

Efficacy of probiotic supplementary therapy for asthma, allergic rhinitis, and wheeze: a meta-analysis of randomized controlled trials

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ABSTRACT

Background: Probiotic supplementary therapy to prevent allergic diseases, including asthma in children, has been widely explored in many randomized controlled trials. However, there is conflicting evidence on the effect of probiotic supplementation during pregnancy and infancy to the incidence of asthma and allergic rhinitis.

Method: This study was designed to systematically explore the potential effects of probiotic supplementation on the occurrence and development of asthma, wheeze, and allergic rhinitis. Randomized controlled trials were searched in several medical literature data bases. A meta-analysis was undertaken by using the fixed-effects model or the random effects model to calculate the pooled risk of significant heterogeneity. Two writers were designated to perform the study selection and data extraction. The primary outcome was clinically diagnosed asthma; the secondary outcomes included wheeze, allergic rhinitis, and a positive aeroallergen skin-prick test result.

Results: Seventeen randomized controlled trials, which composed a total of 5264 children, were analyzed. The pooled data for risk of developing asthma after probiotic supplementation showed no significant reduction compared with controls (risk ratio [RR] 0.86 [95% confidence interval {CI}, 0.73–1.01]; $I^2 = 0\%$; $p = 0.06$). A subgroup of strains indicated that *Lactobacillus rhamnosus* GG supplementation only had a reduction to the occurrence of asthma (RR 0.75 [95% CI, 0.57–0.99]; $I^2 = 11\%$; $p = 0.04$). The supplement in the postnatal group had a similar result, but the incorporated data were limited. Meanwhile, it is failed to identify that probiotic supplementary therapy have a clear benefit to the secondary outcomes: wheeze, allergic rhinitis, positive aeroallergen skin-prick test result.

Conclusion: This study showed a significant benefit that supplementation with probiotics in pre- and postnatal periods was likely to play an essential strategic role in the prevention of asthma. However, these effects were based on the type of probiotics used, which also need more large-sample and high-quality RCTs to confirm the reliability of this study.

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Asthma is a chronic respiratory disease characterized by bronchial hyperresponsiveness, chronic airway inflammation, and airway remodeling.^{1,2} Due to its high morbidity and substantial economic burden, asthma has caused a widespread concern in the past decades, especially in childhood.^{3,4} According to results of the International Study of Asthma and Aller-

gies in Childhood (ISAAC) questionnaires, asthma prevalence increases by 0.18% in the 6–7-year-old group and 0.28% in the 13–14-year-old group every year. It is worth noting that recurrent wheeze frequently precedes the diagnosis of asthma.⁵ Especially, allergic rhinitis (AR) has been estimated to be a risk for the development of asthma, which shares common pathophysiologic elements with asthma.^{6,7}

Asthma has been verified to be the consequence of complicated interactions between genetic and environmental factors.¹ Strachan⁸ first proposed a hygiene hypothesis that interpreted that the rise in allergic diseases might be associated with reduced microbial exposure. Such a hypothesis may give an explanation for the raised incidence of atopic diseases in the 20th century.^{9–11} Then, further, the “old friends” hypothesis proposed by Rook¹² argued that the fundamental microbial exposures were present in primate development and the time of the hunter gatherer, when the human immune system evolved.¹³ Ecological species and some other microbes which inhabit indoor and

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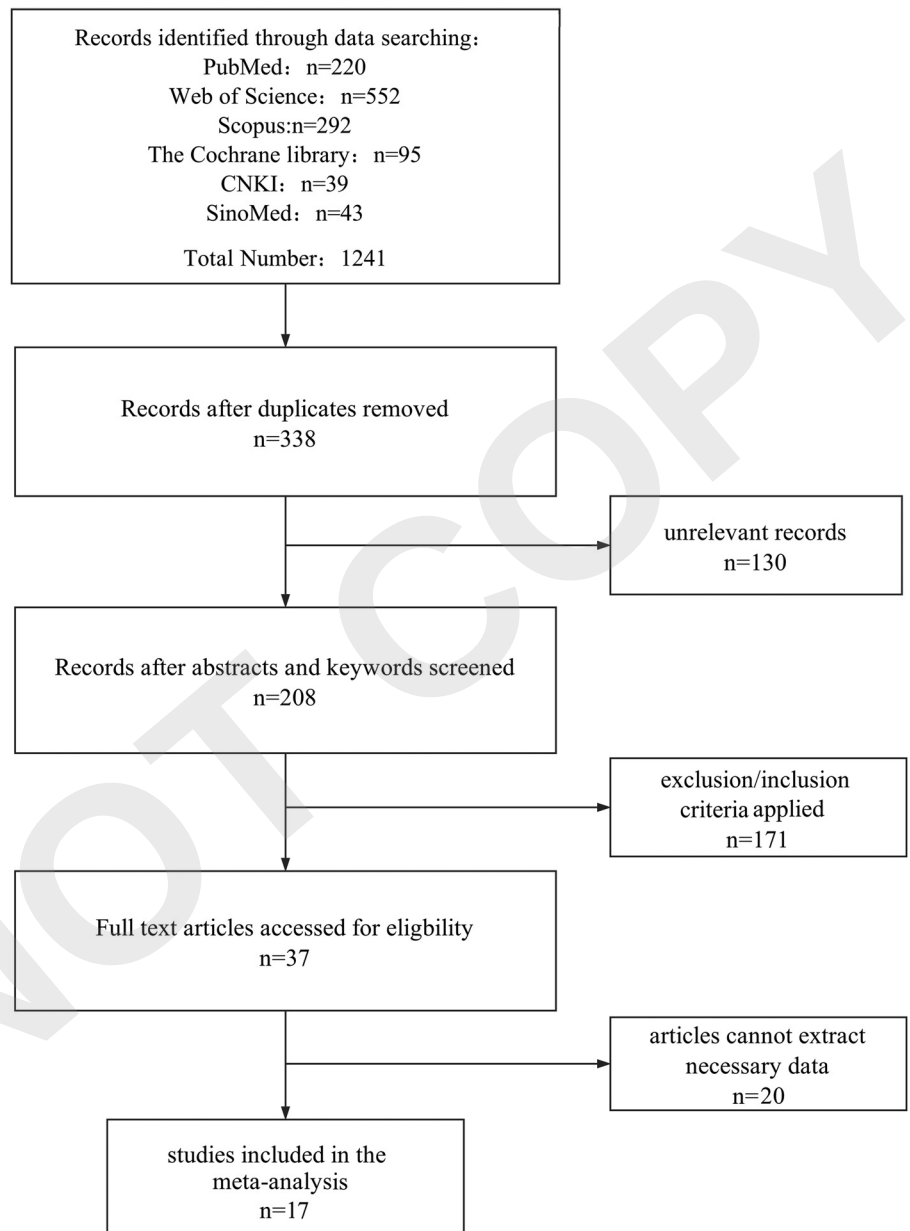


Figure 1. Flow chart of the selection process by following the PRISMA criteria.

outdoor environments, are generally harmless comensal microbes, and can be acquired from the skin, gut and respiratory tract of other people. Exposure to typical microbial flora in early life is considered as an effective incentive for T-helper cell type 1 and type 2 balance.¹⁴ In addition, the most essential circumstances for “old friends” exposure is the early life in development, including pregnancy, delivery, and the first few days or months of infancy.¹⁵ Based on these pivotal revelations, a number of researchers focused on the altering gut colonization by pre- or probiotic supplementation.^{16,17}

Probiotics, live microorganisms, are considered to confer a health benefit to the host through an interac-

tion with gut microbiota. Gut microbiota has been verified to be involved in the modulation of the immune response in early life.¹⁸ Supplementation of probiotics has been regarded as an effective strategy to prevent allergies. Of note, the use of probiotics to prevent allergic diseases, including asthma in children, has been widely explored in many randomized controlled trials (RCT).¹⁹ However, there is still no confirming evidence to support the use of probiotics to prevent asthma. Therefore, we performed a meta-analysis to systematically explore whether probiotic supplementation used in pregnant women and/or infants could reduce the incidence of asthma and AR in children.

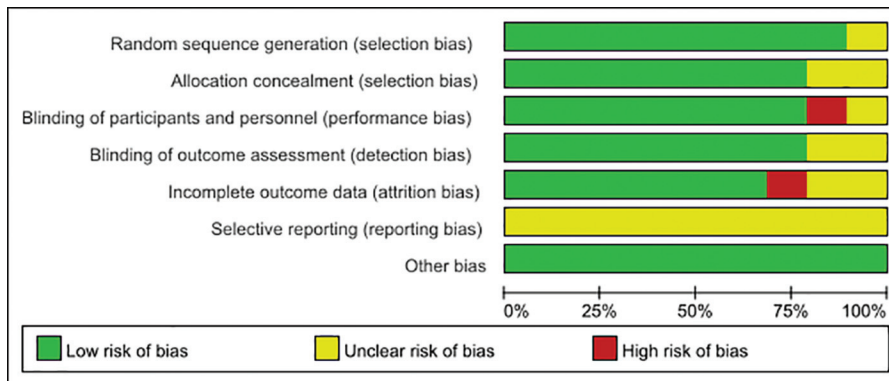


Figure 2. Quality assessment of randomized controlled trials (RCT) included in the meta-analysis by using the Cochrane Collaboration tool for assessing risk of bias.

METHOD

Search Strategy

We conducted a comprehensive search in the PubMed, Web of Science (Institute for Scientific Information, Philadelphia, USA), the Cochrane Library (John Wiley & Sons, Hoboken, USA), Scopus (Elsevier, Amsterdam, The Netherlands), and Chinese data bases (CNKI (National Knowledge Infrastructure, Beijing, China) and SinoMed (Institute of medical information, Beijing, China)). These data bases were searched according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁸ for RCTs to evaluate the effect of probiotic supplement therapy for asthma, AR, and wheeze in pre- and postnatal periods. The language limits set for studies were those published in English or Chinese. Studies that could be converted into an English version were also allowed. The search string was built up through the most-appropriate Boolean operators by combining all terms related to asthma, AR, wheeze, and probiotics by using PubMed Medical Subject Headings, and free-text words and their combinations. Studies obtained by virtue of the above-mentioned search strategy were imported into EndNote (Thomson Corporation, Stanford, USA), in which duplicates were removed. Also, we manually screened references in the chosen articles by using the citation snowballing technique. The complete search strategies are reported in the flow chart (Fig. 1).

All the authors, who are in the Department of Physiology, Xiangya School of Medicine, conceived and designed the study protocol. X Du and L Wang performed the literature search and selection, and assessed study details, which were checked by S Wu and L Yuan. L Yuan and S Tang evaluated the study quality. X Du and L Wang wrote the first draft of the paper, which was critically revised by all the other authors (Y Xiang, X Qu, H Liu, X Qin). All the authors gave final approval of the version to be submitted and agreed to be accountable for the whole paper.

Study Selection

The primary outcome measure was asthma diagnosed by the clinician. The secondary outcomes included wheeze, AR, allergic symptoms, lower respiratory tract infections, and total immunoglobulin E level. The screening process was done independently by two individuals (X D and L W) and then summarized. The disputed part was finally decided by the third person (L Yuan).

Inclusion criteria were the following:

1. RCTs were blinded.
2. The subjects were healthy children, with or without a high risk of developing allergic diseases and without concurrent treatments.
3. Probiotics were supplemented since the pre- and/or postnatal periods, with > 3 months of intervention duration; the details of the specific probiotic strains and dose were given in the articles. The control subjects were children who received a placebo.
4. There were clear descriptions of the missed condition and eventual completion of the trial population in the studies.
5. The studies were approved by the ethics committee, and the full name of the approving institution was provided.

Exclusion criteria were the following:

1. Inappropriate study design, population, intervention, comparison, and/or outcome, which did not meet the inclusion criteria.
2. Inappropriate article type: letter or review, meeting abstract, laboratory studies, or case report.
3. Nonhuman research.
4. Lack of necessary outcome measures: sample size, incidence, hazard ratio (HR) or risk ratio (RR), 95% CI, or data could not be analyzed.

Data Extraction and Quality Assessment

For the final selection of articles, two researchers (L Y and S T) independently extracted data and reached a consensus. The extracted data included the first author,

Table 1 Characteristics of RCTs included in the meta-analysis (quality score accessed by the Jadad scale)

Study	No. Participants/ High Risk	Pre- and/or Postnatal Intervention	Intervention/Dose ×10 ⁸ CFU/Duration	Placebo	Follow- up, y	AR/Wheeze/Positive Aeroallergen SPT Result	Quality Score
Lundelin et al ⁴² , 2016	221/✓	Pre- and postnatal	LGG, mixture/100/36 WG until delivery, first 6 mo	Not stated	4-5,10-15	—	5, 3, 4, 5 (4 studies)
Peldan et al ³⁰ , 2017	1223/✓	Pre- and postnatal	Mixture/100/36 WG until delivery, first 6 mo	Not stated	10	AR	5
Melanie et al ²⁹ , 2015	215/✓	Pre- and postnatal	Mixture/50/36 WG until delivery, first 6 mo	Not stated	6	Wheeze	4
Berni et al ³⁴ , 2016	193/✓	Postnatal	LGG/unclear/first 12 mo	EHCF	3	—	4
Paula et al ³¹ , 2014	796/✓	Pre- and postnatal	Mixture/100/35 WG until delivery, first 6 mo	Not stated	3.5	—	3
Stephen J et al ³⁷ , 2014	454/×	Pre- and postnatal	Mixture/100/36 WG until delivery, first 6 mo	Maltodextrin	2	AR/wheeze/positive aeroallergen SPT result	5
Michael et al ³⁵ , 2017	184/✓	Postnatal	LGG/100/first 6 mo	Inulin	2	—	4
Robert et al ³⁶ , 2011	250/✓	Pre- and postnatal	LGG/180/36 WG until delivery, first 3 mo	Maltodextrin	1	Wheeze/postive aeroallergen SPT result	5
Dotterud et al ³³ , 2010	278/✓	Pre- and postnatal	Mixture/1050/35 WG until delivery, first 3 mo	Not stated	2	—	5
Kalliomäki et al ⁴¹ , 2007	116/✓	Pre- and postnatal	LGG/100/36 WG until delivery, first 3 mo	Not stated	7-8	AR	4
Ou et al ³⁹ , 2012	191/✓	Pre- and postnatal	LGG/100/24 WG until delivery, first 6 mo	Microcrystalline cellulose	3	Wheeze	2
Jensen et al ³² , 2012	123/×	Postnatal	LGG/30/first 6 mo	Maltodextrin	5	AR/wheeze/postive aeroallergen SPT result	4
Prescott et al ⁴⁰ , 2008	105/✓	Postnatal	LGG/30/first 6 mo	Not stated	2.5	Wheeze/postive aeroallergen SPT result	4
Taylor et al ³² , 2007	178/✓	Postnatal	LGG/30/first 6 mo	Maltodextrin	6	Wheeze	4
West et al ³⁸ , 2009	171/×	Postnatal	LGG/1/first 6 mo	Not stated	6	—	2

Table 1 Continued

Study	No. Participants/ High Risk	Pre- and/or Postnatal Intervention	Intervention/Dose $\times 10^8$ CFU/Duration	Placebo	Follow-up, y	AR/Wheeze/Positive Aeroallergen SPT Result	Quality Score
Wickens et al ²⁷ , 2018a	278/√	Pre- and postnatal	LGG/60/35 WG until delivery, first 24 mo	Not stated	11	AR/wheeze	5
Wickens et al ²⁷ , 2018b	288/√	Pre- and postnatal	<i>Bifidobacterium</i> /90/35 WG until delivery, first 24 mo	Not stated	11	AR/wheeze	5

RCT = Randomized controlled trial; AR = allergic rhinitis; SPT = skin-prick test; √ = with high risk of allergic disease; LGG = *Lactobacillus rhamnosus* GG; WG = weeks of gestation; EHCF = enzymic hydrolysis casein formula; × = without high risk of allergic disease.

year of publication, number of subjects, subjects' high risk of allergy (first- or second-level family members had a history of asthma, rhinitis, allergic sensitivity), early infection history, duration of the experimental intervention, mode of intervention in the experimental group and the control group, the type of probiotics, the dose, and the follow-up outcome indicators (asthma, wheezing, and the incidence of AR). We used two approaches to assess the quality of inclusion documents. One is the Jadad scale,²⁰ which describes the allocating studies with a score between 0 (very poor) and 5 (rigorous) by assessing three aspects: randomization and concealment, blinding, and the reason and number of withdrawals and dropouts. However, the Jadad scale ignores the importance of hidden allocation, so we introduced another approach: the Cochrane Collaboration tool (John Wiley & Sons, Hoboken, USA) for accessing risk of bias.²¹ The Cochrane Collaboration tool illustrates the quality of all included RCTs by assessing six aspects: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each indicator was judged in the degree of low, unclear, or high risk of bias (Fig. 2). All our analyses were based on the incorporated previous studies that were all approved by relevant ethical committee.

Statistical Analysis

Meta-analysis was constructed by following the methods outlined in a previously published meta-study with slight modifications.²² Stata 14.0 (StataCorp LLC, College Station, Texas, USA) and Revman 5 (John Wiley & Sons, Hoboken, USA) were used in the meta-analysis.^{23–26} Data were combined as appropriate and displayed in forest plots. RRs were used to assess risk in the cohort studies. Study heterogeneity was tested by using the 32 χ^2 test and I^2 statistics. Subgroup and sensitivity analyses were used to identify the source of heterogeneity. Confounding factors were segregated for further analysis.

RESULTS

Trials Included Study Characteristics and Quality of Reporting.

As shown in Fig. 1, a total of 949 articles were obtained: 220 from PubMed, 552 from Web of Science, 95 from the Cochrane Library, 292 from Scopus, and 82 from Chinese data bases (CNKI and SinoMed). After exclusion of duplicate articles, 338 articles were identified, and 208 of these were retained after abstract and screening of keywords. There were 37 articles that reached the criteria after reading the full texts. Finally, 17 studies were included in this analysis, which engaged 5246 participants; all the studies were RCTs and published from 2000 to 2018.^{27–42} In 11 of the 17 studies (26, 28, 29, 30, 32, 35, 36, 38, 40, 41), given was given for

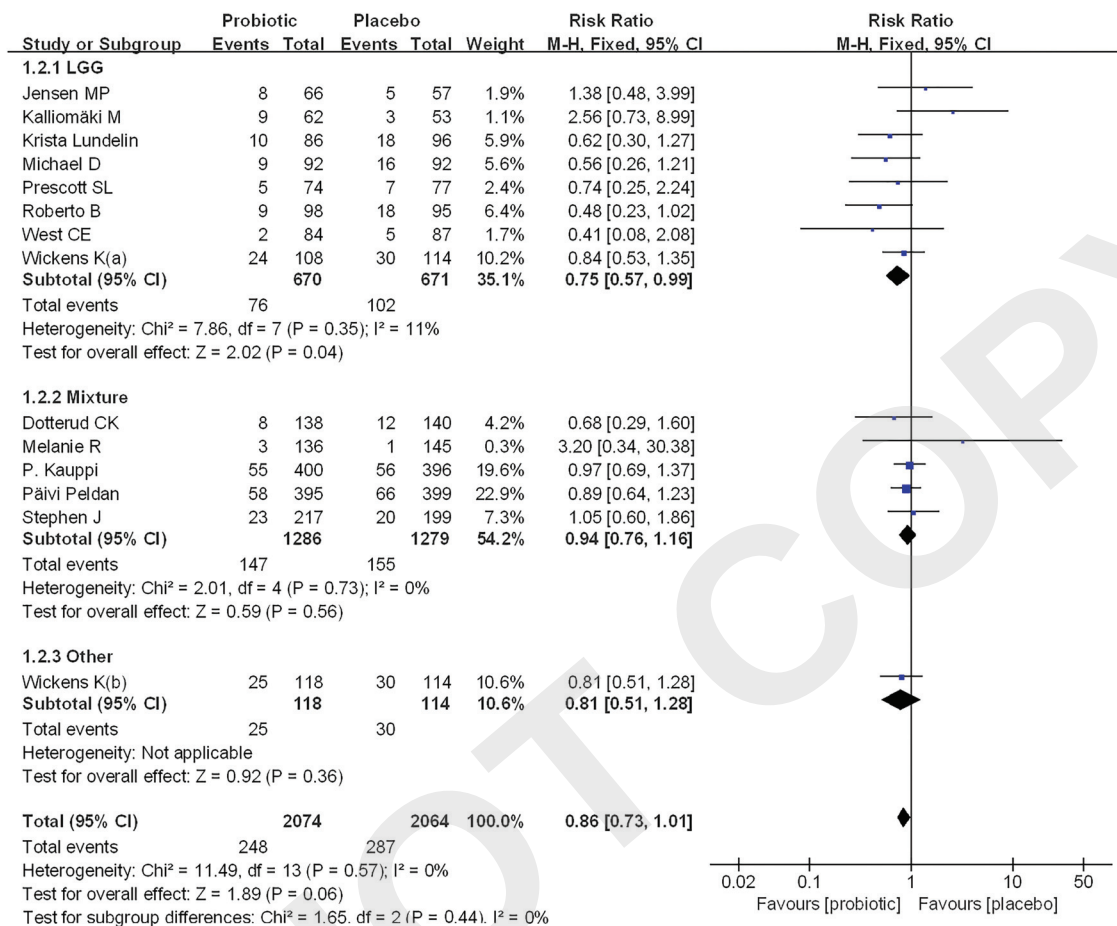


Figure 3. Subgroup analysis of the association between probiotic supplementation and asthma. Forest plot, showing the comparison of probiotic supplementation versus placebo for asthma when using different probiotic strains: (1) mixture, (2) *Lactobacillus rhamnosus* GG (LGG), (3) other probiotics.

both pre- and postnatal period, whereas intervention was given only for postnatal period in the 6 remaining studies (27, 31, 33, 34, 37, 39). There were 14 studies (26–30, 32–35, 38–41) aimed at infants with a high risk of allergy (4516), and 3 studies (31, 36, 37) aimed at children who were not high risk (748). Further details for the included studies are described in Table 1. In addition, a study includes two different cohorts characterized by specific strain (LGG or *Bifidobacterium*).²⁷ Notwithstanding, these cohort studies were included only once in the distinctive investigations (the latest report in each case).

Probiotic Intervention

The detailed probiotic interventions in each study included in our meta-analysis are shown in Table 1. There also were different species of probiotics in these studies. Of the 14 trials (two of them are from the same article), 8 used *Lactobacillus rhamnosus* GG (LGG), 1 used *Bifidobacterium*, and 5 used a mixture (mixture of a variety of probiotics). The daily dose of probiotics ranged from 50 to 100×10^8 CFU. Durations of the

intervention were at least 6 months. The ways of supplementation include adding the suspension to breast milk and infant formula, and adding maltodextrin or insulin into the control group. However, some studies did not give a detailed description of the placebo treatment.

The Primary Outcome

Among the 14 studies^{27,29–35,37,38,40–42}, the data of asthma incidence among 4645 children were included. The results of the meta-analysis are presented in a forest plot (Fig. 3). The pooled data for the risk of developing asthma after probiotic supplementation showed no significant reduction compared with those who received placebo: RR 0.86 (95% CI, 0.73–1.01); $I^2 = 0\%$; $p = 0.06$. However, our pooled analysis did not indicate a significant effect of probiotic supplementation to asthma prevention.

Subgroup Analysis

We predefined subgroups based on the different strain of probiotic used (LGG, mixture, other probiot-

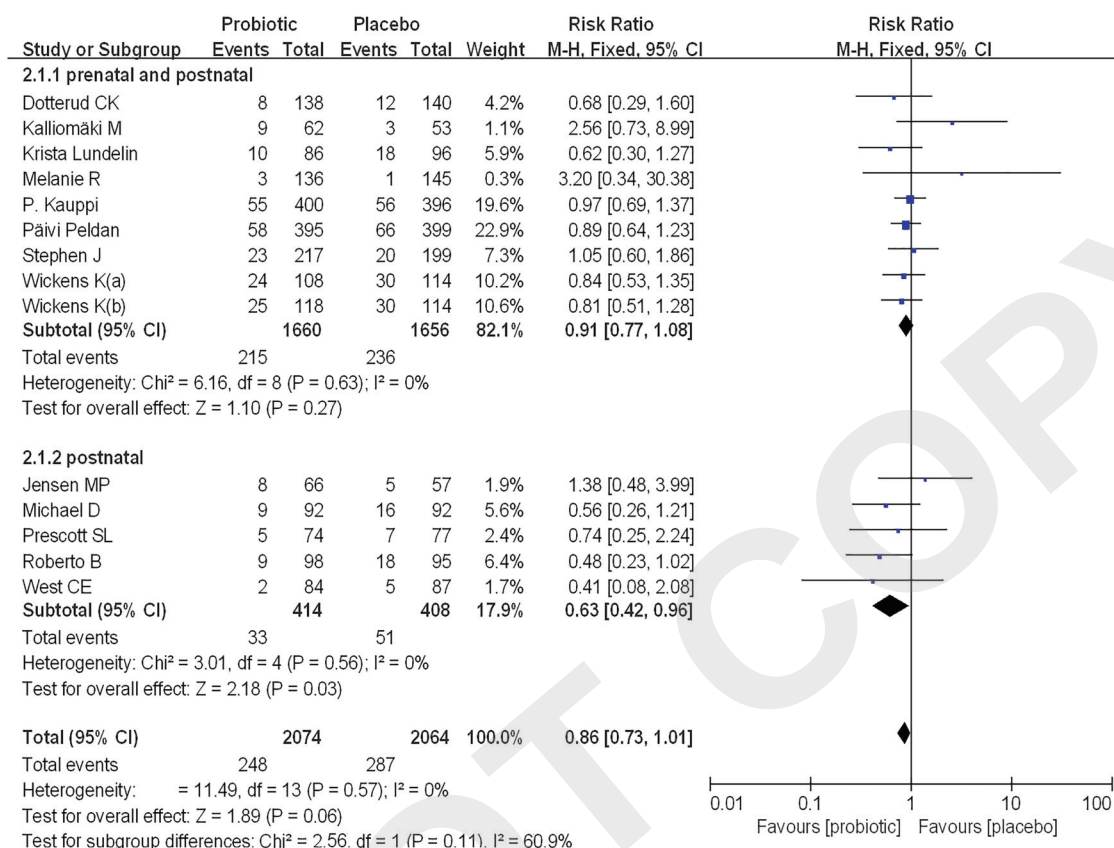


Figure 4. Forest plot, showing the comparison of probiotic supplementation versus placebo for asthma according to the period of intervention: (1) prenatal and postnatal, (2) postnatal.

ics) and the period of interventions (prenatal, postnatal, or both) to assess the efficiency of different subgroup probiotic supplementation on asthma (Figs. 3 and 4). Because the heterogeneity among individual research results was not significant, we used a fixed-effects model to analyze the subgroups. The results showed that there was a difference between the LGG group and placebo group (RR 0.75 [95% CI, 0.57–0.99]; $I^2 = 11\%$; $p = 0.04$). The subgroup of intervention in postnatal period had a similar result (RR 0.63 [95% CI, 0.42–0.96]; $I^2 = 0\%$; $p = 0.03$). However, the evidence was low due to its limited incorporated data. In addition, we conducted a sensitivity analysis of the studies subject to high-risk groups, and the results did not show any statistical difference.

The Secondary Outcomes

Nine studies reported wheeze outcome^{27–29,32,36,37,39,40}, and the pool analysis did not show any significant effect (RR 0.94 [95% CI, 0.51–1.15]; $I^2 = 20\%$; $p = 0.36$). In addition, six articles assessed AR^{27,30,32,37,41} and four were about positive aeroallergen SPT^{32,36,37,40} results. Result did not show that it has significant prophylactic effects of probiotic supplementation on these outcomes (AR: RR 1.03 [95% CI, 0.77–1.39]; $I^2 = 68\%$; $p = 0.83$;

and SPT: RR 0.74 [95% CI, 0.57–1.09]; $I^2 = 0\%$; $p = 0.13$) (Fig. 5).

Study Quality

We used two approaches to assess the quality of inclusion studies. One was the Jadad scale, which is used to rate the quality of each RCT, as shown in Table 1. However, the Jadad scale has a limitation; it ignores the importance of allocation concealment. We then used another approach (the Cochrane Collaboration tool) to illustrate the quality of the RCTs (Fig. 2). Because we could not judge the existence of selective reporting by screening the full texts, all the studies had an unclear risk of bias in this aspect. Apart from this, two studies^{38,39} had a high risk of bias in the aspects of blinding performance and attrition.

Risk of Bias

A funnel plot was used to assess a publication bias of >10 (Fig. 6). We investigated the publication bias of the 14 studies^{27,29–35,37,38,40–42} (studies that only reported second outcomes were not included) in this meta-analysis. The funnel plot did not show any clear asymmetry. There was no evidence of publication bias for our outcome.

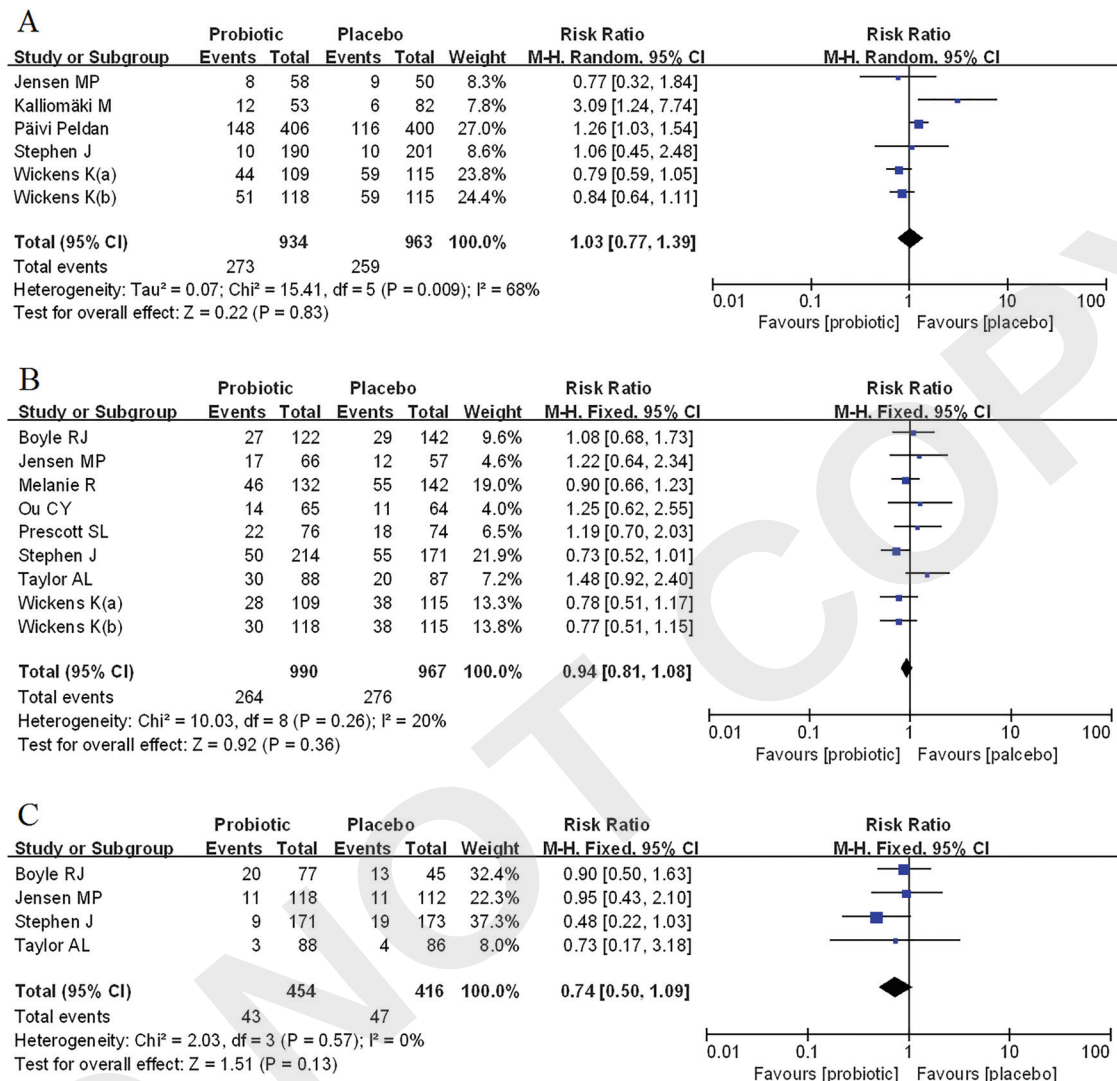


Figure 5. Forest plot, showing the comparison of probiotic supplementation versus placebo for secondary outcomes. (A) Allergic rhinitis. (B) Wheeze. (C) Positive aeroallergen skin-prick test (SPT) result.

DISCUSSION

Despite significant ongoing research, the efficacy of probiotic supplementary therapy for asthma, AR, and wheeze remains unclear. In this work, we conducted a comprehensive search of RCTs in six data bases and eventually summarized 17 studies,^{27–42} which engaged a total of 5246 subjects. Furthermore, we reported the basic characteristics of the selected studies. The available evidence did not verify that the use of probiotics in the pre- and postnatal period helps reduce the incidence of childhood asthma. However, from the subgroup pooled analysis based on the sort of probiotic strains, Subgroup analysis of the comparison of probiotic supplementation versus placebo for asthma when using different probiotic strains showed that the risk of developing asthma was reduced in the LGG treatment group compared with the placebo group. Subgroup analysis by duration time (pre- and postnatal, or post-

natal only) showed that the postnatal-only group had a decrease in asthma occurrence. AR, wheeze, and positive aeroallergen SPT results were measured as secondary outcomes. These results demonstrated that the early administration of probiotics did not reduce these symptoms.

The potential mechanisms of numerous health benefits from probiotic supplementation are manifold. One mechanism is that probiotics can affect the microbial metabolism by modulating the levels of short chain fatty acid (SCFAs). These metabolites have many positive effects, such as downregulating inflammation and improving gut barrier function. Another mechanism is that commensal microbes could communicate with the immune system via pattern recognition receptors, which are expressed on the intestinal epithelial cells and dendritic cells in the gut.⁴³ Notably, results of many studies indicated the hypothesis that probiotics

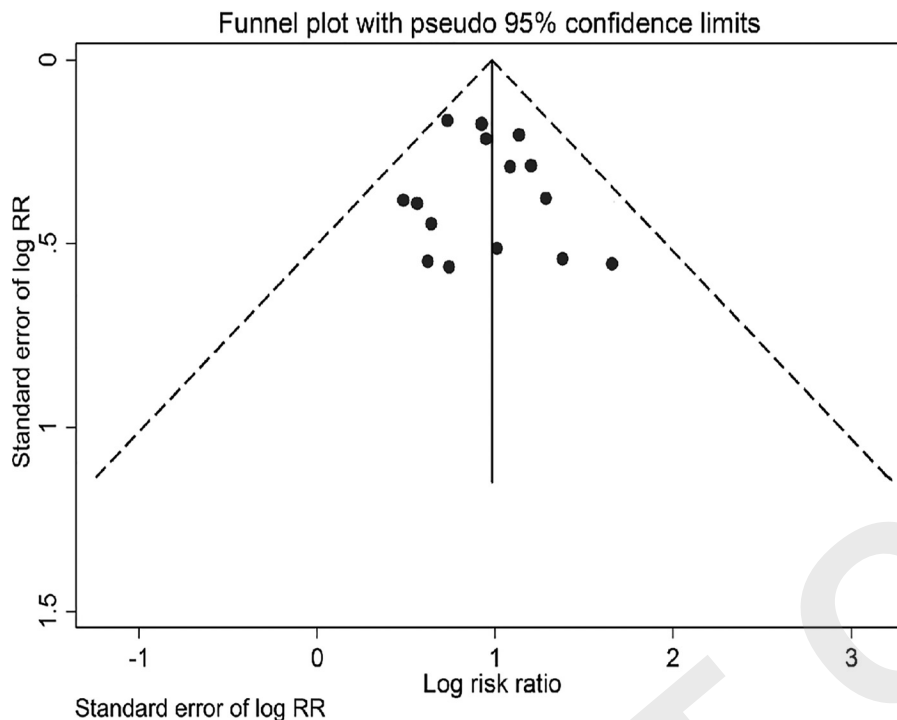


Figure 6. Funnel plots of the meta-analysis of probiotics with asthma.

might be protective for asthma^{16,17,18,22,25}. In the birch pollen-induced mice model, preventive treatment with LGG resulted in a decrease in bronchoalveolar lavage eosinophil counts, lung interleukin 13 and interleukin 5 levels, and airway responsiveness.⁴⁴ Similar results were also reported with other asthma-induction protocols.⁴⁵

Compared with previous studies, The improvement of our analysis is that the studies we included is updated studies with the longer follow-up. Subgroup analysis showed that LGG supplementation facilitates the prevention of asthma. These results illustrated that, depending on specific strain used, the probiotic treatment effects varied. Moreover, probiotics used during the postnatal period can also reduce the risk of asthma. Because the postnatal group studies all belonged to the LGG group, the influence of duration time on probiotic effectiveness is uncertain. Although a previous meta-analysis by Wei *et al.*⁴⁶ did not show a direct association between pre- and postnatal probiotic administration and asthma incidence in infants, whereas there was also no obvious effect of LGG as a specific strain of probiotic on asthma prevention. We believe that this discrepancy was mainly due to the different criterial settings of the included studies.⁴⁶

The systematic reviews of prevention effects of probiotics on allergic diseases was first published in 2007.^{47,48} These reviews demonstrated that probiotic supplementation to infant feeds was not helpful in the prevention of allergic diseases. However, the small sample size may have affected the reliability of results. A later review, published in 2013, showed that prenatal

and/or early-life probiotic administration can reduce the risk of atopic sensitization and lower the total immunoglobulin E level in children.⁴⁹ Other meta-analyses drew a consistent conclusion that probiotic supplementation may be effective to some specific allergic diseases, such as eczema atopic dermatitis or food allergy.^{50–53} The latest report of the World Allergy Organization indicates that probiotic supplementation should be considered for pregnant women or infants at high risk for allergy. Current RCTs also found that the probiotic supplementation in late infancy can reduce the incidence of eczema.⁵⁴ Also, adding probiotics to budesonide could significantly improve quality of life in patients with persistent AR.⁵⁵ However, it remained unclear whether probiotic supplementation could result in reducing the episodes of respiratory allergic disease.

Herein, we conducted a comprehensive search of the latest data bases published before November 2018. There were strengths in our study. First, some articles that were included in a previous review were updated and have a longer follow-up to record the progress of asthma and other respiratory tract allergic diseases and symptoms.^{26,28,29,32,34} Second, we took asthma as the primary outcome and performed further subgroup analysis. Third, we used AR as the secondary outcome in our pooled analysis because there was a connection between AR and asthma in epidemiologic, physiologic, immunopathologic, and common therapeutic approaches.⁵⁶ However, our study had limitations. First, the criteria for judging changes in the clinical outcomes were not completely uniform in the available RCTs; this may have caused the

divergence of data and even the final decision in the meta-analysis. Second, the mixtures used in our included studies had different compositions, which may have induced uncertain heterogeneity in different subgroups.

Conclusion

We showed that probiotic supplementation may reduce the occurrence of asthma. In the subgroup analysis, LGG supplementation had a positive effect on the prevention of asthma. Moreover, there was no significant advantage of probiotic supplements on AR and other respiratory allergic symptoms. However, a larger sample size and well-designed RCTs need to be conducted to evaluate the exact role that probiotics play in the prevention of asthma in the future.

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