

Review

Treatment efficacy of probiotics on atopic dermatitis, zooming in on infants: a systematic review and meta-analysis

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Abstract

Probiotic treatment of atopic dermatitis is widely studied with controversial results. The objective of this study is to review the efficacy of probiotics for the treatment of atopic dermatitis in infants. PubMed, Embase, and Cochrane Central Register of Controlled Trials databases, and reference lists were searched up to July 2017. Double-blinded randomized clinical trials were included. The primary outcome was the Scoring Atopic Dermatitis index. Subgroups analyses were conducted on probiotic species, treatment duration, participant age, and disease severity. Eight clinical trials (741 infants) were included in the quantitative synthesis. The overall pooled change in Scoring Atopic Dermatitis index (95% CI) in infants was -5.71 (-8.37 , -3.04), $P < 0.01$. Subgroup analysis revealed that the effect was protective in moderate-to-severe patients -8.32 (-16.35 , -0.28), with preparations containing *Lactobacillus* -5.76 (-9.21 , -2.30). Probiotics for the treatment of infantile atopic dermatitis is beneficial.

Introduction

Atopic dermatitis (AD), also known as eczema, is a chronic inflammatory, relapsing skin disease that is known to affect nearly 20% of children in both developed and developing countries.¹ The hygiene hypothesis, or the lack of exposure to microbial stimuli in early life which programs the immune system toward a Th2-type allergic response, is suggested to be a major mechanism in AD.² Probiotic supplementation has been shown to be effective in the treatment of AD. Probiotics contain cultures of living microorganisms that, when ingested in adequate amounts, can modulate gut microbiota.³ A recent meta-analysis showed that the administration of mixed strains of bacteria is beneficial to the treatment of AD.³ However, evidence of its efficacy is less conclusive in infantile AD.^{4,5} This study sets out to conduct a systematic literature review and meta-analysis of randomized clinical trials investigating the efficacy of probiotics for the treatment of infantile AD.

Methods**Data sources**

Literature searches were undertaken in PubMed/MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases from the inception to July 25, 2017. Thorough manual search was conducted for existing reviews, and relevant articles

were retrieved from references. Index words included the terms: eczema or atopic dermatitis, and infant or infantile or children, and probiotics or probiotic. Articles using synbiotics or a mixture of prebiotic and probiotics were excluded. Non-human studies or articles published in languages other than English were excluded. Relevant references were reviewed to retrieve articles that might have been missed in the initial searches.

Study selection

We included all published double-blind randomized clinical trials evaluating the effect of probiotics on AD treatment in infants. For this study, infancy was defined as subjects aged 36 months or less because a more rigorous definition of <2 years would exclude even more studies and make quantitative synthesis impossible. Studies investigating preventive effects were excluded. To be included, a publication needed to have included an assessment of AD disease severity using SCORAD index. Case reports, letters, and review articles were excluded from this study.

Two reviewers (Mutong Zhao and Chunping Shen) independently screened titles, abstracts, and full texts. Disagreements about inclusion were resolved by consensus or by consulting a third reviewer (Lin Ma).

Quality assessment

The risk of bias in individual studies was assessed using Revman 5.3. Studies were evaluated for six aspects: sequence

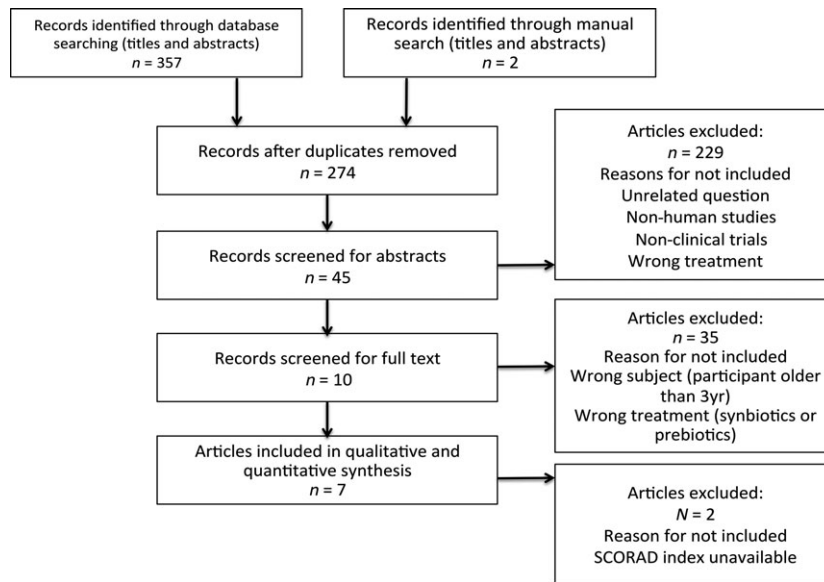


Figure 1 Selection of publications for the meta-analysis

generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the quality of evidence. The quality rating for studies assessed using the GRADE approach has four levels: high, moderate, low, or very low.

Statistical analysis

The statistical analysis was performed using Stata version 12.0 as indicated. The primary outcome was reported as SCORAD index at the end of treatment administration, in the treatment and placebo groups. Grade of evidence was estimated with the GRADE system using GRADEpro. Pooled weighted mean differences (WMDs) and the 95% confidence intervals were estimated using a random-effects model. Forest plots were depicted for visual interpretation of the individual study-specific and pooled estimates with respective 95% confidence intervals. The I^2 statistics ($>75\%$) were defined to assess heterogeneity. Subgroup analyses were conducted based on different species of probiotics, treatment duration, participant age, and disease severity. Publication bias was evaluated using a funnel plot for the visual assessment of asymmetry, along with statistical estimates from the Begg test.

Ethics

No ethics approval was required.

Results

A total of 357 articles (abstracts) were retrieved through the primary searches, and an additional two articles were retrieved

through the reference list. Seven studies were included in the final analysis, accruing 609 children^{4–10} (Fig. 1). Three studies were excluded because only graphical^{11,12} or binary¹³ measures of SCORAD index were available. The study characteristics of these seven selected trials are summarized in Table 1. No evidence of publication bias was found by the funnel plot or by the Begg test ($P = 0.18$) (Fig. 2).

The seven included articles were appraised critically for quality of methodology, design, and data analysis using GRADE (Table 2). The quality of these studies was low (Table 3). Some studies were unclear of blinding of outcome measurement and their randomization generation method. Patient withdrawals were severe for two studies. Heterogeneity persisted albeit subgroup analysis. Thus, we assumed that its possible that the potential limitations might lower the confidence in estimation of effects.

In the main analysis, we pooled estimates of SCORAD index at the end of treatment. A random-effects model revealed a significant decrease in the WMD of SCORAD values in the probiotic group compared with the control group (WMD and 95% CI, -5.71 ; -8.37 to -3.04 ; $P < 0.01$) (Fig. 3). However, significant heterogeneity among studies was observed ($I^2 = 97.4\%$; $P < 0.01$).

Six studies used *Lactobacillus* containing preparations, while three used *Bifidobacterium* containing preparations. Subgroup analyses investigating species-specific effects showed that only *Lactobacillus* species, but not *Bifidobacterium* ones, are beneficial (WMD and 95% CI -5.76 [-9.21 , -2.30]; $P = 0.001$) (Table 4).

We then conducted subgroup analyses exploring different treatment durations and found a significant decrease in SCORAD values in infants treated 8 weeks or less (the WMD and 95% CI -8.65 [-14.32 , -2.98]; $P = 0.003$) (Table 4).

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Study design	Severity	Control treatment	Participant age, months	Probiotic species	Treatment/Control, No.	Dose	Duration, weeks	Weaning status
Isolaure, E ⁶	2000	RCT	NA	Extensively hydrolyzed whey formula	Mean age 4.6 months	<i>Lactobacillus GG</i> <i>Bifidobacterium lactis</i>	9/9 9/9	8 × 10 ⁸ CFU; daily 1 × 10 ⁹ CFU; daily	8 weeks	Weaned
Viljanen, M ⁷	2005	RCT	Moderate-to-severe AD (baseline SCORAD >30)	Microcrystalline cellulose	0–12 months	<i>Lactobacillus GG</i>	80/74	5 × 10 ⁹ CFU; twice daily	4 weeks	Not weaned
Weston, S ⁸	2005	RCT	Moderate-to-severe AD (baseline SCORAD ≥25)	Maltodextrin	6–18 months	<i>Lactobacillus fermentum</i> VRI-003 <i>PCC</i>	26/27	1 × 10 ¹⁰ CFU; twice daily	8 weeks	Not clear
Gruber, C ⁹	2007	RCT	Mild-to-moderate AD (baseline SCORAD 15–40)	Cellulose, saccharose, and magnesium stearate mix	3–12 months	<i>Lactobacillus GG</i>	54/48	5 × 10 ⁹ CFU; twice daily	12 weeks	Not weaned
Gore, C ⁵	2012	RCT	Mild-to-moderate AD, SCORAD category undefined	Maltodextrin	3–6 months	<i>Lactobacillus paracasei</i>	43/46	1 × 10 ¹⁰ CFU; daily	12 weeks	Not clear
Lin, R. J ⁴	2015	RCT	NA	NA	12–36 months	<i>Bifidobacterium lactis</i> <i>Bifidobacterium bifidum</i>	44/46 20/20	1 × 10 ¹⁰ CFU; daily Unclear	4 weeks	Not clear
Rose, M. A ¹⁰	2010	RCT	NA	NA	6–24 months	<i>Lactobacillus GG</i>	56/44	1 × 10 ¹⁰ CFU; twice daily	24 weeks	Not clear

RCT, randomized control trial; AD, atopic dermatitis; NA, placebo preparation not available, that is, not clearly stated; CFU, colony-forming units.

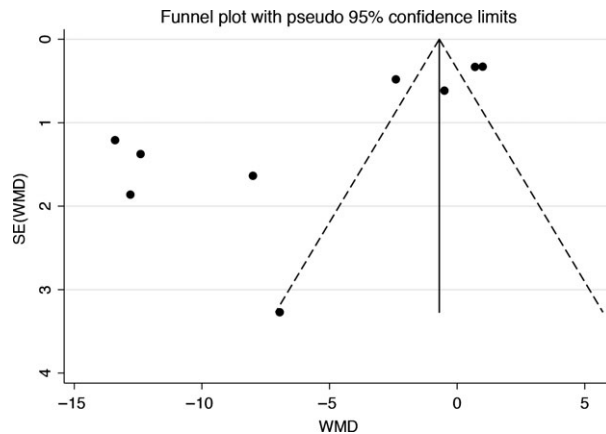


Figure 2 Funnel plot of eight RCTs (broken down into nine analyses) of probiotic use for infant atopic dermatitis. WMD: weighted mean difference, s.e. WMD: standard error of weighted mean difference. Minimal asymmetry indicates lack of publication bias

We next explored if treatment efficacy differs for early infancy and later. Probiotic treatments are of borderline significance for children aged 1 year or less ($P = 0.055$) but not so much for older infants ($P = 0.125$) (Table 4).

Finally, we pooled estimates based on different disease severities. Two trials focused on mild-to-moderate AD while another two focused on moderate-to-severe disease. We found that probiotics might confer differential effect to infants with different disease severities, that is, in those with moderate-to-severe diseases, probiotics were protective (WMD and 95% CI, -8.32 (-16.35 , -0.28), $P = 0.043$) (Table 4), while in those with mild conditions, the effect was marginal (WMD and 95% CI, -2.38 (-5.20 , 0.45), $P = 0.07$) (Table 4).

Discussion

In recent years, studies have found that probiotics modulate the body's immune status and improve the gut barrier function that contributes to the prevention and treatment of atopic diseases.⁴ At birth, the gastrointestinal tract of the newborn is sterile, and

the developing microflora in the early postnatal period is involved in the activation of innate and adaptive immunity.¹⁴ Inadequate microbial stimulus results in unbalanced gut microflora, which favors the persistence of a neonatal Th2-dominant immune response, precipitating the development of atopy.^{15,16} Studies have shown that probiotic supplementation is effective in the prevention of AD.¹⁷ However, findings are less conclusive for its treatment efficacy, especially in infants.^{18,19} Meanwhile, concerns have been raised that in severely ill or immunocompromised patients, sepsis, endocarditis, and liver abscess might occur.²⁰ Thus, it is of crucial importance to explore the efficacy of probiotic supplementation in younger children whose immune system is still under development. Unnecessary administration might be redundant and even incur serious complications. To the best of our knowledge, this is the first meta-analysis focusing on the treatment effect of probiotics in infants. In the current meta-analysis, we found a significant effect of probiotics in the management of infantile AD.

In our subgroup analysis, we found that only *Lactobacillus* strains are protective in the treatment of AD. However, only three studies, accruing 148 subjects for the treatment and the control group combined, investigated the effect of *Bifidobacterium* species. As such, results of *Bifidobacterium* should be viewed with caution due to the smaller size and heterogeneity of studies. In addition, earlier studies did show that *bifidobacteria* strains are decreased in the stools of infants with AD.^{21,22} It might be fruitful to further explore the effect of *bifidobacteria* in combination with *Lactobacillus* or alone in larger trials.

We found that disease severity was associated with the effect of probiotic supplementation treatment. In infants with moderate-to-severe diseases, we observed a WMD (95% CI) of -8.32 (-16.35 , -0.28), indicating a significantly protective effect, whereas in participants with milder diseases, the effect was not significant, which was in accordance with previous meta-analysis where older children were studied.¹⁹ Among the studies included in the quantitative synthesis of the current meta-analysis, four studies incorporated disease severity as their participant recruitment criterion, while three others did not. As severe AD tends to improve over time, leading to the regression of SCORAD to the mean, disease severity might be a

Table 2 Quality assessment of the included studies

Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Isolaure, E ⁶	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
Viljanen, M ⁷	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Weston, S ⁸	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Gruber, C ⁹	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Gore, C ⁵	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Lin, R. J ⁴	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Rose, M. A ¹⁰	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk

Table 3 Grade assessment of studies. Question: should probiotics versus placebo be used for infantile atopic dermatitis?

Certainty assessment		No of patients					Effect (95% CI)	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
8	Randomised trials	Serious ^a	Serious ^b	Not serious	Not serious	None	-5.71 (-8.37, -3.04)	⊕⊕○○ LOW	IMPORTANT

^aSome studies were unclear of blinding of outcome measurement and their randomization generation method. Patient withdrawal was severe for two studies.

^bHeterogeneity persists albeit subgroup analysis.

confounder and should be accounted for in future studies. Similarly, the mysterious finding that treatment of 8 weeks or less is protective and treatment of longer duration did not confer equal protection as expected. This might also be explained by the natural progression of AD, which diminishes the effect of any treatment over time.

Another finding is that probiotic treatment might be more effective in infants aged less than 12 months with a borderline *P* value of 0.055. One possible explanation is that children of 1 year of age or less are less subjective to other dietary supplements, which at older ages might become allergens and contribute to exacerbation. On the contrary, children less than 1-year-old are less prone to unmeasured confounders.

Our analysis revealed great heterogeneity that could not be reduced by subgroup analyses. One possible source of heterogeneity might originate from the dosage variance. As a recent review pointed out, there seems to be dose-response effects of probiotics in antibiotic-associated diarrhea,²³ and treatment effects might also be dose-dependent. As shown in Table 1, the dosages of probiotic bacteria ingested by the patients vary by two orders of magnitude, and further evidences are required to resolve this heterogeneity that might be caused by variation in dosage. One other consideration was that current studies have been using doses ranging from 10⁸ to 10¹¹, which is common in probiotic studies targeting adults.²³ However, this might not be the optimal dose for infants. Future studies testing other dosages in this age group could be promising.

We also found that the safety profile of probiotic treatment is not adequately studied. Incidents of common side effects of probiotics, including constipation, nausea, infection, and rash, are not registered. In a study investigating effects of symbiotic treatment in older children, no severe side effect was observed.¹³ However, in younger children, this question remains to be answered. In addition, recurrence data were lacking in these studies. The only study that tried to address this issue by following the infants up to 6 months after treatment found no effect of probiotics on recurrences of AD.¹⁰ Furthermore studies are required to assess both the safety profile and long-term effects of probiotics for the treatment of AD infants.

Some limitations of this study are the small number of RCTs available for quantitative synthesis as well as the small sample sizes of each study. Also, the inclusion criteria might be too stringent as we excluded studies published in other languages and abstract publications from conferences. We acknowledge our inclusion criteria might incur possible publication bias; however, with Begg's test and the funnel plot, we did not find any. This paper did not go through consumer review, and thus our academic and clinical concern might not stand for that of the consumers (i.e., parents of AD infants). Albeit these limitations, our study is, to the best of our knowledge, the first to assess the efficacy of probiotic treatment in infantile atopic dermatitis (<3 years).

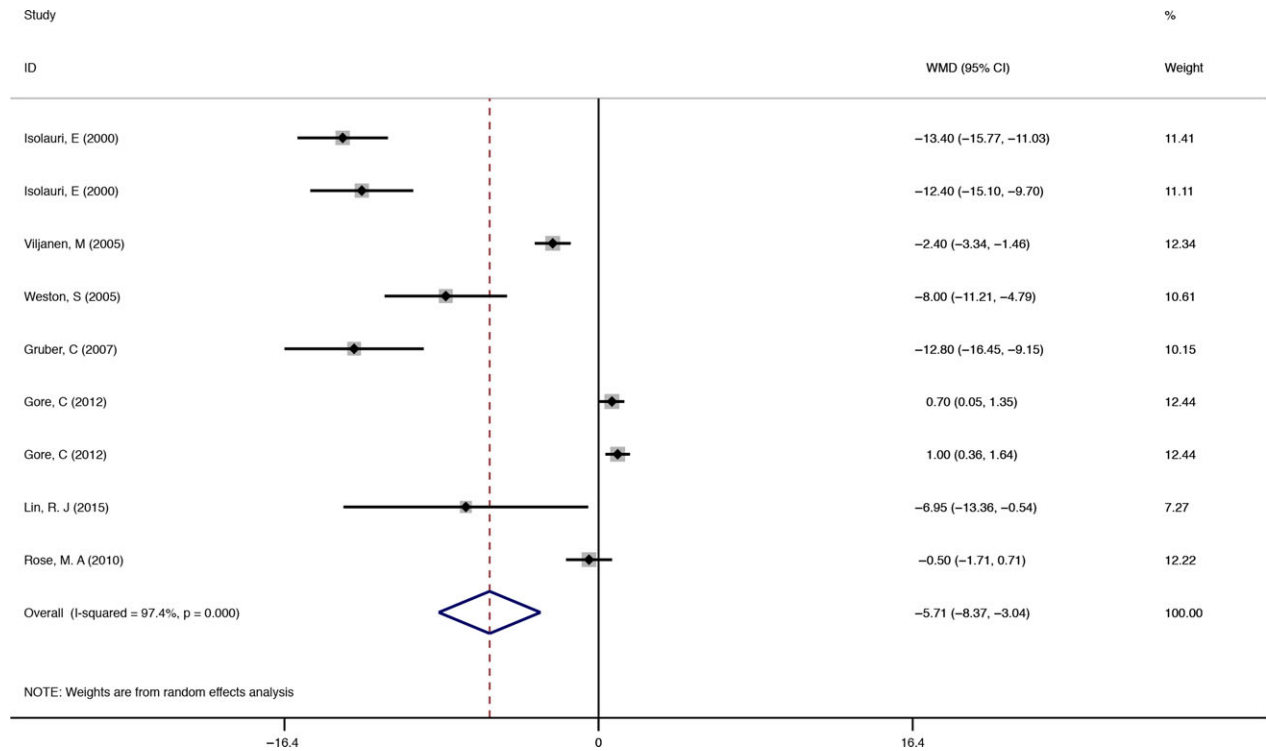


Figure 3 Forest plot of studies describing the treatment efficacy of probiotic use for infant atopic dermatitis from seven RCTs. Dots represent the weighted mean difference (WMD) of SCORAD index in the probiotic group compared to the placebo group in each study, and horizontal lines represent the 95% CI for the WMD. Size of the square around each WMD is proportional to the study weight. I^2 , the inconsistency index, represents the degree of heterogeneity in the included studies. Pooled WMD (diamond) was calculated using a random effects model

Table 4 Subgroup analysis of randomized clinical trials of synbiotics for treatment of atopic dermatitis

Parameters	Studies, NO.	Treatment/Control, NO.	WMD (95% CI)	P value	I^2 , %
Probiotic species					
Containing <i>Lactobacillus</i>	6	268/248	-5.76 (-9.21, -2.30)	0.001	97.5
Containing <i>Bifidobacterium</i>	3	73/75	-6.03 (-16.33, 4.26)	0.251	97.9
Treatment duration, weeks					
≤8	4	144/130	-8.65 (-14.32, -2.98)	0.003	96.4
>8	3	197/138	-1.68 (-3.83, 0.46)	0.125	94.7
Participant age, years					
≤1	3	221/168	-2.41 (-4.87, 0.05)	0.055	96.5
>1 included	3	102/91	-4.85 (-10.77, 1.08)	0.109	90.6
Disease severity					
Mild AD	2	141/94	-2.38 (-5.20, 0.45)	0.074	97.9
Moderate-to-severe AD	2	106/101	-8.32 (-16.35, -0.28)	0.043	90.7
Unclear	3	117/100	-2.38 (-5.20, 0.45)	0.1	96.3

AD, atopic dermatitis; WMD, weighted mean difference; CI, confidence interval.

Conclusion

The current analysis favors the employment of probiotics in children. However, caution should be raised when treating children

less than 1 year of age. Moreover, mild subjects constitute exceptions of this beneficial effect. More studies investigating efficacy of *Bifidobacterium* strains could be informative. Also, further larger studies are needed to address the safety, dose-

response profile, and long-term effect of probiotics in the treatment of pediatric AD.

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