

REVIEW ARTICLE

Probiotics supplementation in children with asthma: A systematic review and meta-analysis

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Asthma, the most common chronic inflammatory respiratory disease, can affect people of any age, especially children.¹ In 2010, 25.7 million people, including at least 7 million children, had bronchial asthma in the USA.²

Key Points

- 1 Current studies showed that probiotics may affect immunological cells and may be helpful for allergic diseases. However, there was no systematic review evaluating the effects of probiotics supplementation for asthmatic children.
- 2 Probiotics supplementation may decrease the episodes of asthma, and significant improvements in childhood asthma control test, asthmatic symptom in the day and night, the number of symptom-free days and pulmonary function of children with asthma were not obtained; however, obvious heterogeneity leads to the low quality of results.
- 3 Probiotics may significantly decrease the level of IL-4 and increase the level of interferon- γ of children with asthma, but obvious heterogeneity exists.

Recently, there is an enormous amount of research targeting the effects of probiotics on allergic diseases as they might modulate the intestinal microbiota and regulate the inflammatory response. Probiotics may affect macrophages cells, dendritic cells, T cells natural and killer cells,^{3–7} inducing a subset of regulatory T cells and suppressing allergen induced in inflammatory response.³ In the past decades, several clinical studies have examined the association between the intake of probiotics and allergic diseases. The findings from these studies suggested that probiotics play an important role in treating allergic diseases. Recent meta-analyses revealed the benefits of probiotics in the treatment of allergic rhinitis and dermatitis.^{8–11} Previous clinical trials were conducted to explore the effects of probiotic supplementation on asthmatic children; nevertheless, the results were inconsistent.^{12–22} There was no systematic review of probiotics supplementation for asthmatic children. In view of the lack of evidence-based review, we aimed to assess the effects of probiotics on asthmatic children in this systematic review and meta-analysis of currently available randomised control trials (RCTs).

Methods**Search strategy**

Six databases, including PubMed, EMBASE, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure Database, CQ VIP Database and Wanfang Data, were searched by two reviewers (J Lin and Y Zhang) until November

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2017 without any limitation. Keywords such as probiotics, children and asthma were used in the English databases. The corresponding Chinese key terms were used in three Chinese databases. Additional information was retrieved via a manual search of the reference lists of the published original studies to supplement our search. We contacted the primary authors of the included studies for detailed information.

Study selection

Studies were included only if they met the following inclusion criteria: (i) the study was designed as an RCT; (ii) the children were diagnosed with asthma, and the age of involved children in study ranged from 0 to 18 years old; and (iii) probiotics were consumed as the only intervention in the probiotics group without restrictions on dosage and type.

The whole process was conducted independently by two reviewers (J Lin and Y Zhang). If disagreements occurred, discussions were held until agreements were achieved.

Data extraction

Study characteristics were extracted independently by two reviewers (J Lin and Y Zhang) using a self-designed data extraction sheet. The first author's name, year of publication, study design, geographic area where the research was conducted, duration of therapy, sample size (experimental/control group), the characteristics of patients, probiotic intervention and main outcomes were extracted. A discussion was held if there were differences about the interventions and outcomes until agreement was reached between reviewers before the data analysis. The data extracted were presented in the descriptive review and/or meta-analysis.

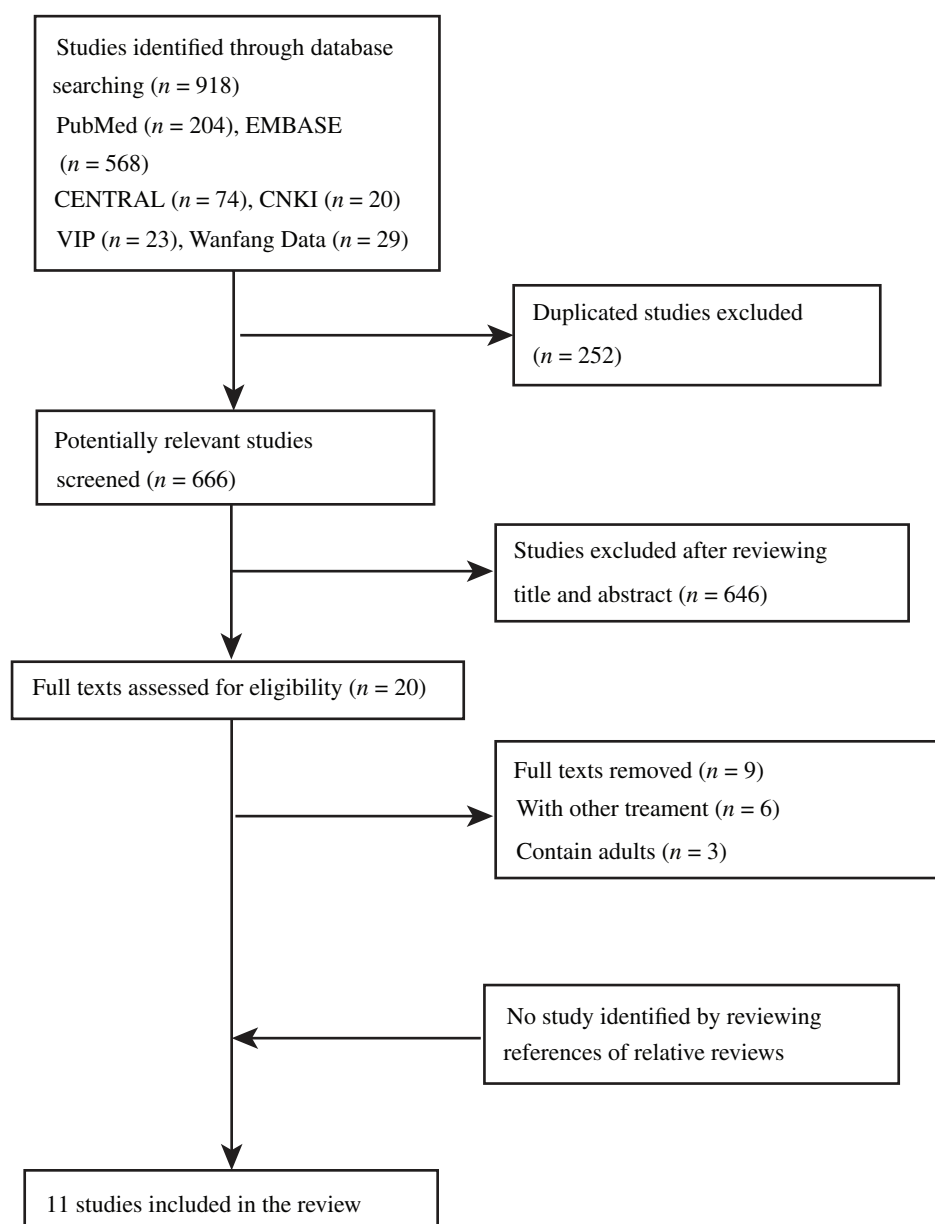


Fig. 1 The flow diagram of identifying relevant studies. CNKI, China National Knowledge Infrastructure Database; VIP, CQ VIP Database.

Table 1 The characteristic of included trials

	Anhanchian 2016	Bin 2016	Bing 2016	Chen 2010	Giovannini 2007	Gutkowski 2010	Hui 2016	Miraglia 2012	Miraglia 2017	Rose 2010	Xianjun 2014
Study design	Double-blind, randomised, placebo-controlled study	Randomised controlled study	Randomised parallel-controlled study	Double-blind, randomised, placebo-controlled study	Double-blind, randomised, placebo-controlled study	Double-blind, randomised, placebo-controlled study	Randomised controlled study	Double-blind, randomised, placebo-controlled study	Double-blind, randomised, placebo-controlled study	Double-blind, randomised, placebo-controlled study	Randomised controlled study
Geographic area	Mashhad, Iran, 2012–2014	Jiangsu, China, 2013–2015	Guangdong, China, 2014–2015	Taiwan, 2006–2007	Milan and surroundings, Northern Italy, 2003–2004	Warsaw, Poland, 2002–2005	Shanghai, China, 2014–2015	Naples, Italy, 2009–2010	Naples, Italy, 2015	Frankfurt/Main, Germany, 2002–2003	Hubei, China, 2012–2014
Sample size (exp/con), n	36/36	50/50	23/22	49/56	81/77	22/24	43/43	22/21	20/20	65/66	42/42
Participant	Children (6–12 years) with mild persistent asthma and a history of recurrence	Children (under 14 years old) with bronchial asthma combined with AR	Children (8–14 years old) with bronchial asthma	Children (6–12 years old) with a history of mild to moderate persistent asthma (GINA steps 2–3) accompanied by persistent AR	Children (2–5 years old) diagnosed of allergic asthma and/or rhinitis	Children (4–10 years old) with mild to moderate atopic asthma	Outpatient children (5–12 years old) with bronchial asthma	Children (6–14 years old) affected by mild persistent asthma (GINA step 2) under control in treatment with montelukast (5 mg/day) for at least 2 weeks and were allergic to HDM	Children (9 ± 2.2 years old) suffering from SAR and well-controlled asthma	Children (6–24 months old) with a history of at least two episodes of wheezing during the past 12 months, with at least one of these exacerbations in the 3 months before enrolment, and a first-degree family history	Children (7–16 years old) with cough variant asthma
Intervention	One billion CFU capsule of <i>Lactobacillus casei</i> , <i>Lactobacillus rhamnosus</i> , <i>Streptococcus thermophilus</i> , <i>Bifidobacterium breve</i> , <i>Lactobacillus acidophilus</i> , <i>Bifidobacterium infantis</i> , <i>Lactobacillus bulgaricus</i> and Fructooligosaccharide	Live combined <i>Bifidobacterium</i> and <i>Lactobacillus</i> tablets (1 pack/time, twice a day)	Oral probiotics supplementation + routine aerosolised budesonide inhalation	One capsule of <i>Lactobacillus goseri</i> twice a day	<i>L. bulgaricus</i> , <i>S. thermophilus</i> and the probiotic strain <i>L. casei</i> DN-114001	<i>L. acidophilus</i> , <i>Bifidobacterium bifidum</i> and <i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> (b.i.d)	Oral administration of probiotics, 1.5 g, b.i.d on the basis of control group	Oral supplementation containing <i>Bifidobacteria</i> mixture, <i>Bifidobacteria longum</i> B8536, <i>B. infantis</i> M-63 and <i>B. breve</i> M-16 V as powder in 3 mg sachet	Oral supplementation containing <i>Bifidobacteria</i> mixture, <i>Bifidobacteria longum</i> B8536, <i>B. infantis</i> M-63 and <i>B. breve</i> M-16 V as powder in 3 mg sachet	Supplementation with <i>L. rhamnosus</i> strain GG ATCC 53103 (b.i.d.)	<i>Lactobacillus salivarius</i> PMA0006

Table 1 (Continued)

	Ahanchian 2016	Bin 2016	Bing 2016	Chen 2010	Giovannini 2007	Gutkowski 2010	Hui 2016	Miraglia 2012	Miraglia 2017	Rose 2010	Xianjun 2014
Duration of therapy, months	2	6	1.5	2	12	3	3	2	2	6	2
Main outcomes	Viral respiratory infection, salbutamol consumption, oral prednisolone, school absenteeism, outpatient visits, hospital admissions	CACT, ACT, FEV1% predicted, PEF, IFN- γ , IL-4	IgE, IL-4, IFN- γ , Th1/Th2, CD4+/CD+8, asthmatic symptom scores, QOL, effective rate	Pulmonary function (FEV1, FVC, PEF, FEV1/FVC (%), MEF25/75), CACT, IgE, cytokine production	Diarrhoea, fever, IgA, IgG, IgM, IgE	Asthma, exacerbations, Effective rate, bronchodilators used, FEV1%VC, HLA-DR %, CD8/CD45RA %	recurrence rate	FEV1% predicted, FeNO Symptoms, QOL, salbutamol use in ppb CACT	Number of wheezing episodes, days with wheeze, days on inhalative betamimetics, days on inhalative steroids, number of rescue-free days, number of symptom-free days, asthma symptom score, IgE	Effective rate, recurrence rate	

ACT, asthma control test; AR, allergic rhinitis; b.i.d, twice daily; CACT, childhood asthma control test; CFU, colony-forming units; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; HDM, house dust mite; HLA-DR, human lymphocyte antigen – antigen D related; IFN- γ , interferon- γ ; IL-4, interleukin-4; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; PEF, peak expiratory flow; SAR, severe allergic rhinitis; QOL, quality of life; VC, vital capacity.

Assessment of methodological quality

We assessed the risk of bias in included studies using the criteria of the Cochrane Handbook for Systematic Reviews of Interventions²³: (i) random sequence generation; (ii) allocation concealment; (iii) blinding of participants and personnel; (iv) blinding of outcome assessment; (v) incomplete outcome data; (vi) selective reporting; and (vii) other bias. Each item was graded as 'low', 'high' or 'unclear' risk of bias. Any disagreement was settled by two data extractors (J Lin and C He) and all the team members would discuss if agreement could not be achieved between the two data extractors.

Data synthesis and statistical analysis

In this review, outcomes were presented as continuous variables. Mean differences (MD) or standard mean difference (SMD) was used for continuous variables. Risk ratio was used for dichotomous variables. We calculated 95% confidence interval (CI) for each effect size estimate, and a random-effects model or fixed-effects model was used depending on the heterogeneity. A *P* value <0.05 was considered to be statistically significant. The heterogeneity among studies was tested with the *I*-statistic. The result of an *I*-statistic analysis is *I*², which describes the percentage of total variation across studies that is due to heterogeneity rather than due to chance: it demonstrates a low heterogeneity if *I*² is less than 50%.²⁴ The following treatment comparison was made: probiotics therapy (experimental group) versus placebo (control group). All statistical analyses were performed using Review Manager, version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Literature search

A total of 918 studies were included through electronic searching, although only 666 studies remained after duplicates were removed. Following this, 646 of the 666 were deemed ineligible after titles and abstracts were reviewed. The full texts of the remaining 20 studies were studied by two reviewers, 9 of which were eliminated because of failure to meet the inclusion criteria. Six of them used other intervention with probiotics, and three of them included adults in studies. No study was included through manual searching. In total, 11 studies met eligibility criteria and were included in the present review. The flow chart for literature screening is shown in Figure 1.

Characteristics of included studies

All the included studies are RCTs. Of the 11, 7 were presented in English, while the remaining 4 studies were presented in Chinese. A total of 910 children patients with asthma (453 in the experimental group vs. 457 in the control group) aged from 0.5 to 16 years were involved in this review. The 11 studies were carried out in diverse geographical areas, including Asian and European countries. All the research was conducted from 2002 to 2015. Sample sizes ranged from 40 to 158. Different probiotics

were applied in the experimental groups through the included studies. Duration of therapy ranged from 1.5 to 6 months. The details are shown in Table 1.

Quality of RCTs

Risk of bias of the included studies was assessed according to the *Cochrane Handbook*. Five studies^{12–15,19} reported adequate methods in random sequence generation. None reported the adequate method of allocation concealment. Seven studies^{12–18}

reported adequate blinding of participants and personnel, while the blinding of outcome assessment remained unclear in all included studies. In terms of incomplete outcome data, 10 studies were at low risk of bias for no data were missing, or eligible reasons for withdrawal were reported. Only one study¹⁶ reported a high number of missing data and did not provide the reason. Two included studies^{13,14} had a high risk of selective reporting. Other risks including potential source of bias were not found in all included studies. The details are shown in Figure 2.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ahanchian 2016	+	?	+	?	+	+	+
Bin 2016	+	?	?	?	+	+	+
Bing 2016	?	?	?	?	+	+	+
Chen 2010	+	?	+	?	+	–	+
Giovannini 2007	+	?	+	?	+	+	+
Gutkowski 2010	?	?	+	?	–	+	+
Hui 2017	?	?	?	?	+	+	+
Miraglia 2012	?	?	+	?	+	+	+
Miraglia 2017	+	?	+	?	+	–	+
Rose 2010	?	?	+	?	+	+	+
Xianjun 2014	?	?	?	?	+	+	+

Fig. 2 Summary of risk of bias assessment of included studies.

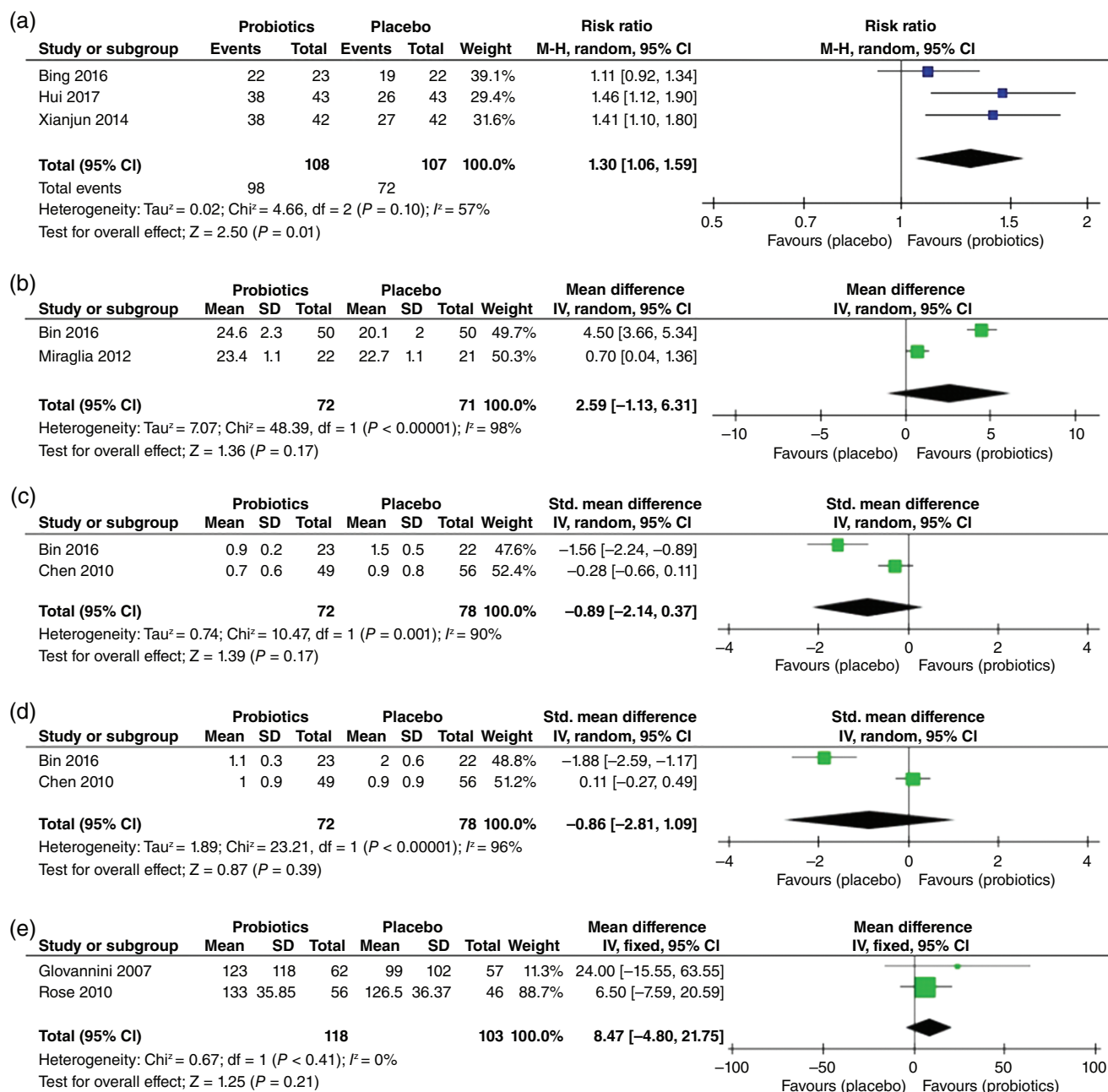


Fig. 3 Outcome of probiotics versus control: (a) Episodes of asthma. (b) Childhood Asthma Control Test. (c) Scores of asthmatic symptoms in the day. (d) Scores of asthmatic symptoms in the night. (e) The number of symptom-free days. CI, confidence interval; SD, standard deviation; Std., standard.

Effect of intervention

Changes in the clinical outcomes

1 Episodes of asthma: Meta-analysis indicated that the proportion of children with fewer episodes of asthma was obviously higher in probiotics groups than in control groups, which was consistent with three studies.^{20–22} The pooled risk ratio was 1.3 (95% CI 1.06–1.59, $P = 0.01$) (Fig. 3a). Significant heterogeneity existed across studies ($I^2 = 55\%$). Three studies^{15–17} assessed the number of asthma exacerbations. Two of them demonstrated that there was no significant difference between

the two arms,^{15,17} while the other¹⁶ reported that the asthma exacerbations were statistically more frequent in the probiotics group. We could not pool the data of the three studies^{15,16} as two of them did not provide detailed data.

2 Childhood Asthma Control Test (CACT): Three studies^{13,17,19} reported the effects of probiotics on CACT. While one study¹³ did not provide the detailed score, it reported that the proportion of patients with an improvement in CACT was higher in the probiotics group than in control group. Two studies^{17,19} provided statistical data regarding the CACT results in both the

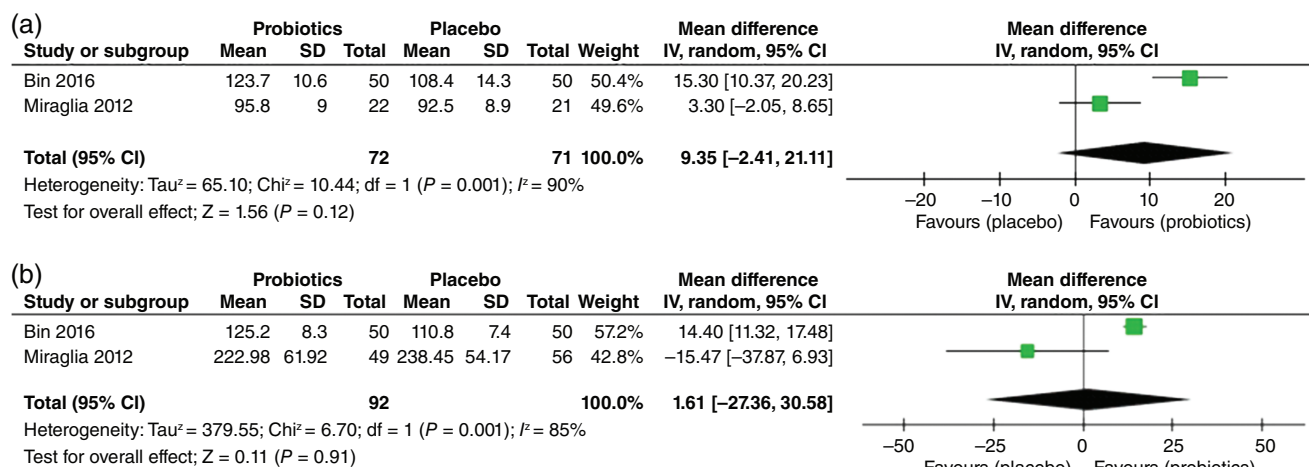


Fig. 4 Comparison probiotics versus control outcomes: (a) Forced expiratory volume in the first second; (b) peak expiratory flow. CI, confidence interval; SD, standard deviation; Std., standard.

probiotics and control groups. The pooled data revealed that there was no statistical difference between children treated with probiotics compared with children treated with placebo (MD 2.59, 95% CI -1.13, 6.31, $P = 0.17$, I^2 98%) (Fig. 3b).

- Asthmatic symptoms: Two studies^{13,20} reported statistical data about the effects of probiotics on asthmatic symptoms. SMD was used in data analysis because the criteria for evaluating asthmatic symptoms in children in two studies were different. No statistical difference was found comparing scores of asthmatic symptoms in the day (SMD -0.89, 95% CI -2.14, 0.37; $P = 0.001$, I^2 90%) (Fig. 3c) or night (SMD -0.86, 95% CI -2.81, 1.09, $P = 0.39$, I^2 96%) (Fig. 3d).
- The number of symptom-free days: Two studies^{15,17} provided data regarding the number of symptom-free days in both the probiotics and control groups. The pooled results demonstrated that there was no significant difference between the two arms (MD 8.47, 95% CI -4.8, 21.75, $P = 0.21$, I^2 0%) (Fig. 3e).

Effects on pulmonary function

- Forced expiratory volume in the first second (FEV1): Four of the included studies^{13,14,16,19} assessed post-treatment FEV1 using different scales. The data were reported in two of them.^{14,19} The pooled data revealed that children treated with probiotics did not have a significantly higher score in FEV1 predicted compared with children treated with placebo (MD 9.35, 95% CI -2.41, 21.11, $P = 0.12$, I^2 90%) (Fig. 4a). Although the effects of probiotics for FEV1/FVC(%) in children were both positive in the other two studies, the critical data were not attained in one study,¹⁶ and we could not conduct a meta-analysis for FEV1/FVC(%) in children.
- Peak expiratory flow (PEF): PEF was reported in two studies.^{13,19} The pooled results based on the two studies showed that there was no statistically significant difference between the probiotics group and the control group (MD -0.95, 95% CI -3.08, 1.19, $P = 0.38$, I^2 88%) (Fig. 4b).

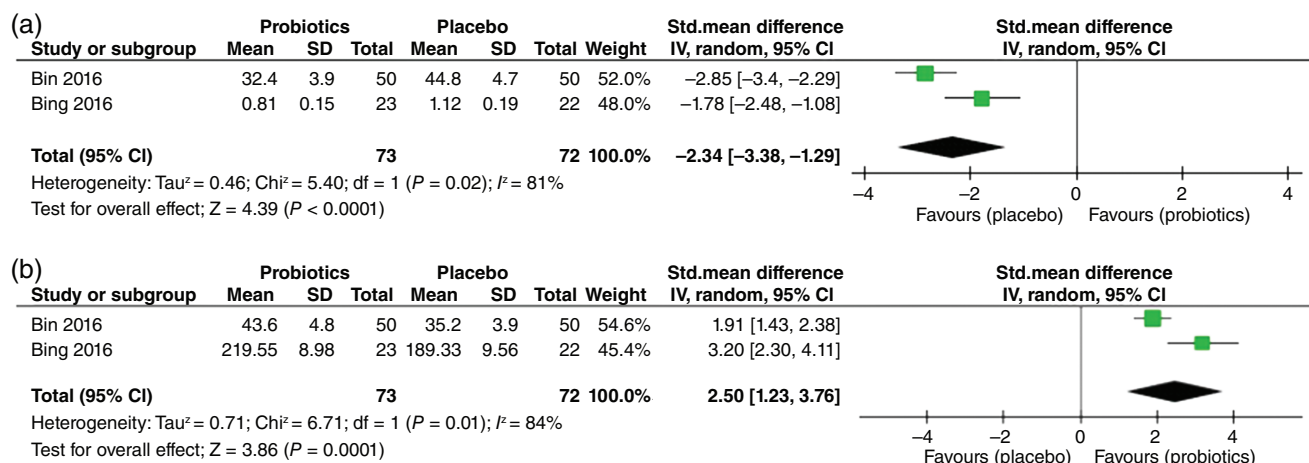


Fig. 5 Outcomes of probiotics versus control: (a) Interleukin-4; (b) interferon- γ . CI, confidence interval; SD, standard deviation; Std., standard.

Changes in the laboratory data

- 1 Interleukin (IL)-4: IL-4 was assessed in two studies,^{19,20} The pooled results based on the two studies showed that there was a statistically significant reduction of IL-4 in the probiotics group compared with the control group (MD -2.34, 95% CI -3.38, -1.29, $P < 0.01$, I^2 81%) (Fig. 5a).
- 2 Interferon (IFN)- γ : IFN- γ was assessed in three studies,^{13,19,20} one of which lack the detailed data. We opted to pool the data of the other two studies and found that there was a statistically significant difference between the probiotics group and the control group (MD 2.5, 95% CI 1.23–3.76, $P < 0.01$, I^2 84%) (Fig. 5b).
- 3 Immunoglobulin E (IgE): Four studies^{13,15,17,20} assessed the serum IgE, and only one study showed that there was a significant difference between the probiotic-treated and the placebo group. Meta-analysis was not conducted as the data in three studies were not normally distributed, and all measurements were different.

Discussion

We conducted a systematic review of RCTs to evaluate the effects of probiotics supplementation for children with asthma. To our knowledge, it is the first systematic review assessing the effects of probiotics supplementation in children with asthma. We applied a systematic review methodology in the process of selecting, synthesising and assessing the published evidence.

Pooled data of the three studies^{20–22} provided evidence that probiotic supplementation significantly decreased the proportion of childhood, with fewer episodes of asthma, but whether the criteria evaluating the reduction of episodes of asthma were the same across the three studies remained unclear. On the contrary, significant differences in the improvement of asthmatic symptoms in the daytime or nighttime and CACT scores between two groups were not found, with significant heterogeneity existing across included studies. We could not conduct a subgroup analysis because of the limited number of included studies. Consequently, the results might be affected by clinical heterogeneity such as different baseline of selected children, different subspecies of probiotics and duration of intervention. It led to low quality of the evidence. Similar to the asthmatic symptoms score, the administration of probiotics was not found to significantly increase the number of symptom-free days by analysing data. The results of the use of bronchodilators were inconsistent in different studies. Two studies^{12,16} showed that the frequency was statistically reduced after probiotics supplementation. However, Rose *et al.*¹⁷ indicated that there was no significant difference when using inhalative betamimetics during the daytime in two arms.

The pulmonary function test was regarded as a relatively objective method for asthma assessment. The pooled results did not showed significant improvement in FEV1 predicted and PEF in asthmatic children between the two groups. Significant heterogeneity existed between studies. It is contrary to evidence demonstrated in two other studies,^{13,16} which indicated a significant effect of probiotics supplementation on FEV1%FVC. The participants of the study where the result is contrary to the other three studies included children affected by mild persistent asthma under control. It suggested that the effectiveness of probiotics on

the pulmonary function of children with asthma may be affected by the severity of the disease. Two studies^{13,19} gave different evidence on the effect of probiotics on PEF of asthmatic children. The obvious discrepancy of original data may be caused by the characteristics of the child participants, such as age and height. One study¹⁸ demonstrated that the fractional exhaled nitric oxide in the probiotics group decreased significantly than in control group, suggesting that probiotics may have beneficial effects on ameliorating airway inflammation in children with asthma.

In recent years, several studies have confirmed that the immune response mediated by T helper cells plays an important role in allergic diseases, and the immune imbalance of Th1/Th2 cells is considered to be an important mechanism for inducing respiratory allergic diseases.^{25,26} Th1/Th2 imbalance exists in asthmatic children in the remission stage. IL-4 is a representative cytokine secreted by Th2 cells, which promotes the aggregation and activation of eosinophils (EOS), while IFN- γ is secreted by Th1 cells and inhibits airway inflammation. The Th2 subgroup of asthmatic patients was mainly induced, increasing the level of IL-4 and decreasing IFN- γ /IL-4. By pooling the data of IL-4 and IFN- γ , we found a significant reduction of IL-4 and an increase of IFN- γ after probiotics supplementation with significant heterogeneity. The pooled results were consistent with Bin *et al.*'s¹⁹ and Bing *et al.*'s²⁰ results. Although there was no detailed data, the result of the serum level of IFN- γ in the other study¹³ was also significantly increasing. Th1/Th2 was increasing in one study.²⁰ However, the different kinds of probiotics in studies may lead to significant heterogeneity. Due to the limited number of studies, we cannot conduct a subgroup analysis, and this led to the low quality of the pooled results. Four studies assessed the level of IgE, which is an important indicator of anaphylaxis in body, but most of them revealed that there was no significant difference between probiotic-treated and placebo groups; only one study¹⁷ showed a significant decrease of IgE between the two arms. However, meta-analysis was not considered as two of them were not normally distributed, and all measurements were different.

The main limitation of our study is the small number and low quality of the available RCTs. We cannot pool more outcomes in every meta-analysis of the outcomes as many studies did not provide precise results. There are various kinds of probiotics applied; lactobacillus, streptococcus, bifidobacterium and their subspecies were widely used in included studies. It may result in high heterogeneity for different probiotics, and distinct combinations would cause the divergence of data and even the final decision in the review. Due to the limited number of studies, subgroup analyses could not be conducted to explain the heterogeneity. We opted to not conduct the sensitivity analyses and publication bias tests, such as funnel plot, Egger's test and Begg's test,²⁴ due to insufficient studies in every meta-analysis. Likewise, the relatively small sample sizes limited the precision of our analysis.

It is important to assess the safety of probiotics, especially in young children. There may be side effects of probiotics in patients with critical illness or bone marrow/stem cell transplantation.²⁷ One included study reported that probiotics might not significantly increase the incidence of fever and diarrhoea.¹² Among all included RCTs, rare cases of severe complications occurred, with a certain association with probiotics consumption. No participant died in any study.

Conclusions

The systematic review and meta-analysis suggested that probiotics supplementation may reduce the proportion of childhood, with fewer episodes of asthma, while no significant benefits were obtained regarding CACT, asthmatic symptoms in daytime or nighttime and pulmonary function such as FEV1 and PEF. However, a high level of heterogeneity existing among studies may lead to the low quality of the evidence. More well-designed RCTs with larger sample sizes need to be conducted to evaluate the effects of probiotics in children with asthma in the future.

All participants or their guardians gave their consent prior to their inclusion in the studies included in this review.

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