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REVIEW ARTICLE

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Systematic review and meta-analysis of probiotics in the treatment of allergic rhinitis

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KEYWORDS
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Abstract
Background: The purpose of this meta-analysis is to systematically evaluate the efficacy of probiotics on allergic rhinitis (AR).
Methods: Collecting randomized controlled trials (RCTs) with probiotics as intervention measures for AR, two researchers independently screened the literature, extracted the data and evaluated the methodological quality of the included studies, and used RevMan 5.3 software for meta-analysis to observe the effects of probiotics on Rhinitis Quality of Life (RQLQ) scores, Rhinitis Total Symptom Scores (RTSS), blood eosinophil count, total and antigen-specific serum immunoglobulin E (IgE) levels by using the fixed- or the random-effects model to calculate the pooled risk for significant heterogeneity.
Results: A total of 2708 patients were included in 30 RCTs. Meta-analysis results showed that the RQLQ global scores (mean difference [MD] = −9.43; P < 0.00001), RQLQ nasal scores (MD = −1.52; P = 0.03), and RTSS nasal scores (MD = −1.96; P = 0.02) significantly improved in the probiotic group when compared with those in the placebo group. There was no significant difference in blood eosinophil count (MD = −0.09; P=0.82), RQLQ eye scores (MD = −1.45; P = 0.07), RTSS global scores (MD = −2.24; P = 0.26), RTSS eye scores (MD = −0.39; P = 0.31), total and antigen-specific serum IgE levels (MD = −0.04; P = 0.7 and MD = −0.08; P = 0.81) between the probiotic and the placebo group.
Conclusion: Compared with the placebo group, the quality of life and symptoms of patients with AR significantly improved in the probiotic group, thus providing a new potential method for the application of probiotics in AR. However, because of the limited evidence for the current study outcomes, the heterogeneity of research, and the differences in research results, more high-quality studies are needed to in the future.

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Introduction

Allergic rhinitis (AR) is a nasal mucosal disease caused by immunoglobulin E (IgE)-mediated allergic reactions. Exposure to allergens can cause AR symptoms including sneezing, nasal itching, upper respiratory tract obstruction, runny nose, and itchy or watery eyes which are featured as T helper (Th) 2-dominant inflammation of the nasal mucosa.[1] The prevalence of AR exceeds 10% worldwide and has risen rapidly in the past few decades, severely affecting the quality of life and increasing the economic burden of patients.[2] The modern medical treatments available for AR include avoiding allergens, antihistamines, decongestants, intranasal corticosteroids, etc. Some side effects like dry mouth, drowsiness, and insomnia are noticed.

Recently, Kim et al.[3] suggested that probiotics especially, those with lesser side effects, such as lactic acid bacteria and bifidobacteria, can be a new treatment for AR. Many studies have shown that the intestinal microbiota may play a pivotal role in immune and allergic diseases.[4] Probiotics are living microorganisms that exist in yogurt, sauerkraut, and kimchi. They inhibit lung airway inflammation, mast cell degranulation, airway remodeling, ovalbumin (OVA)-specific IgE/IgG1 expression, Th1/Th2 imbalance reversal and enhance anti-inflammatory cytokine interleukin (IL)-10.[5]

Dendritic cells are antigen-presenting cells that play a critical role in guiding the transition of Th cells to Th1 and Th2. Probiotics can induce the maturation of dendritic cells, regulate Th1/Th2 balance by producing IL-12 and interferon (IFN), or inhibit Th2 by reducing the production of IL-4, specific IgE (sIgE), IgG1, and IgA in mice with OVA-induced food allergy.[6,7] Another study reported that probiotics could also improve the quality of life of patients and reduce drug use.[8]

Currently, the research scheme of measuring the results of probiotics in the treatment of AR is mixed. Some probiotics have improved the rhinitis quality of life questionnaire score in several studies, and some had no significant effect on the total symptom score or symptom drug score of rhinitis was reported.[9] Therefore, there is no consensus on whether probiotics can be applied in the treatment of AR. Hence, this study strictly evaluated and analyzed the existing randomized controlled trials (RCTs) of probiotics in the treatment of AR and provided reasonable and safe evidence-based medical evidence for the clinical treatment of AR by probiotics.

One of the main limitations of this review is the nondemonstration of the therapeutic effect of probiotics on allergies/atopic diseases. The study by Szajewska and Horvath[10] showed that probiotics (regardless of the time of administration) do not reduce the risk for eczema. Another study found that taking a combination of probiotics after birth has no effect on the incidence of allergic diseases or atopic sensitization in the first two years of preterm infants.[11] Similar differences in efficacy have also been found in a comparative randomized controlled trial of atopic dermatitis treatment. It showed that a single probiotic strain was effective in the treatment of atopic dermatitis, whereas the other was completely ineffective.[12]

Materials and methods

Search strategy

RCTs on probiotics for AR published from inception to May 2021 were reviewed using PubMed, Web of Science (Institute for Scientific Information, Philadelphia, USA), and Cochrane Library (John Wiley & Sons, Hoboken, USA) with the keywords "rhinitis and probiotics."

Study selection

The EndNote X5 literature management software was used for deduplication. Two researchers (S Yan and L Huang) screened the literature strictly in accordance with the inclusion and exclusion criteria and finally cross-checked the results of the two screening. If there was a difference in opinion, one of the corresponding authors (X Zhuang) was consulted.

Inclusion criteria

1. Articles published in English and RCTs of probiotics as interventions for AR in humans.
2. The included subjects were all through specific IgE and/or skin pricks patients diagnosed with AR in the trial, including seasonal and perennial AR, and had a medical history of more than 1 year; age and gender were not limited.
3. Patients in the experimental group received different doses of probiotic products (milk, capsules, or powder containing probiotics, etc.), and the control group was given the equivalent doses of placebo products.
4. Outcome indicators: total and antigen-specific serum IgE levels, blood eosinophil count, Rhinitis Quality of Life (RQLQ) global scores, RQLQ nasal and eye scores, Rhinitis Total Symptom Scores (RTSS) global scores, and RTSS eye and nasal scores.

Exclusion criteria

1. Nonrandomized controlled experiments.
2. Animal experiments and case reports.
3. Clinical studies with unclear outcome indicators.
4. Clinical studies with incomplete data and nonavailability of the author for original data cross-check.

Data extraction and quality evaluation

For the final inclusion of RCTs, two researchers (F Zhang and N He) extracted data and reached a consensus. The data extracted from the literature included the first author, publication year, author country, single-blind or double-blind RCTs, the number of participants, age, experimental intervention measures, intervention time, observation indicators, and experimental results. Meanwhile, the methodological quality of each study was assessed independently. If there were a difference, another author (X Zhuang) was consulted.

Studies that met the inclusion criteria are evaluated using the revised seven-point Jadad scale,[13] that included four aspects: the generation of allocation sequence (2 points), allocation concealment (2 points), blind method (2 points), and dropout (1 point). A total score of <4 and ≥ 4 indicated low and high quality, respectively.

Statistical analysis

The P and I^2 values were calculated using the heterogeneity analysis between studies. When I^2 was ≤ 50%, the fixed-effects model was used for weighted combination, and I^2 was > 50%, the random-effects model was used for weighted combination. RevMan 5.3 software was used for statistical analysis. The effect analysis statistics of enumeration data were expressed by mean difference (MD) or standardized mean difference (SMD), and $P < 0.05$ indicated that the difference was statistically significant.

Results

Search outcome

A total of 219 articles were preliminarily retrieval recorded 219 articles, and 45 were obtained through software deduplication, reading papers, and abstracts. Then, the uncertain literature of the selected articles was downloaded. Further, after reading the complete article text, it was screened according to the inclusion and exclusion criteria. Finally, 30 papers were included with about 2708 patients (the specific screening process is shown in Figure 1).

Basic characteristics of the included studies

The complete details of the included literature are shown in Table 1. The treatment time of the probiotics was between 4 weeks and 16 months. All studies described the baseline data of the patient's gender, age, region, and race in detail, whose differences were not statistically significant and comparable. The commonly used observation indicators were RQLQ (six studies), RTSS (three studies), blood eosinophil count (seven studies), total IgE level (eight studies), and antigen-specific serum IgE levels (seven studies).

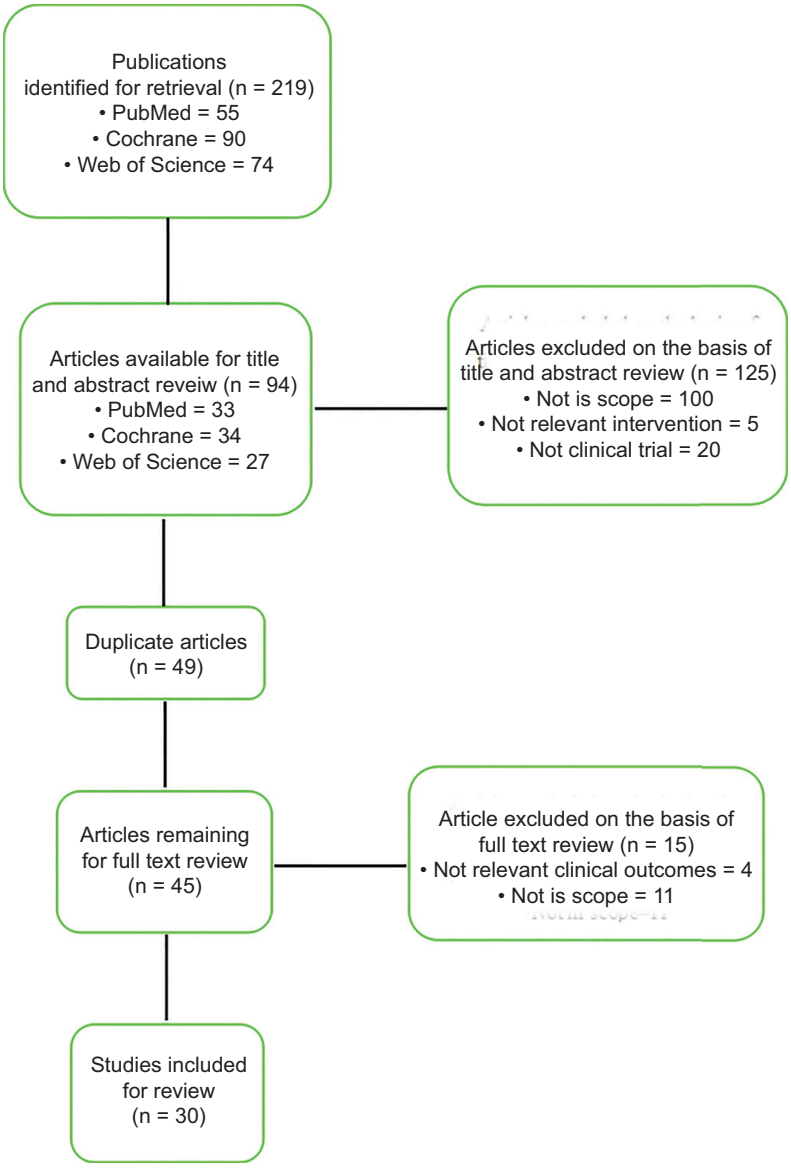

Figure 1 Article selection criteria.

Table 1 Characteristics of the included studies.

	Study	country	Type	Patients (n)(T/C)	Ages	Intervention (probiotic strain)	Outcomes	Results	Jadad scores
1	Tamura et al.[22]	Japan	RCT-DB	55/54	39.3 ± 8.0 years (probiotic) and 39.5 ± 10.9 years (placebo)	*Lactobacillus casei* strain Shirota × 8 weeks	Change in SMS and blood eosinophil count	No benefits.	5
2	Kang et al.[23]	Korea	RCT-DB	41/43	33.61 ± 1.23 years (probiotic) and 33.49 ± 1.33 years (placebo)	*B. longum* IM55 and *L. plantarum* IM76 × 4 weeks	Change in TNSS, *D. pteronyssinus*-specific IgE, and blood eosinophil count	Reduction in the total nasal symptom scores and sIgE, but no significant difference in the blood eosinophil count.	5
3	Meng et al.[24]	China	RCT	27/24	33.34 ± 3.21 years (probiotic) and 29.33 ± 4.13 years (placebo)	OM85-Broncho-Vaxom × 8 weeks	Change in TNSS	Reduction in the total nasal symptom scores, itching score, nasal rhinorrhea score, and sneezing score; no change in nasal congestion score.	4
4	Giudice et al.[25]	Italy	RCT-DB	18/22	9 ± 2.2 years	*Bifidobacterium* mixture (*B. longum* BB536, *B. infantis* M-63, and *B. breve* M-16V) × 4 weeks	Change in QOL and TSS	Decease in QOL and TSS.	4
5	Dennis-Wall et al.[26]	American	RCT-DB	81/80	18-60 years	*Lactobacillus gasseri* KS-13, *Bifidobacterium bifidum* G9-1, and *Bifidobacterium longum* MM-2 × 8 weeks	Change in MRQLQ and the total IgE	Decease in MRQLQ; no change in the total IgE.	6
6	Jerzynska et al.[27]	Poland	RCT-DB	20/17	5–12 years	SLIT-L. rhamnosus GG × 5 months	Change in symptom-medication score	Decease in symptom-medication scores.	4
7	Costa et al.[28]	France	RCT-DB	215/210	38.05 ± 12.25 years (probiotic) and 37.19±11.82 years (placebo)	*Lactobacillus paracasei* LP-33 × 5 weeks	Change in RQLQ and RTSS	Decease in RQLQ; no change in RTSS.	4
8	Lin et al.[29]	Taiwan	RCT-DB	32/28	9.5 ± 2.0 years (probiotic) and 9.3 ± 2.3 years (placebo)	*Lactobacillus paracasei* × 8 weeks	Change in PRQLQ and RTSS	No benefit in the initial 8 weeks; decrease PRQLQ scores and individual symptoms scores for sneezing, itchy nose, and swollen eyes at 12 weeks.	5
9	Singh et al.[30]	Switzerland	RCT-DB	10/10	20–65 years	*Bifidobacterium lactis* NCC2818 × 8 weeks	Change in TNSS	Reduction in the total nasal symptom scores.	5

(*continues*)

Table 1 Continued

	Study	country	Type	Patients (n)(T/C)	Ages	Intervention (probiotic strain)	Outcomes	Results	Jadad scores
10	Lin et al.[31]	Taiwan	RCT-DB	99/100	8.0 ± 1.9 years (probiotic) and 8.0 ± 2.1 years (placebo)	*Lactobacillus salivarius* × 12 weeks	Change in SSS, SMS, and the total IgE	Reduction in the nasal, eye, and medication scores; no change in total IgE.	5
11	Lue et al.[32]	Taiwan	RCT	30/27	8.82 ± 1.64 years (probiotic) and 8.88 ± 1.54 years (placebo)	*Lactobacillus johnsonii* EM1 × 12 weeks	Change in TSS, PRQLQ, total IgE and blood eosinophil count	Reduction in TSS; no change in PRQLQ, the total IgE, and blood eosinophil count.	4
12	Chen et al.[33]	Taiwan	RCT-DB	49/56	8.1 ± 3.0 years (probiotic) and 9.4 ± 4.1 years (placebo)	*Lactobacillus gasseri* A5 × 8 weeks	Change in the clinical symptom scores and total IgE	Decease in the clinical symptom scores; no change in the total IgE.	7
13	Ouwehand et al.[34]	Finland	RCT-DB	20/21	4–13 years	*Lactobacillus acidophilus* NCFMTM and *Bifidobacterium lactis* Bl-04 × 4 months	Change in subjective symptoms and blood eosinophil count	No benefits.	7
14	Nishimura et al.[35]	Japan	RCT-DB	15/15	33.8 ± 2.0 years (high dose probiotic); 36.7 ± 1.2 (low probioticdose); and 36.5 ± 2.8 years (placebo□	*Tetragenococcus halophilus* Th221 × 8 weeks	Change in disease severities, the total IgE, TNSS, and allergen specific IgE	Decease in the TNSS and total IgE at high doses only; no change in allergen specific IgE, sneezing, and rhinorrhea.	4
15	Giovannini et al.[36]	Italy	RCT-DB	49/50	2–5 years	*Lactobacillus casei* × 12 months	Change in time free from and the number of episodes of asthma/rhinitis and the total IgE	Decease in annual number of rhinitis episodes; no change in the total IgE.	7
16	Peng and Hsu[37]	Taiwan	RCT-DB	30/30	16.07 ± 2.11 years (live-probiotic); 14.50 ± 1.78 years (heat-killed probiotic); and 16.60 ± 2.02 years (placebo)	*Lactobacillus paracase*i 33 × 30 days	Change in modified PRQLQ	Decease in PRQLQ and bothersome symptoms and reduction in the frequency and dosage required for medical treatment.	5
17	Ciprandi et al.[38]	Italy	RCT-DB	10/10	12–15 years	*Bacillus clausii* × 3 weeks	Change in TSS	No benefits.	4
18	Wang et al.[39]	Taiwan	RCT-DB	60/20	15.87 ± 1.53 years (probiotic) and 14 ± 1.90 years (placebo)	*Lactobacillus paracasei*-33 × 30 days	Change in modified PRQLQ	Decease in PRQLQ.	5

19	Harata et al.[40]	Japan	RCT-DB	14/11	36.9 ± 6.9 years (probiotic) and 36.5 ± 6.1 years (placebo)	*Lactobacillus rhamnosus GG* and *L. gasseri* TMC0356 × 10 weeks	Change in gut microbiota composition and blood lipid levels	With beneficial effects on the blood lipid levels and gut microbiota composition.	4
20	Kawase et al.[41]	Japan	RCT-DB	20/18	20–57 years	*Lactobacillus rhamnosus* GG and *L. gasseri* TMC0356 × 10 weeks	Change in the mean symptom score, meansymptom-medication scores and the total IgE, sIgE, and the blood eosinophil count.	Decease in mean symptom score and meansymptom-medication scores;no change in the total IgE, sIgE, and the blood eosinophil count.	4
21	Xiao et al.[42]	Japan	RCT-DB	20/20	36.5 ± 7.8 years (probiotic) and 36.7 ± 9.5 years (placebo)	*Bifidobacterium longum* BBS36 × 14 weeks	Change in subjective symptom scores and blood eosinophil count	Decease in eye symptoms; no change in other symptoms and blood eosinophil count.	5
22	Xiao et al.[43]	Japan	RCT-DB	20/12	36.5 ± 8.1 years (probiotic) and 36.0 ± 7.3 years (placebo)	*Bifidobacterium longum* BBS36 × 13 weeks	Change in subjective symptom scores and blood eosinophil count	Decrease in rhinorrhea, nasal blockage, and composite scores; no change in blood eosinophil count.	5
23	Sadeghi-Shabestari et al.[44]	Iran	RCT	14/14	12.08 ± 34.15 years (probiotic) and 12.32 ± 29.64 years (placebo)	Kant's 109 CFU probiotics × 8 weeks	Change in clinical symptoms	No benefits.	4
24	Ahmed et al.[45]	Pakistan	RCT-DB	106/106	26 ± 16.64 months	*Lactobacillus paracasei* (LP-33) × 6 weeks	Change in clinical symptoms	No benefits.	6
25	Perrin et al.[46]	Switzerland	RCT-DB	15/13	18–35 years	*Lactobacillus paracasei* NCC2461 × 4 weeks	Change in objective and subjective clinical symptoms	Decrease in nasal pruritus; no benefit on nasal congestion.	6
26	Xu et al.[47]	China	RCT-DB	44/20	25/26 years(median)	SIT with *Clostridium butyricum* × 6 months	Change in NSS, medication scores,serum specific IgE levels and recurrence of clinical symptoms	Decrease in NSS, medication scores, serum specific IgE levels, and recurrence of clinical symptoms; maintained at least for 12 months.	4
27	Nembrini et al.[48]	Switzerland	RCT-DB	63/68	18–65 years	*Lactobacillus paracasei* NCC 2461 × 8 weeks	Change in symptoms scores, quality of life, and the specific IgE levels	No benefits.	5

(*continues*)

Table 1 Continued

	Study	country	Type	Patients (n)(T/C)	Ages	Intervention (probiotic strain)	Outcomes	Results	Jadad scores
28	Jan et al.[49]	Taiwan	RCT-DB	98/100	8.1 ± 4.4 years (probiotic) and 8.0 ± 4.3 years (placebo)	*Lactobacillus rhamnosus* × 12 weeks	Change in SSS and the total IgE	No benefits.	4
29	Anania et al.[50]	Italy	RCT-DB	117/86	10.5 ± 3.1 years (probiotic) and 8.8 ± 3.5 years (placebo)	*Bifidobacterium* animalis Subsp. Lactis BB12 and *Enterococcus faecium* L3 × 16 months	Change in NSS	Decrease in NSS.	5
30	Helin et al.[51]	Finland	RCT-DB	15/16	14–36 years	*Lactobacillus rhamnosus* × 5.5 months	Change in RTSS, respiratory and eye symptoms, and use of medications scores	No benefits.	4

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; QOL=Quality of Life; TSS=Total Symptom Score; MRQLQ=Mini Rhinoconjunctivitis Quality of Life Questionnaire; NSS=Nasal Symptoms Score

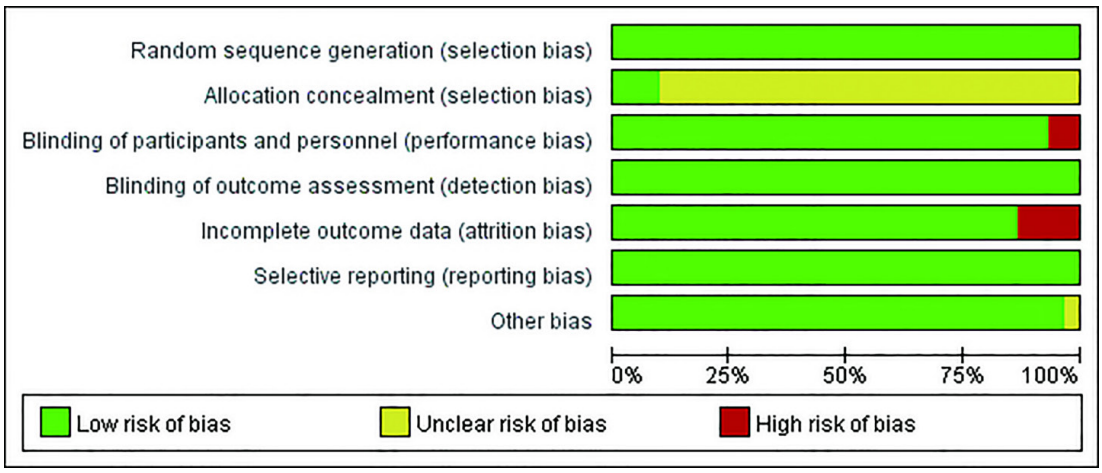

Figure 2 Quality assessment of the included randomized controlled trials using the Cochrane Collaboration tool for assessing risk for bias graph.

The outcomes of the 22 studies showed that compared with placebo, probiotics had a therapeutic effect on at least one outcome index and eight studies showed no therapeutic significance.

Risk assessment for bias in included studies

According to the bias risk assessment method recommended by the Cochrane library, 30 of the included studies had random allocation methods; 27 were double-blind; and only three mentioned the allocation concealment. About 20 studies had lost follow-up data, and four were unclear about the reason for the loss to follow-up. None of the studies had selective reporting results; post assessment, one study might have other biases. Figures 2 and 3 indicate the bias risk graph, and a summary of the risk for bias for each study.

Total and antigen-specific serum IgE

The probiotic effects on total and antigen-specific serum IgE levels were assessed in eight and seven studies, respectively (Figure 4). Meta-analysis results showed no significant difference between the total IgE levels of the probiotic group versus the placebo group (SMD = −0.04; 95% confidence interval [CI], −0.23 to 0.15; P = 0.70), and the antigen-specific serum IgE level (SMD = −0.08; 95% CI, −0.72 to 0.56; P = 0.81). Using a fixed-effect model and weighted combined analysis, the meta-analysis of the total IgE level indicated I^2 = 0%, indicating no statistical heterogeneity between the two groups. On using the random-effects model and weighted combined analysis, the antigen-specific serum IgE showed I^2 = 85%, indicating a significant difference between the two groups.

Blood eosinophil count

Seven studies evaluated the effect of probiotics on blood eosinophil count (Figure 5). About 206 patients included in these studies received the probiotic treatment, and 195 patients received the placebo treatment. The results of a meta-analysis of blood eosinophil levels showed no statistical difference between the probiotic group and the placebo group (SMD = −0.09; 95% CI, −0.81 to 0.64; P = 0.82). The random-effects model and the weighted combined analysis showed an I^2 = 91%, suggesting no heterogeneity between the two groups.

RQLQ

RQLQ is a widely used and validated quality of life questionnaire that measures the effectiveness of the disease on the daily activities of patients with rhinitis[14]. Among the seven studies using RQLQ, six studies allowed direct comparison and meta-analysis of descriptive data (Figure 6). The data of these six studies included 434 patients receiving probiotic treatment and 389 patients receiving placebo treatment. Meta-analysis results showed that RQLQ global scores of the probiotic group was significantly improved when compared with the placebo group (MD = −9.43 (95% CI, −11.71 to −7.15); P < 0.00001) and RQLQ nasal symptoms (MD = −1.52 (95% CI, −2.89 to −0.15); P = 0.03). RQLQ eye symptoms had a trend of improvement, but the study results showed no statistical significance (MD = −1.45 (95% CI, −3.04 to 0.14); P = 0.07). Meta-analysis of RQLQ global scores and nasal and eye symptom scores with random-effects model and weighted combined analysis showed an I^2 of >50%, indicating significant heterogeneity.

Rhinitis total symptom score

RTSS mainly measures the nasal symptoms and nonnasal symptoms related to AR patients. Three studies with sufficient quantitative data using the RTSS were used for this meta-analysis (Figure 7). They included 260 patients receiving probiotic treatment and 253 patients receiving placebo treatment. Meta-analysis results showed that RTSS global scores and RTSS eye symptom scores of the probiotic group

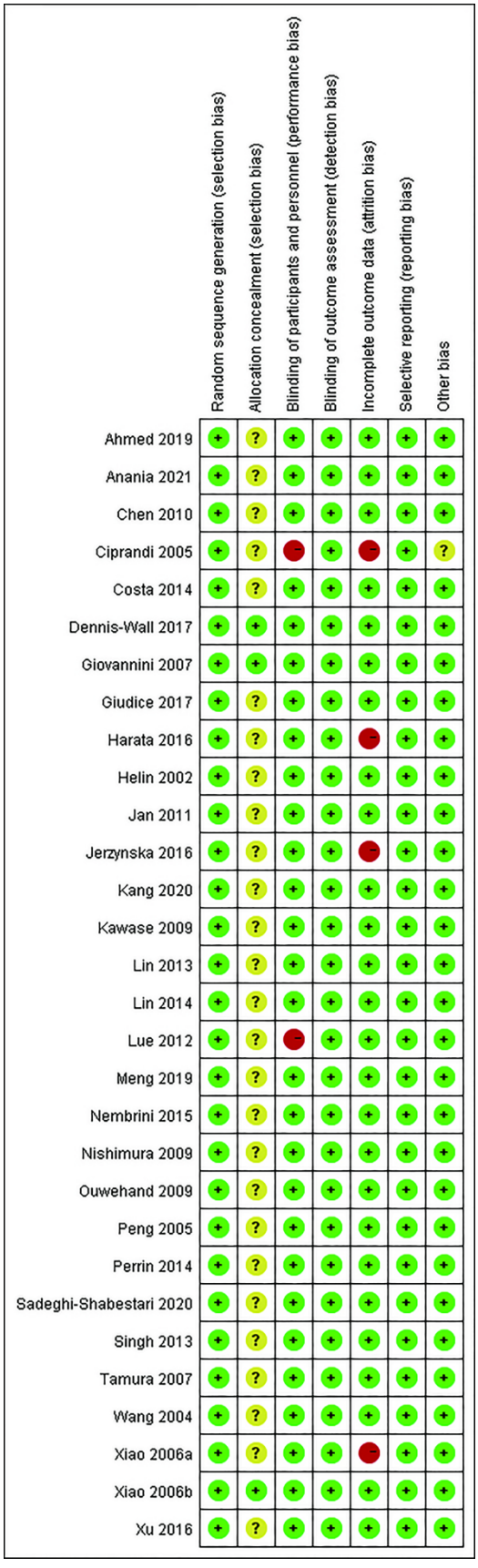

Figure 3 Quality assessment of the included randomized controlled trials using the Cochrane Collaboration tool for assessing risk for bias summary.[22-51]

was not significantly different from the placebo group (MD = −2.24; 95% CI, −6.15 to 1.68; P = 0.26; and MD = −0.39; 95% CI, −1.13 to 0.36; P = 0.31). However, the meta-analysis of RTSS nasal symptom scores showed a significant improvement in the probiotic group compared with the placebo group, which was statistically significant (MD = −1.96; 95% CI, −3.61 to −0.32; P = 0.02). Meta-analysis of RTSS global scores and nose and eye symptom scores showed an I^2 of >50%, suggesting significant heterogeneity using the random-effects model and weighted combined analysis.

Adverse events

Seven of the included studies reported adverse events, such as abdominal pain, diarrhea, conjunctival itching, sublingual itching, vomiting, etc. These symptoms could alleviate spontaneously in a short period and were not related to the probiotic intervention. No serious or life-threatening adverse events were reported, and no patients required additional treatment or intervention.

Discussion

The current systematic review and meta-analysis are the latest and most comprehensive analyses of the use of probiotics to treat AR to date. The meta-analysis results showed that most studies found that probiotics have a certain clinical effect in the treatment of AR compared with placebo. The probiotic group has significant improvements in RQLQ global and nasal scores and RTSS nasal scores, which were statistically significant. However, probiotics do not affect total IgE, antigen-specific serum IgE levels, RTSS global and eye scores, and RQLQ eye scores.

Lilly et al. in early 1965 proposed the concept of probiotics.[15] After continuous research and clinical practice, the role of probiotics in treating intestinal floral imbalance was reported. Yamanishi et al.[16] showed that the inferior turbinate nasal mucosal microbiota imbalance, like the increase of *Staphylococcus aureus* and the decrease of *Propionibacterium acnes*, was related to the increase of total IgE level in patients with AR, indicating that the inferior turbinate microbiota may be caused by environmental allergens, change in response to allergic inflammation, and microbial changes in specific parts may play a role in the pathophysiology of AR.[15] Specific probiotic strains can change the composition of the intestinal microbiota and alter the host immune system, showing strong Th2 inhibitory ability, certain probiotic strains may have the ability to affect the development of tolerant dendritic cells, Stimulates Toll-like receptors and promotes immunosuppressive regulatory T cell lineage.[17] From the studies researched in this meta-analysis, the probiotics currently used in treating diseases mainly include *Lactobacillus* and *Bifidobacterium*. Several RCTs suggest that probiotics may be a potential new treatment for AR.

The mechanism of probiotics for the treatment of AR is not completely clear. Treatment with *B. longum* IM55, IM76, or their probiotic mixture (PM) can significantly reduce OVA-induced allergic nasal symptoms, mouse blood IgE, nasal tissue, and bronchoalveolar lavage fluid (BALF)

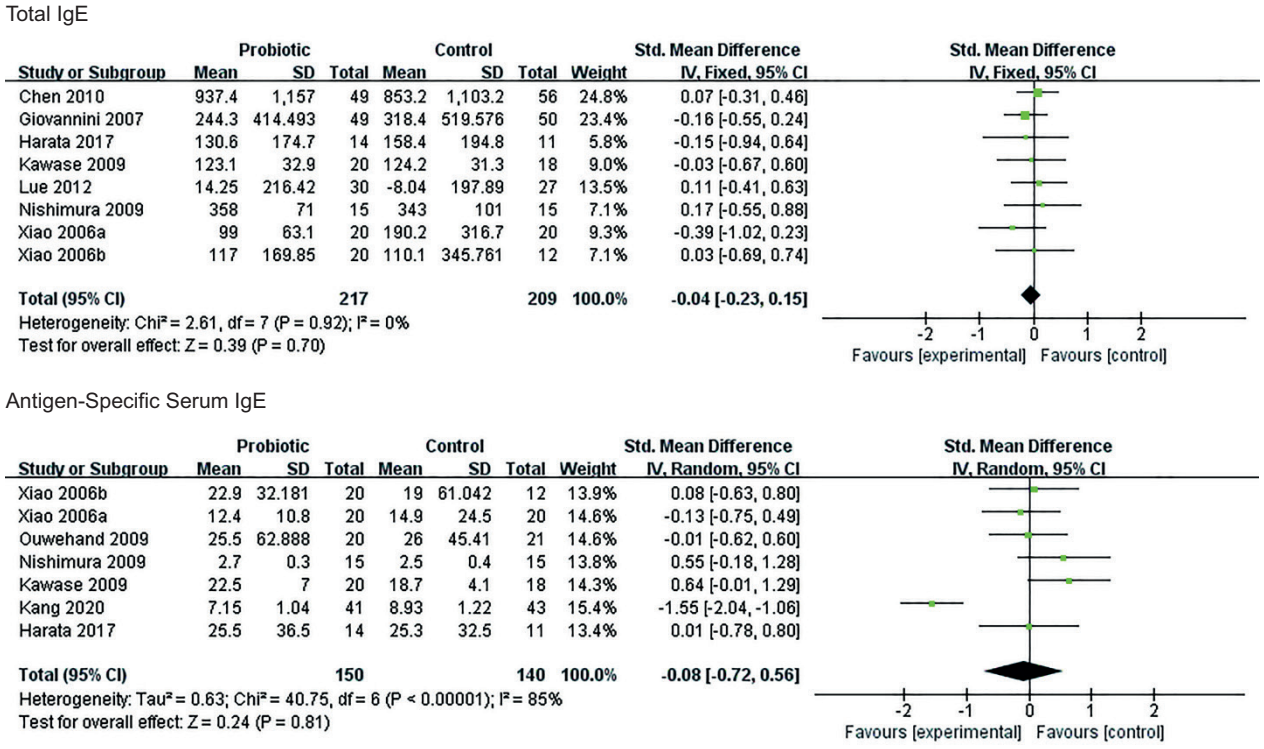

Figure 4 Forest plot showing the comparison of probiotic versus placebo outcomes in the total and antigen-specific immunoglobulin E.

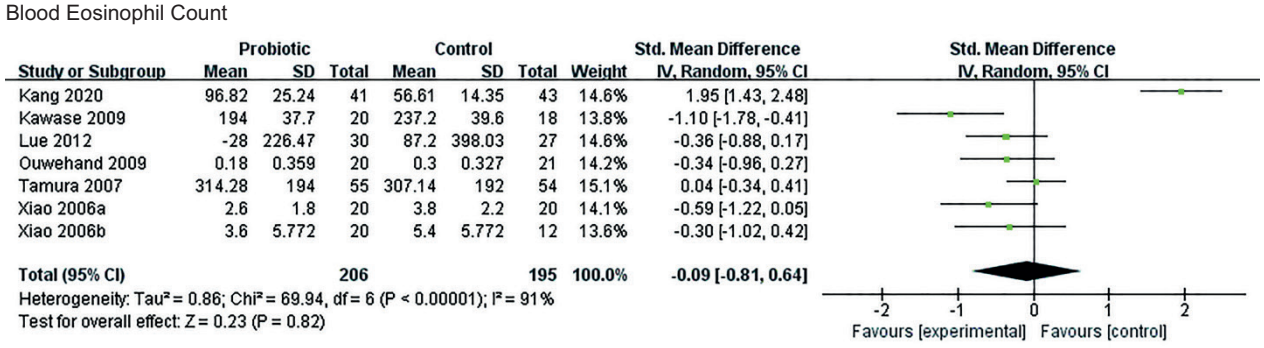

Figure 5 Forest plot showing the comparison of probiotic versus placebo outcomes in the blood eosinophil count.

OVA-induced IL-4 and IL-5 levels. But increased OVA inhibited IL-10 levels and restored the composition of the gut microbiota *Proteobacteria*, *Bacteroidetes*, and *Actinobacteria* disrupted by OVA. These results indicate that *B. longum* IM55 and IM67 can alleviate AR by restoring Th2/Treg imbalance and intestinal microbiota disturbance.[18] BALF and draining lymph node samples from mice given *L. plantarum* CJLP133 and CJLP243 showed a decrease in the number of immune cells and Th2 cytokines (IL-4, IL-5, and IL-13) secretion. But reported an increase in Th1 cytokine (IFN-γ) secretion, indicating that this PM can restore Th1/Th2 balance by enhancing Th1 immune response and reducing the symptoms of AR caused by birch pollen in mice.[19] Johansson et al.[20] found that the supernatant of lactic acid bacteria can attenuate the activation of all subtypes of immune cells caused by *S. aureus* superantigens, including $CD4^+$, $CD8^+$, and mucosal-associated constant T cells, and NK cells. *Lactobacillus* PM inhibits the proliferation and degranulation of these cells, which proves that probiotics can regulate autoimmunity by affecting Treg cells and Th17 cells. Therefore, in the future, the potential mechanism of intestinal immunity should be further studied and explored for better use of the therapeutic role of probiotics in AR.

The current meta-analysis showed the role of probiotics in improving the quality of life and disease symptoms of patients. Only a few of the included studies reported adverse events, and most studies only reported positive treatment results. This systematic review and meta-analysis included 30 studies involving 2708 patients. However,

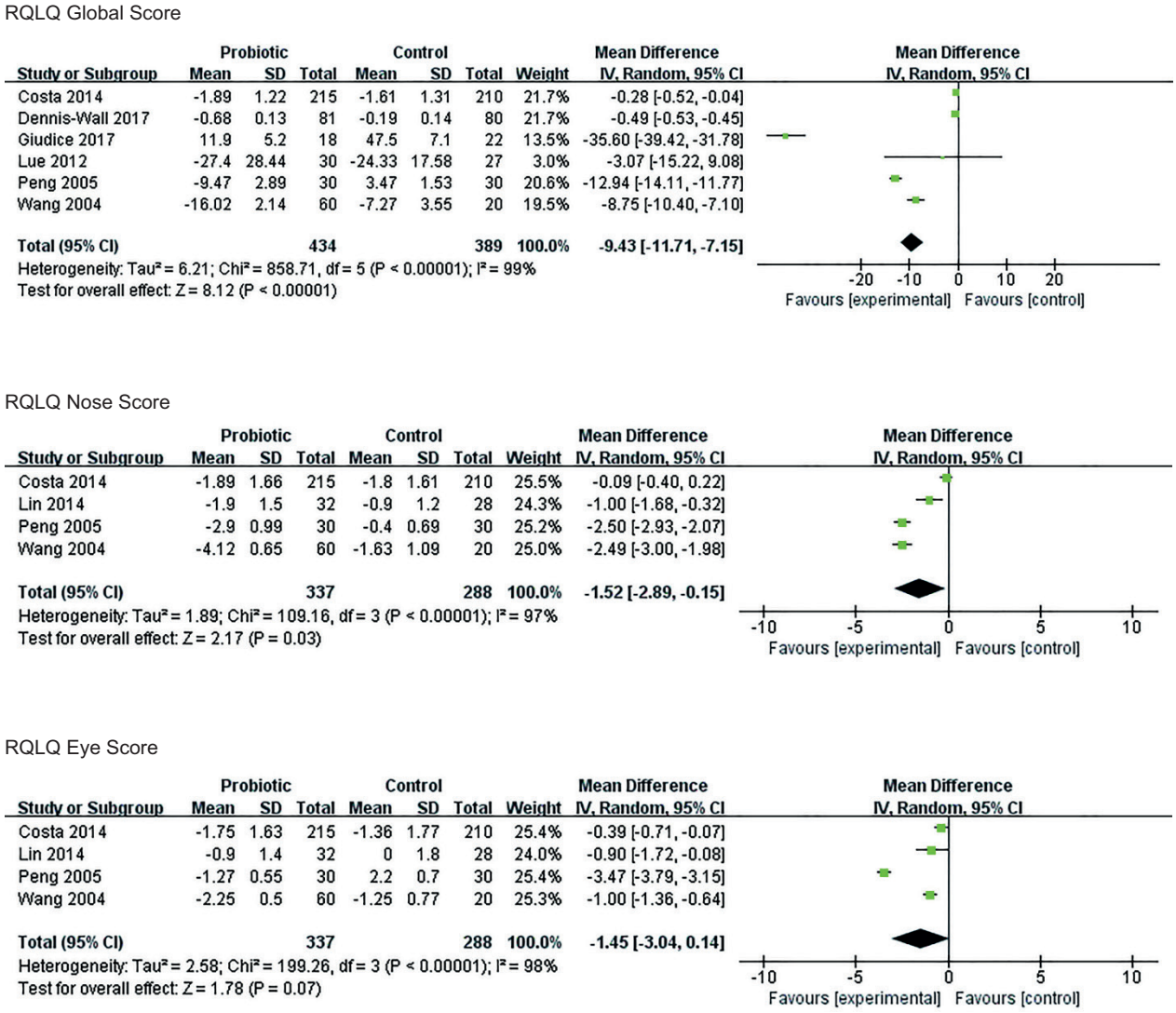

Figure 6 Forest plot showing the comparison of probiotic versus placebo outcomes in the Rhinitis Quality of Life Questionnaire.

because of the lack of quantifiable data in some studies, the study outcomes were incomplete, and more studies could not be included in this meta-analysis. Although there are some limitations, this systematic review and meta-analysis can still draw several important findings. First, there are differences in the composition of probiotics, measurement results, and intervention time among the studies. However, most RCTs suggest that probiotics can improve at least one measurement result. Second, the research results suggest that the RQLQ global and nasal scores and RTSS nasal scores in the probiotic group are significantly improved, with a significant difference. But no significant effect was noted on the RQLQ eye scores. The RTSS global and eye scores in probiotics group suggest that probiotics can relieve the nasal symptoms of patients with AR, but it is not obvious for the eye symptoms of patients with AR. The results may be related to the following points: First, intestinal microbes strengthen the connection with lung diseases through the "lung-intestine axis."[21] Nose belongs to the lung system and, eyes do not belong to the lung system. Second, the possible mechanisms of AR associated with eye symptoms include allergen deposition in the conjunctiva, nasolacrimal duct obstruction, and naso-ocular reflex. But the probiotics may not have corresponding targets, so they cannot alleviate eye symptoms. Of course, further clarification on the specific mechanism is required in the future. In most of the included studies, the number of patients with complications is limited. Finally, the probiotic group has no significant effect on total, antigen-specific serum IgE, and blood eosinophil count, which indicate that probiotics can improve the quality of life and the clinical symptoms are not significantly related to the regulation of total, antigen-specific serum IgE, and blood eosinophil count, that agreed with the study of Tamura et al.[22] who found that probiotics might improve subjective symptoms, even if there was no difference in the immunological parameters between the probiotic and the placebo groups, such as the imbalance in the allergen-specific IgE level or Th1/Th2.

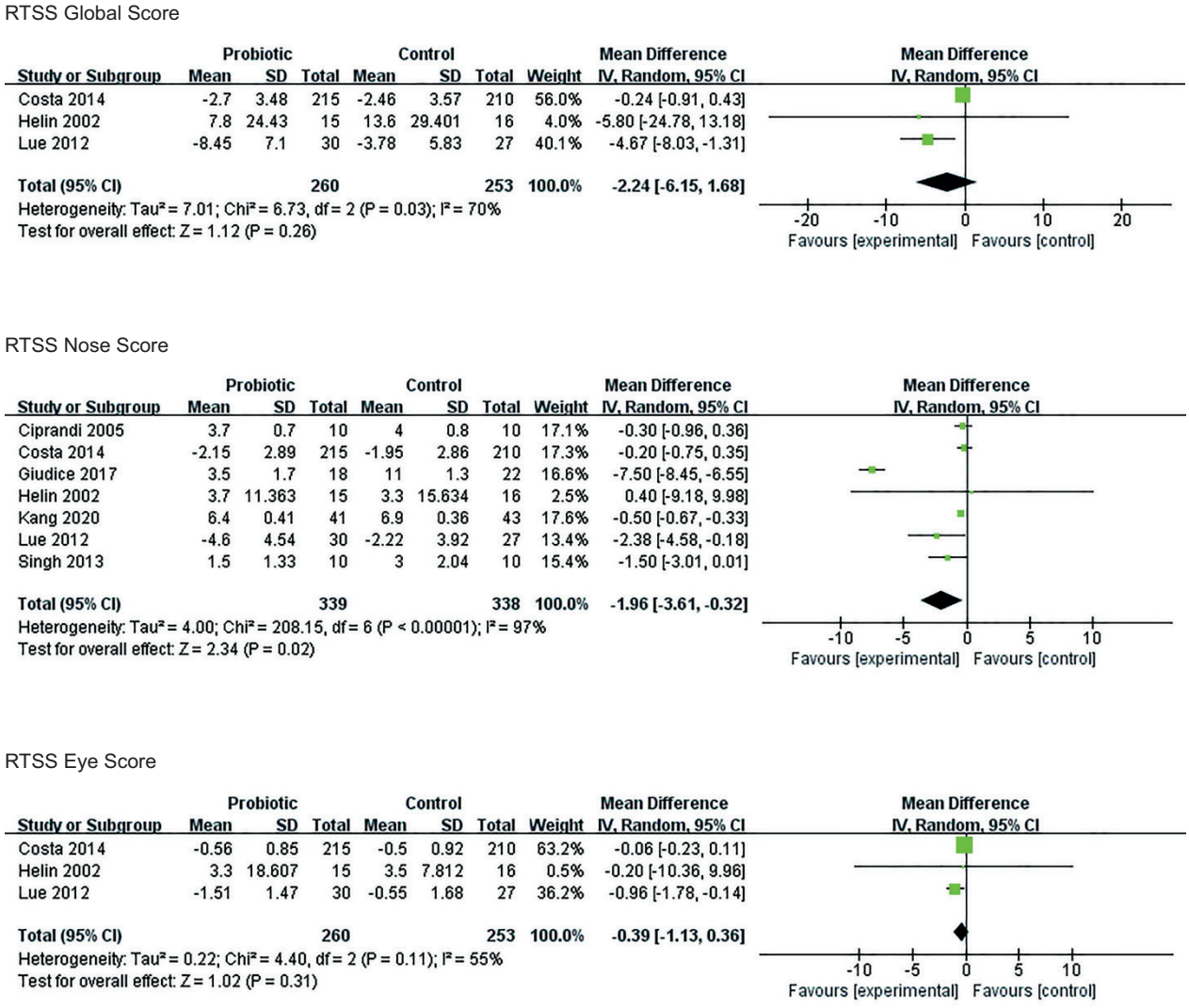

Figure 7 Forest plot showing the comparison of probiotic versus placebo outcomes in the Rhinitis Total Symptom Score.

Conclusion

Although the included RCTs are heterogeneous in the formulation of probiotics, study design, and outcome measurement, this systematic review and meta-analysis indicate that probiotics have a certain effect on the treatment of AR. At present, probiotics cannot be recommended as an independent method for the treatment of AR, but as a new potential therapy, it is believed that it can eventually be used as an adjuvant therapy for the treatment of AR. Therefore, more large sample sizes, consistent measurement results, and high-quality prospective randomized controlled studies are needed to provide more meaningful evidence-based medicine support for AR treatment.

Author contributions

S Yan and L Huang searched and screened the literature. F Zhang and N He extracted the literature data, and evaluated the research quality. The first draft of this article was written by S Yan, and was critically revised by other authors. All authors finally approved to submit the version and agreed take responsibility of the whole article.

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