS, *Lactobacillus sakei*; LS2, *Lactobacillus salivarius*; NA, not available; SCORAD, Scoring of Atopic Dermatitis.

^aCrossover study. Data from the first 6 weeks of treatment were used.

^bMedian (range).

^cMedian (interquartile range).

^dGeometric mean (95% confidence interval).

^eMean (SD).

^fInfants treated with heat-inactivated LGG were not included in the meta-analysis.

^gInterquartile range.

^hLGG 5 × 10⁹ cfu, LR 5 × 10⁹ cfu, BB 2 × 10⁸ cfu, and *Propionibacterium freudenreichii* 2 × 10⁹ cfu.

ⁱDe-transformed mean of square root-transformed data (95% confidence interval).

^jMean (SEM).

^kMean.

^lLC, LR, *Streptococcus thermophilus*; BB, LA, *Bifidobacteria infantis*; and *Lactobacillus bulgaricus*.

Table 2
Methodologic quality of the trials by Jadad scale and quality assessment of controlled clinical trials

Study	Jadad scale						Quality assessment of controlled clinical trials			
	Representation of randomization	Appropriateness of method for randomization	Representation of double blinding	Appropriateness of method for double blinding	Representation of withdrawals	Total score	Generation of allocation sequences	Concealment adequate	Patient blinding adequate	ITT performed
Majamaa and Isolauri, 1997	1	0	1	1	0	3	unclear	unclear	yes	no
Kirjavainen et al, 2003	1	0	1	1	0	3	unclear	unclear	yes	yes
Rosenfeldt et al, 2003	1	1	1	1	1	5	yes	yes	yes	no
Viljanen et al, 2005	1	1	1	1	1	5	yes	yes	yes	no
Weston et al, 2005	1	1	1	1	1	5	yes	yes	yes	yes
Brouwer et al, 2006	1	0	1	0	1	3	unclear	unclear	yes	yes
Fölster-Holst et al, 2006	1	0	1	0	1	3	unclear	unclear	yes	yes
Passeron et al, 2006	1	–1	1	1	1	3	unclear	unclear	yes	no
Sistek et al, 2006	1	1	1	1	1	5	yes	yes	yes	yes
Gruber et al, 2007	1	1	1	1	1	5	yes	yes	yes	yes
Rössler et al, 2008	1	0	1	1	1	4	unclear	yes	yes	yes
Chernyshov et al, 2009	1	–1	0	0	1	1	no	unclear	unclear	yes
Cukrowska et al, 2010	1	0	1	0	0	2	unclear	yes	yes	no
Gerasimov et al, 2010	1	1	1	1	1	5	yes	yes	yes	yes
Gobel et al, 2010	1	0	1	0	0	2	unclear	unclear	yes	unclear
van der Aa et al, 2010	1	1	1	1	1	5	yes	yes	yes	yes
Woo et al, 2010	1	0	1	1	1	4	unclear	unclear	yes	no
Yoshida et al, 2010	1	0	1	1	1	4	unclear	yes	yes	yes
Drago et al, 2011	1	1	1	1	1	5	yes	yes	yes	yes
Farid et al, 2011	1	0	1	1	1	4	unclear	unclear	yes	no
Wu et al, 2011	1	1	1	1	1	5	yes	yes	yes	yes
Gore et al, 2012	1	0	1	0	1	3	yes	yes	yes	yes
Han et al, 2012	1	1	1	1	1	5	yes	yes	yes	yes
Iemoli et al, 2012	1	0	1	0	1	3	unclear	unclear	yes	yes
Yesilova et al, 2012	1	1	1	1	1	5	yes	yes	yes	yes

Abbreviation: ITT, intention to treat.

the IgE-sensitized subjects over the placebo group. The other studies showed a significant decrease in SCORAD value only in IgE-sensitized subjects and not in the placebo group.

Sensitivity Analysis of Studies Including Only High-Quality Trials

To take into account the effect of study quality on the outcome of this analysis, each trial was evaluated according to the Jadad score and categorized as high or low. The 22 trials that scored at least 3 were categorized as high, and the other 3 trials with scores of 1 or 2 were categorized as low.^{35–37} The exclusion of low-quality trials showed similar results to those of the overall result (WMD –5.02, 95% CI –7.48 to –2.56, $P < .001$, $I^2 = 88\%$), implying the robustness of this meta-analysis. Also, in the children population, similar significant effects were maintained after excluding 1 study with a Jadad score of 3³¹ (WMD –5.79, 95% CI –7.33 to –4.24, $P < .001$, $I^2 = 37\%$).

Adverse Events of Probiotics

Of the 25 trials included in this meta-analysis, 9 trials reported adverse events (AEs).^{14,16,23,26,29,31,32,34,40} However, in a study by Kirjavainen et al,²⁸ AEs were noticed only in a group using a heat-inactivated *Lactobacillus rhamnosus* strain GG. In other studies, most AEs were associated with gastrointestinal symptoms (eg, diarrhea, vomiting) and did not show any significant differences in the incidence of AEs between the probiotic and placebo groups. The reported AEs other than gastrointestinal symptoms were fever, infections, skin disorders, wheezing, and coughing. Some studies reported serious AEs, such as acute enteritis, eczema herpeticum, food poisoning, and respiratory syncytial virus bronchiolitis.^{13,15,33} However, it was mentioned that these events were not associated with the study medication. The incidence of AEs varied among studies, from 30.7% to 91.1% in the probiotic group.

Discussion

The present meta-analysis of 25 RCTs suggests that the administration of probiotics might have a positive effect on the treatment of AD. Although the result of a –4.51-point difference in SCORAD value for the overall subject population was greater than that of a previous meta-analysis,¹⁸ its clinical significance is still questionable. In addition, the authors could not conclude the positive effect of probiotics in the overall subject population owing to the high heterogeneity among studies. However, from the current study, we could conclude the positive effect of probiotics on the treatment of AD in children (1–18 years old) and adults based on the analysis of clinical trial results that were stratified by age of participants and had low heterogeneity.

Conversely, the current evidence does not favor the use of probiotics in infants (<1 year old). The age range of infants can be assumed as birth to 12 months or birth to 2 years. In this meta-analysis, infancy was defined as birth to 1 year of age because some studies investigating the effects of probiotics in children

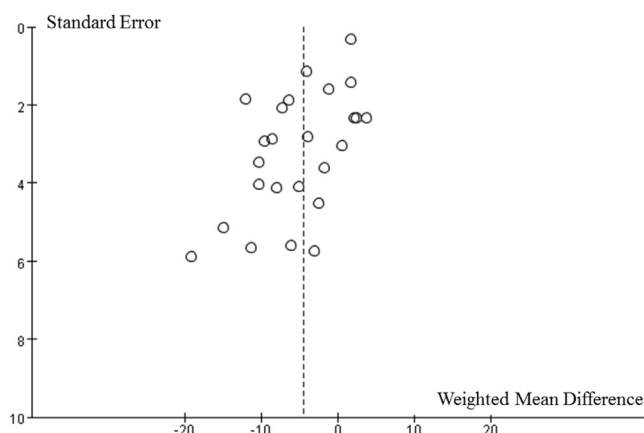


Figure 2. Funnel plot of SE by weighted mean difference. Each dot represents 1 trial.

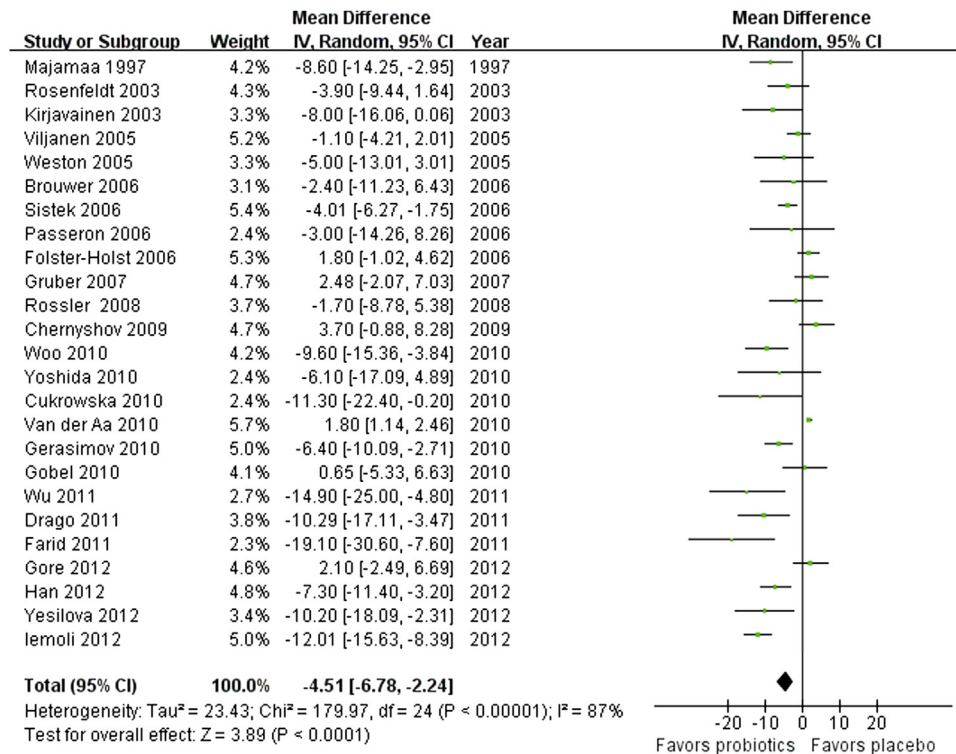


Figure 3. Pooled statistical analysis on the random-effects model of weighted mean difference of Scoring of Atopic Dermatitis values with probiotics treatment compared with control in patients with atopic dermatitis overall. CI, confidence interval.

ranged from 1 to 10 years old. When 11 studies that included infants up to 2 years old were analyzed, a similar nonsignificant benefit was observed with high heterogeneity (WMD -1.57 , 95% CI -4.17 to 1.02 , $P = .28$, $I^2 = 70\%$). Previous meta-analyses by Boyle et al¹⁶ and Michail et al¹⁸ that included 1 to 4 studies in each age group with specific age criteria (<2 vs 2 – 12 years and <1 year vs 1 – 13 years, respectively) observed no significant difference in total SCORAD values between probiotic and control treatments in the 2 age groups with a high level of heterogeneity. In the present meta-analysis, 8 studies of children in which participants were 1 to 13 years old showed a statistically significant -5.74 -point difference in total SCORAD values between the probiotics and placebo groups.

This is the first meta-analysis investigating probiotic effects in adults with AD. Four RCTs were included and showed a -9.69 -point difference in total SCORAD value, which was greatest among all age groups. However, considering the small number of subjects analyzed, this finding should be interpreted with caution.

The observed small gap in the decrease of total SCORAD value between the control and treatment arms, which is of questionable clinical significance, can be explained in part by a prebiotic intervention as placebo in some studies, as suggested by the previous meta-analysis.¹⁸ Indeed, research published in 2009 by Shibata et al¹¹ showed that ketose, a prebiotic, exerted a beneficial effect on the clinical symptoms of AD. The present post hoc comparative analysis of the effect of placebo using prebiotics such as maltodextrin, cellulose, fructo-oligosaccharide, etc vs a nonprebiotic placebo showed that the studies using a nonprebiotic placebo showed greater mean differences in SCORAD value changes (WMD -5.58 , 95% CI -9.42 to -1.74 , vs -3.81 , 95% CI -6.82 to -0.80).

A general and justified criticism that most meta-analyses assess the effect of probiotics by pooling all data on different probiotic strains, doses, etc, also applies to the present study and is its main limitation.⁴⁶ In this meta-analysis, considerable heterogeneity among studies ($I^2 = 87\%$, $P < .001$) was noticeable in the overall

analysis. A test for heterogeneity was significant for 2 subgroup categories: target patient age and probiotic bacterial species.

Subgroup analysis by the type of bacterial species showed that the greatest effect was observed in studies using a mixture of different bacterial species, followed by *Lactobacillus* species alone. However, based on the results of subgroup analysis, no beneficial effect was found with a *Bifidobacterium* species supplement. These findings confirmed previous reports that probiotic strains can affect the clinical outcomes of treatment with probiotics.¹⁶

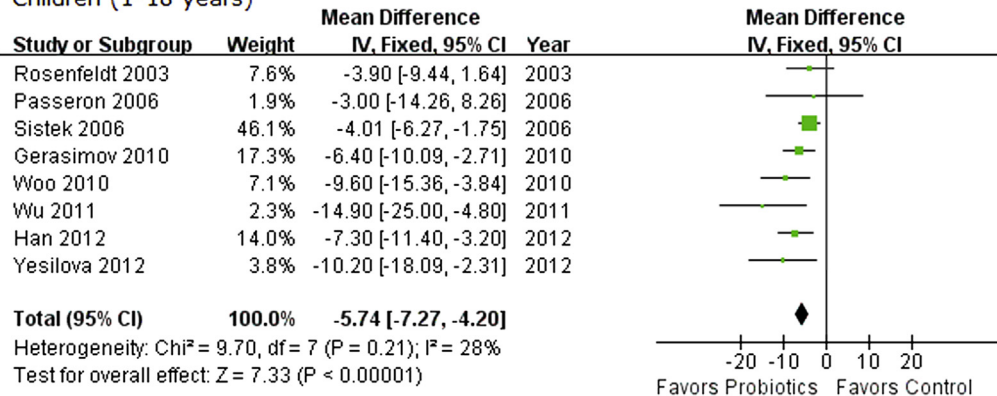
Although there was no study comparing synbiotics directly with probiotics on the effect of AD treatment, the subgroup analysis in children suggests that synbiotics appear to be more effective in alleviating clinical symptoms of AD as reflected by a greater SCORAD value decrease than probiotics (-7.02 vs -5.5). This finding has not been reported in a previous meta-analysis regarding treatment of AD. A similar trend was observed in a recent meta-analysis, in which a more pronounced effect with the use of synbiotics compared with the use of probiotics in decreasing the incidence of postoperative sepsis in an elective general surgical setting was suggested.⁴⁷ In contrast, 1 study investigating the therapeutic effect of a synbiotic formula on the severity of AD in infants did not show beneficial effects.¹⁵

The present subgroup analysis also suggests that longer treatment durations (>8 weeks) might be possible factors affecting the effect of probiotics on the treatment of AD. In addition, the use of probiotics would be most beneficial to patients with moderate to severe AD based on available data.

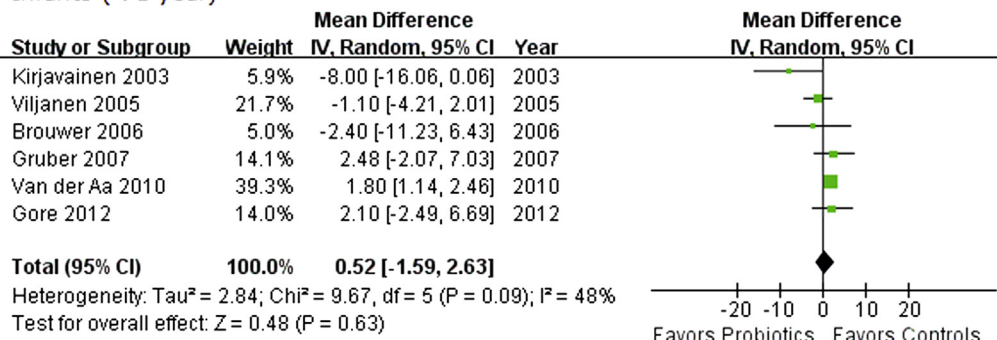
All these findings from subgroup analysis need to be confirmed by prospective large-scale trials that address these questions directly.

The dose of probiotic preparation used in the trials ranged from 0.3 billion to 20 billion colony-forming units. This might contribute to the heterogeneity among the included studies. However, the authors did not investigate the effect of probiotic dose because

Children (1–18 years)



Infants (< 1 year)



Adults (> 18 years)

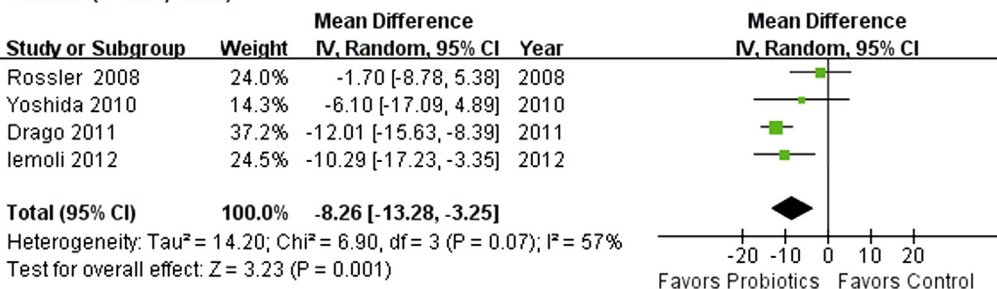


Figure 4. Statistical analysis of weighted mean difference of Scoring of Atopic Dermatitis values with probiotics treatment compared with control in patients with atopic dermatitis stratified by age group. CI, confidence interval.

applying the same dose criteria to various products that consist of different strains might be inappropriate. To find the optimal dose of probiotic preparation, a direct head-to-head comparison study is required.

Some factors can be considered for the residual, unexplained heterogeneity. The various treatment options performed simultaneously with the probiotic intervention could yield different outcomes. However, the amount of topical agent used was different in each study. For example, several studies included subjects who were allowed to use emollients,^{14,16,28,30,32,36,38} topical steroids,^{14,16,23–25,31,31,35,38} or even topical calcineurins¹⁵ during their intervention with probiotics.^{15,21,22,30,31,35,38}

Ten trials reported the use of topical steroids in subjects during the intervention period. Six trials observed changes in the amount of steroids from baseline to the end of the intervention.^{13,22,30,31,38,44} Five of them reported no statistical difference between the placebo and treatment groups in the amount of steroid usage. Gerasimov et al¹³ reported significantly lower steroid use in the probiotic group than in the placebo group ($P = .006$). Three trials observed the frequency of steroid use in subjects.^{13,15,24}

Although frequency decreased in the probiotic treatment groups, it was not statistically provable when compared with the control group. Sistek et al²³ reported no changes in the ratio of probiotic users to control subjects using topical steroids. However, Chernyshov³⁵ reported a smaller ratio of subjects using topical steroids in the probiotic group than in the placebo group.

Heterogeneity also could be explained by the limits for food intake in each study. Compliance is another important factor in measuring the real treatment effect. Only a few trials had observed compliance rates higher than 90%.^{30,31,38}

With regard to safety, AEs were generally under-reported. Only 9 trials reported AEs, mainly gastrointestinal symptoms, with no significant difference between the treatment and control groups. Because most participants were otherwise healthy, serious AEs related to the use of probiotics were not observed.

This meta-analysis has some limitations. The main limitations are residual unexplained heterogeneity, which is described above. In addition, the evaluation of the funnel plot and the Egger test showed the possibility of publication bias. A lack of small studies with negative results may have led to a substantial overestimation

Table 3
Subgroup meta-analysis results

Factor	Studies, n	Subjects, n		Effect size of WMD (95% CI)	P value	Heterogeneity (I^2), %
		Treatment	Control			
Synbiotics ^a						
Yes	3	87	96	−7.02 (−10.33 to −3.71)	<.001	32
No	5	171	163	−5.56 (−7.29 to −3.83)	<.001	26
Type of probiotics						
Mixed	7	226	210	−6.60 (−10.42 to −2.79)	<.001	80
<i>Lactobacillus</i>	17	550	516	−3.81 (−6.42 to −1.21)	.004	71
<i>Bifidobacterium</i>	4	120	114	1.75 (1.10 to 2.40)	<.001	0
Duration						
≥8 wk	20	660	559	−4.98 (−7.69 to −2.77)	<.001	88
<8 wk	4	222	136	−2.20 (−6.75 to 2.36)	.34	75
Baseline SCORAD						
Mild	5	143	96	−0.81 (−4.21 to 2.60)	.25	26
Moderate/severe	19	721	572	−4.66 (−7.33 to −1.99)	<.001	89

Abbreviations: CI, confidence interval; SCORAD, Scoring of Atopic Dermatitis; WMD, weighted mean difference.

^aOwing to high heterogeneity, the subgroup analysis of synbiotic usage used synthesized trials for the children population.

of the true probiotic effects. Another limitation to this meta-analysis is that the authors could not obtain all raw data from the included studies, although the study authors were contacted, so some subgroup analysis had to be performed using the available data.

In summary, the overall result of this meta-analysis of available evidence suggests that probiotics could be an option for the treatment of AD, especially moderate to severe AD in children and adults, despite heterogeneity in the type of probiotic strain, combination with prebiotics, dose, and duration. The current evidence does not appear to support the beneficial role of probiotics in infants. In addition, an important finding from the present subgroup analysis is that probiotic effects are strain specific, and probiotics containing a single *Bifidobacterium* species may not confer therapeutic effects in AD.

The effectiveness of synbiotics compared with probiotics, optimization of the dosing strategy, and strain-specific benefits must be addressed by future studies.

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