Original Investigation

Synbiotics for Prevention and Treatment of Atopic Dermatitis
A Meta-analysis of Randomized Clinical Trials

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IMPORTANCE Atopic dermatitis (AD) is a highly prevalent condition that may be associated with an altered gastrointestinal microbiota that promotes an immune environment more susceptible to allergic disease. Synbiotics, a mixture of prebiotics and probiotics, have been used for the prevention and treatment of AD.

OBJECTIVE To investigate the efficacy of synbiotics for primary prevention and treatment of AD.

DATA SOURCES PubMed/MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and the CAB Abstracts Archive searchable database were searched from the inception of all databases to October 15, 2015, with no language restrictions.

STUDY SELECTION We included all published randomized clinical trials of synbiotics for prevention and/or treatment of AD. To be included, a publication needed to clearly define the intervention as oral administration of synbiotics (combination of probiotics and prebiotics) and must have included an assessment of AD disease severity, such as the Severity Scoring of Atopic Dermatitis (SCORAD) index, or the incidence of AD as an outcome measure. Only 8 of 257 initially identified studies (3%) met selection criteria.

DATA EXTRACTION AND SYNTHESIS Data extraction was independently done by multiple observers and cross-checked to avoid errors. The quality of the selected studies was critically examined following the Cochrane guidelines. Data were pooled using a random-effects model.

MAIN OUTCOMES AND MEASURES The primary outcomes were the SCORAD index (treatment studies) and the relative risk of AD (prevention studies). The hypothesis was formulated before data collection.

RESULTS A total of 257 abstracts were screened to identify 6 treatment studies (369 children enrolled; aged 0 months to 14 years) and 2 prevention studies (1320 children enrolled; up to age 6 months in one study and term neonates aged <3 days in the other). From the 6 treatment studies included for random-effects meta-analysis, the overall pooled change in SCORAD index in those treated with synbiotics at 8 weeks of treatment was −6.56 (95% CI, −11.43 to −1.68; P = .008). Heterogeneity was significant (I^2 = 77.1%; P = .001). Subgroup analysis showed that the beneficial effect was significant only when using mixed strains of bacteria (weighted mean difference, −7.32; 95% CI, −13.98 to −0.66; P = .03) and when used in children aged 1 year or older (weighted mean difference, −7.37; 95% CI, −14.66 to −0.07; P = .048). From the 2 prevention studies included, the pooled relative risk ratio of AD in those treated with synbiotics compared with placebo was 0.44 (95% CI, 0.11 to 1.83; P = .26).

CONCLUSIONS AND RELEVANCE This meta-analysis shows evidence that supports the use of synbiotics for the treatment of AD, particularly synbiotics with mixed strains of bacteria and for children aged 1 year or older. Further studies are needed to evaluate the effectiveness of synbiotics for primary prevention of AD.

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The prevalence of infant and childhood allergic disease is on the rise, with the recent estimated prevalence of atopic dermatitis (AD) at 15% to 20%.[1] One possible explanation for this increased prevalence is an alteration in gastrointestinal microbiota that promotes an immune environment more susceptible to allergic disease. It has been found that the gut microbiota may be different in infants with AD and that this difference may precede the development of eczema. Specifically, 2 studies found that infants with eczema had decreased bifidobacteria species in their stool.[2,3] Given this, prebiotic and probiotic supplements, which can modulate intestinal microbiota, have been tested as prevention and treatment methods for AD.

Probiotics contain cultures of living microorganisms that, when ingested in adequate amounts, can modulate gut microbiota and provide health benefits beyond nutrition.[4-6] They have been used for several diseases including inflammatory bowel disease, asthma, allergies, and AD under the hypothesis that microbiota has a global allergy-protective effect.[4-6] Children with genetic risk for AD who are given probiotic supplements early in life will be exposed to antigenic competition, immune regulation, and stimulation of innate immunity, all of which might decrease susceptibility to certain disorders.[7] The results of isolated trials using probiotics to prevent or treat AD have been inconsistent, and the large variability in bacterial strains and quantity ingested in these studies makes interpretation challenging. Two meta-analyses have demonstrated that probiotics might reduce the incidence of AD in infants, with the pooled relative risk ratio ranging from 0.69 to 0.79.[4,6] A recent meta-analysis also concluded that treatment with probiotics significantly decreased the Severity Scoring Atopic Dermatitis (SCORAD) index in children with AD[8]; however, other meta-analyses showed inconsistent results.[9-11]

Prebiotics contain nonliving indigestible fibers that may give certain bacterial strains a selective advantage to live and grow.[12] They stimulate the growth of healthy bacteria in the colon. A meta-analysis showed that prebiotics alone significantly reduced the development of AD in infants (relative risk ratio = 0.68; 95% CI, 0.48-0.97).[12] Few studies have investigated the efficacy of prebiotics for the treatment of AD, but a beneficial effect has also been reported.[13] Because probiotics feed off of prebiotics, the two are sometimes combined in a supplement to act synergistically to promote healthy gastrointestinal bacteria. Called *synbiotics*, the combination has a potentially stronger effect on gut microbiota than either probiotics or prebiotics alone. Synbiotics have also been used for either prevention or treatment of AD, but the results are inconsistent and have not been extensively reviewed. Our objective was to conduct a systematic literature review and meta-analysis of randomized clinical trials investigating the efficacy of oral synbiotics in the prevention and treatment of AD in children.

Methods

The conduct and reporting of the current systematic review and meta-analysis conform to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[14,15]

At a Glance

- Atopic dermatitis is a highly prevalent condition that may be associated with an altered gastrointestinal microbiota; synbiotics, a mixture of prebiotics and probiotics, have been used for the prevention and treatment of atopic dermatitis.
- To investigate the efficacy of synbiotics for prevention and treatment of atopic dermatitis, we performed a meta-analysis including all published randomized clinical trials of synbiotics for prevention and/or treatment of atopic dermatitis.
- We found evidence that supports the use of synbiotics for the treatment of atopic dermatitis, particularly mixed strains of bacteria (mean change in Severity Scoring of Atopic Dermatitis index, −7.32; 95% CI, −13.98 to −0.66) and for children aged 1 year or older (mean change, −7.37; 95% CI, −14.66 to −0.07). Further studies are needed to evaluate the effectiveness of synbiotics for primary prevention of atopic dermatitis.

Search Strategy

Comprehensive literature searches were undertaken in PubMed/MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and the CAB Abstracts Archive (a searchable database by the Centre for Agriculture and Biosciences International), from the inception of all databases to October 15, 2015. Thorough manual search was conducted for existing reviews, and relevant articles were retrieved from references. The entire search strategy was evaluated by an independent librarian and is provided in the eAppendix in the Supplement. Three independently working groups (M.T.G.-R. and M.K.T.; A.J. and Y.-S.C.; Y.-F.L. and L.D.) evaluated all retrieved articles using the inclusion criteria as described later. All differences in opinion were resolved through consensus.

Study Selection

We included all published randomized clinical trials evaluating the effect of synbiotics on AD, either for the treatment or prevention of the disease. No language restrictions were imposed on study selection; both English and non-English articles were reviewed. To be included, a publication needed to clearly define the intervention as oral administration of synbiotics (combination of probiotics and prebiotics) and must have included an assessment of AD disease severity, such as the SCORAD index, or the incidence of AD as an outcome measure.

Data Extraction

The data extraction for each study was independently done by 2 authors and cross-checked to avoid errors. Details of study methods included aims and objectives, study population, inclusion and exclusion criteria, period of enrollment, type of study, blinding (yes or no) and type (single or double), random sequence generation, allocation concealment, type of analysis, specific intervention (synbiotic combination used, dose, and route of administration), specific placebo or any alternative intervention used in the control arm (dose and route of administration), number of participants screened and number randomized (total and in each arm), primary outcome measure, secondary outcome measures, and duration of follow-up after intervention. The numbers of participants in each

Table 1. Characteristics of Studies Included in the Meta-Analysis

Source (Country)	Treatment/ Control Participants, No.	Participant Age	Synbiotics Used, Probiotic + Prebiotic	Control Used	Dose	Duration	Main Results
Treatment studies							
Passeron et al,[16] 2006 (France)	17/22	2-12 y	*Lactobacillus rhamnosus* + skimmed milk powder, potato starch, and lactose	Prebiotic (skimmed milk powder, potato starch, and lactose)	1.2×10^9 CFU; 3 times daily	12 wk	Mean total SCORAD index significantly decreased in both groups, but at end of treatment, no statistically significant difference between the 2 groups was found
Gerasimov et al,[17] 2010 (Ukraine)	43/47	12-36 mo	*Lactobacillus acidophilus* DDS-1, *Bifidobacterium lactis* UABLA-12 + fructo-oligosaccharide	Placebo (rice maltodextrin)	1×10^{10} CFU; daily	8 wk	Children receiving synbiotics showed greater decrease in mean SCORAD index than did children from placebo group at wk 8
van der Aa et al,[18] 2010 (Netherlands)	42/43	0-7 mo	*Bifidobacterium breve* + mixture of 90% scGOS and 10% lcFOS	Placebo	1.3×10^9 CFU; on demand	12 wk	No difference in SCORAD index improvement between synbiotic and placebo groups; synbiotic group did have significantly higher percentage of specific fecal bacteria
Shafiei et al,[19] 2011 (Iran)	18/18	1-36 mo	7 Strains of probiotics + fructo-oligosaccharide	Placebo (sucrose)	1×10^9 CFU; once daily	8 wk	Mean total SCORAD index decreased by 56% in all patients, but no difference between placebo and synbiotic groups
Farid et al,[20] 2011 (Iran)	19/21	3 mo to 6 y	*Lactobacillus casei*, *L rhamnosus*, *Streptococcus thermophilus*, *B breve*, *L acidophilus*, *Bifidobacterium infantis*, *Lactobacillus bulgaricus* + fructo-oligosaccharide	Placebo	1×10^9 CFU; twice daily	8 wk	Significantly greater reduction in SCORAD index of synbiotic group compared with placebo group
Wu et al,[21] 2012 (Taiwan)	27/27	2-14 y	*Lactobacillus salivarius* + fructo-oligosaccharide	Prebiotic (fructo-oligosaccharide, corn starch)	2×10^9 CFU; twice daily	10 wk	At 10 wk, SCORAD index was significantly lower in treatment group compared with control group (>50% change)
Prevention studies							
Kukkonen et al,[22] 2007 (Finland)	459/463	Pregnant women 2-4 wk before delivery + their infants (for 6 mo)	*L rhamnosus* GG (ATCC 53103) and LC705 (DSM 7061), *B breve* Bb99 (DSM 13692), *Propionibacterium freudenreichii* subsp *shermanii* JS (DSM 7076) + galacto-oligosaccharides	Placebo (microcrystalline cellulose and sugar syrup without galacto-oligosaccharides)	ATCC 53103, 5×10^9 CFU; DSM 7061, 5×10^9 CFU; DSM 13692, 2×10^8 CFU; DSM 7076, 2×10^9 CFU	6 mo	Synbiotic treatment reduced eczema (OR = 0.74; 95% CI, 0.55-0.98; $P = .04$)
Rozé et al,[23] 2012 (France)	39/45	Term neonates <3 d	*L rhamnosus* LCS-742, *Bifidobacterium longum* subsp *infantis* M63 + 96% galacto-oligosaccharides and 4% scFOS	Control infant formula	1.4×10^8 CFU/100 mL of formula	6 mo	Synbiotic treatment reduced AD (OR = 0.11; 95% CI, 0.01-0.94; $P < .05$)

Abbreviations: CFU, colony-forming units; lcFOS, long-chain fructo-oligosaccharides; OR, odds ratio; scFOS, short-chain fructo-oligosaccharides; scGOS, short-chain galacto-oligosaccharides; SCORAD, Severity Scoring of Atopic Dermatitis.

arm who were included in analysis, noncompliant, and lost to follow-up in each arm were also recorded.

The primary outcome for the treatment studies was measured by the mean and standard deviation of change in the SCORAD index from baseline to the primary end point, contrasted between the intervention and control arms. Secondary outcomes considered by the studies included pruritus and sleep disturbance subscores within the SCORAD, changes in topical medication use and frequency, total serum IgE level and specific IgE levels to allergens, total eosinophil count, skin prick test results, stool frequency and consistency, changes in fecal microbiota composition, and adverse effects. For the prevention studies, the primary outcome was the incidence of AD, and secondary outcomes included total serum IgE level and specific IgE levels to allergens, total eosinophil count, skin prick test results, stool frequency and consistency, and changes in fecal microbiota composition. A summary of the study characteristics is included in **Table 1**.

Statistical Analysis

The statistical analysis was performed using Stata version 12.0 statistical software (StataCorp LP). For treatment studies, the

primary outcomes were reported as mean change in SCORAD index from baseline, in the intervention and placebo groups. In studies where the mean change was not reported, standard statistical techniques were followed to calculate this information from the reported data.[24] For prevention studies, the primary outcomes were reported as incidence of AD. Pooled weighted mean differences (WMDs) or relative risk ratios and the 95% confidence intervals were estimated using a random-effects model based on the DerSimonian-Laird method. Forest plots were depicted for visual interpretation of the individual study-specific and pooled estimates with respective 95% confidence intervals. The χ^2 test of homogeneity (Cochran Q statistic, $P < .05$) and I^2 statistic (>75%) were defined to assess statistical significance and degree of heterogeneity.[24]

Risk of Bias

The quality of the selected studies and the risk of bias were critically examined following the Cochrane guidelines.[24] The quality parameters included the type of analysis, random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Exploration of Heterogeneity and Further Analysis

We made an a priori decision to conduct analyses of the primary outcome based on different durations of treatment (4 weeks, 8 weeks, and end of study) and use the result from the longest common treatment duration as the main outcome effect. We also decided to conduct subgroup analysis based on control used (placebo or prebiotics), probiotic strain component (single strain or mixed), and participant age (whether including infants aged <1 year).

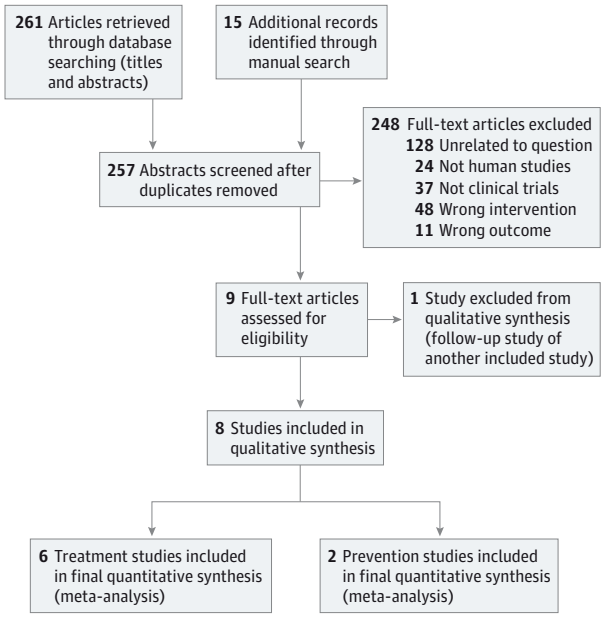
Publication bias was evaluated by constructing a funnel plot for the visual assessment of asymmetry, along with statistical estimates from the Egger test. Influence analysis was performed to examine the effect of individual studies on the pooled mean difference.

Results

Study Characteristics

A total of 261 articles (abstracts) were retrieved through the database searches, and an additional 15 were retrieved through the manual reference search. However, after excluding duplicates, 257 articles were considered for the first stage of screening. We excluded 249 articles at this stage, the principle reasons being studies unrelated to our research question, wrong intervention, and not being a randomized clinical trial (**Figure 1**). For the final meta-analysis, 6 treatment studies (369 children enrolled)[16-21] and 2 prevention studies (1320 children enrolled)[22,23] were included. The study characteristics of these 8 selected trials are summarized in Table 1. The selected studies were all double-blind, randomized clinical trials. Quality assessment of the studies is summarized in the eTable in the Supplement. No evidence of publication bias was found by the funnel plot and the Egger linear regression test (intercept, −1.94; 95% CI, −9.85 to 5.97; $P = .53$) (eFigure 1 in the Supplement).

Figure 1. Flowchart of the Stepwise Procedure for Study Selection



Synbiotics for the Treatment of AD

Overall Clinical Effects

There was variety in the treatment duration for each of the 6 studies, ranging from 8 to 12 weeks. In our main analysis, we determined weighted pooled estimates for the change in SCORAD index at 8 weeks because this is the longest treatment period at which results were reported for all of the included studies. A random-effects model meta-analysis of all 6 trials showed a significant decrease in the WMD of SCORAD values in the synbiotics group compared with the control group (WMD, −6.56; 95% CI, −11.43 to −1.68; $P = .008$) (**Figure 2**). However, significant heterogeneity among studies was observed ($I^2 = 77.1\%$; $P = .001$).

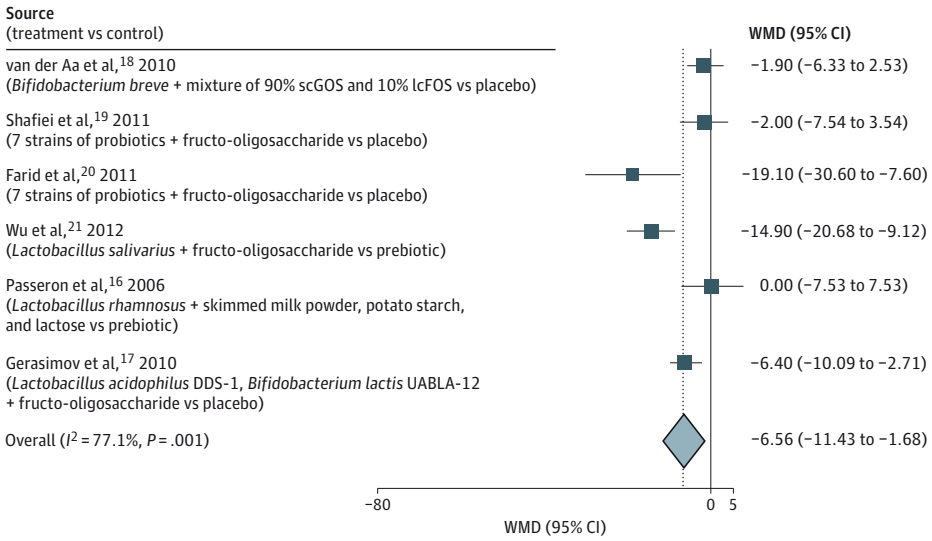
Clinical Effect by Treatment Duration

We explored the effects at different measurement times. From the 5 studies that reported the SCORAD index at 4 weeks (n = 308),[16-18,20,21] there was a trend of improvement in the SCORAD index at 4 weeks for the synbiotic vs control groups, but it did not reach statistical significance (WMD, −5.53; 95% CI, −11.23 to 0.17; $P = .06$). At the end of study, which ranged from 8 to 12 weeks, there was a significant decrease in the WMD of SCORAD values in the synbiotics group compared with the control group (WMD, −5.86; 95% CI, −10.94 to −0.79; $P = .02$). Subgroup analysis by treatment duration showed that treatment for more than 8 weeks did not confer additional benefit (**Table 2**).

Clinical Effect by Type of Probiotic Bacterial Species

Three studies used single-strain bacterial species in the probiotic content of the synbiotics (n = 178),[16,18,21] while 3 studies used mixed-strain bacterial species (n = 166).[17,19,20] Mixed-strain bacterial species had a significant effect on improving the SCORAD index (WMD, −7.32; 95% CI, −13.98 to −0.66;

Figure 2. Forest Plot for Weighted Mean Difference (WMD) in Change in Severity Scoring of Atopic Dermatitis (SCORAD) Index at 8 Weeks of Treatment With Synbiotics



Weights are from random-effects analysis. lcFOS indicates long-chain fructo-oligosaccharides; scGOS, short-chain galacto-oligosaccharides.

Table 2. Subgroup Analysis of Randomized Clinical Trials of Synbiotics for Treatment of Atopic Dermatitis

Factor	Studies, No.	Treatment/ Control Participants, No.	WMD (95% CI)	*P* Value	I^2, %
Treatment duration, wk					
≤8	3	80/86	−7.32 (−13.98 to −0.66)	.03	71.6
>8	3	86/92	−4.46 (−13.64 to 4.72)	.34	83.5
Participant age					
Only ≥1 y	3	87/96	−7.37 (−14.66 to −0.07)	.048	80.8
Includes infants <1 y	3	79/82	−5.74 (−13.16 to 1.67)	.13	74.5
Type of probiotics					
Single strain	3	86/92	−5.69 (−14.79 to 3.41)	.22	86.4
Mixed strains	3	80/86	−7.32 (−13.98 to −0.66)	.03	71.6
Control used					
Placebo	4	122/129	−5.46 (−10.24 to −0.67)	.03	67.7
Prebiotics	2	44/49	−7.65 (−22.25 to 6.94)	.30	89.4

Abbreviation: WMD, weighted mean difference.

P = .03), while single-strain bacterial species did not improve the SCORAD index significantly (*P* = .22) (Table 2).

Clinical Effect by Participant Age

Three studies enrolled only participants aged 1 year or older[16,17,21] and 3 studies also enrolled infants younger than 1 year.[18-20] Synbiotics significantly improved the SCORAD index for children aged 1 year or older with AD (WMD, −7.37; 95% CI, −14.66 to −0.07; *P* = .048) but did not have a significant effect in the studies that also included infants younger than 1 year (*P* = .13) (Table 2).

Effect of Synbiotics vs Prebiotics

Four studies compared the effect of synbiotics vs placebo,[17-20] while 2 studies used prebiotics for the control group rather than placebo.[16,21] Synbiotics improved the SCORAD index significantly compared with placebo (WMD, −5.46; 95% CI, −10.24 to −0.67; *P* = .03); however, compared with prebiotics, synbiotics did not have a significant effect (*P* = .30) (Table 2).

Synbiotics for the Prevention of AD

Only 2 prevention studies met our criteria for inclusion in the meta-analysis. The pooled relative risk ratio of AD in those treated with synbiotics compared with those treated with placebo was 0.44 (95% CI, 0.11-1.83; *P* = .26). Heterogeneity was moderate (I^2 = 56.7%; *P* = .13) (eFigure 2 in the Supplement).

Discussion

In this meta-analysis, we found a significant effect of synbiotics compared with placebo for the treatment of AD in children, especially when using a mixed-strain probiotic component and for children aged 1 year or older. However, we did not

find strong evidence to suggest the use of synbiotics for the prevention of AD.

The roles of probiotics, prebiotics, and synbiotics in AD have been a popular area of study. Previous meta-analyses evaluating the effect of probiotics on the treatment of AD had inconsistent results.[8-11] Of these meta-analyses, the most recent one concluded that probiotics significantly improved the SCORAD index in patients aged 1 year or older with AD (mean difference, −4.51; 95% CI, −6.78 to −2.24),[8] but the clinical significance of these findings has been questioned and therefore the role of probiotics in the treatment of AD has not been established. Prebiotics alone have been found to be able to lower the SCORAD index in children with AD in a small randomized clinical trial (RCT),[13] and in the meta-analysis by Kim et al,[8] a post hoc comparative analysis showed that the studies using a nonprebiotic placebo showed greater mean differences in SCORAD value changes than those using a prebiotic placebo (nonprebiotic placebo: WMD, −5.58; 95% CI, −9.42 to −1.74; prebiotic placebo: WMD, −3.81; 95% CI, −6.82 to −0.80), suggesting a beneficial effect of prebiotics for AD. Synbiotics exert both probiotic and prebiotic effects and theoretically work better than either alone.[25] A recent meta-analysis found that synbiotics have a more pronounced effect than probiotics in reducing the incidence of postoperative sepsis in the elective general surgery setting. In our pooled analysis, synbiotics significantly reduced the SCORAD index by a WMD of −6.56 after 8 weeks of treatment. The beneficial effect of synbiotics seems greater than the pooled effect of probiotics in the previous meta-analysis.[8] However, there were no studies performing head-to-head comparison between synbiotics and probiotics, and the clinical significance of the benefit could still be questionable.

There were several interesting findings from our subgroup analyses. First, the studies that used mixed-strain bacterial species had a significant effect on improving the SCORAD index (WMD, −7.32), while those that used single-strain bacterial species did not. Previous meta-analyses on the effect of probiotics also found that mixed strains improved the SCORAD index better than single strains for either the treatment or prevention of AD.[6,8] There could be a possible synergistic effect of mixed strains of bacteria in regulating the gut microbiota and thus the immune system, and further research is needed. The effect of synbiotics with a mixed-strain probiotic component found in our study also seems more pronounced than the effect of mixed-strain probiotics alone found in the meta-analysis by Kim et al[8] (mean difference,−7.32 vs −6.60, respectively). Again, head-to-head comparison studies are needed for clarification.

We also found that synbiotics significantly improved the SCORAD index for children aged 1 year or older with AD but did not have a significant effect when infants were also included. This is consistent with previous findings of probiotics by Kim et al,[8] suggesting that benefit from probiotics or prebiotics is limited in infants younger than 1 year. However, not all of the studies that included infants presented separate results for children younger than 1 year and those aged 1 year or older. Therefore, we were unable to directly compare the effect of synbiotics for these 2 age groups.

We found that synbiotics improved the SCORAD index significantly compared with placebo but did not have a significant effect compared with prebiotics. However, only 2 studies with small sample sizes used prebiotics as the control, and it has been shown that prebiotics might by themselves have a possible beneficial effect for the treatment of AD.[13] Therefore, these findings should be interpreted with caution as we might not have had enough power to detect a difference.

Another finding was that treatment duration longer than 8 weeks with synbiotics did not confer additional benefit. This is inconsistent with prior studies in which longer probiotic administration was beneficial for both the treatment and prevention of AD.[7,8,26] This inconsistency may be due to the significant heterogeneity between studies.

Because one of the included studies[20] had such a large effect size but did not provide important details of the study design such as baseline SCORAD index, we decided to exclude it from the analysis and obtain results without it as a sensitivity analysis. The result remained significant (WMD, −5.162; 95% CI, −9.845 to −0.478; $P = .03$), which supports the evidence that synbiotics provide a benefit for treating AD.

Regarding primary prevention of AD, a recent meta-analysis of 14 studies found that probiotics reduced the incidence of AD in infants younger than 2 years (pooled relative risk ratio, 0.69; 95% CI, 0.62-0.78).[12] In our study, the pooled relative risk ratio of AD in those treated with synbiotics compared with those treated with placebo was 0.441 but was not significant owing to a wide 95% confidence interval. Only 2 prevention studies were included in our analysis,[22,23] and there was moderate heterogeneity between them. In one study, pregnant mothers were treated 2 to 4 weeks before delivery and then their infants were treated for 6 months.[22] In the other study, treatment was started less than 3 days after birth and continued for 6 months.[23] The bacterial strains, prebiotic components, and dose were also different between these 2 studies. Therefore, although both of the individual studies showed that synbiotic treatment significantly reduced the incidence of AD, the pooled relative risk ratio was insignificant. This underscores the necessity of more RCTs assessing the role of synbiotics for the prevention of AD.

To our knowledge, this is the first meta-analysis of RCTs of synbiotics for the treatment and prevention of AD. We did not find evidence of publication bias, and according to our quality assessment there were not many opportunities for other kinds of biases. Some of the limitations of our meta-analysis are the small number of RCTs that were available for analysis as well as the small sample sizes of each study. Another limitation is the large heterogeneity between studies. The probiotics and prebiotics as well as the placebo components and dose used varied between the studies. Important heterogeneity might also stem from diverse factors such as variable populations, different ages of the study participants, and different levels of strict study execution. All the treatment studies allowed for concomitant steroid use for AD but did not control amounts or frequency; this could also be an important source of heterogeneity.

Conclusions

Currently, the evidence supports the use of synbiotics for the treatment of AD, particularly in children aged 1 year or older with synbiotics composed of mixed strains of bacteria. More studies are needed to specify the strains of probiotics and type of prebiotics that are more effective. Also, further larger studies are needed to address the efficacy of synbiotics for the prevention of this common pediatric disease.

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Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
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Study supervision: Chang, Jha.

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