

The role of probiotics in prevention and treatment for patients with allergic rhinitis: A systematic review

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ABSTRACT

Background: Allergic rhinitis (AR) is a disease of respiratory allergy, and probiotics can provide a potential strategy for its management. The purpose of this study was to carry out a systematic review to investigate the role of probiotics in the prevention and treatment of AR.

Methods: We searched for randomized controlled trials (RCTs) of the use of probiotics for the prevention and treatment of AR in the major electronic databases up to March 2014. The quality of the included RCTs was evaluated, and the data were independently extracted by two assessors. Meta-analyses were performed. Continuous data were expressed as the mean difference (MD) or standardized MD with 95% confidence interval (CI). Dichotomous data were expressed as odds ratio with the 95% CI. A *p* value <0.05 was considered significant.

Results: A total of 11 RCTs were included in the analysis. Probiotic intake was associated with a significant overall improvement of the quality of life scores and nasal symptom scores of patients with AR (MD -2.97 [95% CI, -4.77 to -1.16]; *p* = 0.001). No improvements with regard to prevention or immunologic parameters were noted in the patients with AR.

Conclusions: The current evidence is not sufficiently strong to verify a preventive role of probiotics in AR, but probiotics may improve the overall quality of life and nasal symptom scores. Because the available data were generated from only a few trials with a high degree of heterogeneity, routine use of probiotics for prevention and treatment in patients with AR cannot be recommended.

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Recently, the incidences of both perennial allergic rhinitis (AR) and seasonal AR have been increasing worldwide,¹ and according to morbidity reports for AR, the incidence ranges from 10 to 20%.² As the disease progresses, it may impair the quality of life (QOL) of patients with chronic disease to varying degrees, increasing their medical burden. Therefore, it is important to understand the mechanisms that underlie AR to control its symptoms effectively and reduce medical expenditure.

AR is characterized by T-helper (Th) 2 polarization, as elevated levels of Th2-derived cytokines, including interleukin (IL) 4, IL-5, and IL-13, have been implicated in AR.³ Th2 cytokines play a pathogenic role through inducing immunoglobulin (Ig) E synthesis and eosinophil infiltration. Th2 polarization in subjects with allergy may occur as a consequence of reduced pressure of microbial agents in the gut, which is referred to as the hygiene hypothesis.⁴ However, some studies recently revisited the hygiene hypothesis and suggested that the decline in childhood infections is less important than how modern societal practices have caused the disappearance of ancestral indigenous microbiota species that might confer benefits beyond our current understanding,⁵ which constitutes the so-called microbial hypothesis. Microbial exposure during the perinatal period is linked to epigenetic regulation of genes involved in allergic inflammation and alters susceptibility to allergic diseases.⁶ Based on these observations, there is reason to believe that some types of microorganisms can modulate the immune systems of patients with AR and impact their symptoms and QOL.

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host.⁷ Recent clinical and animal studies support the hypothesis that lactobacilli, particu-

larly certain selected strains with immunomodulatory properties, can modify the responses of the host, thereby inducing beneficial effects against AR. For example, Ishida *et al.*⁸ reported that the oral administration of *Lactobacillus acidophilus* strain L-92 suppresses serum antigen-specific IgE levels in mice and verified the antiallergic effect of *L. acidophilus* strain L-92 in patients with perennial AR. Moreover, it has been shown that *Lactobacillus paracasei* may improve the QOL of adolescents with perennial AR and that *Lactobacilli* spp. can be beneficial for the respiratory tract in individuals who consume probiotic milk for a long period of time.¹⁰ However, numerous clinical trials that investigated the prevention and treatment of allergic respiratory diseases, including asthma and AR, demonstrated that the beneficial effects of probiotics are not significant. A preventive study of probiotic use during the first 7 years of life showed that the overall risk of developing eczema was significantly decreased in the *Lactobacillus rhamnosus* strain GG (Gorbach and Goldin), which paralleled their earlier findings with a shorter follow-up. However, AR and asthma tended to be more common in the probiotic group; further studies are required in other populations and with other probiotic strains.¹¹ A Finnish study that tested *Lactobacillus rhamnosus* GG versus placebo for the treatment of birch pollen-induced AR showed no significant difference in the obtained rhinitis symptom scores.¹²

Thus, the effect of probiotics on rhinitis remains controversial, and questions remain regarding whether probiotics have an effect on AR and whether they play a role in prevention and treatment. To investigate these issues, a review of the current literature was conducted to determine whether the use of probiotics benefits patients with AR.

METHODS

Types of Studies: Randomized Double-Blind Controlled Trials

Types of Participants

Preventive studies of AR included pregnant women with a family history of allergy and term infants with no prior allergic manifestations. A family history of allergy was defined as a family member (mother, father, or older sibling) with atopic dermatitis, AR, or asthma, and confirmed allergic sensitization against an inhalant allergen. Treatment studies of AR were of patients with AR, regardless of age.

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Table 1 The risk evaluation of included studies in the review

Study	Year	Clinical Trial Registration	Ethical Compliance	Random Methods Appropriate	Random Allocation	Patients with Double-Blind Treatment	Blind Inspectors or Curative Effect Appraisal	Results of Incomplete Data	Selective Reports	Other Bias
Dotterud <i>et al.</i> , ¹⁷	2010	Yes	Yes	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk
Kukkonen <i>et al.</i> , ¹³	2011	No	Yes	Lower risk	Unclear	Unclear	Unclear	Lower risk	Lower risk	Unclear
Xiao <i>et al.</i> , ¹⁸	2006	No	Yes	Lower risk	Lower risk	Lower risk	Unclear	Lower risk	Lower risk	Lower risk
Wang <i>et al.</i> , ¹⁹	2004	No	Yes	Unclear	Unclear	Lower risk	Unclear	Lower risk	Lower risk	Unclear
Peng <i>et al.</i> , ²⁰	2005	No	Yes	Unclear	Unclear	Unclear	Lower risk	Lower risk	Lower risk	Unclear
Xiao <i>et al.</i> , ²¹	2006	No	Yes	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk
Nagata <i>et al.</i> , ²²	2010	No	Yes	Unclear	Unclear	Lower risk	Unclear	Lower risk	Lower risk	Unclear
Kuitunen <i>et al.</i> , ¹⁴	2009	No	Yes	Lower risk	Unclear	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk
Ishida <i>et al.</i> , ²³	2005	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Lower risk	Lower risk	Unclear
West <i>et al.</i> , ¹⁵	2013	Yes	Yes	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk
Kalliomäki <i>et al.</i> , ¹⁶	2003	No	Yes	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Unclear

Types of Interventions and Controls

The treatments in the intervention and control groups were probiotics and placebo or other probiotics, respectively. The start time, period, dose, and administration route for prevention or treatment were not restricted.

Types of Outcome Measurements

The primary outcome measurement was the incidence of AR (diagnosed by a structured medical history, clinical examination, atopic sensitization). The secondary outcome measurements were the symptomatology (nasal symptoms and overall QOL) and immunologic assessments (specific IgE, IL-10, interferon [IFN] γ , Th1/Th2 ratio, eosinophil rates) (see the Results section).

Exclusions were of (1) meeting abstracts, case reports, reviews, and review articles; (2) articles with data that could not be extracted or were unreported or unclear; (3) original literature with nonhuman research subjects; and (4) duplicate reports of data or unclear depictions of study characteristics.

Search Strategy

We systematically searched PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and previous reviews, including cross-references (all articles referenced), abstracts, and conference proceedings for all relevant articles up to March 2014. Search strategy included the following: ("probiotics" or "lactobacillus" or "Bifidobacterium" or "bacteriotherapy" or "fermented milk" or "lactic acid bacteria") and ("prevention" or "treatment") and ("allergy" or "respiratory allergy" or "allergic rhinitis" and "children" or "pediatric" or "adults") and ("clinical trial" or "randomized controlled trial" or "randomized controlled trial") in the keywords and/or Medical Subject Heading terms. We then combined all of the searches and retrieved the relevant articles. This study was considered exempt by the Medical College of Luzhou's institutional review board.

Data Collection and Methodologic Quality

Two of the authors (Y.P., A.L.) of this review independently assessed the quality of each trial, and any disagreement was resolved through discussion. The design of the trial, comparators, characteristics of the study participants, number of participants, type of intervention (dose, duration), and major outcomes were evaluated. We assessed trial quality according to methods set out in the Cochrane

Handbook for Systematic Reviews of Interventions.⁹ This scale assigns points as follows:

1. Selection bias: Were the randomization procedure and allocation concealment adequate?
2. Performance bias: Were the participants and personnel involved in the treatment masked to the intervention?
3. Detection bias: Were the outcome assessors masked to the intervention?
4. Attrition bias: (a) Were withdrawals and dropouts completely described, and (b) was the analysis conducted based on intention-to-treat, or was it an "available case" analysis?
5. Reporting bias: Was there selective reporting?
6. Other biases: Were there biases other than those listed above?

There were three types of evaluation results: low risk, unclear risk, and high risk. Trials graded as showing a low risk of bias or an unclear risk of bias were included in the review, whereas trials that presented a high risk of bias were excluded (Table 1).

Data Synthesis

Review Manager version 3.2 Cochrane Collaboration Network (London, United Kingdom), was used for the meta-analysis. First, the heterogeneity of the literature was determined, followed by extracting of the data according to the type of test result. Dichotomous data were expressed as an odds ratio. The weighted MD was used to analyze the outcomes of continuous variables, which were measured by using standard test methods. The standardized mean difference (SMD) was used to analyze the continuous data variables with different measurement units that were obtained from different measurement tools. The 95% confidence intervals (CI) were calculated, and $p < 0.05$ was considered to be statistically significant. When the included studies were not heterogeneous ($p \geq 0.05$; $I^2 < 50\%$), a fixed-effects model was used for the analysis; otherwise, a random-effects model was used.

RESULTS

Screening of the Articles

When the combined Medical Subject Heading terms were used, a total of 496 studies were identified from primary electronic databases,

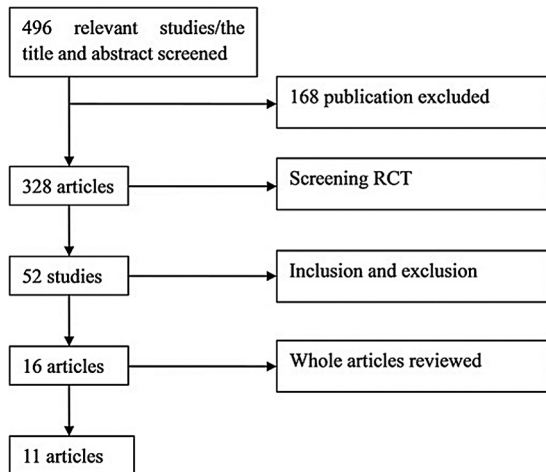


Figure 1. Flow diagram of search results.

including PubMed and EMBASE, and the Cochrane Library. After examining the title and abstract, 168 publications were excluded as irrelevant (because they did not address treatment or prevention). Then, the articles were read again, and 52 studies were considered potentially eligible for randomized control led trial (RCT). Subsequently, we applied the inclusion and exclusion criteria, and 36 trials were excluded. Finally, we read the whole articles; a total of 11 trials were eligible for this systematic review (Fig. 1). According to the Cochrane Handbook⁴⁸, the test bias in the risk assessment required a preliminary evaluation. All of the studies were randomized, double-blind controlled trials and were based in Norway, Finland, Italy, Taiwan, Japan, or Sweden.

Basic Characteristics of the Included Studies: The Preventive and Therapeutic Role of Probiotics in AR

Five studies that addressed the preventive role of probiotics in AR were evaluated. The subjects in the control group were administered a placebo (skimmed fermented milk), microcrystalline cellulose, or cow's milk protein. A total of 1527 mothers and children were enrolled, including 758 in the probiotics group and 769 in the control group. The detailed intervention, time when intervention began, outcome measurements and exclusion criteria are presented in Table 2.^{13–17} In these studies, the immune markers studied included fractional exhaled nitric oxide, specific IgE, total IgE, IgE-associated rhinitis morbidity, and a positive skin-prick test, among others, but only IgE-associated rhinitis morbidity could be combined. Six studies that addressed AR treatment were enrolled, which included 306 patients with AR, 173 of whom participated in probiotics groups and 133 in control groups. The control drugs, types of probiotics, and duration of treatment varied within these studies (Table 2),^{18–23} and the evaluation index included nasal symptom scores, quality-of-life scores, specific IgE, IL-10, IFN- γ , Th1/Th2 ratios, and eosinophil rates.

Analysis of the Effects of Probiotics on AR

There were five trials from which information about AR prevention could be extracted, and no significant heterogeneity was found ($I^2 = 29\%$; $p = 0.23$). The outcome of the meta-analysis revealed that no difference in the incidence of AR was found between the probiotic and placebo groups (odds ratio 1.07 [95% CI, 0.81–1.42]; $p = 0.64$, fixed-effects model), and no significant difference in the prevention of AR was observed (Fig. 2).

There were two RCTs that addressed nasal symptoms and QOL, which included 140 patients: 90 subjects in the intervention groups and 50 in the control groups. The random effect model was adopted

to conduct a meta-analysis regarding heterogeneity between the two trials ($I^2 = 97–99\%$; $p < .00001$). There was no significant change in frequency and severity in nasal symptom score (MD -0.96 [95% CI, -3.78 to 1.96], $p = 0.51$; and MD -1.11 [95% CI, -3.38 to 1.17], $p = 0.34$) or in QOL (MD -5.60 [95% CI, -16.92 to 5.72], $p = 0.33$; and MD -4.40 [95% CI, -9.84 to 1.04]; $p = 0.11$). The total analysis favored the intervention groups (MD -2.97 [95% CI, -4.77 – 1.16]; $p = 0.001$), which indicated that probiotics may globally relieve symptoms of patients with AR (Fig. 3).

Among numerous RCTs that involved immunology, four articles that addressed specific IgE, IL-10, IFN- γ , Th1/Th2 ratios, and eosinophil rates were enrolled.^{18,21–23} The data on eosinophil rates showed significant heterogeneity ($I^2 = 0.56$; $p = 0.10$) and presented no significant difference (SMD -0.39 [95% CI, -0.95 to 0.17]; $p = 0.18$). Similarly, no significant difference was found for specific IgE, IL-10, IFN- γ , and the Th1/Th2 ratio (SMD 0.10 [95% CI, -0.29 to 0.49], $p = 0.62$; SMD 0.43 [95% CI, -0.05 to 0.90], $p = .008$; SMD 0.15 [95% CI, -0.32 to 0.62], $p = 0.53$; and SMD 0.39 [95% CI, -0.05 to 0.83], $p = 0.08$), and the total outcome was also negative (SMD 0.10 [95% CI, -0.13 to 0.32]; $p = 0.15$) (Fig. 4). These outcomes indicate that probiotics lack an effect on the immunologic indices of AR.

DISCUSSION

This review analyzed the role of probiotics in the prevention and treatment of AR and revealed that probiotics have not been found to be able to decrease the incidence of AR. Although the ingestion of probiotics was not observed to change nasal symptoms or QOL scores, probiotic use was able to relieve the overall symptoms of AR. However, with regard to the immunologic data, probiotics have not shown significant benefits.

Probiotics that consist of a series of active bacteria could change the composition of intestinal microflora, such as lactic acid bacteria and *Bifidobacterium* species. In clinical practice, these organisms can potentially be used to treat lactose maldigestion, acute diarrhea, and inflammatory bowel diseases. In addition to digestive diseases, probiotics may also improve symptoms related to rheumatoid arthritis, respiratory infection in children, allergic reactions (specifically, atopic dermatitis), and diabetes.²⁴ Although the precise mechanisms that underlie the favorable effects of probiotics on allergy are not entirely known, several mechanisms have been observed in *in vitro* and *in vivo* studies. In addition to modulation of the intestinal microbiota, probiotics have been found to improve the barrier function of the intestinal mucosa and reduce the leakage of antigens through the mucosa and, thus, exposure to these antigens.^{25,26}

Direct modulation of the immune system may occur through the induction of anti-inflammatory cytokines or through increased production of secretory IgA, which contributes to the exclusion of antigens from the intestinal mucosa. Furthermore, enzymatic degradation of dietary antigens by enzymes produced by probiotics will reduce the load of, and exposure to, antigens.²⁷ Probiotics have been demonstrated to exhibit anti-inflammatory properties associated with changes in cytokine expression that could potentially facilitate the Th1 immune response, which might inhibit the development of an allergic Th2 response and allergic antibody (IgE) production.^{28,39} Selected species of the *Bifidobacterium* genus have been demonstrated to prime *in vitro*-cultured neonatal dendritic cells to polarize T-cell responses. Therefore, these species may be potential candidates for use in the primary prevention of allergic diseases.³⁰ Some researchers consider the protection offered by probiotics against allergic diseases to be based on stimulation of Toll-like receptors, which produce mediators, *e.g.*, IL-6, and induce further IgA differentiation from naive B cells.³¹ In addition, some studies demonstrated that neonatal application of probiotic bacteria inhibits subsequent allergic sensitization and airway disease in a murine model of asthma via the induction of regulatory T cells (Tregs) and transforming growth factor- β production.³² In summary, the local influences of probiotics

Table 2 Characteristics of included studies in the review

Study, year	Methods	Intervention	Time When Intervention Began	Outcome Measurement	Exclusion Criteria
Dotterud <i>et al.</i> , ¹⁷ 2010	RCT	Milk contained <i>L. rhamnosus</i> GG, <i>Bifidobacterium animalis</i> subspecies lactis BB-12, and <i>L. acidophilus</i> La-5 250 mL/day for 4 mo	Mothers from 36 wk of gestation to 3 mo postnatal	Allergic rhinoconjunctivitis morbidity	Pregnant women were ineligible if they had been taking probiotic supplements during the past 4 wk or were planning to move away from Trondheim, Norway <25 mo after randomization
Kukkonen <i>et al.</i> , ¹³ 2011*	RCT	Mother took capsules that contained <i>L. rhamnosus</i> GG, <i>L. rhamnosus</i> LC705, <i>Bifidobacterium breve</i> Bb99, <i>Propionibacterium freudenreichii</i> ssp. shermanii JS (CDSM7076) twice daily; the newborn infants received the same probiotics plus 0.8 g of prebiotic galactooligosaccharides once daily for 6 mo	Mothers from 36th wk of gestation, infants from birth	AR morbidity	No exclusion criteria stated
Xiao <i>et al.</i> , ¹⁸ 2006	RCT	Yogurt contained <i>Bifidobacterium longum</i> strain BB536, <i>S. thermophilus</i> and <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> 200 g per day for 14 wk	Intervention age, years 36.5 ± 7.8; control age, years 36.7 ± 9.5	Change in specific IgE, IL-10, IFN- γ , Eosinophil rate	Subjects with extreme severe symptom of Japanese cedar pollinosis
Wang <i>et al.</i> , ¹⁹ 2004	RCT	Fermented formula that contained <i>Streptococcus thermophilus</i> and <i>Lactobacillus bulgaricus</i> and <i>L. paracasei</i> (LP-33) 200 mL per day for 30 days	Intervention age, years 15.87 ± 1.53; control age, years 14.00 ± 1.90	Nasal symptoms scores and QOL of patients with AR scores	Pregnancy, steroid treatment, smoking, neuropsychiatric disease or congenital immunodeficiency or cow's milk allergy
Peng <i>et al.</i> , ²⁰ 2005	RCT	Capsule contained live LP-33 colony-forming units, 2 capsules per day for 30 days	Intervention age, years 16.07 ± 2.11; control age, years 16.60 ± 2.02	Nasal symptoms scores and QOL of patients with AR scores	Steroid treatment, neuropsychiatric disease or congenital immunodeficiency, probiotic allergy
Xiao <i>et al.</i> , ²¹ 2006	RCT	Powder contained <i>Bifidobacterium longum</i> BB536, 100 mL of milk twice daily for 13 wk	Intervention age, years 36.5 ± 8.1; control age, years 36.0 ± 7.3	Change in specific IgE, IL-10, IFN- γ , eosinophil rate	Subjects with extreme severe symptom of Japanese cedar pollinosis
Nagata <i>et al.</i> , ²² 2010	RCT	Powder contained LP14 0.5 g per day for 6 wk	Intervention age, years 22.0 ± 3.9; control age, years 21.9 ± 5.6	Change in specific IgE, Th1/Th2 ratio	No exclusion criteria stated
Kuitunen <i>et al.</i> , ¹⁴ 2009*	RCT	Mothers took a capsule that contained freeze-dried <i>L. rhamnosus</i> GG, <i>L. rhamnosus</i> LC705, <i>Bifidobacterium breve</i> Bb99, <i>Propionibacterium freudenreichii</i> ssp. shermanii JS (CDSM7076) twice daily for 1 mo; infants received the same probiotic capsule mixed with 20 drops of syrup that contained 0.8 g of galactooligosaccharides once daily for 6 mo	Last month of pregnancy, infants from birth	AR morbidity	Birth at less than 37 wk of gestation, major malformations, and the second born of twins
Ishida <i>et al.</i> , ²³ 2005	RCT	100 mL of heat-treated milk fermented by <i>Lactobacillus acidophilus</i> L-92 per day for 8 wk	Intervention age, years 34.0 ± 3.4; control age, years 36.9 ± 3.0	Change in specific IgE, Th1/Th2 ratio, eosinophil rate	No exclusion criteria stated
West <i>et al.</i> , ¹⁵ 2013*	RCT	Daily intake of infant cereals with <i>Lactobacillus paracasei</i> ssp. <i>paracasei</i> F19 (1 × 10 ⁸ CFU) for 9 mo	Infants from 4 mo of age	AR morbidity	Cesarean delivery and medications or supplements that could have affected the gut microbiota
Kalliomäki <i>et al.</i> , ¹⁶ 2003*	RCT	Mothers received 2 capsules of <i>Lactobacillus GG</i> daily for 2–4 wk before expected delivery; after delivery, mothers who were breastfeeding could take the capsules, otherwise children received the capsule contents were mixed with water, then given by spoon for 6 mo	Mothers from 4 wk before due date; infants postnatal until 6 mo	AR morbidity	No family history of atopic disease

LP14 = *Lactobacillus plantarum* no. 14.

*Four RCTs provided (source refs: 14, 15, 16, 18) whereas one RCT did not provide any allergic history (source ref: 17).

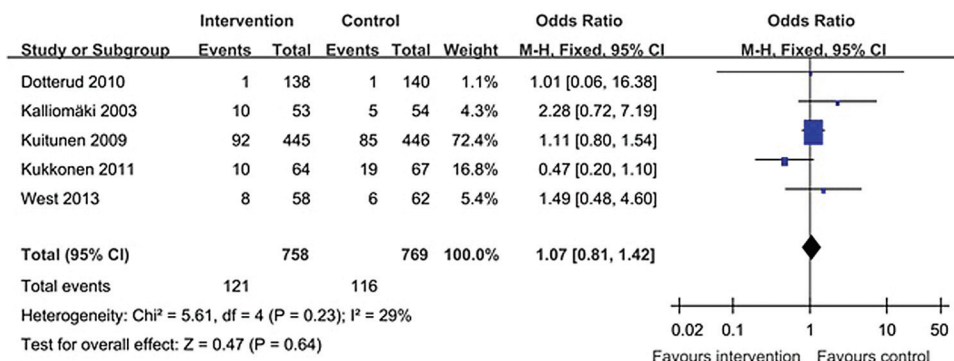


Figure 2. Analysis of the preventive role of probiotics in AR morbidity. Forest plot of pooled analyses of morbidity in randomized controlled trials of mothers and infants treated with probiotics.

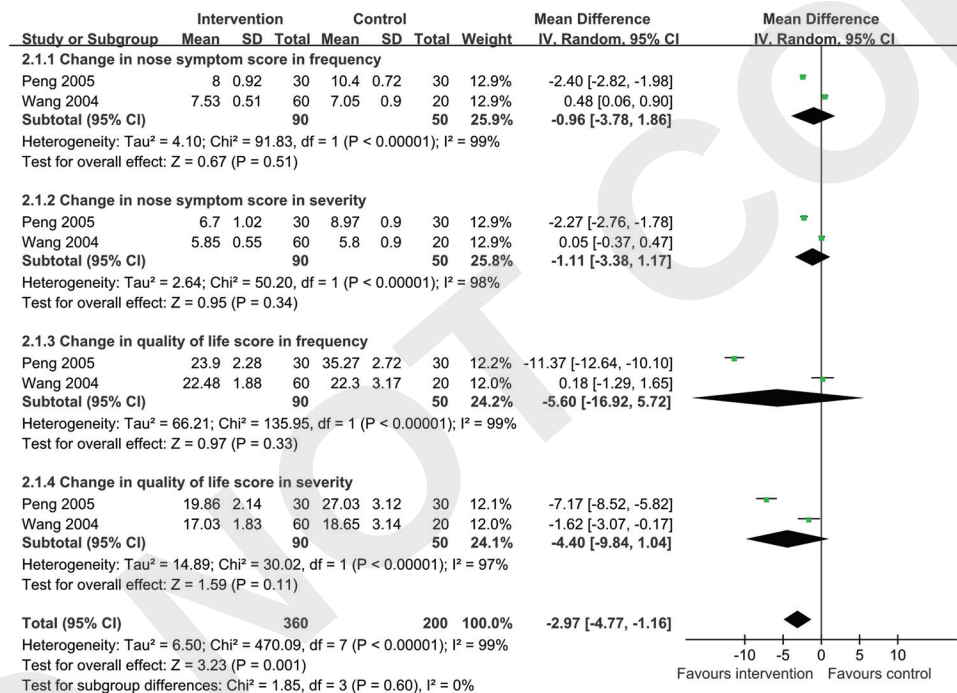


Figure 3. Analysis of nasal symptoms and QOL. Forest plot of data analysis of nose symptom score and QOL score in randomized controlled trials of patients with AR who were treated with probiotics.

potentially include reduction of permeability and systemic penetration of antigens, increased local IgA production and changes in local inflammation or tolerance induction. Some possible systemic effects include anti-inflammatory effects mediated by Toll-like receptors, Th1 skewing of the responses to allergens, and the activation of tolerogenic dendritic cells, in addition to Treg production.

With regard to our findings, probiotics may alleviate the symptoms of patients with AR for the above reasons, although the immunologic parameters did not show significant differences. Furthermore, our findings indicated that probiotics showed no effect on the prevention of AR. However, some trials included in our study showed that probiotics could improve nasal and ocular symptoms.^{33–35} Furthermore, other researchers concluded that probiotics could influence immunologic characteristics,^{7,10,33,36–40} but their data could not be analyzed because they could not be combined or extracted. Hence, the question of why probiotics can treat, but not prevent, AR remains unknown. When considering the mechanisms that underlie the effects of probiotics on allergy and atopy in humans, we postulated potential reasons for the observed impacts. Atopic eczema is usually the first manifestation of atopy and may coincide with a food allergy. Asthma often follows and is followed in turn by AR,⁴¹ which constitutes the

so-called atopic course, which is a period in which the immune system becomes mature and allergic disease may gradually develop. During this period, patients who develop atopic eczema earlier in life may benefit from the intake of probiotics.^{42,43}

There is a lack of an effect of the use of probiotics in older individuals with asthma and AR, which indicates that any beneficial effects may be confined to early life, before allergic disease becomes established.⁴⁴ In the majority of the trials reviewed, the duration of AR prevention was approximately 4 to 6 months, after which there was no significant clinical effect, and no change in allergen-specific IgE was detected because the half-life of receptor-bound IgE is approximately 3 weeks.⁴⁵ In addition, in the perinatal and after-birth period, when the immune system becomes mature, if probiotics cannot inhibit the atopic course, then they may only affect patients' symptoms and blood inflammation parameters for a short time. Furthermore, combinations of probiotics are alleged to cause paradoxical Th2 stimulation similar to what is observed in chronic and balanced helminth infection, which is associated with the activation of Tregs, which suppresses allergic inflammation. Because colonization is transient, the observed Treg induction is not permanent. Thus, when these

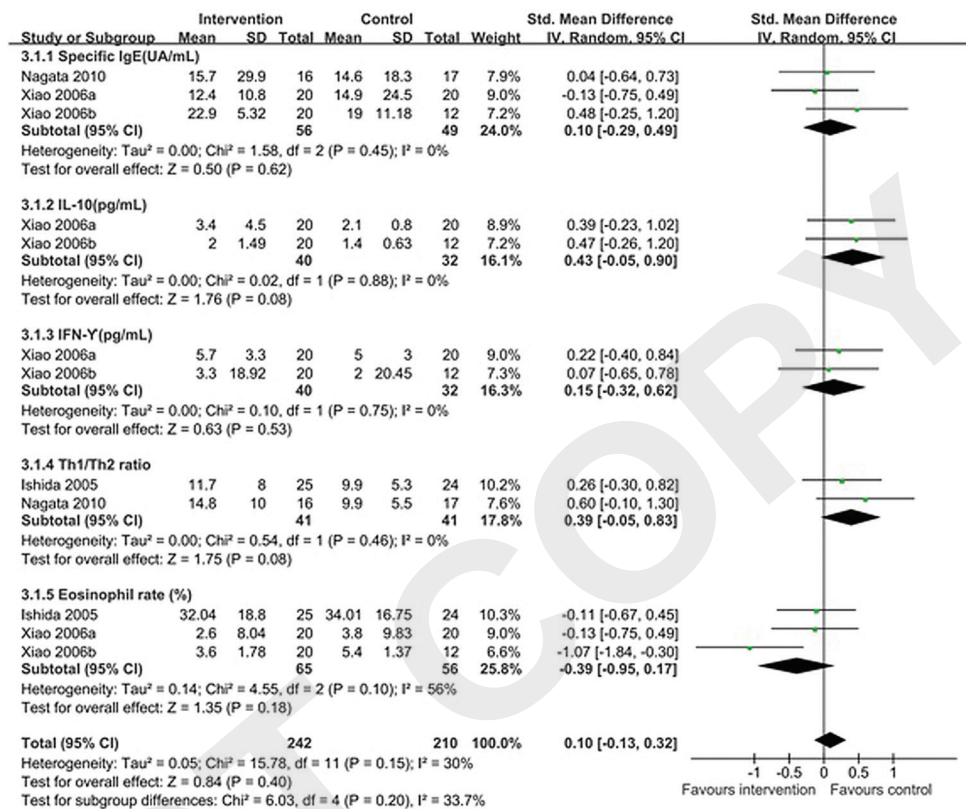


Figure 4. Analysis of the immune system. Forest plot of pooled analyses of specific IgE, IL-10, IFN- γ , Th1/Th2 ratios and eosinophil rates in randomized controlled trials of patients with AR who were treated with probiotics.

immunologic effects no longer operate, the clinical effect is simultaneously lost.³¹

In our review, 11 RCTs were enrolled, in which the control groups were administered placebo, milk, or other probiotics including skim fermented milk, microcrystalline cellulose, cow's milk protein with placebo yogurt, or heat-killed lactic acid bacteria. All of the studies adopted random, double-blind methods, and heterogeneity was found in our data. We also identified some problems within these studies. First, the probiotics administered to the intervention groups were not all the same, which may affect the outcome of the analysis. Second, the number of the types of probiotics used varied from one to three, which made it difficult to determine the effect of any single probiotic agent. Third, the intervention times were different, which made it difficult to determine how long probiotics should be administered, especially in studies that addressed treatment. Fourth, there was a wide range of probiotic doses applied. Fifth, the evaluation methods were different among the studies, which limited the ability to combine and analyze the data. For example, some investigators found that the nasal symptoms and QOL of patients with AR could be improved even if any immunologic or blood cell variable was not affected.^{46,47} Their research outcomes supported our conclusions in this review on overall symptom scores and immunologic indices; however, those data could not be used because of different study methods and immunologic parameters. Therefore, multicenter, randomized, controlled clinical trials with identical methods, the same indices, and detailed data will aid the evaluation of the beneficial effects of probiotics. For example, all the trials should be the same doses, durations, and strains of probiotics, and the same immunologic parameters for evaluation.

The present review revealed that probiotics may improve overall symptom scores in patients with AR, although there is no evidence that they improve nasal symptom scores or QOL scores independently. In the meantime, probiotics show no preventive role or immunologic effects. The evidence given here was generated from sev-

eral trials with high heterogeneity. Although we drew a more conservative conclusion by using the random-effect model, which might reduce the influence of heterogeneity, our outcomes should be judged accordingly. The available evidence does not recommend probiotics as a therapy in AR. We believe that the therapeutic roles of probiotics on AR will be verified when additional high-quality trials become available and other mechanisms are revealed for probiotics to alleviate allergies.

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