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A Systematic Review and Meta-analysis of Probiotics for the Treatment of Allergic Rhinitis

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Abstract

Objective—Probiotics have proven beneficial in a number of immune-mediated and allergic diseases. Several human studies have evaluated the efficacy of probiotics in allergic rhinitis, however, evidence for their use has yet to be firmly established. The current systematic review seeks to synthesize the results of available randomized trials.

Study Design—Systematic review and meta-analysis.

Methods—The Medline, EMBASE, and Cochrane Library databases were reviewed and randomized controlled trials were extracted based on defined inclusion criteria. The effect of probiotics on Rhinitis Quality of Life (RQLQ) scores, Rhinitis Total Symptom Scores (RTSS), as well as total and antigen-specific serum IgE levels were evaluated by meta-analysis.

Results—A total of 23 studies with 1919 patients were identified, including 21 double-blind randomized controlled trials and 2 randomized crossover studies. Multiple probiotic strains, study populations, and outcome measures were utilized in individual trials. Seventeen studies showed a significant clinical benefit from the use of probiotics in at least one outcome measure when compared to placebo, while 6 trials showed no benefit. Among the trials eligible for meta-analysis, the use of probiotics resulted in significant improvement in RQLQ scores compared to placebo [standard mean difference (SMD) −2.23; p = 0.02]. Probiotics had no effect on RTSS [SMD −0.36; p = 0.13] or total IgE levels [SMD 0.01; p = 0.94], while there was a trend toward a reduction in antigen-specific IgE [SMD 0.20; p = 0.06] in the placebo group compared to probiotic.

Conclusions—Probiotics may be beneficial in improving symptoms and quality of life in patients with allergic rhinitis, however, current evidence remains limited due to study heterogeneity and variable outcome measures. Additional high-quality studies are needed to establish appropriate recommendations.

Keywords

Allergic rhinitis; probiotics; allergy; atopy; lactobacillus; randomized trial; meta-analysis

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INTRODUCTION

Allergic rhinitis (AR) is a common disease estimated to affect between 10% and 30% of the general population.[1] The disease process itself is initiated when an individual is exposed to an allergen that stimulates IgE-mediated inflammatory responses in the nasal mucosa. This leads to allergen sensitization and the development of an atopic reaction that symptomatically manifests as rhinorrhea, pruritus, sneezing, and nasal congestion. These symptoms can have major impacts on patient quality of life and result in significant economic burdens.[2,3] Although typically a self-limited disease, medical intervention is often required for symptomatic relief, with current treatment regimens including allergen avoidance, antihistamines, decongestants, and intranasal corticosteroids. Unfortunately, complete symptom resolution of AR is typically very difficult to achieve with a recent prospective international survey finding adequate symptom control in as few as 38.8% of patients on varied regimens of antihistamines and intranasal corticosteroids.[4]

Probiotics are novel treatment options for AR and have recently generated considerable interest in the scientific community. At the writing of this manuscript, when the term ‘probiotic’ is queried in PubMed, 13,273 results are returned with over half of publications occurring in the past 5 years. Probiotics are living microorganisms that confer a physiologic benefit following host administration[5] and are naturally found in foods such as yogurt, miso soup, sauerkraut, pickles, and dark chocolate.[6] Probiotics have been utilized effectively in a number of immune and allergen-mediated conditions and recent evidence suggests that they may be preventative adjuvants for conditions such as atopic dermatitis, infectious and antibiotic-associated diarrhea, and vaginal infections during pregnancy.[7–10]

Numerous studies have evaluated the putative efficacy of probiotics for the treatment of AR, typically with mixed conclusions. Consequently, a consensus for or against the use of probiotics in AR has yet to be reached. Recent reviews have suggested that probiotics may have significant beneficial effects on AR management, with the potential to improve patient quality of life and reduce medication use.[11,12] Additional randomized controlled trials have since been performed, however differences in study parameters and individual probiotics used has made synthesis of this data very difficult. The current study seeks to systematically review the role of probiotics as an adjuvant treatment for AR.

MATERIALS AND METHODS

A comprehensive systematic literature review was performed using the Medline, EMBASE, and Cochrane Library databases. The search was limited to articles published in the English language and studies performed on humans. Only randomized controlled trials were reviewed. The search criteria included the MESH terms ‘rhinitis’ and ‘probiotic’.

Retrieved titles and abstracts were reviewed by two study authors (A.Z., J.T.). A full text review was then performed on selected articles by both authors to confirm that inclusion and exclusion criteria were met. All randomized controlled trials that examined the effects of probiotic administration on the treatment of a population with AR – both seasonal and perennial - were considered eligible for inclusion. Studies with a treatment duration longer

than 4 weeks were included. Only studies between the year 2000 and 2014 that included defined and comparable outcome measures, particularly the Rhinitis Quality of Life Questionnaire, Rhinitis Total Symptom Score, total IgE, and antigen-specific IgE, were included. Studies that analyzed prenatal data or had the mother ingest probiotics to determine effects on their child were excluded. Mixed populations where individual outcomes could not be extracted were excluded. RCTs that examined mixed AR, nonallergic AR, or rhinosinusitis were also excluded. No studies were excluded on the basis of participant gender/age.

Each included study was evaluated with the 5-point Jadad scale[13] to assess the quality of included manuscripts. This scale assigns points in the following manner:

1. Was the study described as randomized? (0 = no; 1 = yes)
2. Was the study described as double blind? (0 = no; 1 = yes)
3. Was there a description of withdrawals and dropouts? (0 = no; 1 = yes)
4. Was the method of randomization well described and appropriate? (0 = no; 1 = yes)
5. Was the method of double blinding well described and appropriate? (0 = no; 1 = yes)
6. Deduct 1 point if methods for randomization or blinding were inappropriate.

Out of a maximum possible 5 point score, studies with a score ≥ 3 are considered to be of well-regarded quality and were included in this review.

Data was then extracted from individual studies and assembled in a standardized database using Cochrane Review Manager 5.3 software. Mean values, standard deviations, and sample sizes were utilized for each comparable objective criterion. This data was then formatted into forest and funnel plots to illustrate the relative strength of treatment effects and assessment of publication bias, respectively. Quantitative assessment of publication bias using the Begg and Mazumdar's Rank Correlation Test and Egger's Regression were performed using Comprehensive Meta Analysis 2.2 software. When applicable, results are described in accordance with the PRISMA guidelines for reporting systematic reviews and meta-analyses,[14] with 95% confidence intervals reported throughout. A P value of <0.05 was considered significant for all statistical tests.

RESULTS

Systematic Review

The literature search retrieved a total of 153 articles. A title and abstract review followed by exclusion of any duplicate publications resulted in 42 remaining articles for full text review. Twenty-three articles were ultimately included in the study, with the majority of studies being excluded due to a lack of quantifiable data or insufficient study description. The selection process is detailed in Figure 1. Studies identified during the systematic review included 21 double-blind randomized controlled trials and 2 randomized crossover studies.

Study Details

Details regarding the individual studies identified during the systematic review can be found in Table 1. Sixteen studies used *Lactobacillus* strains while six studies used *Bifidobacterium*. *Escherichia coli* (Nissle 1917), *Tetragenococcus halophilus* (Th221), and *Bacillus clausii* were used in single studies. The duration of probiotic administration varied between studies and ranged from 4 weeks to 12 months. The most commonly used outcome measures were the Rhinitis Quality of Life Questionnaire (6 studies), Symptom Medication Score (5 studies) and Rhinitis Total Symptom Score (5 studies). Seventeen of 23 studies showed significant improvement in at least one measured outcome with the use of probiotics, while 6 studies showed no benefit. Measurement of total or antigen specific IgE was included in 8 and 7 studies, respectively. The quality of included studies was assessed using the 5-point Jadad scoring system. 9 (39.13%) trials had a total score of 3, while 13 (56.52%) trials had a total score of 4, and 1 (4.35%) trial had a total score of 5.

Rhinitis Quality of Life

Of the 6 studies that utilized the RQLQ, four included descriptive data that allowed for direct comparison and meta-analysis. This particular metric was created to assess functional problems (physical, emotional, social, and occupational) associated with AR. Data from the four studies included a total of 335 patients treated with probiotics and 287 patients treated with placebo (Figure 2). The meta-analysis demonstrated a significant improvement in RQLQ global scores in the probiotic group compared to placebo (SMD −2.23 (95% CI −4.07, −0.40); P = 0.02) as well as in RQLQ nasal symptoms (SMD −1.21 (95% CI −1.42, −0.99); P <0.00001). There was a trend toward improvement in RQLQ eye symptoms (SMD –1.45 (95% CI –3.04, 0.15); P = 0.08), though this did not reach statistical significance. As a frame of reference, Juniper et al.[15] showed that mean changes in RQLQ greater than 0.5 can generally be considered clinically significant. For example, Demoly et al.[16] examined the effect of desloratadine on RQLQ in patients with AR and showed a change of −1.4. Of note, significant heterogeneity was observed with an I^2 statistic of 97% or above for RQLQ global and symptom-specific scores. Risk of bias was quantitatively assessed using the Begg and Egger tests. Both tests were nonsignificant (p = 0.09 and p =0.16, respectively). However, the fairly low p-values and significant heterogeneity suggests that the effect identified in this meta-analysis may be at least partially due to confounding factors and differences between studies. This is highlighted by the fact that the two older, small studies showed a fairly significant difference between placebo and probiotic, while the two larger, more recent studies identified either a small difference or no difference between groups.

Rhinitis Total Symptom Score

Of the six studies that assessed RTSS, four reported quantitative data that was sufficient for meta-analysis. The RTSS measures both nasal and non-nasal symptoms associated with AR. The eligible studies included 270 patients in the probiotic group and 263 patients in the placebo group (Figure 3). No significant differences in RTSS global scores (SMD −0.36 (95% CI −0.83, 0.10); P = 0.13) were identified between the probiotic and placebo groups. Likewise, RTSS eye symptoms (SMD −0.10 (95% CI −0.26, 0.07); P = 0.25) and RTSS nose symptoms (SMD −0.82 (95% CI −2.41, 0.78; P = 0.32) were not significantly different

between groups. Moderate heterogeneity was noted among the study population (I^2 = 45–58%) and no significant bias was identified using the Begg and Egger tests (p = 0.73 and p = 0.23, respectively).

Total and Antigen-Specific IgE

The effect of probiotics on total and antigen-specific IgE was assessed in 8 and 7 studies, respectively (Figure 4). A meta-analysis of included studies did not demonstrate any significant differences between the probiotic and placebo groups for total IgE (SMD 0.01 (95% CI −0.18, 0.19); P = 0.94). A trend toward a reduction in antigen-specific IgE levels was observed in the placebo group compared to the probiotic group (SMD 0.20 (95% CI −0.01, 0.41); P = 0.06). Minimal heterogeneity was identified (I^2 = 0%) and no significant study bias was detected with the Begg and Egger tests (total IgE, p = 1.0 and p = 0.78; antigen-specific IgE, p = 0.76 and p = 0.63, respectively).

Adverse Events

Few adverse events were reported among the included studies. Complaints including diarrhea, abdominal pain, and flatulence were reported in select studies, but at rates that typically mirrored the placebo group. There were no serious/life-threatening adverse events and no patients required additional treatment or intervention. Among the 23 included studies, only one patient did not compete the study due primarily to an adverse event (flatulence).

DISCUSSION

The current systematic review and meta-analysis represents the most comprehensive analysis to date of the use of probiotics for the treatment of AR. A majority of studies resulted in at least some clinical benefit with the use of probiotics compared to placebo. A meta-analysis resulted in contrasting findings, with the probiotic group showing a statistically significant improvement in global and symptom-specific RQLQ scores, but no improvement in RTSS scores. Probiotics did not have any effect on either total or antigen-specific IgE levels.

Probiotic supplementation has been shown to improve clinical outcomes in a variety of inflammatory disorders. For example, a review article examining the therapeutic potential of probiotics in irritable bowel syndrome found that in roughly two-thirds of controlled clinical trials, probiotic supplementation lead to an improvement in symptoms.[17] Delivery of oral probiotics has also shown benefit for the treatment of food allergy,[18,19] and atopic dermatitis.[20] Probiotics have even been proven to reduce the development of hepatic encephalopathy in patients with liver cirrhosis.[21] As summarized in this review, multiple randomized controlled trials have now also demonstrated potential benefits of probiotics for the treatment of AR.

The mechanism by which probiotics may modulate atopic diseases has yet to be completely defined. In mouse models, probiotics have the potential to promote T helper type 1 (Th1) immunity while suppressing Th2 responses.[22] Other evidence suggests that probiotics may increase the predominance of regulatory T cells (Tregs) by altering the composition of the

gut microflora.[23] Multiple animal studies have found that probiotics can modify levels of antigen-specific serum IgE levels.[24,25] However, our meta-analysis showed no significant change in total or antigen-specific IgE levels between study participants receiving probiotics versus placebo. Collectively, these data suggest that probiotics may serve as immunomodulators that alter systemic innate and adaptive immune responses. Much about the role of probiotics in the human immune response remains poorly understood and additional translational studies will likely be needed to clarify this in the future.

The current study suggests that probiotics have the potential to alter disease severity, symptoms, and quality of life in patients with AR. Positive outcomes were reported in a majority of studies with no significant adverse events. However, several limitations prevent us from making generalized recommendations based on this data. Despite including 23 studies with almost 2000 patients, the overall cohort remained fairly heterogeneous. Furthermore, a lack of quantifiable data prevented inclusion of most studies in the meta-analysis, a fact that restricted the power of these analyses. The term ‘probiotic’ is an all encompassing term, but the efficacy of particular formulations is largely dependent on geography, dietary practices, and prevailing gut microflora. This is echoed in the current study, with certain strains (*Lactobacillus paracasei* 33) proving effective for treatment of grass pollen allergies, while others (*Escherichia coli* strain Nissle 1917) proved ineffective.[26,27] Similar differences in efficacy have been noted in other atopic diseases, with one probiotic strain proving effective for the treatment of atopic dermatitis in a comparative randomized controlled trial, while another was completely ineffective.[28]

Despite these self-evident limitations, this study was able to synthesize current literature and report several important findings. First, the majority of randomized-controlled studies reported improvement in patient symptoms or quality of life in at least one measured outcome. This was despite variability in study design, probiotic formulation, and outcome measures. A meta-analysis demonstrated improvement in patient quality of life as assessed by the RQLQ. This is perhaps the most commonly used and accepted quality of life metric for assessing the symptomatic impact of AR, and has been validated in multiple studies.[15,29] While a similar improvement was not noted for the RTSS, there was a trend toward improvement with probiotic compared to placebo. These particular meta-analyses were likely limited by study heterogeneity and the small number of incorporated patients in most of the included studies. In particular, significant heterogeneity and possible bias were identified in the meta-analysis of RQLQ scores, issues which limit any conclusions that can be reported based on these results. Finally, a meta-analysis assessing the impact of probiotics on total and allergen-specific IgE levels did not result in any significant differences between the probiotic and placebo groups. Interestingly, there was a trend toward a reduction in antigen-specific serum IgE in the placebo group, an unexpected finding in light of prior animal studies.[24,25] This would suggest that the physiologic effects of probiotics in humans may be unrelated to their putative modulatory effect on IgE levels.

Probiotics appear to have beneficial effects in a number of inflammatory and immunologic diseases. The current systematic review suggests that they may be similarly effective in AR, though the mechanism and duration of this effect remains unclear. Future studies will need to address the limitations of randomized trials to date, specifically the variability in study

design and probiotic formulations, both of which make comparison between individual studies difficult. While the use of probiotics as a stand-alone therapy cannot be advised at this point, they may ultimately prove to be an effective adjuvant therapy for the treatment of recalcitrant AR in select populations.

CONCLUSIONS

Currently available trials evaluating the efficacy of probiotics for the treatment of AR suffer from variability in probiotic formulations, study designs, and outcome measures. Despite these shortcomings, current evidence suggests that probiotics may have some beneficial effects in this patient population. Additional randomized controlled trials using specific probiotic strains and consistent outcome measures are needed to confirm this putative efficacy and allow for evidence-based recommendations.

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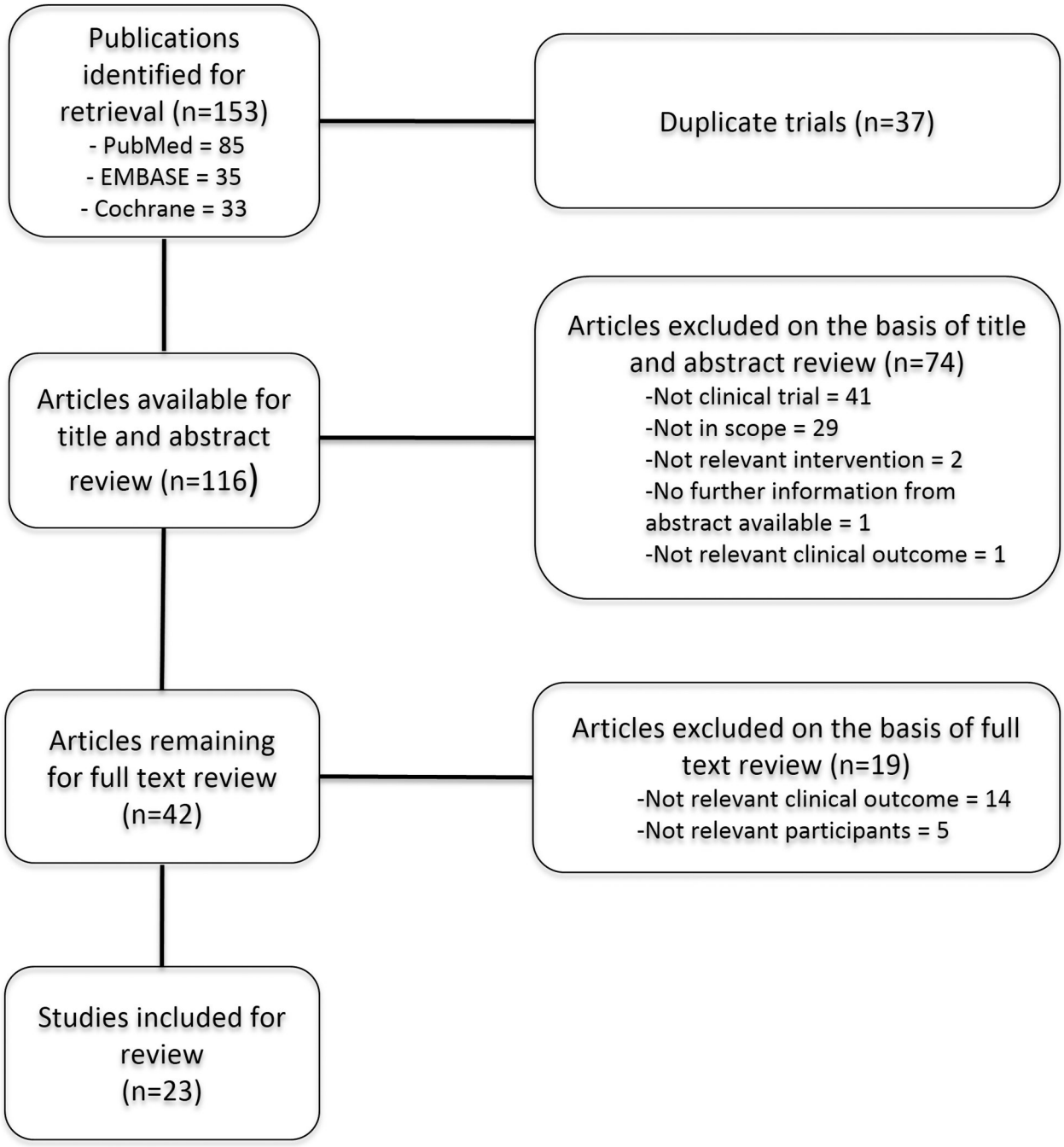
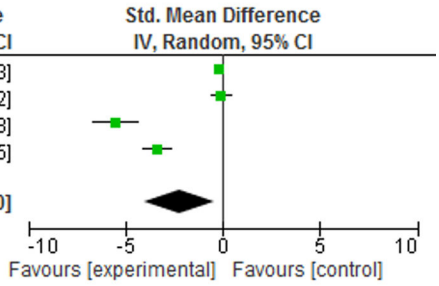


Figure 1.
Article Selection Process for Systematic Literature Review

RQLQ Global Score

Study or Subgroup	Probiotic Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Costa 2014	-1.89	1.22	215	-1.61	1.31	210	25.9%	-0.22 [-0.41, -0.03]
Lue 2012	-21	29.41	30	-18.37	21.41	27	25.5%	-0.10 [-0.62, 0.42]
Peng 2005	-9.47	2.89	30	3.47	1.53	30	23.6%	-5.52 [-6.66, -4.38]
Wang 2004	-16.02	2.14	60	-7.27	3.55	20	25.0%	-3.39 [-4.13, -2.65]
Total (95% CI)			**335**			**287**	**100.0%**	**-2.23 [-4.07, -0.40]**

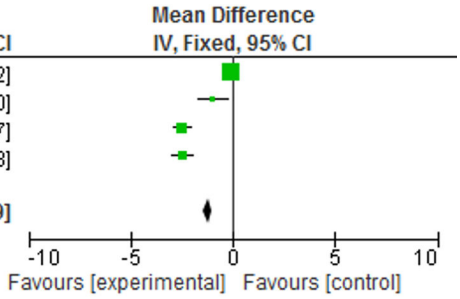
Heterogeneity: Tau² = 3.36; Chi² = 143.72, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.39 (P = 0.02)



RQLQ Nose Score

Study or Subgroup	Probiotic Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Costa 2014	-1.89	1.66	215	-1.8	1.61	210	47.8%	-0.09 [-0.40, 0.22]
Lin 2014	-1.9	1.5	30	-0.9	1.2	27	9.4%	-1.00 [-1.70, -0.30]
Peng 2005	-2.9	0.99	30	-0.4	0.69	30	24.8%	-2.50 [-2.93, -2.07]
Wang 2004	-4.12	0.65	60	-1.63	1.09	20	18.1%	-2.49 [-3.00, -1.98]
Total (95% CI)			**335**			**287**	**100.0%**	**-1.21 [-1.42, -0.99]**

Heterogeneity: Chi² = 109.14, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 11.00 (P < 0.00001)



RQLQ Eye Score

Study or Subgroup	Probiotic Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Costa 2014	-1.75	1.63	215	-1.36	1.77	210	25.4%	-0.39 [-0.71, -0.07]
Lin 2014	-0.9	1.4	30	0	1.8	27	23.9%	-0.90 [-1.74, -0.06]
Peng 2005	-1.27	0.55	30	2.2	0.7	30	25.4%	-3.47 [-3.79, -3.15]
Wang 2004	-2.25	0.5	60	-1.25	0.77	20	25.3%	-1.00 [-1.36, -0.64]
Total (95% CI)			**335**			**287**	**100.0%**	**-1.45 [-3.04, 0.15]**

Heterogeneity: Tau² = 2.59; Chi² = 199.12, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.78 (P = 0.08)

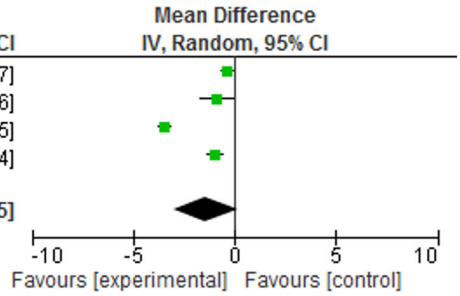
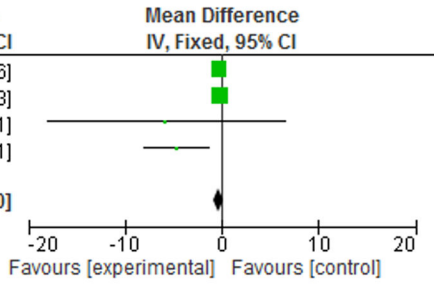


Figure 2.
Rhinitis Quality of Life Questionnaire

RTSS Global Score

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Ciprandi 2005	3.7	0.7	10	4	0.8	10	49.8%	-0.30 [-0.96, 0.36]
Costa 2014	-2.7	3.48	215	-2.46	3.57	210	48.1%	-0.24 [-0.91, 0.43]
Helin 2002	7.8	15.5296	15	13.6	19.3296	16	0.1%	-5.80 [-18.11, 6.51]
Lue 2012	-8.45	7.1	30	-3.78	5.83	27	1.9%	-4.67 [-8.03, -1.31]
Total (95% CI)			**270**			**263**	**100.0%**	**-0.36 [-0.83, 0.10]**

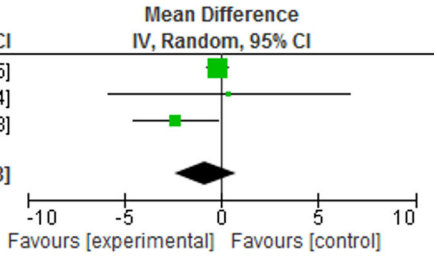
Heterogeneity: Chi² = 7.23, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 1.53 (P = 0.13)



RTSS Nose Score

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Costa 2014	-2.15	2.89	215	-1.95	2.86	210	64.0%	-0.20 [-0.75, 0.35]
Helin 2002	3.7	7.2231	15	3.3	10.3216	16	6.0%	0.40 [-5.84, 6.64]
Lue 2012	-4.6	4.54	30	-2.22	3.92	27	30.0%	-2.38 [-4.58, -0.18]
Total (95% CI)			**260**			**253**	**100.0%**	**-0.82 [-2.41, 0.78]**

Heterogeneity: Tau² = 0.96; Chi² = 3.61, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 1.00 (P = 0.32)



RTSS Eye Score

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Costa 2014	-0.56	0.85	215	-0.5	0.92	210	95.9%	-0.06 [-0.23, 0.11]
Helin 2002	3.3	11.9181	15	3.5	5.067	16	0.1%	-0.20 [-6.72, 6.32]
Lue 2012	-1.51	1.47	30	-0.55	1.68	27	4.0%	-0.96 [-1.78, -0.14]
Total (95% CI)			**260**			**253**	**100.0%**	**-0.10 [-0.26, 0.07]**

Heterogeneity: Chi² = 4.40, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 1.14 (P = 0.25)

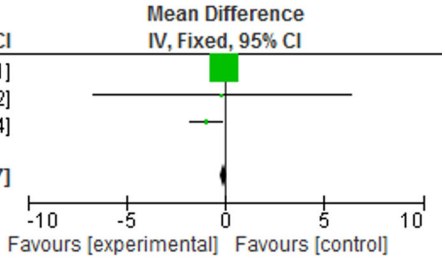
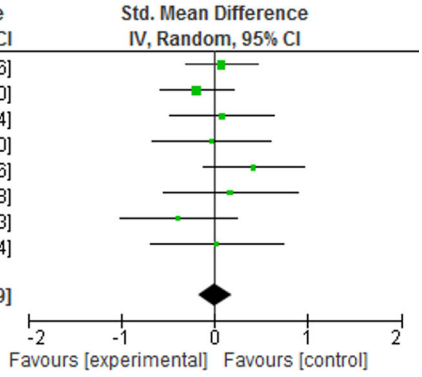


Figure 3.
Rhinitis Total Symptom Score

Total IgE

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chen 2010	937.4	1,157	49	853.2	1,103.2	56	23.7%	0.07 [-0.31, 0.46]
Giovannini 2007	244.3	330.3932	49	318.4	416.6126	50	22.4%	-0.20 [-0.59, 0.20]
Ishida 2005	562.2	757	25	504	646.6653	24	11.1%	0.08 [-0.48, 0.64]
Kawase 2009	123.1	32.9	20	124.2	31.1	18	8.6%	-0.03 [-0.67, 0.60]
Nagata 2010	515.9	850.5	26	238.4	384.8	27	11.7%	0.42 [-0.13, 0.96]
Nishimura 2009	358	71	15	343	101	15	6.8%	0.17 [-0.55, 0.88]
Xiao 2006a	99	63.1	20	190.2	316.7	20	8.9%	-0.39 [-1.02, 0.23]
Xiao 2006b	117	213.6686	20	110.1	320.7581	12	6.8%	0.03 [-0.69, 0.74]
Total (95% CI)			**224**			**222**	**100.0%**	**0.01 [-0.18, 0.19]**

Heterogeneity: Tau² = 0.00; Chi² = 5.13, df = 7 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)



Antigen-specific IgE

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ishida 2005	24.3	23	25	21.2	19.5959	24	13.8%	0.14 [-0.42, 0.70]
Kawase 2009	22.5	7	20	18.7	4.1	18	10.2%	0.64 [-0.01, 1.29]
Nagata 2010	16.3	32	27	13.9	16.1	27	15.3%	0.09 [-0.44, 0.63]
Nishimura 2009	2.7	0.3	15	2.5	0.4	15	8.2%	0.55 [-0.18, 1.28]
Xiao 2006a	12.4	10.8	20	14.9	24.5	20	11.3%	-0.13 [-0.75, 0.49]
Xiao 2006b	22.9	42.3064	20	19	55.4008	12	8.5%	0.08 [-0.64, 0.80]
Yonekura 2009	82.5	124.6	58	63.2	67.5	58	32.7%	0.19 [-0.17, 0.56]
Total (95% CI)			**185**			**174**	**100.0%**	**0.20 [-0.01, 0.41]**

Heterogeneity: Tau² = 0.00; Chi² = 4.00, df = 6 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.87 (P = 0.06)

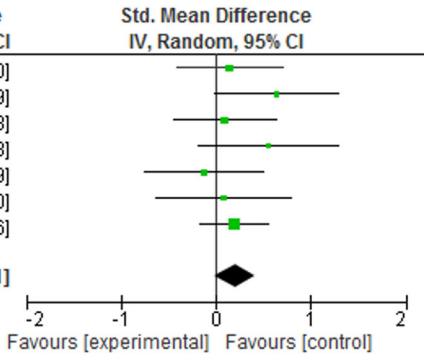


Figure 4.
Total and Antigen-Specific IgE

Table 1

Characteristics of Included Studies

Study	Type	Patients	Ages	Intervention (Probiotic Strain)	Outcomes	Results	Jadad Score
Lue 2012[30]	RC	63	7–12 yrs	*Lactobacillus johnsonii EM1*	Changes in RTSS and PRQLQ	Decreased RTSS; no change in PRQLQ	3
Wang 2004[31]	RCT-DB	80	15.87±1.53 yrs (probiotic) and 14.00±1.90 yrs (placebo)	*Lactobacillus paracasei-33 × 30 days*	Change in modified PRQLQ	Decreased PRQLQ (decreased frequency, level of bother)	4
Peng 2005[32]	RCT-DB	90	16.07±2.11 yrs (live-probiotic), 14.50±1.78 yrs (heat-killed probiotic), 16.60±2.02 yrs (placebo)	*Lactobacillus paracasei × 30 days*	Change in modified PRQLQ	Decreased PRQLQ (decreased frequency, level of bother)	3
Costa 2014[27]	RCT-DB	425	18–60 yrs	*Lactobacillus paracasei LP-33 × 5 weeks*	Change in RQLQ, RTSS	Decreased RQLQ; no change in RTSS	4
Lin 2013[33]	RCT-DB	199	6–12 yrs	*Lactobacillus salivarius × 12 weeks*	Change in SSS, SMS, total IgE	Reduction in nasal, eye, medication scores; no change in total IgE	4
Singh 2013[34]	RCT-DB	20	20–65 yrs	*Bifidobacterium lactis NCC2818 × 8 weeks*	Change in TNSS	Reduction in total nasal symptom scores	4
Nishimura 2009[35]	RCT-DB	45	33.8±2.0 yrs (high dose probiotic), 36.7±1.2 yrs (low dose probiotic), 36.5±2.8 yrs (placebo)	*Tetragenococcus halophilus Th221 × 8 weeks*	Change in disease severities, TNSS, total IgE, antigen-specific IgE	Decreased total nasal symptom scores at high dose only; no change in sneezing rhinorrhea, or antigen-specific IgE	4
Kawase 2009[36]	RCT-DB	40	20–57 yrs	*Lactobacillus GG and L. gasseri TMC0356 × 10 weeks*	Change in mean symptom score, mean symptom-medication score, total IgE, antigen-specific IgE	Decreased nasal blockage and medication score for nasal blockage; no change in total or antigen-specific IgE	4
Giovannini 2007[37]	RCT-DB	187	2–5 yrs	*Lactobacillus casei × 12 months*	Change in time free from and number of episodes of asthma/rhinitis, total IgE	Decrease in annual rhinitis episodes; no change in total IgE	5
Tamura 2007[38]	RCT-DB	120	39.3±8.0 yrs (probiotic) and 39.5±10.9 yrs (placebo)	*Lactobacillus casei Shirota × 8 weeks*	Change in SMS	No benefit	4
Xiao 2006a[39]	RCT-DB	40	23–61 yrs (probiotic) and 24–55 yrs (placebo)	*Bifidobacterium longum BB536 × 14 weeks*	Change in subjective symptoms	Decreased eye symptoms; no benefit in other symptoms;	4

Study	Type	Patients	Ages	Intervention (Probiotic Strain)	Outcomes	Results	Jadad Score
Xiao 2006b[40]	RCT-DB	44	26–57 yrs (probiotic) and 22–48 yrs (placebo)	*Bifidobacterium longum BB536 × 13 weeks*	Change in subjective symptoms	Decreased symptom scores for rhinorrhea, congestion, and composite scores	4
Helin 2002[41]	RCT-DB	36	14–36 yrs	*Lactobacillus rhamnosus × 5.5 months*	Change in allergic nose, eye, lung, and RTSS	No benefit	3
Xiao 2007[42]	RC	24	41.0±8.0 yrs (placebo 1st) and 37.6±7.5 yrs (probiotic 1st)	*Bifidobacterium longum BB536 × 4 weeks*	Change in subjective symptoms	No change in nasal symptom score; reduced throat and ocular symptoms	3
Dölle 2013[26]	RCT-DB	34	19–54 yrs	*Escherichia coli strain Nissle 1917 × 6 months*	Change in SMS	No benefit	4
Nagata 2010[43]	RCT-DB	55	18–27 yrs	*Lactobacillus plantarum No. 14 × 6 weeks*	Change in SMS, total IgE, antigen-specific IgE	Decreased SMS and itchy eyes; no effect on medication intake	3
Chen 2010[44]	RCT-DB	105	6–12 yrs	*Lactobacillus gasseri A5 × 8 weeks*	Change in subjective symptoms, total IgE	Decreased nasal allergic symptoms	4
Ouwehand 2009[45]	RCT-DB	47	4–13 yrs	*Lactobacillus acidophilus NCFM and Bifidobacterium lactis BI-04 × 4 months*	Change in subjective symptoms	No benefit	4
Lin 2014[46]	RCT-DB	60	6–13 yrs	*Lactobacillus paracasei HF.A00232 × 8 weeks*	Change in RTSS and PRQLQ	No benefit thru 8 wks; lower PRQLQ scores and individual symptom scores (sneezing, itchy eyes, swollen eyes) at 12 wks	3
Yonekura 2009[47]	RCT-DB	116	20–50 yrs	*Lactobacillus paracasei KW3110 × 3 months*	Change in RQLQ, antigen-specific IgE	Improved quality of life when pollen scattering low.	4
Ishida 2005[48]	RCT-DB	49	34.0±3.4 yrs (probiotic) and 36.9±3.0 yrs (placebo)	*Lactobacillus acidophilus L-92 × 8 weeks*	Change in SMS, total IgE, antigen-specific IgE	Improvement in nasal symptom-medication scores, no change in total IgE or antigen-specific IgE	3
Ciprandi 2005[49]	RCT-DB	20	12–15 yrs	*Bacillus clausii × 3 weeks*	Change in RTSS and medication use	No significant difference in RTSS; reduced medication use	3
Aldinucci 2002[50]	RCT-DB	20	19–44 yrs	*Lactobacillus acidophilus and Bifidobacterium × 4 months*	Change in subjective symptoms	Decreased nasal symptoms	3
	Total	1919					

PRQLQ = Pediatric Rhinoconjunctivitis Quality of Life Questionnaire
RQLQ = Rhinitis Quality of Life Questionnaire
RTSS = Rhinitis Total Symptom Score
SSS = Specific Symptoms Score
SMS = Symptom Medication Score
TNSS = Total Nasal Symptom Score