Do probiotics have a role in the treatment of allergic rhinitis? A comprehensive systematic review and meta-analysis

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ABSTRACT

Objective: *To investigate clinical evidence for the efficacy of probiotics in the treatment of allergic rhinitis (AR).*

Methods: *A systematic search was conducted to review the results of all randomized, double-blind, placebo-controlled trials by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. Primary outcome measurements were total nasal and ocular symptom scores (SS) and quality of life (QoL) questionnaires. Secondary outcome measurements were individual nasal SS and immunologic parameters.*

Results: *Twenty-two randomized, double-blind, placebo-controlled studies were included. Seventeen trials showed significant benefit of probiotics clinically, whereas eight trials showed significant improvement in immunologic parameters compared with placebo. All five studies with Lactobacillus paracasei (LP) strains demonstrated clinically significant improvements compared with placebo. Probiotics showed significant reduction in nasal and ocular SS (standardized mean difference [SMD], −1.23, $p < 0.001$; and SMD, −1.84, $p < 0.001$; respectively), total, nasal, and ocular QoL scores compared with placebo (SMD, −1.84, $p < 0.001$; SMD, −2.30, $p = 0.006$; and SMD, −3.11, $p = 0.005$; respectively). Although heterogeneity was high, in subgroup analysis, SMD for total nasal and ocular symptoms with patients with seasonal AR and for nasal QoL scores for studies with LP-33 strain were significant and homogenous. Scores of nasal blockage, rhinorrhea, and nasal itching were significantly lower in the probiotic group compared with placebo. The meta-analysis studies SS the Japanese guidelines revealed a significant, homogenous SMD score of −0.34 for individual nasal SS, above the minimal important clinical difference value of 0.3. The T-helper 1 to T-helper 2 ratio was significantly lower in the probiotic group compared with placebo (SMD, −0.78; $p = 0.045$).*

Conclusion: *Despite high variability among the studies, synthesis of available data provided significant evidence of beneficial clinical and immunologic effects of probiotics in the treatment of AR, especially with seasonal AR and LP-33 strains. With the rising pool of studies, the most promising strains in specific allergies can be revealed and adjuvant therapy with probiotics can be recommended for the treatment of AR.*

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The prevalence of allergic rhinitis (AR) has been substantially increasing over the past 4 decades in all the world.[1] According to the "hygiene hypothesis," atopic march may be altered by feeding probiotics to infants at risk for allergic diseases.[2] Probiotics are living microorganisms that provide a health benefit to the host when administered in adequate amounts.[3] Well-known probiotics are most commonly *Lactobacillus* and *Bifidobacterium* species, but *Lactococcus*, *Streptococcus*, *Enterococcus* species, some nonpathogenic strains of *Escherichia coli*, and certain yeast strains, *viz.*, *Saccharomyces* are also listed.[4]

Probiotics are believed to induce immunomodulatory mechanisms by the stimulation of gut-associated lymphoid tissue.[5] Dendritic cells are potent antigen-presenting cells and have a critical role in directing T-helper (Th) cell responses toward Th1, Th2, or regulatory pathways.[4] Probiotics induce dendritic cell maturation so that the Th1:Th2 balance is restored by induction of Th1 responses through the production of interleukin (IL) 12 and interferon (IFN) γ, or by suppression of Th2 responses through the reduction of IL-4, specific immunoglobulin E (sIgE), IgG1, and IgA production. Induction of T-regulatory cells by dendritic cells results in the secretion of IL-10 and transforming growth factor β, and thereby oral tolerance is induced.[5]

Although a 50% decrease in the frequency of clinical eczema to that of the placebo with supplementation of *Lactobacillus rhamnosus* strain GG (ATCC 53103) (LGG)[6] was reported, the development of asthma and AR was found to be increased to 3.5- and 2.3-fold, respectively, by the age of 7.[7] A recent meta-analysis reported no significant difference in terms of prevention of asthma or rhinoconjunctivitis.[8] Analysis of these data built serious concerns about the assumed preventive effects of probiotics for allergic diseases. The reviews that studied the efficacy of probiotics on the treatment of AR elicited contradictory results. We decided that a comprehensive meta-analysis of these studies could highlight this controversy and conducted a systematic search to gather the results of all randomized, double-blind, placebo-controlled (RDBPC) trials on the effects of probiotics in the treatment of AR.

METHODS

This meta-analysis was prepared by following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.[9] The review question was framed according to Patients, Intervention, Comparator, Outcomes, Study design criteria.

Criteria for Considering Studies for This Review

Study Population. Participants in the trials were of either sex and of any age diagnosed with AR and/or rhinoconjunctivitis. Diagnosis had been based on clinical history and on positive objective tests, such as a skin-prick test or a radioallergosorbent test.

Interventions and Comparators. Interventions consisted of daily treatment with probiotics or placebo administered at the beginning of the study and continued for a minimum of 4 weeks, with or without

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standard antiallergic medications. Studies with inappropriate placebo were excluded. All formulations of probiotics (irrespective of the species, strain, and concentration) were considered. Studies that concerned both seasonal and perennial allergies were included, but, for studies on seasonal allergies, studies held in an environmental exposure unit or out of season were not considered eligible.

Outcome Measurements. Our primary outcome measurements for determining the efficacy of probiotics were the change in nasal and ocular symptom scores (SS) and quality of life (QoL) questionnaires before and after the intervention compared with placebo. Separate analyses were planned for studies that provided only the difference between pre- and postmeasurement values. SS collected by using the nasal provocation test were not considered eligible. Secondary outcome measurements were the effect of probiotics on specific nasal SS and on immunologic parameters.

Study Design. RDBPC trials, irrespective of publication status, date of publication, or language, were reviewed. RDBPC trials were preferred for analysis because our primary outcome scores were subjective, and, therefore, may be subjected to performance and detection bias.

Search Methods for Identification of Studies. The review process was managed and conducted by two Ear, Nose, Throat (ENT) surgeons (I.A.G., E.E.). The results were further consulted by an advisory ENT professor (C.C.) who specialized in allergy. Medline (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library Issue 4, 2009), and the search engine of Baskent University known as Baskent Academic Search Engine, which allows investigation of the data bases for Academic Search Complete, Cambridge journals, Elsevier Clinical Key, OVID, Oxford Journal, Sage Journals, Science Direct, Springer link, Taylor and Francis, and Wiley Online Library were systematically searched for all relevant articles, including reviews, abstracts, and conference proceedings, as well as clinical trials, on February 15, 2015, for the past 20 years and an update search was conducted on September 16, 2015. The following keywords were used for retrieval of articles: (probiotic or *Lactobacillus* or *Bifidobacterium* or "lactic acid bacteria") and ("allergic rhinitis" or "allergic rhinoconjunctivitis" or "hay fever" or "nasal allergy" or "eye allergy" or "rhinitis").

The cross-references of the previous reviews were also scanned for additional studies. After removing duplicates, the abstracts of search results were screened according to the research question, and full texts of eligible articles were retrieved. Also, the references of these articles were screened for any other relevant articles.

Quality Assessment. Each included study was first evaluated with the five-point Jadad scale to assess the quality of the trials by two independent reviewers (I.A.G., E.E.).[10] Then, according to the study eligibility flowchart (Fig. 1), participants' description, intervention description, and outcome measurements were evaluated, and unqualified studies were excluded. The flaws of the excluded studies are listed in Table 1.[11–29]

Data Extraction. For all of the included studies, data were extracted independently by an ENT surgeon and a meta-analyst (I.A.G., F.S.M., respectively). For each outcome, sample sizes, and pre- and postmeasurement of means with standard deviations and/or differences of pre- and postmeasurement means were extracted for placebo and intervention group. For seasonal studies, peak season means were extracted as postmeasurement values. Data were recorded on a prestructured data extraction form. Any differences in reporting were reconciled by jointly revisiting the relevant publication. Whenever the data shared in a relevant study were unavailable for analysis (*e.g.*, data in diagrams, lack of posttreatment values), efforts were made to contact the study authors so that full study details could be obtained. For all of the included studies, the risk of bias was evaluated according to The Cochrane Collaboration's tool[30] for assessing risk of bias. Selection bias, blinding of participants and outcome assessment, incomplete outcome data, selective reporting, and other bias were evaluated as low, high, or unclear.

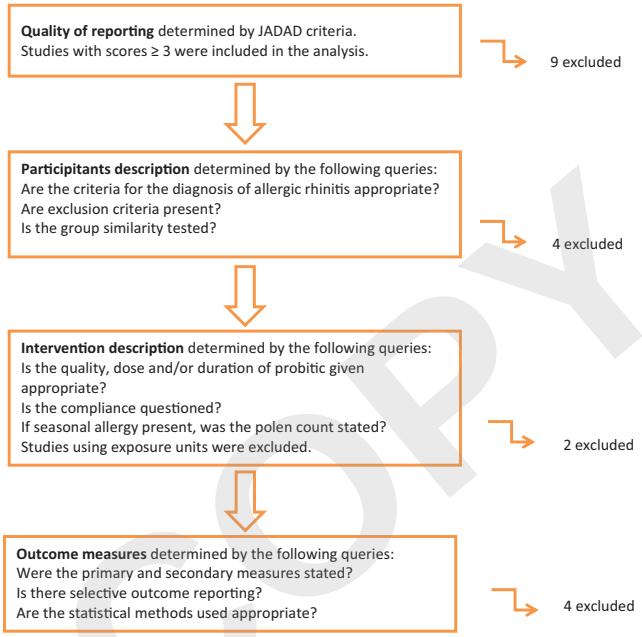


Figure 1. *The study eligibility flowchart.*

Data Synthesis and Meta-Analyses. The outcome data extracted were continuous, but different scoring systems and scales for SS were used by the researchers. Therefore, to compare the results, data were expressed as mean (standard deviation), and the method of standardized mean difference (SMD) was performed. The data from various studies were pooled and expressed as pooled SMD with 95% confidence interval (CI). A random effects model was initially conducted. Statistical heterogeneity was measured by using the Q statistic, and $p < 0.10$ was considered to be representative of statistically significant heterogeneity. The Q statistic measures the degree of inconsistency in the studies by calculating the percentage of total variation across studies. These data were then formatted into forest and funnel plots to illustrate the relative strength of treatment effects and assessment of publication bias, respectively. The statistical analysis was conducted by using Stata 11.0 (Stata-Corp, College Station, TX), and $p < 0.05$ was considered to be statistically significant. We performed further analyses in *a priori* defined subgroups of trials to explain the observed between-study heterogeneity and to identify subgroup-specific differences in the effect of the intervention.

RESULTS

Study Selection

The literature search retrieved a total of 451 articles. A title and abstract review followed by exclusion of any duplicate publications resulted in 36 remaining articles for full-text review. The review of full texts with references identified five other related articles, which resulted in a total of 41 articles. After elimination according to methodologic quality and eligibility criteria, 22 RDBPC articles were ultimately included in the study. The selection process is detailed in Fig. 2.

Study Characteristics

Twenty-two RDBPC trials were included in the systematic analysis. Twenty-two trials enrolled a total of 2242 participants (1953 after losses to follow-up), which involved all age groups and both sexes. Details regarding the individual studies identified during the systematic review can be found in Tables 2 and 3.[31–52] Overall, 22 trials included patients from 2 to 65 years of age. Fourteen trials included

Table 1 **Excluded studies**

Study	Reasons for Exclusion
Van de Water *et al.*,[11] 1999	Criteria for the diagnosis of allergic rhinitis unclear; outcome measurements were inappropriate; symptom scores were not collected
Aldunicci *et al.*,[12] 2002	Randomization and blinding methods were inappropriate
Shimida *et al.*,[13] 2004	Randomization and blinding methods were inappropriate
Fujiwara *et al.*,[14] 2005	Randomization and blinding methods were inappropriate
Ishida *et al.*,[15] 2005	Randomization and blinding methods were inappropriate
Ciprandi *et al.*,[16] 2005	Randomization and blinding methods were inappropriate
Morita *et al.*,[17] 2006	Preliminary human study; no control group present
Xiao *et al.*,[18] 2007	Intervention inappropriate; environmental exposure unit was used
Moreira *et al.*,[19] 2007	Criteria for the diagnosis of allergic rhinitis were inappropriate
Martínez-Cañavate *et al.*,[20] 2009	Criteria for the diagnosis of allergic rhinitis were inappropriate
Hasegawa *et al.*,[21] 2009	Randomization and blinding methods were inappropriate
Koyama *et al.*,[22] 2010	Criteria for the diagnosis of allergic rhinitis were inappropriate
Snel *et al.*,[23] 2011	Intervention was inappropriate; the study was conducted out of the pollen season
Wassenberg *et al.*,[24] 2011	Outcome measurements were inappropriate; nasal provocation test was used
Lue *et al.*,[25] 2012	Randomization and blinding methods were inappropriate
Kimura *et al.*,[26] 2012	Full text in Japanese
Ivory *et al.*,[27] 2013	Outcome measurements were inappropriate; nasal allergen challenge was used
Perrin *et al.*,[28] 2014	Outcome measurements were inappropriate; nasal provocation test was used
Harima-Mizusawa *et al.*,[29] 2014	Randomization and blinding methods were inappropriate

adults, and eight included children. Inclusion criteria were stated clearly in all of the studies. All of the patients had AR confirmed with sIgE and/or skin-prick test. Exclusion criteria, such as no severe food allergies or other serious health problems, and no previous immunotherapy, steroids, or other medications for AR before the trial, were stated in all the studies except two.[35,46]

Thirteen studies included patients with seasonal AR (SAR) allergic to pollens: seven with patients allergic to Japanese cedar pollen (JCP),[32,37,41,43,46,50,51] four with patients allergic to grass,[33,40,44,52] and two studies of patients with allergies to birch pollens.[34,49] Seven studies included patients with perennial AR (PAR) to house-dust mites,[31,35,38,42,47,48] and two studies included patients with SAR and PAR.[36,45] Four of the SAR studies did not provide pollen counts.[33,34,40,44]

Sixteen studies used *Lactobacillus* strains,[31,34–48] three studies used *Bifidobacterium* strains,[33,50,51] one study used *E. coli* (Nissle 1917)[52], and two studies used mixtures of probiotics.[32,49] Although most of the probiotics in the studies differed in their strains, three studies used *Lactobacillus paracasei*-33 (LP-33),[38–40] two used *Lactobacillus paracasei* Shirota,[43,44] and two used LGG.[34,35] Patients received milk, yogurt, powder, or capsules that contained probiotics. The placebo consisted of products with the same acidity and taste but without the probiotics. In three of the studies, probiotics and placebo included yogurt fermented with the usual bacteria (*Streptococcus thermophilus* and *Lactobacillus delbrueckii*),[32,38,50] and, in one study, only the probiotic yogurt was fermented with the usual bacteria, whereas the placebo was unfermented milk.[45] The duration of probiotic treatment of the studies ranged from 4 weeks to 12 months.

In 18 of the trials, both clinical and immunologic outcomes were measured,[31–37,41–43,45–52] 3 focused on only clinical,[38–40] and 1 only on immunologic outcomes.[44] There was high variety among studies in terms of how the clinical outcomes were expressed. Clinical outcomes were expressed as total daily SS in 17 studies[31–37,40–43,46–51] and as QoL scores in 7 studies.[37–41,47,52] Medication scores and symptom medication scores were also expressed in nine[31,32,36,37,41,43,46–48] and eight studies,[32,35,37,41,43,46,48,52] respectively. Seven studies[31,32,37,41,43,46,48] used Japanese guidelines for AR,[53] and two studies[35,47] used Scoring for AR to evaluate their results. One study assessed the number and duration of rhinitis episodes.[45] Compliance was assessed and reported as good in 14 of the studies.[33,35,37–40,42,44,46,47,49–52] Fecal microbiota was assessed in five of the studies.[45,46,49–51]

Risk of Bias Assessment in the Included Studies

The quality of the included studies was assessed by using the five-point Jadad scoring system: 3 trials (13.6%) had a total score of 3 whereas 9 trials (40.9%) had a total score of 4, and 10 trials (45.5%) had a total score of 5 (Table 3). Two studies used intention-to-treat analysis,[40,51] and all the studies were RDBPC, although the methods used to ensure adequate allocation concealment and blinding were not clearly reported in most studies. According to the analysis with the Cochrane Collaboration's tool for assessing risk of bias, 15 of the studies scored high[31,32,35,36,38,40–43,45–47,50–52] and 5 studies scored unclear in one or two components of risk of bias,[34,39,44,48,49] 2 studies had a low risk of bias.[33,37] The reasons for scoring a high or unclear risk of bias for individual studies are described in detail in Table 3. Each trial reported dropouts and withdrawals, and analyzed patients who completed the trial; the dropout rate ranged from 0 to 25%.

Results of Individual Studies

In 10 of 21 studies[31–33,37–41,47,51] that evaluated clinical parameters, probiotics showed significant improvement compared with placebo in at least two parameters. In six studies,[36,42,45,46,48,50] probiotics showed significant improvement compared with placebo in only one parameter. In two studies,[43,49] clinical parameters for probiotics tended to improve compared with placebo, and, in three studies,[34,35,52] there were no differences between probiotic and placebo groups (Tables 2 and 3). In 3 of 19 studies[33,44,49] that evaluated immunologic parameters, probiotics showed significant improvement compared with placebo in at least two parameters; in 6 studies,[36,41,46,50–52] probiotics showed significant improvement compared with placebo in only one parameter. In one study,[37] immunologic parameters for probiotics tended to improve compared with placebo, and, in nine studies,[31,32,34,35,42,43,45,47,48] there were no differences between probiotic and placebo groups (Tables 2 and 3).

Six[36,38,39,42,45,47] of the 8 and 2[36,49] of the 6 trials with children showed significant improvements in clinical and immunologic outcomes, respectively, whereas 10[31–33,37,40,41,46,48,50,51] of the 13 trials and 7[33,41,44,46,50–52] of the 13 trials with adults showed significant improvements in clinical and immunologic outcomes, respectively. Two studies with LGG[34,35] and one study with *E. coli*[52] showed no improvements in clinical parameters with treatment. Three studies with *Lactobacillus gasseri* strains,[32,36,37] five studies with LP strains,[38–42] one

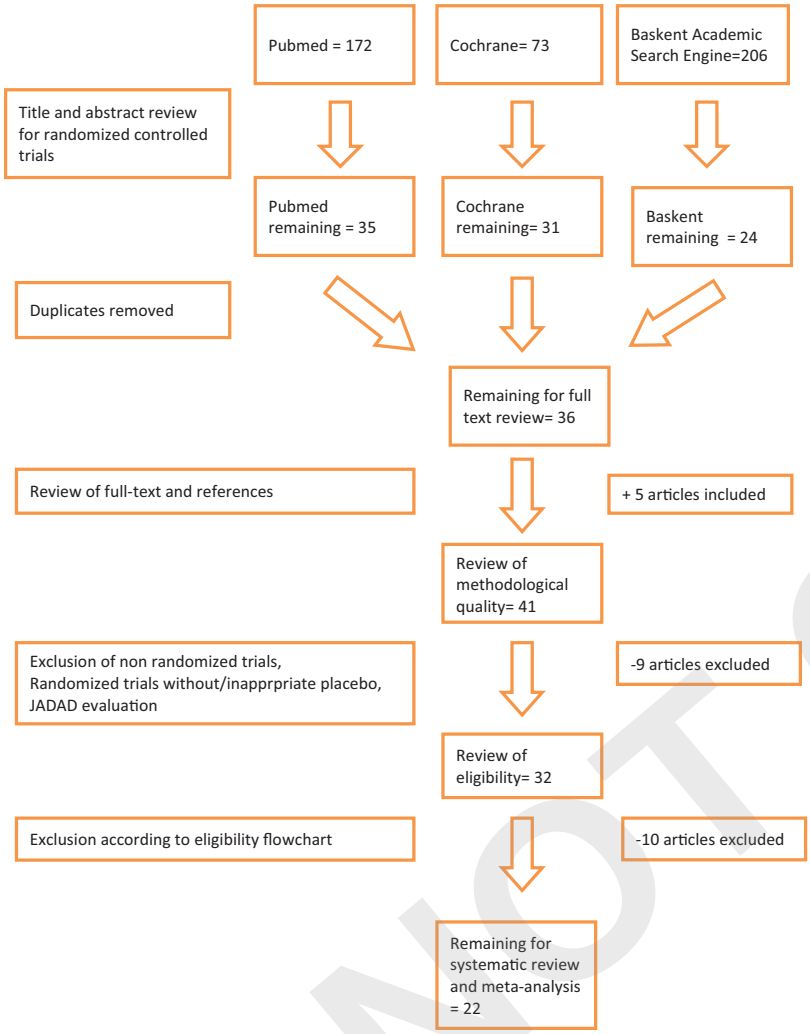


Figure 2. *The flowchart of study selection.*

of the two studies with *Lactobacillus casei* strains,[45] one with *Lactobacillus plantarum*,[46] one with *Tetragenococcus halophilus* Th221,[31] one with *Lactobacillus salivarius*,[47] one with *Lactobacillus acidophilus*,[48] one with *Bifidobacterium lactis*,[33] and two with *Bifidobacterium longum* strains[50,51] demonstrated clinically significant improvements compared with placebo. Detailed information extracted from the individual studies is summarized in Table 3.

Adverse effects were questioned in 12 of the studies, but most studies reported no adverse effects, 3 reported minor gastrointestinal effects[41,46,52] and 1 reported severe adverse effects.[40]

SYNTHESIS OF RESULTS

Primary Outcome Parameters

SS. There was a wide variety of scoring systems among the studies that were included in the analysis. We first tried to include all of the scores for total nasal and ocular symptoms reported in the studies to gather as many studies as we could in one meta-analysis, therefore, in the first analysis, we included all of the studies that reported daily SS and/or QoL scores.

Of the 21 studies that evaluated nasal symptoms, 10 reported pre- and posttreatment data available for meta-analysis.[31–33,38,39,41,42,47,50,51] Data from these 10 studies included a total of 801 patients with AR. Two of the studies evaluated two different forms of probiotic (heat-killed and live form of LP-33,[39] low-dose and high-dose of *Tetragenococcus halophilus* Th221,[31] and their results were extracted in the analysis as if they were two separate studies (Fig. 3). The combined SMD of the total nasal SS of the probiotic- and placebo-treated group was −1.23 (95% CI, −1.84 to −0.62; $p < 0.001$), which indicated a significant decrease in nasal symptoms in the probiotic-treated group compared with placebo. A test of homogeneity was conducted to assess the variance of true effect sizes by using the Q statistic, a measure of weighted standard deviations. In this case, the Q statistic is significant (Q = 143.14, d.f. = 11, $p < 0.001$), and any variance in effect sizes can be confidently attributed to sampling error, which indicated heterogeneity.

Quantitative assessment of publication bias by using Begg's and Egger's tests revealed the estimated bias coefficient as −1.33, with a standard error of 3.21 ($p = 0.687$, Egger's test), thus provided no evidence for the presence of small study effects. Influence analysis identified the studies by Wang *et al.*,[38] Peng and Hsu,[39] Nishimura *et al.*[31] (low dose), and Lin *et al.*[47] as the influential studies. The value for heterogeneity, excluding these studies, decreased to Q = 9.44 (d.f. = 6, $p = 0.150$), becoming homogenous with an SMD value of −0.60 (95% CI, −0.89 to −0.31; $p < 0.0001$).

We performed subgroup analyses to evaluate whether there was evidence of different effects of probiotics in predefined subgroups of patients. We analyzed studies on SAR and PAR separately (Fig. 3). For five SAR studies[32,33,41,50,51] with 286 patients, the combined SMD of the total nasal SS was −0.62 (95% CI, minus]0.93 to −0.31; $p < 0.001$), which indicated a significant decrease in nasal symp-

Table 2 **Characteristics of the included RDBPC trials**

No.	Study, y (country)	No. Patients	Dropout, no. patients	Age range, y (C or A)	Type of Allergic Rhinitis	Intervention (probiotic) vs Placebo	Probiotic Dose and Duration	Improvement in Clinical Parameters*	Improvement in Immunologic Parameters*
1	Helin *et al.*,[34] 2002 (Finland)	36	5	14–36 (A)	Seasonal (birch pollen)	Capsules that contained LGG vs capsules that contained microcrystalline cellulose	At least 5×10^9 CFU/capsules 2×2 capsules for 5.5 mo (2.5 mo before pollen season, 1 mo during the season, 2 mo after the season)	0	0
2	Jan *et al.*,[35] 2011 (Tawain)	240	42	Mean, 8 (C)	Perennial (Dp, Df or dust)	Capsule that contained LGG vs capsules that consisted of microcrystalline cellulose	4×10^9 CFU/g/day for 12 wk	0	0
3	Kawase *et al.*,[32] 2009 (Japan)	44	4	36.9 (A)	Seasonal (JCP)	Fermented milk that contained the usual bacteria and LGG and *L. gasseri* TMC0356 vs yogurt that contained the usual bacteria	110 g/day for 10 wk	3	0
4	Chen *et al.*,[36] 2010 (Taiwan)	118	13	6–12 (C)	Mild to moderate, persistent	Capsules that contained LG-A5 vs capsules with starched powder made from rice	2×10^9 CFU/capsule $2 \times$ 1/day for 8 wk	2	2
5	Gotoh *et al.*,[37] 2009 (Japan)	107	7	19–50 (A)	Seasonal (JCP)	Tablets that contained heat-killed *L. gasseri* OLL2809 vs tablets that consisted of dextrin	1×10^{10} CFU/100 mg/day for 8 wk	3	1
6	Wang *et al.*,[38] 2004 (Taiwan)	80	0	>5; mean, 15.4 (C)	Perennial (Dp)	Yogurt that contained the usual bacteria and LP-33 vs yogurt that contained the usual bacteria	2×10^9 CFU/200- 400 mL/day for 30 days	3	—
7	Peng *et al.*,[39] 2005 (Taiwan)	90	0	>5; mean, 15.7 (C)	Perennial (Dp)	Capsule that contained live LP-33 vs capsule that contained heat-killed LP-33 vs capsule that contained only milk powder	5×10^9 CFU/capsule $2 \times$ 1/day for 30 days	3	—
8	Costa *et al.*,[40] 2014 (France)	425	81	18–60 (A)	Seasonal (grass)	Capsules that contained LP-33 plus loratadine vs identical placebo capsules plus loratadine	2.0×10^9 CFU/capsule/day for 5 wk	3	—
9	Yonekura *et al.*,[41] 2009 (Japan)	138	22	20–50 (A)	Seasonal (JCP)	Powder that contained *L. paracasei* KW3110T vs powder that contained dextrin	$1–3 \times 10^{12}$ CFU/g daily for 3 mo +4-wk observation period	3	2
10	Lin *et al.*,[42] 2014 (Taiwan)	60	0	6–13 (C)	Perennial (mite)	Capsules contained *L. paracasei* (HF.A00232) plus levocetirizine vs capsules that contained plus levocetirizine maltodextrin	5×10^9 CFU/capsule/day for 8 wk	2	0

Continued

Table 2 **Continued**

No.	Study, y (country)	No. Patients	Dropout, no. patients	Age range, y (C or A)	Type of Allergic Rhinitis	Intervention (probiotic) vs Placebo	Probiotic Dose and Duration	Improvement in Clinical Parameters*	Improvement in Immunologic Parameters*
11	Tamura *et al.*,[43] 2007 (Japan)	120	11	Mean, 39.4 (A)	Seasonal (JCP)	Fermented milk that contained *L. casei* Shirota vs unfermented milk	4×10^{10} CFU/80 mL/day for 8 wk	1	0
12	Ivory *et al.*,[44] 2008 (U.K.)	20	1	18–45 (A)	Seasonal (grass)	Milk that contained *L. casei* Shirota vs milk without probiotics	10^8 CFU/mL, 65 mL daily for 5 mo	—	3
13	Giovanni *et al.*,[45] 2007 (Italy)	187	29	2–5 (C)	Perennial and seasonal	Fermented milk that contained the usual bacteria and *L. casei* DN-114 001 vs unfermented milk	10^8 CFU/mL, 100 mL/day for 12 mo	2	0
14	Nagata *et al.*,[46] 2010 (Japan)	Spring, 35; Autumn, 20	Spring, 2; Autumn, 0	18–27 (A)	Seasonal (JCP)	Branched dextrin that contained *Lactobacillus plantarum* No. 14 vs branched dextrin	8.7×10^8 CFU/0.5 g/day for 6 wk	2	2
15	Nishimura *et al.*,[31] 2009 (Japan)	45	7	16–60 (A)	Perennial (house-dust and mite)	Low-dose vs high-dose tablets that contained *Tetragenococcus halophilus* Th221 vs identical placebo tablets	Low-dose tablets that contained 3.4 mg/tablet, 6 tablets/day for 8 wk; high-dose tablets that contained 10 mg/tablet, 6 tablets/day for 8 wk	3	0
16	Lin *et al.*,[47] 2013 (Taiwan)	240	41	6–12 (C)	Perennial (Dp, Df or dust)	Powder that contained *Lactobacillus salivarius* vs microcrystalline cellulose powder	4×10^9 CFU/g, 500 mg daily for 12 wk	3	0
17	Ishida *et al.*,[48] 2005 (Japan)	52	3	Mean, 35.4 (A)	Perennial (house dust and mite)	Heat-treated fermented milk that contained *L. acidophilus* (L-92) vs acidic milk without lactic acid bacteria	3×10^{10} CFU/100 mL/day for 8 wk	2	0
18	Ouwehand *et al.*,[49] 2009 (Finland)	47	6	4–13 (C)	Seasonal (birch)	Capsules that contained 25% *L. acidophilus* NCFM (ATCC 700396) and 75% *B. lactis* Bl-04 (ATCC SD5219) vs capsules that contained microcrystalline cellulose	5×10^9 CFU/day for 4 mo	1	3
19	Singh *et al.*,[33] 2013 (Switzerland)	20	0	20–65 (A)	Seasonal (grass)	*B. lactis* NCC2818 blended in maltodextrin vs maltodextrin alone	2×10^9 CFU/g daily for 8 wk, in the peak season of allergy	3	3
20	Xiao *et al.*,[50] 2006 (Japan)	40	0	23–61 (A)	Seasonal (JCP)	Yogurt that contained the usual bacteria and *B. longum* BB536 vs yogurt that contained the usual bacteria	$>2 \times 10^7$ CFU/100 mL $2 \times$ 1/day for 14 wk	2	2

Continued

Table 2 **Continued**

No.	Study, y (country)	No. Patients	Dropout, no. patients	Age range, y (C or A)	Type of Allergic Rhinitis	Intervention (probiotic) vs Placebo	Probiotic Dose and Duration	Improvement in Clinical Parameters*	Improvement in Immunologic Parameters*
21	Xiao *et al*,[51] 2006 (Japan)	44	11	22–56 (A)	Seasonal (JCP)	Lyophilized powder that contained *B. longum* BB536 vs powder that contained only an internal matrix, mainly dextrin	5×10^{10} CFU/2 $\times$ g 2 $\times$ 1 / day for 13 wk	3	2
22	Dölle *et al*,[52] 2014 (Germany)	34	4	19–54 (A)	Seasonal (grass)	Capsules that contained *Escherichia coli* strain Nissle 1917 vs identical placebo capsules	$2.5–25 \times 10^9$ CFU/capsule/ day for 6 mo	0	2

RDBPC = Randomized, double-blind, placebo-controlled; C = children; A = adult; LGG = Lactobacillus rhamnosus (ATCC 53103); ATCC = ; Dp = Dermatophagoides pteronyssinus; Df = Dermatophagoides farinae; JCP = Japanese cedar pollen; L. gasseri = Lactobacillus gasseri; LP-33 = Lactobacillus paracasei-33; L. paracasei = Lactobacillus paracasei; L. casei = Lactobacillus casei; L. acidophilus = Lactobacillus acidophilus; B. lactis = Bifidobacterium lactis; B. longum = Bifidobacterium longum.

**0, No effect; 1, At least one clinical and/or immunologic parameter tended to improve in the probiotic group compared with placebo; 2, only one clinical and/or immunologic parameter significantly improved in the probiotic group compared with placebo; 3, more than one clinical and/or immunologic parameter significantly improved in the probiotic group compared with placebo; —, not evaluated in the trial.*

toms in the probiotic-treated group compared with placebo. A test of homogeneity indicated a homogenous effect (Q = 5.47, d.f. = 4, $p = 0.242$).

Five studies[31,38,39,42,47] with 515 patients with PAR were included in the subgroup analysis of total nasal SS (Fig. 3). The combined SMD of the total nasal SS for the subgroup of patients with PAR was −1.61 (95% CI, −2.56 to −0.65; $p < 0.001$), which indicated a significant decrease in nasal symptoms in the probiotic-treated group. The degree of heterogeneity was high (Q = 104.82, d.f. = 6, $p < 0.001$).

Two[38,39] of the above-mentioned 10 studies,[31–33,38,39,41,42,47,50,51] reported their results also as a change in pre- and posttreatment nasal symptoms, and three other studies[34,40,46] reported only the change. These five studies, which included a total of 666 patients, were evaluated in a separate meta-analysis (Fig. 4). Compared with placebo, probiotics also showed significant improvement in nasal symptoms (SMD −1.68 [95% CI, −3,07 to −0.29]; $p = 0.018$). There was a high degree of heterogeneity for this outcome (Q = 164.27, d.f. = 5, $p < 0.001$).

Of the 21 studies that evaluated ocular symptoms, 7 reported[38,39,41,42,47,50,51] pre- and posttreatment data available for meta-analysis. Data from these studies included a total of 692 patients with AR (Fig. 5). The combined SMD of the total ocular SS for these studies was −1.84 (95% CI, −2.83 to −0.84; $p < 0.001$), which indicated a significant decrease in ocular symptoms in the probiotic group compared with placebo, but heterogeneity was high (Q = 104.82, d.f. = 6, $p < 0.001$).

In the subgroup analysis, three SAR studies[41,50,51] with 226 patients were evaluated for ocular symptoms (Fig. 5). Ocular symptoms were significantly reduced in the probiotic-treated subgroup of patients with SAR compared with placebo, and the results were homogenous (SMD −0.39 [95% CI, −0.67 to −1.11]; $p = 0.006$) (Q = 0.53, d.f. = 2, $p = 0.766$).

Four studies[38,39,42,47] with 470 patients with PAR were included in subgroup analysis of total ocular SS (Fig. 5). The combined SMD of the total ocular SS for the subgroup of patients with PAR was −2.78 (95% CI, −4.27 to −1.29; $p < 0.001$), which indicated a significant decrease in ocular symptoms in the probiotic-treated group. The degree of heterogeneity was high (Q = 123.22, d.f. = 4, $p < 0.001$).

Two[38,39] of the above-mentioned seven studies[38,39,41,42,47,50,51] reported their results also as the change in pre- and posttreatment ocular symptoms, and three other studies[34,40,46] reported only the change. These five studies, which included a total of 666 patients were evaluated in a separate meta-analysis (Fig. 4). Compared with placebo, the probiotic group also showed a significant improvement in ocular symptoms (SMD −2.37 [95% CI, −4.08 to −0.66]; $p = 0.006$). There was a high degree of heterogeneity (Q = 214.06, d.f. = 5, $p < 0.001$). Separate analyses were done for total daily nasal and ocular SS, nasal and ocular QoL scores, and total QoL scores.

Daily Total SS. Eight studies with 631 patients provided enough data to allow quantitative evidence synthesis based on daily total nasal SS.[31–33,41,42,47,50,51] Overall, probiotics induced a significant reduction in the total nasal SS compared with placebo (SMD −0.67 [95% CI, −1.15 to −0.19]; $p = 0.007$). The degree of heterogeneity was high (Q = 53.08, d.f. = 8, $p < 0.001$). Daily total ocular SS were available for analysis in four studies with 384 patients.[42,47,50,51] Probiotics induced a significant reduction in the total ocular SS compared with placebo (SMD −0.70 [95% CI, −1.81 to −0.45]; $p < 0.001$). There was a high degree of heterogeneity (Q = 58.72, d.f. = 3, $p < 0.001$). Of the seven studies[31,32,37,41,43,46,48] that used Japanese guidelines[53] for AR for the evaluation of daily total nasal SS, three of them, with 227 patients,[31,32,41] provided quantitative data for meta-analysis. A SMD score of −0.34, which was significant (95% CI, −0.62 to −0.07; $p = 0.015$) and homogenous (Q = 2.64; d.f. = 3; $p = 0.451$) was obtained for daily total nasal SS (Fig. 6).

QoL. Three studies, with 308 patients, provided pre- and posttreatment data for analysis of nasal QoL scores.[38,39,41] Overall, probiotics significantly improved the nasal QoL (SMD −2.30 [95% CI, −3.93 to

Table 3 **Characteristics of the included RDBPC trials**

Study No.	Study, y (country)	Outcome Measurements: Primary Outcome (1°) and Secondary Outcome (2°)	Jadad Score	Cochrane Risk of Bias Assessment*	Results	Improvement in Clinical Parameters#	Improvement in Immunologic Parameters#
1	Helin *et al.*,[34] 2002 (Finland)	1°: Nasal, eye, and lung symptom and medication diary; and 2°: oral apple challenge	4	RSG unclear; AC unclear	1°: No significant changes between groups in nose, eye, and lung symptoms or use of medication; and 2°: no significant changes in the results of apple challenge	0	0
2	Jan *et al.*,[35] 2011 (Taiwan)	1°: The SCORing Allergic rhinitis index, specific symptoms (nasal, eye, lung) scores and SMS; and 2°: total IgE and blood eosinophil counts	3	AC unclear; IOD high (dropout rate of 17.5%, intention-to treat analysis was not done); OB unclear (no exclusion criteria stated)	1°: No significant reduction in symptom scores; and 2°: no significant change in immunologic parameters	0	0
3	Kawase *et al.*,[32] 2009 (Japan)	1°: Nasal, eye, and throat symptom scores; medication scores; SMS; nasal examination according to Japanese guidelines for AR; and 2°: blood tests for total IgE, sIgE, Th1:Th2 ratio, TARC, CRP, eosinophils	4	RSG unclear; AC unclear; OB high (usual bacteria used in intervention and placebo, not possible to conclude about the effect of BB536 per se, some antiallergic effects of the placebo yogurt cannot be excluded)	1°: Significant decrease in the nasal blockage after 9 wk in the probiotic group compared with placebo; no difference in sneezing, rhinorrhea, and itching between the groups; significant decrease in the mean SMS for nasal blockage after 9 and 10 wk; and 2°: no significant difference in blood tests	3	0
4	Chen *et al.*,[36] 2010 (Taiwan)	1°: Symptom and medication diary, daily PEFR, PFT; 2°: assessment of cytokine (TNF-α, IFN-γ, IL-10, IL-12p40, IL-13) production by PMNCs stimulated with PHA, Dp or Dp supplemented with LG-A5 production and Total IgE	4	AC unclear; OB high (steroid used as rescue medication, which influenced immunologic parameters)	1°: Significant difference in number of patients that showed improvement of asthmatic and AR symptoms between probiotic and placebo groups; significant improvement of AR symptoms compared with the beginning of the study; and 2°: no significant difference in change of total IgE between the groups, Th1 and Th2 cytokines decreased significantly in probiotic group compared with placebo	2	2
5	Gotoh *et al.*,[37] 2009 (Japan)	1°: Nasal and eye SMS, intranasal findings; according to the Japanese guidelines for AR; and 2°: Japan RQLQ total IgE, sIgE, eosinophils, Th1:Th2 ratio	5		1°: Significant reduction in nasal SMS scores in probiotic group in the second wk; in subgroup analysis of the patients with RAST scores of 4 and 5, significant reduction in nasal SMS scores in wk 1, 5, 6, 7, 8, and nasal congestion and itching scores in RQLQ in wk 8 in the probiotic group compared with placebo; and 2°: no difference in blood parameters, Th1:Th2 ratio tended to increase in the probiotic subgroup compared with placebo	3	1

Continued

Table 3 **Continued**

Study No.	Study, y (country)	Outcome Measurements: Primary Outcome (1°) and Secondary Outcome (2°)	Jadad Score	Cochrane Risk of Bias Assessment*	Results	Improvement in Clinical Parameters#	Improvement in Immunologic Parameters#
6	Wang *et al.*,[38] 2004 (Taiwan)	1°: Modified PRQLQ	4	RSG unclear; AC high (subjects were aware that there was a greater chance of receiving active treatment); OB high (use of yogurt that contained the usual bacteria as medium for intervention and placebo, significantly higher baseline nasal scores in the probiotic group)	1°: Significant decrease in frequency and level of bother of the overall QoL score in the probiotic group compared with placebo	3	—
7	Peng and Hsu,[39] 2005 (Taiwan)	1°: Modified PRQLQ	4	RSG unclear; AC unclear	1°: Significant reduction in the overall QoL score for live and heat-killed probiotic groups compared with the placebo group, in terms of both frequency and level of bother; the efficacy of the heat-killed LP-33 was not inferior to the live variant	3	—
8	Costa *et al.*,[40] 2014 (France)	1°: RQLQ global score; and 2°: nasal and ocular symptoms (individual and total symptom scores), visual analog scale, and time of first exacerbation of the symptoms when loratadine was stopped	5	OB high (study was done in 2 years because of insufficient recruitment of enough subjects in the first year)	1°: RQLQ global score decreased significantly more in the LP-33 group than in the placebo group; and 2°: no significant differences were noted for the change of the rhinitis total symptom score, but significant differences in RQLQ in ocular symptoms domain and in the individual score of rhinorrhea were observed between the groups in favor of the probiotic group	3	—
9	Yonekura *et al.*,[41] 2009 (Japan)	1°: Symptom scores, medication scores, intranasal findings according to Japanese clinical guidelines, Japan RQLQ; and 2°: immunologic markers: total IgE and sIgE levels, serum eosinophil count and ECP, Th1: Th2 ratio were measured in PMNC; adverse effects	5	IOD high (dropout numbers were high)	1°: SMSs tended to be lower in the probiotic group during intake, significantly lower during the observation period compared with placebo, runny nose significantly lower in the probiotic group in 12 wk of intake (improved QoL when pollen scattering was low); significant difference in interference with outdoor activities after 12 wk and significantly suppressed nasal discharge after 4 and 12 wk in examination in the probiotic group compared with placebo; and 2°: significantly lower blood ECP level after 4 and 12 wk, Th1:Th2 ratio, which showed a tendency to be higher throughout the intake period in the probiotic group compared with placebo; no significant difference in adverse effects	3	2

Continued

Table 3 **Continued**

Study No.	Study, y (country)	Outcome Measurements: Primary Outcome (1°) and Secondary Outcome (2°)	Jadad Score	Cochrane Risk of Bias Assessment*	Results	Improvement in Clinical Parameters#	Improvement in Immunologic Parameters#
10	Lin *et al.*,[42] 2014 (Taiwan)	1°: Nasal, eye, throat, and TSS; PRQLQ; and 2°: sIgE, IL-4, IFN- γ, IL-10, and TGF-β	4	RSG unclear; AC unclear; OB high (levosetirizine use may have masked the probiotic effect)	1°: No difference between the 2 groups in TSS, NTSS, ETSS, TTSS, or PRQLQ scores; in the follow-up period, a significant reduction in PRQLQ and individual symptoms of sneezing, itchy nose, and swollen puffy eyes in the probiotic group compared with placebo; and 2°: no significant changes in cytokine levels between the 2 groups	2	0
11	Tamura *et al.*,[43] 2007 (Japan)	1°: Symptom and medication score, examination of nasal cavity according to the Japanese clinical guidelines, and 2°: anti-JCP IgE, eosinophil count, ECP, and Th1:Th2 ratio	5	OB high (placebo is unfermented milk)	1°: No significant difference in clinical parameters; in subgroup analysis, the patients with moderate-severe nasal symptoms, LcS tended to reduce nasal SMS; and 2°: no significant difference in immunologic parameters between the groups	1	0
12	Ivory *et al.*,[44] 2008 (U.K.)	1°: Pre–, peak–, and post–grass-pollen season plasma levels of total IgE and grass-pollen sIgG and sIgE levels, PMNC cytokines (IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IFN-γ, TNF-α)	3	RSG unclear	1°: Lower elevations of cytokines of Th2 pathway (IL-5, IL-6), IFN-γ, sIgE levels, whereas higher levels sIgG were in the probiotic group compared with placebo; these parameters demonstrated the beneficial effects of LcS, in downregulation of Th1- and Th2-type cytokines and beneficially alter the balance of IgE and IgG levels in SAR	—	3
13	Giovanni *et al.*,[45] 2007 (Italy)	1°: Time free from episodes of rhinitis and/or asthma, cumulative number and duration of episodes; and 2°: the number and duration of episodes of diarrhea or fever, and total serum IgA, IgE, IgG, and IgM	5	OB high (compliance low; intervention, fermented milk vs placebo nonfermented milk; not possible to conclude about the effect of *Lactobacillus casei* per SE)	1°: No significant difference between the groups found in children with asthma for any outcome measure; number of rhinitis episodes per year significantly lower in the probiotic group compared with placebo; and 2°: the mean duration of an episode of diarrhea was significantly lower in the probiotic group; no significant difference in the immunologic profile	2	0

Continued

Table 3 **Continued**

Study No.	Study, y (country)	Outcome Measurements: Primary Outcome (1°) and Secondary Outcome (2°)	Jadad Score	Cochrane Risk of Bias Assessment*	Results	Improvement in Clinical Parameters#	Improvement in Immunologic Parameters#
14	Nagata *et al.*,[46] 2010 (Japan)	1°: Symptom and medication scores according to the Japanese clinical guidelines, SMS; and 2°: total IgE, anti-JCP IgE, eosinophil count, CRP; and Th1 percentage, Th2 percentage, and Th1:Th2 ratio, antiragweed, anti–house-dust mite IgE, fecal microbiota, GI symptoms	4	RSG unclear; AC unclear; SR unclear (results of the nasal scores for the Autumn study were not mentioned); OB high (pollen count remained low until the fifth wk of intake, limited number of subjects, no exclusion criteria mentioned)	Spring study: 1°: Mean ocular SMS was significantly lower in the probiotic group compared with placebo in the first week of intake; and 2°: percentage of Th1 cells increased significantly with the intake of probiotic; postintake eosinophils increased significantly in placebo with the 3-fold increase in pollen counts but not in the probiotic group; the score for sensation of defecation was significantly higher after 3 wk of intake in the probiotic group compared with placebo; Autumn study: 1°: nasal and ocular scores tended to be reduced in the probiotic group compared with placebo; and 2°: no differences in blood parameters between the 2 groups; the score for sensation of defecation was significantly lower at postintake in the probiotic group compared with placebo	2	2
15	Nishimura *et al.*,[31] 2009 (Japan)	1°: Nasal symptoms, QoL, disease severity, nasal signs (examination), medication scores according to the Japanese clinical guidelines; and 2°: serum total IgE and sIgE levels, eosinophil count, nasal eosinophil and neutrophil counts, TARC	3	RSG unclear; AC unclear; IOD was high (2 subjects from the placebo group and 3 subjects from the high-dose group were excluded for sneezing >100 times); OB high (higher baseline total IgE scores in the probiotic group)	1°: Disease severity examined by the physicians, total score for nasal symptoms significantly improved in the high-dose group at the end of the trial compared with the beginning; nasal signs improved in all the groups at the end of the trial compared with the beginning; and 2°: a significant decrease in the serum total IgE level at the end of the trial compared with the beginning; no significant differences between the groups	3	0
16	Lin *et al.*,[47] 2013 (Taiwan)	1°: The SCORing Allergic rhinitis index: specific symptoms score for nasal blockage, nasal itching, sneezing, rhinorrhea, eye irritation and watering, wheezing, cough, and asthma, medication score; and 2°: eosinophil count, total IgE level	5	AC unclear; IOD was high (dropout numbers were high, intention-to-treat analysis was not done)	1°: Significant reduction in eye and nasal specific symptom scores, no significant reduction in asthma symptoms; and 2°: no significant statistical differences in blood eosinophils or IgE levels	3	0
17	Ishida *et al.*,[48] 2005 (Japan)	1°: Nasal and ocular symptom scores, SMS, examination of nasal cavity according to the Japanese clinical guidelines; and 2°: blood samples for total IgE and sIgE levels, Th1:Th2 ratio in blood, eosinophils	4	RSG unclear; AC unclear	1°: Significant improvement in nasal SMS, whereas ocular SMS tended to improve in the probiotic group compared with placebo; significant reduction in scores for swelling and color of mucosa for probiotic group compared with placebo at 8th and 6th wk, respectively; and 2°: no differences in total IgE or sIgE levels, Th1:Th2 ratio, or eosinophil count	2	0

Continued

Table 3 **Continued**

Study No.	Study, y (country)	Outcome Measurements: Primary Outcome (1°) and Secondary Outcome (2°)	Jadad Score	Cochrane Risk of Bias Assessment*	Results	Improvement in Clinical Parameters#	Improvement in Immunologic Parameters#
18	Ouwehand *et al.*,[49] 2009 (Finland)	1°: Presence of nasal, respiratory, or ocular symptoms; and 2°: serum sIgE level, blood and nasal eosinophil counts, cytokines IL-4, IL-5, IL-6, IL-10, TNF-α, TGF-β2, soluble CD14, analysis of fecal microbiota, calprotectin, and IgA	4	RSG unclear	1°: Fewer subjects tended to report runny nose and nasal blocking in the probiotic group; eye symptoms were slightly more frequent in the probiotic group; and 2°: significant reduction in nasal eosinophils and fecal IgA with probiotics compared with placebo	1	3
19	Singh *et al.*,[33] 2013 (Switzerland)	1°: TNSS; and 2°: IL-2, IL-5, IL-10, IFN-γ, IL-13, IL-1β, and TNF-α in whole-blood cell cultures; total IgE and sIgE levels	5	—	1°: Significant decrease in TNSS scores in probiotic group compared with placebo after 8 wk of treatment; and 2°: significant decrease in the levels of IL-5, IL-13, TNF-α in *ex vivo* stimulated whole-blood cultures in probiotic group compared with placebo, levels of sIgE tended to be lower in the probiotic group	3	3
20	Xiao *et al.*,[50] 2006 (Japan)	1°: Nasal, eye, and throat symptom scores, self-care measures (wearing mask, nasal sprays, eye drops); and 2°: blood samples for total IgE, sIgE, IL-10, IFN- γ values, and eosinophil ratio	5	AC unclear; OB high (total amount of pollen scattered was low, the usual bacteria was used in the intervention and placebo, not possible to conclude about the effect of BB536 per se, some antiallergic effects of the placebo yogurt cannot be excluded)	1°: Significant alleviation in eye symptoms compared with placebo; other nasal symptoms, except for sneezing and throat symptoms tended to decrease in the probiotic group compared with placebo, lower frequencies of self-care measures of mask wearing and eye drops were observed in the probiotic group compared with the placebo; and 2°: significant suppression of IFN-γ decrease in probiotic group compared with placebo in the 4th wk; levels of IL-10 tended to be higher and levels of eosinophil increase tended to be lower in the probiotic group	2	2
21	Xiao *et al.*,[51] 2006 (Japan)	1°: Nasal, eye, and throat symptom scores, self-care measures (wearing mask, nasal sprays, eye drops); and 2°: blood samples for total IgE, sIgE, IL-10, IFN- γ, and eosinophil ratio, TARC	5	SR high (use of prescribed pollinosis drug was set as a dropout criterion, but intention-to-treat analysis was done)	1°: Significant reduction in the number of subjects who were prematurely terminated with probiotic intake compared with placebo; significant alleviation of rhinorrhea, nasal obstruction and composite scores in the probiotic group compared with placebo; and 2°: significant suppression of elevation of the TARC levels and mild suppression of elevations of sIgE and decreases in IFN- γ levels in probiotic group	3	2

Continued

Table 3 **Continued**

Study No.	Study, y (country)	Outcome Measurements: Primary Outcome (1°) and Secondary Outcome (2°)	Jadad Score	Cochrane Risk of Bias Assessment*	Results	Improvement in Clinical Parameters#	Improvement in Immunologic Parameters#
22	Dölle *et al.*,[52] 2014 (Germany)	1°: SMS during grass-pollen season; and 2°: skin-prick test, conjunctival provocation test, RQLQ, total IgE, sIgE, sIgA levels	5	OB high (low pollen count)	1°: SMS scores with coseasonal treatment with probiotic was not superior to placebo; and 2°: significant increase in sIgA in the probiotic group compared with placebo, which indicated an immunoregulatory response with EcN	0	2

RDBPC = Randomized, double-blind, placebo-controlled; RSG = random sequence generation; AC = allocation concealment; SMS = symptom-medication score; IgE = immunoglobulin E; IOD = incomplete outcome data; OB = other bias; AR = allergic rhinitis; sIgE = specific immunoglobulin E; Th = T-helper; TARC = thymus activation regulated chemokine (Th2 marker); CRP = C-reactive protein; BB536 = Bifidobacterium longum BB536; PEFR = peak expiratory flow rate; PFT = pulmonary function test; TNF = tumor necrosis factor; IFN = interferon; IL = interleukin; PMNC = polymorphonuclear leucocyte; PHA = phytohemagglutinin; Dp = Dermatophagoides pteronyssinus; LG-A5 = Lactobacillus gasseri A5; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; RAST = radioallergosorbent test; LP-33 = Lactobacillus paracasei-33; ECP = eosinophil cationic protein; TSS = total symptom score; PRQLQ = Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; TGF = transforming growth factor; NTSS = nasal total symptom score; ETSS = eye total symptom score; TTSS = throat total symtom score; JCP = Japanese cedar pollen; LcS = Lactobacillus casei Shirota; SAR = seasonal AR; GI = gastrointestinal; QoL = quality of life; TNSS = total nasal symptom score; SR = selective reporting; EcN = Escherichia coli strain Nissle 1917; 1° = primary outcome; 2° = secondary outcome.
**Assessments are categorized as low, high, or unclear risk; only the reasons for high and unclear risks are listed.*
#0, no effect; 1, at least one clinical and/or immunologic parameter tended to improve in the probiotic group compared with placebo; 2, only one clinical and/or immunologic parameter significantly improved in the probiotic group compared with placebo; 3, more than one clinical and/or immunologic parameter significantly improved in the probiotic group compared with placebo; —, not evaluated in the trial.

Figure 3. *Meta-analysis of the change extracted from pre- and posttreatment values of daily nasal SS and/or QoL scores (Refs. 31–33,38,39,41,42,47,50,51). SS = Symptom score; QoL = quality of life; CI = confidence interval; SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis.*

−0.67]; $p = 0.006$). The degree of heterogeneity was high (Q = 86.60, d.f. = 3, $p < 0.001$). Three studies, with 308 patients, provided data for analysis of ocular QoL scores.[38,39,41] Overall, probiotic significantly improved the ocular QoL (SMD −3.11 [95% CI,

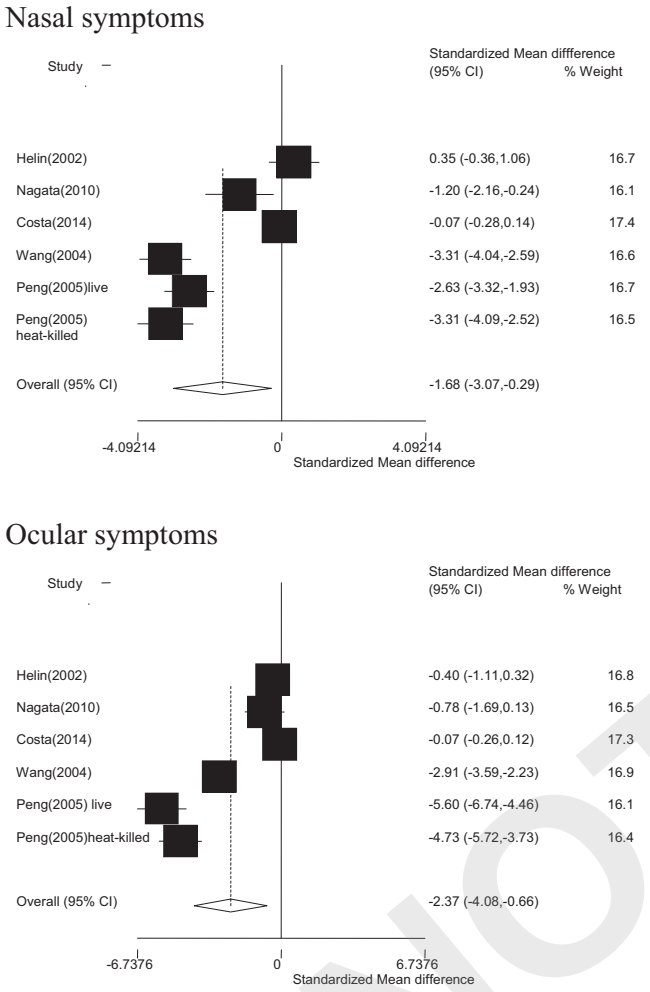


Figure 4. *Meta-analysis of the values given as change of daily SS and/or QoL scores (Refs. 34,38–40,46). SS = Symptom score; QoL = quality of life; CI = confidence interval.*

−5.27 to −0.95]; $p = 0.005$). The degree of heterogeneity was high (Q = 123.65, d.f. = 3, $p < 0.001$).

Two studies, with 170 patients, that used LP-33 as the probiotic strain provided data for analysis of nasal and ocular QoL scores.[38,39] LP-33 significantly reduced nasal and ocular QoL scores with an SMD of −2.96 (95% CI, −3.38 to −2.55; $p < 0.001$) and −4.03 (95% CI, −6.23 to −1.83; $p < 0.001$), respectively. The distribution was homogenous for nasal QoL scores (Q = 1.40, d.f. = 2, $p = 0.498$) but heterogeneous for ocular QoL scores (Q = 37.45 d.f. = 2, $p < 0.001$). These two studies[38,39] reported their results also as a change in pre- and post-treatment nasal and ocular QoL scores, and another study[40] reported only the change. In all of these three studies,[38–40] LP-33 was used as the probiotic strain. Analysis of these studies, which included a total of 595 patients, revealed that LP-33 significantly reduced nasal QoL scores (SMD −2.31 [95% CI, −4.43 to −0.27]; $p = 0.026$) and ocular QoL scores (SMD −3.33 [95% CI, −5.97 to −0.69]; $p = 0.013$), both with high degrees of heterogeneity (Q = 163.17, d.f. = 3, $p < 0.001$; and Q = 197.47, d.f. = 3, $p < 0.001$, respectively).

Total QoL scores were also provided for quantitative analysis in five studies,[38–42] which included 793 patients (Fig. 7). Overall, probiotic significantly improved the total QoL scores (SMD −1.84 [95% CI, −2.94 to −0.74]; $p < 0.001$). The degree of heterogeneity was high (Q = 173.35, d.f. = 5, $p < 0.001$) A subgroup analysis of the total QoL scores of the three studies[38–40] that used LP-33, which included 595 patients, revealed a significant reduction of total QoL scores with LP-33 compared with placebo with an SMD of −2.70 (95% CI, −4.90 to −0.49; $p = 0.016$), and the distribution was also heterogeneous (Q = 166.27, d.f. = 3, $p < 0.001$) (Fig. 7).

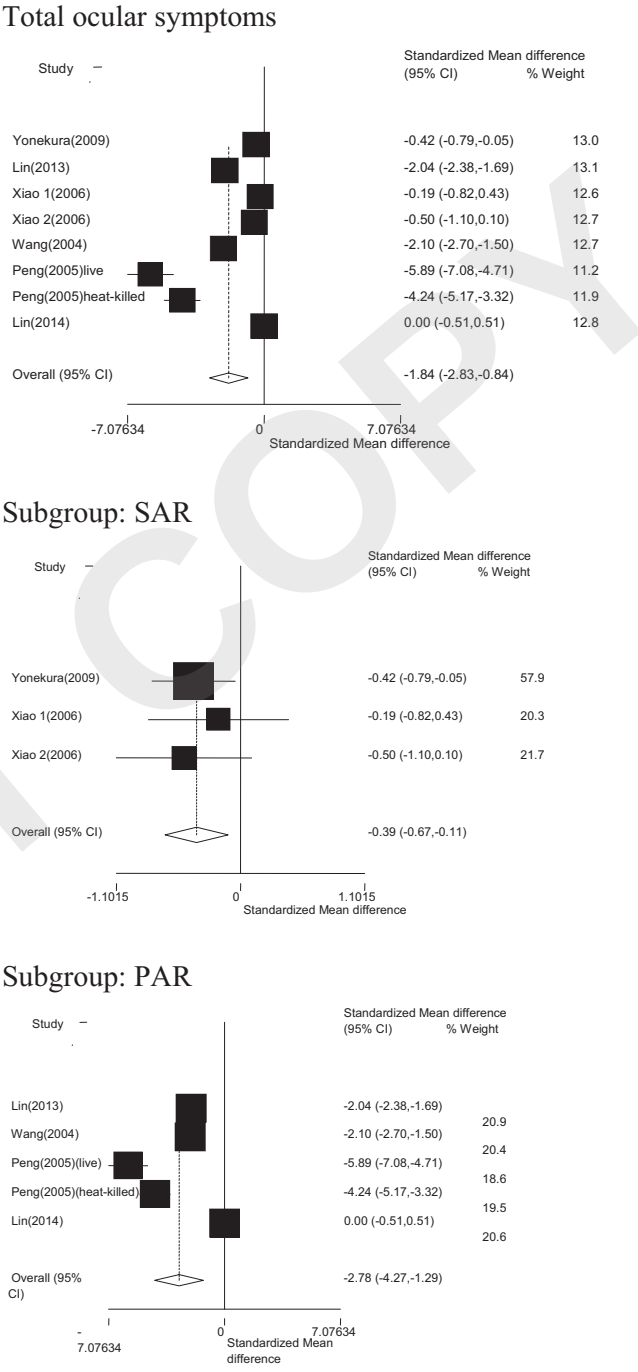


Figure 5. *Meta-analysis of the change extracted from pre- and posttreatment values of daily ocular SS and/or QoL scores (Refs. 38,39,41,42,47,50,51). SS = Symptom score; QoL = quality of life; CI = confidence interval; SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis.*

Secondary Outcome Parameters

Individual nasal SS. Nasal blockage, sneezing, and rhinorrhea SS were assessed in five studies[32,33,41,50,51] with 286 patients and with

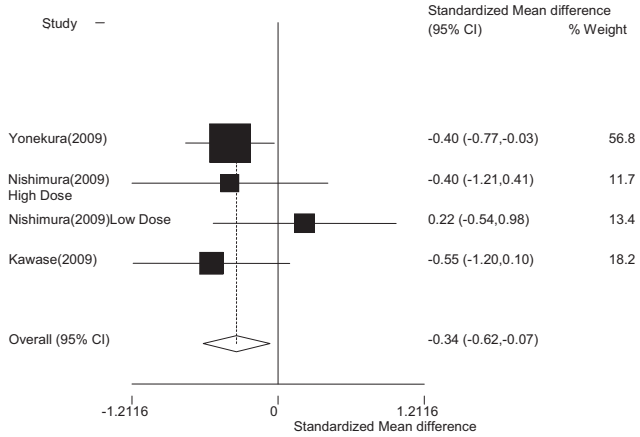
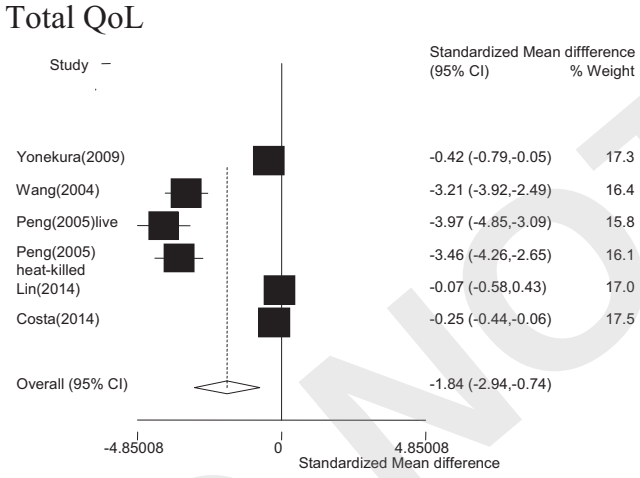


Figure 6. *Meta-analysis of the change extracted from pre- and posttreatment values of daily nasal SS of the studies that used Japanese guidelines for AR (Refs. 31,32,41). SS = Symptom score; AR = allergic rhinitis; CI = confidence interval.*



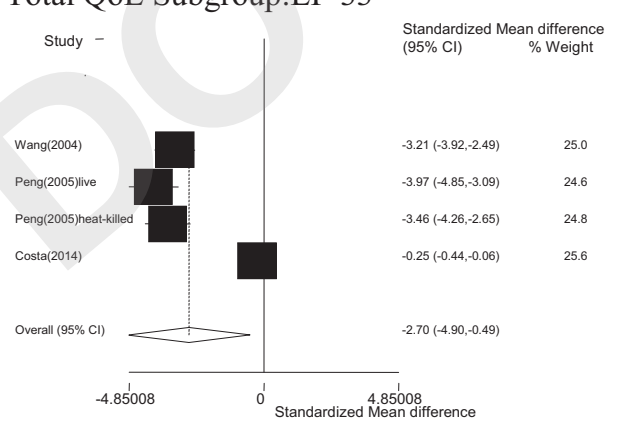


Figure 7. *Meta-analysis of the change in total quality of life (QoL) scores (Refs. 38–42). CI = Confidence interval.*

nasal itching scores in four studies with 148 patients (Fig. 8). Scores of nasal blockage (SMD −0.90 [95% CI, −1.44 to −0.36]; $p = 0.001$), rhinorrhea (SMD −0.51 [95% CI, −0.76 to −0.26]; $p < 0.001$), and nasal itching (SMD −1.02 [95% CI, −1.77 to −0.26]; $p = 0.008$) were

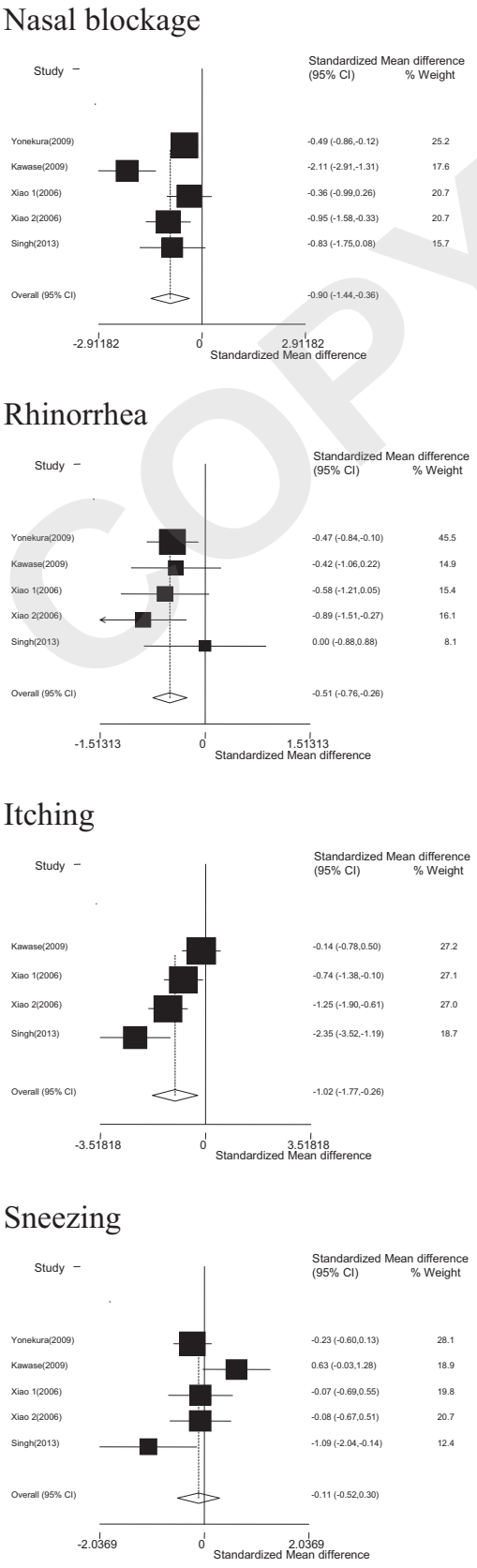


Figure 8. *Meta-analysis of the individual nasal SS (Refs. 32,33,41,50,51). CI = Confidence interval.*

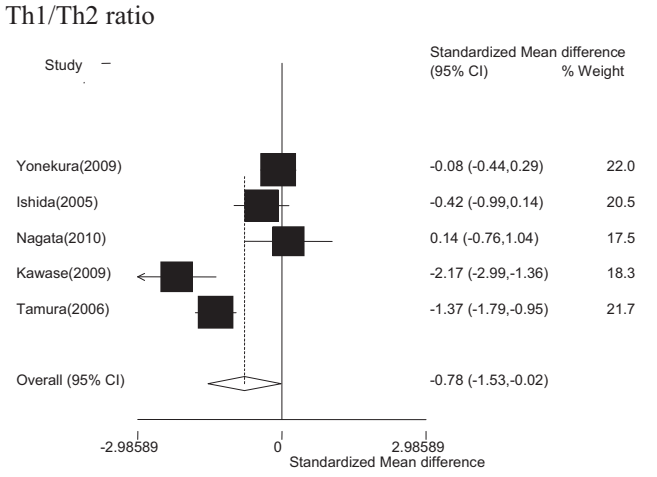


Figure 9. *Meta-analysis of the change in the T-helper 1 to T-helper 2 ratio (Refs. 32,41,43,46,48). CI = Confidence interval.*

significantly lower in the probiotic group compared with placebo. The distribution was homogenous for rhinorrhea (Q = 2.92, d.f. = 4, $p = 0.571$), and heterogeneous for nasal blockage (Q = 14.85, d.f. = 4, $p = 0.005$) and itching (Q = 12.73, d.f. = 3, $p = 0.005$). Sneezing tended to be lower in the probiotic group compared with placebo (SMD −0.11 [95% CI, −0.52 to 0.30]; $p = 0.594$), and the distribution was heterogeneous (Q = 9.46, d.f. = 4, $p = 0.051$).

Immunologic Parameters. The effect of probiotics on total IgE was assessed in nine studies.[31–33,36,45,46,48,50,51] Analysis did not reveal any differences between the probiotic and placebo groups, but the result was homogenous (SMD 0.01 [95% CI, −0.17 to 0.19]; $p = 0.888$) (Q = 3.05, d.f. = 9, $p = 0.962$). sIgE was evaluated in nine studies.[32,33,41,43,46,48–51] No significant difference was observed, and the result was heterogeneous (SMD 0.09 [95% CI, −0.44 to 0.62]; $p = 0.736$) (Q = 60.28, d.f. = 8, $p < 0.001$). The eosinophil count was reported in units of cells/μL in four studies[36,44,47,50] and in units of percentage in three studies.[31,50,51] There were no significant differences in both of the parameters (SMD 0.27 [95% CI, −0.94 to 1.47]; $p = 0.667$; and SMD 0.12 [95% CI, −0.31 to 0.56]; $p = 0.578$, respectively). Five studies provided enough data to allow quantitative analysis for the Th1:Th2 ratio, which was significantly lower in the probiotic group compared with placebo (SMD −0.78 [95% CI, −1.53 to −0.02]; $p = 0.045$), but the heterogeneity was high (Q = 35.829, d.f. = 4, $p < 0.001$) (Fig. 9).

DISCUSSION

This article presented the results of the most comprehensive systematic review and meta-analysis of 22 RDBPC studies on the efficacy of probiotics in the management of AR. Sixteen[31–33,36–42,45–48,50,51] of the trials included in the review showed significant benefit of probiotics on clinical parameters, whereas nine[33,36,41,44,46,49–52] of the trials showed significant improvement in immunologic parameters compared with placebo. The meta-analysis of the trials revealed significant amelioration in nasal and ocular symptoms and QoL scores in patients with AR with probiotic treatment compared with placebo.

In the first meta-analysis, by Yoa *et al.*,[54] the investigators concluded that the studies on the use of probiotics in the treatment of AR produced conflicting results. Cheng *et al.*[55] included four trials and reported significant reduction in nasal SS and improvement in rhinoconjunctivitis QoL in the dietary probiotic-treated group. Das *et al.* published two meta-analysis reports[56,57] in which the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[10] were followed. However, although 7 and 12 randomized controlled trials were included, respectively,[56,57] for analyses, data were extracted and synthesized for meta-analyses from only two[38,39] of the studies. The review was not able to gather the results of the majority of the included studies for the treatment of AR.[56,57]

While we were working on this study, a new meta-analysis was published by Zajac *et al.*[58] which demonstrated a high methodologic quality. They reported a significant improvement in Rhinitis Quality of Life Questionnaire scores compared with placebo, no effect on Rhinitis Total Symptom Scores or total IgE levels, and a trend toward a reduction in antigen sIgE in the placebo group compared with the probiotic group; however, the number of studies included in the meta-analysis again was low, and the synthesis was neither comprehensive nor detailed. Peng *et al.*[59] analyzed 11 randomized-controlled trials and reported that probiotic intake was associated with a significant overall improvement of the QoL scores and nasal SS of patients with AR. Turner *et al.*[60] commented on the study by Peng *et al.*[59] analysis and mentioned that, in the study by Peng *et al.*,[59] a total of six randomized controlled trials were analyzed for the role of probiotics in AR treatment. However, their study identified a total of 23 studies, including 21 randomized controlled trials and 2 crossover studies.[58]

In the present study, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[9] were strictly followed throughout the review. The quality of the studies was analyzed by Jadad scoring[10] and a study eligibility form, and acceptable ones were included in the analyses. In addition, we analyzed nasal symptoms individually for some of the studies. Limitations were heterogeneity of the populations, the diversity of the strains and quantities of probiotics, forms of administration and duration of probiotics, and the diversity of the scoring system used to determine the symptoms of AR. The diversity of methods used in the evaluation of immunologic parameters also resulted in inconsistent results. The use of the weighted mean difference in the meta-analyses compensated in part for this diversity.

Although most of the SMD values in our analysis were significant, showing important benefit of probiotics on symptoms, we could not compare our SMD values for most of the symptom or QoL scores with minimally important difference (MID) values because the symptom scales were different or were not validated; however, with the meta-analysis of three studies[31,32,41] that used the Japanese guidelines,[53] we were able to compare the SMD score with the MID level for nasal symptoms. A significant and homogenous SMD score of −0.34 was obtained for each individual nasal symptom, which is higher than the MID value of 0.3 unit difference per item.[61] The standardization of scoring systems is necessary for data extraction and comprehension of the results of a meta-analysis. The World Allergy Organization recommends the use of a four-point rating scale (from 0 [absent] to 3 [severe]) applied to each symptom.[62] If rescue medications are used, then it is advised to use symptom-medication scores instead of SS. Despite these limitations, the Cochrane Collaboration's tool assessment[30] showed that the general risk of bias of included studies was satisfactory. The heterogeneity was high, but Begg's and Egger's tests provided no evidence for the presence of small study effects. Heterogeneity may be due to confounding factors and differences among studies.

Our analysis demonstrated many important findings. As for primary outcomes, nasal and ocular SS, daily total SS and QoL scores were significantly improved with probiotic treatment compared with placebo. A high degree of heterogeneity was observed in most of these parameters, but the subgroup analysis revealed significant reduction in both nasal and ocular symptoms in patients with SAR and with SMD scores that showed homogenous distribution. This homogeneity may be due to a number of reasons. First of all, for seasonal allergies, the trials were planned in the peak of season, which resulted in maximal allergen exposure, and significant symptom changes were observed compared with perennial allergen studies in which the allergenic exposure may be more variable. It seems that the development of protective probi-

otic response was exaggerated, with greater allergen challenge as described by Schabussova and Wiedermann.[63]

Moreover, four of the five[32,41,50,51] and all three SAR studies[41,50,51] included in subgroup analysis for nasal and ocular symptoms, respectively, were on patients with JCP allergy, which thus resulted in more homogenous analyses. The analysis of nasal scores for the two studies[38,39] from Taiwan, which presented the results of LP-33 supplementation to children and adults allergic to *Dermatophagoides pteronyssinus*, also revealed improvement with homogenous SMD values. These studies were comparable because they were published from the same faculty and had similar methodology and study population.[38,39]

To our knowledge, our study was the first meta-analysis in which the individual nasal scores were analyzed. Scores for nasal blockage,[32,33,41,50,51] rhinorrhea,[32,33,41,50,51] and nasal itching[32,33,50,51] were found to be significantly lower in the probiotic group compared with placebo, and the scores were homogenous for rhinorrhea. Sneezing tended to be lower in the probiotic group compared with placebo.[32,33,41,50,51] Evaluation of the immunologic parameters demonstrated another important finding. The quantitative analysis of the Th1:Th2 ratio resulted in a significantly lower ratio with probiotics compared with placebo.[32,41,43,46,48]

This is the first study, to our knowledge, in which a significant difference was observed in the meta-analysis of an immunologic parameter. Immunologic markers cannot replace symptom and medication scores; however, they provide objective and supportive evidence for the effects of probiotics. The reduction in the Th1:Th2 ratio is associated with a shift from Th2 to Th1 cytokine production, which causes resolution of allergic responses. Analysis for total IgE, antigen sIgE, and eosinophils did not show any differences among groups. There were various other parameters studied in different trials, but, due to the variety of methods of measurement used and scarcity of adequate data, meta-analyses were not possible. Standardization of the measurement methods for immunologic parameters is crucial for comparison. The changes in the parameters may be too small to detect in serum. Alternatively, antigen-specific Th1:Th2 cells in serum or cytokines produced in cultured peripheral blood mononuclear cells can be studied.[44,48]

The systematic review of individual studies also demonstrated significant benefits of probiotic intake, despite the variety of strains. Sixteen of the trials[31–33,36–42,45–48,50,51] showed significant clinical improvement with probiotic compared with placebo, and, in two trials,[43,49] allergic symptoms tended to improve. Moreover, some immunologic improvement was demonstrated in more than half of the trials. It is known that different species of probiotics, even different strains show different effects. LGG is an extensively studied probiotic strain, which was found to be promising in the prevention of atopy and treatment of atopic eczema and food allergy;[6] however, two trials for the treatment of birch pollen and house-dust allergy showed no effects of LGG in the treatment of AR.[33,34]

However, there are numerous trials with different strains and mixtures that showed beneficial effects. LP-33 proved successful in the treatment of allergic rhinoconjunctivitis in two earlier small trials and one recent larger trial in house-dust and grass pollen allergy, respectively.[38–40] Two other strains of LP (KW3110T and HF.A00232) exerted beneficial effects on AR. KW310T effects were apparent, especially on rhinorrhea, QoL scores, and serum eosinophil cationic protein levels, which act on eosinophil function and reduce the eosinophil count.[41] HF.A00232 also had effects on Pediatric Rhinoconjunctivitis Quality of Life Questionnaire scores and individual symptoms, such as sneezing and nasal itching.[42] *L. casei* strain Shirota is also a studied strain, which suppresses IgE production of splenocytes by enhanced IL-12 secretion. A clinical study and an immunologic study by using *L. casei* Shirota demonstrated beneficial effects in pollen allergies.[43,44]

Bifidobacteria are one of the major components of the intestinal microflora that are frequently associated with health-promoting effects. *Bifidobacterium longus* BB536 has been shown to stimulate IFN-γ secretion and inhibit Th2 cytokine and IgE generation. It has proven effective both clinically and immunologically in two trials by Xiao *et al*.[50,51] on patients with JCP allergies. Another trial, with *Bifidobacterium lactis* NCC2818, reported significant decreases in total nasal symptoms and allergic and proinflammatory cytokines in whole-blood cell cultures compared with placebo.[8] A trial of *E. coli* strain Nissle 1917, which displayed preventive and therapeutic potential in allergic diseases, demonstrated no clinical benefit in subjects with grass-pollen allergy, whereas the grass-specific IgA levels were higher in the probiotic-treated group.[52] On the whole, apart from the two unsuccessful trials with LGG alone, all the trials demonstrated some beneficial effects of different probiotic species and mixtures, independent of the type of allergy or age of the study population.

To improve the selection of new candidate probiotic strains or mixtures to be included in new clinical trials, some important points that could reduce the heterogeneity could be remembered: Combining probiotics or using different types (heat killed, live) of probiotics for improving their potency may also cause variant results. Although LGG alone did not show clinical effects in two different trials,[34,35] a combination of LGG with *Lactobacillus gasseri* TMC0356,[32] which suppressed Th2-dominated allergic response and inflammation in experimental studies, alleviated nasal blockage in patients with JCP allergy. The actions of probiotics are dose-dependant.[31]

Moreover, the medium that probiotics are administered in is important. If the probiotic is administered just in water rather than with milk or food, this may increase the susceptibility of the bacteria to gastric acid digestion and reduce the number of viable bacteria that reach the intestine. A fusion protein can be used to increase bacterial uptake and immune responses.[64] The duration and period of probiotic intake are also important. It was shown that beneficial effects of probiotics are seen at least 4 weeks after continuous administration. These effects were evident after 6 weeks of supplementation of an LGG and *L. gasseri* mixture, and only after 8 weeks after supplementation of *B. lactis*.[32,33] There may be a possible "adjustment window" for the action of probiotics that mimics a "low-grade" inflammation when administered first to the host and only after colonization of the probiotic in the gastrointestinal tract may actions on the host immune system be evident.[8]

Host-dependant factors may also affect the results of the studies. The susceptibility to probiotics may differ among individuals with different genetic backgrounds.[65] An ideal model for investigation of immunomodulation for the treatment of allergy would be the segment of population with a suboptimal immune function with moderate symptoms.[66] These differences may explain why probiotics cannot prevent disease in individuals who were not sensitized but are effective in decreasing disease severity in patients who are sensitized. In this aspect, age is also an important factor. In our review, although the level of clinical improvements were similar in studies with children and adults (6/8 versus 10/13, respectively), immunologic parameters seemed to score worse in studies with children compared with adults (2/6 versus 7/13, respectively), which supports the fact that the effect of the probiotic bacteria depends on the maturation of the immunologic status of the host.

Microbial flora also varies, primarily according to age. Care should be taken to construct each study confined to a specific age group to get more reliable results.[67] Sensitization to different allergens may affect the efficacy of a probiotic. For instance, AR due to birch- and timothy-pollen allergies may differ from JCP allergy, and the mechanism of action of LGG in JCP allergy may differ from the effect of LGG in birch-pollen allergy.[32] Therefore, it is crucial to include individuals who are monosensitized in the study population to draw definite conclusions. Environmental factors such as general microbial burden, lifestyle, diet, affected by geographic variances and antibiotic consumption, may alter the gut microflora of the participants and play a cardinal role in the effectiveness of probiotics.[67] The fluctuations in pollen counts may account for the differences in efficacy of probiotics in pollen allergy.[48] Pollen counts must be provided with

SAR studies. Primary outcome analyses can be made for clearly identified relevant periods, *e.g.*, for weeks when the pollen load is higher than a predetermined level (for instance, the peak pollen season, which includes 50% of the total pollen load.[68]

CONCLUSION

The synthesis of available data provided evidence of a potential benefit of probiotics in the treatment of AR, especially with SAR and LP-33 strains. This was demonstrated both clinically and immunologically, despite high variability in study sizes, probiotic formulations, and outcome measurements of the included studies. Our study showed that nasal blockage, nasal itching, and rhinorrhea scores, and the Th1:Th2 ratio were decreased with probiotics. Future studies should address the limitations of previous studies regarding study design, host-dependant factors, and probiotic characteristics, and should focus on studies that can prove the efficacy of single or mixtures of probiotic strains both clinically and immunologically with validated symptom and QoL scores and with objective measurements. With the rising pool of studies that reveal effective strains, adjuvant therapy with probiotics can be recommended for the treatment of AR in the future.

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