



Association between probiotic supplementation and asthma incidence in infants: a meta-analysis of randomized controlled trials

Xiaochen Wei, Ping Jiang, Jiangbo Liu, Rongfei Sun & Liqin Zhu

To cite this article: Xiaochen Wei, Ping Jiang, Jiangbo Liu, Rongfei Sun & Liqin Zhu (2019): Association between probiotic supplementation and asthma incidence in infants: a meta-analysis of randomized controlled trials, Journal of Asthma, DOI: [10.1080/02770903.2018.1561893](https://doi.org/10.1080/02770903.2018.1561893)

To link to this article: <https://doi.org/10.1080/02770903.2018.1561893>



Published online: 18 Jan 2019.



Submit your article to this journal [↗](#)



Article views: 23



View Crossmark data [↗](#)



Association between probiotic supplementation and asthma incidence in infants: a meta-analysis of randomized controlled trials

Xiaochen Wei, MD^a, Ping Jiang, MD, PhD^b, Jiangbo Liu, MD^b, Rongfei Sun, MD, PhD^b, and Liqin Zhu, PhD^a

^aDepartment of Pharmacy, Tianjin First Central Hospital, Tianjin, People's Republic of China; ^bDepartment of Respiration, Tianjin First Central Hospital, Tianjin, People's Republic of China

ABSTRACT

Objective: The increased social and economic burdens for asthma in infants make the prevention of asthma a major public health goal. Probiotics may reduce the risk of asthma in infants. However, randomized controlled trials (RCTs) have shown mixed efficacy outcomes. We performed a meta-analysis of RCTs to investigate whether probiotics are associated with a lower asthma incidence in infants. **Methods:** The PubMed, Cochrane library, and EMBASE databases were systematically searched from the inception dates to August 2018. RCTs comparing the effects of probiotic supplements with a placebo for asthma or wheeze incidence in infants were included. A meta-analysis was performed to calculate risk ratio (RR) and 95% confidence interval (CI) using the Mantel-Haenszel statistical method. **Results:** A total of 19 randomized trials involving 5157 children fulfilled the inclusion criteria. There was no significant association of probiotics with risk of asthma (RR, 0.94 [95% CI, 0.82–1.09]) or wheeze (RR, 0.97 [95% CI, 0.88–1.06]) compared with placebo. Subgroup analysis by asthma risk showed that probiotics significantly reduced wheeze incidence among infants with atopy disease (RR, 0.61 [95% CI, 0.42–0.90]), but no significant associations were found in the other subgroup analyses by participants receiving the intervention, timing of intervention, prevention regimen, probiotic organism, duration of intervention, and duration of follow-up. **Conclusions:** The use of probiotic supplementation compared with placebo was not associated with a lower risk of asthma in infants. These findings do not support recommendation to use probiotics in the prevention of asthma in infants.

ARTICLE HISTORY

Received 5 October 2018
Revised 5 December 2018
Accepted 16 December 2018

KEYWORDS

Probiotic; asthma; wheeze; infant; meta-analysis

Introduction

Asthma is a heterogeneous chronic airway disease very common in childhood, usually characterized by respiratory symptoms including wheeze, breathlessness, chest tightness and cough, together with variable expiratory airflow obstruction [1]. Based on the National Health Interview Survey, the Centers for Disease Control estimated that from 2001 to 2013 the prevalence of asthma increased among children 0–17 years of age in the United States by 0.06% per year reaching 8.91% [2]. Health expenditures for children with asthma are three times higher than for children without asthma [3]. Therefore, today's new parents are faced with the risk that their newborn will be the one out of 10–11 children in the United States diagnosed with asthma [4]. Consequently, newborns today have a high risk of requiring daily medications for years, having to endure numerous visits to doctors

and hospitals, missing an average of 9.2 days of school each year, causing parents to miss work, and having a substantially lower quality of life [5,6].

A revised version of the “hygiene hypothesis” suggests that the pattern of colonization and the diversity of the intestinal microbiota may be an important factor in the increased prevalence of allergic diseases observed over the past several decades [7–9]. Probiotics are defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host [10].” Researchers in recent studies of early probiotic supplementation in infancy have investigated the potential benefit in decreasing the risk of allergic disease. On the basis of the hygiene hypothesis, which suggests that the absence of infectious exposure at a critical point in immune system development could lead to greater risk of allergic disease, it is thought that probiotic exposure could theoretically affect immune system development and

reduce the subsequent risk for the development of allergic disease including asthma [11]. Therefore, the role of probiotics during pregnancy or infancy in the prevention of asthma has received particular scientific interest. Randomized clinical trials (RCTs) using various probiotic species and forms of administration have shown partly conflicting results in the prevention of asthma. In the current study, we performed a meta-analysis of RCTs to assess whether probiotic supplementation during pregnancy or infancy could prevent the occurrence of asthma in infants.

Methods

This meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions [12] and presented based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [13].

Search strategy

We searched the PubMed, Cochrane library, and EMBASE databases for English language publications from the inception dates to August 2018. The search terms were *probiotic*, *infant*, *pediatric*, *newborn*, *asthma*, and *wheeze* with restriction to RCTs designs. Database search was independently performed by two researchers (X.-C.W. and J.-B.L.), and disagreement was resolved by consensus. A manual search was performed for all relevant references including published reviews and meta-analyses. The flow diagram for study selection is shown (Figure 1).

Inclusion criteria

Trials were selected based on the following inclusion criteria: (1) trials enrolled participants with pregnant women or healthy infants who were under 1 year of age at randomization; (2) RCTs comparing probiotics or combined probiotic and prebiotic supplements with a placebo or no intervention group; (3) trials providing asthma or wheeze data; and (4) trials published in the English language. Exclusion criteria were (1) randomized trials without a placebo or treatment group; (2) trials of infants who had been diagnosed asthma by doctors; (3) trials in which supplementation with probiotics or combined probiotics and prebiotics was combined with other medications; and (4) trials in which only prebiotics were used.

Risk-of-bias assessments

Two researchers (X.-C.W. and J.-B.L.) independently assessed the risk of bias of the included RCTs

according to Cochrane risk-of-bias criteria [12], and each quality item was graded as low risk, high risk, or unclear risk. The seven items used to evaluate bias in each trial included the randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Disagreements were resolved by consensus.

Data extraction

Data were extracted using piloted forms, independently and in duplicate by researchers (X.-C.W. and J.-B.L.). The data extracted from each study included first author, year of publication, country of origin, follow-up duration, participant receiving probiotics (mother and/or infant), infant asthma risk (family history, atopic disease (eczema or dermatitis), or cow's milk allergy (CMA)), timing of probiotic supplementation (prenatal and/or postnatal), strain of probiotic administered, dose and duration of supplementation, number of participants and cases in the intervention and control groups and relevant outcomes. The number of infants with asthma was the primary outcome. The secondary outcome was the number of infants with wheeze. Disagreements were resolved by consensus. If the trials had more than two groups or factorial designs and permitted multiple comparisons, we divided them into separate comparison groups. Since the nature of asthma and wheeze can change over time [14], outcome data were extracted for predefined time periods (age ≤ 5 years and >5 years). When a trial reported results for more than one time period, results from the longest follow-up were included in the main meta-analysis; results from earlier time periods were included in subgroup analyses. Data management was performed using Microsoft Excel 2016.

Statistical analysis

Heterogeneity of included studies was assessed with the use of χ^2 test ($p \leq 0.10$ indicating significant heterogeneity) and I^2 test ($I^2 > 50\%$ indicating significant heterogeneity). We calculated the risk ratio (RR) and 95% confidence interval (CI) for asthma incidence and wheeze incidence using the fixed effect model, when there was no significant heterogeneity. Otherwise, a random effect model was chosen. To evaluate whether the association between probiotic supplements and asthma or wheeze was modified by clinical characteristics, we prespecified subgroups based on the participant receiving the intervention

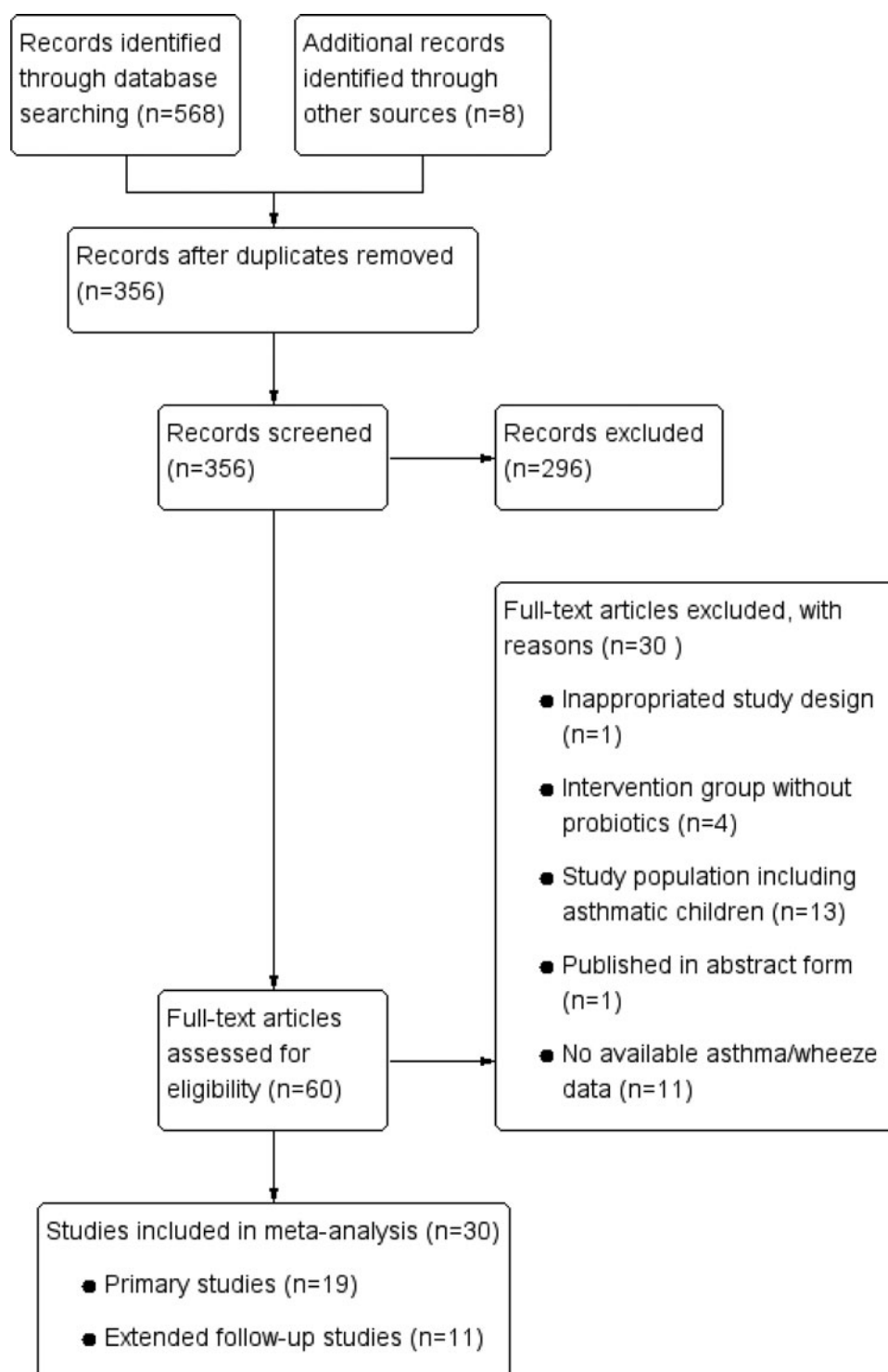


Figure 1. Flow diagram for study selection.

(mother and/or infant), timing of intervention (prenatal and/or postnatal), asthma risk (family history, atopic disease, or CMA), prevention regimen (probiotic and/or prebiotic), probiotic organism (*Lactobacillus* species and/or *Bifidobacterium* species), duration of intervention (≤ 6 months or > 6 months), duration of follow-up or age at assessment (≤ 5 years

or > 5 years). We assessed publication bias by examining funnel plots when the number of trials reporting the primary outcomes was 10 or more [12]. All p values were two-tailed, and statistical significance was defined as $p < 0.05$. All statistical analyses were performed with the use of RevMan version 5.3 (Cochrane Collaboration).

Results

Study characteristics and study populations

The process of literature research and reasons for exclusion are described in Figure 1. A total of 576 articles were obtained from database search. Of the 356 studies reviewed for eligibility, we extracted 60 studies for full-text review. At last, 19 unique trials enrolling a total of 5157 infants were included [15–33]. These trials were represented by 19 primary articles [15–33] and 11 extended follow-up publications [34–44]. These trials were published from 2003 to 2018, and the characteristics of the included trials and participants are summarized in Table 1. Trials were performed mainly in Europe [15,16,19–26,30,31], but also in Asia [27,28], Australia [17,29], New Zealand [32,33], and the United States [18]. One trial exclusively evaluated prenatal maternal supplementation [17], 8 exclusively evaluated postnatal infant supplementation [16,18,20,22,27,29–31], while 10 evaluated a combination of prenatal and postnatal supplementation [15,19,21,23–26,28,32,33]. Sixteen trials evaluated probiotics alone [15–23,25,27–29,31–33], and 3 evaluated probiotics in combination with prebiotics [24,26,30]. Ten trials used *Lactobacillus* species [15–18,23,25,28,29,31,33], one used *Bifidobacterium* species [30], six used probiotic mixtures [19,21,22, 24,26,27], and two used separate *Lactobacillus* species and *Bifidobacterium* species arms compared with 1 placebo group [20,32]. The total duration of intervention ranged from 3 to 24 months except that one trial didn't report [16], and the daily dose of probiotics ranged from 10^8 to 10^{11} colony forming units. Among the included trials, the duration of follow-up ranged from 6 months to 8 years.

Risk of bias and publication bias

Figure 2(A) showed the assessment of the risk of bias in 19 primary studies [15–33]. All primary studies were randomized, double blind, placebo-controlled trials; 16 trials described an adequate random sequence generation process [15–20,22,23,25–27, 29–33]; 14 trials described the methods used for allocation concealment [15,17,19,21–23,25,26,28–33]; and 16 trials described the blinding of outcome assessment [15,17–23,25,26,28–33]. Figure 2(B) showed the assessment of the risk of bias in 11 extended follow-up studies [34–44]. Five trials were at high risk of performance bias due to unblinding of study participants at extended follow-up assessments [34–36,43,44]. The funnel plot was used primarily as an aid for detecting publication bias. Although Figure 3(A) suggested the shapes of funnel plot was seemingly asymmetric, Egger test showed no publication bias for asthma

($p = 0.98$). Figure 3(B) suggested no publication bias was observed with symmetric funnel plot for wheeze that was confirmed by Egger test ($p = 0.38$).

Primary outcome: probiotic supplementation and asthma risk

Thirteen trials including 4021 children compared probiotic supplements with a placebo [16–19,24,27, 34,36,38,39,41,42,44]. Wickens et al. (2013) used separate *L. rhamnosus* HN001 and *B. lactis* HN019 arms compared with one placebo group [44]. Therefore, we divided this trial into two separate comparison groups that were Wickens et al. [44] (*L. rhamnosus* HN001 compared with a placebo) and Wickens et al. [45] (*B. lactis* HN019 compared with a placebo). As shown in Figure 4, there was no significant association of probiotic supplementation with asthma (RR, 0.94 [95% CI, 0.82–1.09]). The subgroup analysis did not show any significant differences within subgroups based on the participant receiving the intervention, timing of intervention, asthma risk, prevention regimen, probiotic organism, duration of intervention or duration of follow-up (Table 2).

Secondary outcomes: probiotic supplementation and wheeze risk

Twelve trials including 2521 children compared results for participants receiving probiotic supplementation versus placebo [17,20,22,25,28,30,33–35,41,42,44]. Gore et al. used separate *L. paracasei* and *B. lactis* arms compared with 1 placebo group [20]. Therefore, we also divided this trial into two separate comparison groups that were Gore et al. (*L. paracasei* compared with a placebo) and Gore et al. (*B. lactis* compared with a placebo). As shown in Figure 5, there was no significant association of probiotic supplementation with wheeze (RR, 0.97 [95% CI, 0.88–1.06]). In subgroup analyses by asthma risk, two trials [20,30] enrolled 225 infants with atopy disease, seven trials [17,25,28,33,34,41,44] enrolled 1795 infants with family history, and one trial [22] enrolled 106 infants with CMA. The results showed probiotic supplementation significantly reduced wheeze incidence among infants with atopy disease (RR, 0.61[95% CI, 0.42–0.90]), but there were no significant associations in infants with family history or CMA. In addition, no significant associations were found in subgroup analyses based on the participant receiving the intervention, timing of intervention, prevention regimen, probiotic organism, duration of intervention or duration of follow-up (Table 2).

Table 1. Characteristics of the included trials and participants.

Included trials	Follow-up (yr)	Participant receiving probiotics	Infant asthma risk	Timing of intervention	Intervention		Added prebiotic	Duration of intervention (mo)		Outcomes	
					Probiotic	Control				Asthma	Wheeze
Abrahamsson et al. [15], 2007 (Sweden)	2	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. reuteri</i> , 1×10^8 , daily ($n = 95$)	Placebo ($n = 93$)	No	13	Yes	Yes	Yes
Abrahamsson et al. [34] ^a , 2013 (Sweden)	7	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. reuteri</i> , 1×10^8 , daily ($n = 94$)	Placebo ($n = 90$)	No	13	Yes	Yes	Yes
Berni Canani et al. [16], 2017 (Italy)	3	Infant	High (CMA)	Postnatal	<i>L. rhamnosus</i> GG ($n = 110$)	Placebo ($n = 110$)	No	NA	Yes	Yes	NA
Boyle et al. [17], 2011 (Australia)	1	Mother	High (family history)	Prenatal	<i>L. rhamnosus</i> GG, 1.8×10^{10} , daily ($n = 125$)	Placebo ($n = 125$)	No	12	Yes	Yes	Yes
Cabana et al. [18], 2017 (United States)	5	Infant	High (family history)	Postnatal	<i>L. rhamnosus</i> GG, 1×10^{10} , daily ($n = 92$)	Placebo ($n = 92$)	No	6	Yes	Yes	NA
Dotterud et al. [19], 2010 (Norway)	2	Mother	Unselected	Prenatal and postnatal	<i>L. rhamnosus</i> GG, 5×10^{10} , <i>B. lactis</i> Bb-12, 5×10^{10} and <i>L. acidophilus</i> La-5, 5×10^9 , daily ($n = 138$)	Placebo ($n = 140$)	No	4	Yes	Yes	NA
Simpson et al. [35] ^a , 2015 (Norway)	6	Mother	Unselected	Prenatal and postnatal	<i>L. rhamnosus</i> GG, 5×10^{10} , <i>B. lactis</i> Bb-12, 5×10^{10} and <i>L. acidophilus</i> La-5, 5×10^9 , daily ($n = 211$)	Placebo ($n = 204$)	No	4	NA	NA	Yes
Gore et al. [20], 2012 (United Kingdom)	3	Infant	High (eczema)	Postnatal	<i>L. paracasei</i> , 1×10^{10} , daily ($n = 45$); <i>B. lactis</i> , 1×10^{10} , daily ($n = 45$)	Placebo ($n = 47$)	No	3	NA	NA	Yes
Niers et al. [21], 2009 (Netherlands)	2	Mother and infant	High (family history)	Prenatal and postnatal	<i>B. bifidum</i> W23, 1×10^9 , <i>B. lactis</i> W52, 1×10^9 and <i>L. lactis</i> W58, 1×10^9 , daily ($n = 50$)	Placebo ($n = 48$)	No	13	NA	NA	NA
Gorissen et al. [36] ^a , 2014 (Netherlands)	6	Mother and infant	High (family history)	Prenatal and postnatal	<i>B. bifidum</i> W23, 1×10^9 , <i>B. lactis</i> W52, 1×10^9 and <i>L. lactis</i> W58, 1×10^9 , daily ($n = 39$)	Placebo ($n = 44$)	No	13	Yes	Yes	NA
Hol et al. [22], 2008 (The Netherlands)	1	Infant	High (CMA)	Postnatal	<i>L. casei</i> , 1×10^7 /g and <i>B. lactis</i> Bb-12, 1×10^7 /g, daily ($n = 59$)	Placebo ($n = 60$)	No	12	NA	NA	Yes
Kalliomäki et al. [23], 2001 (Finland)	2	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. rhamnosus</i> GG, 2×10^{10} , daily ($n = 77$)	Placebo ($n = 82$)	No	6.5–7	Yes	Yes	NA
Kalliomäki et al. [37] ^a , 2003 (Finland)	4	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. rhamnosus</i> GG, 2×10^{10} , daily ($n = 53$)	Placebo ($n = 54$)	No	6.5–7	Yes	Yes	NA
Kalliomäki et al. [38] ^a , 2007 (Finland)	7	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. rhamnosus</i> GG, 2×10^{10} , daily ($n = 53$)	Placebo ($n = 62$)	No	6.5–7	Yes	Yes	NA
Kauppi et al. [24], 2014 (Finland)	5	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. rhamnosus</i> GG, 5×10^9 , <i>B. breve</i> Bbi99, 5×10^9 and <i>Propionibacterium freudenreichii</i> ssp <i>shermanii</i> JS, 2×10^9 , twice daily ($n = 400$)	Placebo ($n = 396$)	Yes	7	Yes	Yes	NA
Kopp et al. [25], 2008 (Germany)	2	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. rhamnosus</i> GG, 5×10^9 , twice daily ($n = 50$)	Placebo ($n = 44$)	No	7	NA	NA	Yes
Kukkonen et al. [26], 2007 (Finland)	5	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. rhamnosus</i> GG, 5×10^9 , <i>L. rhamnosus</i> LC705, 5×10^9 , daily ($n = 400$)	Placebo ($n = 464$)	Yes	7	Yes	Yes	NA

(Continued)

Table 1. Continued.

Included trials	Follow-up (yr)	Participant receiving probiotics	Infant asthma risk	Timing of intervention	Intervention		Added prebiotic	Duration of intervention (mo)	Outcomes	
					Probiotic	Control			Asthma	Wheeze
Kuitunen et al. [39] ^a , 2009 (Finland)	5	Mother and infant	High (family history)	Prenatal and postnatal	<i>B. breve</i> Bb-99, 2×10^8 and <i>Propionibacterium freudenreichii</i> JS, 2×10^9 , twice daily for mothers and daily for infants ($n = 461$) <i>L. rhamnosus</i> GG, 5×10^9 , <i>L. rhamnosus</i> LC705, 5×10^9 , <i>B. breve</i> Bb-99, 2×10^8 and <i>Propionibacterium freudenreichii</i> JS, 2×10^9 , twice daily for mothers and daily for infants ($n = 445$)	Placebo ($n = 446$)	Yes	7	Yes	NA
Loo et al. [27], 2014 (Singapore)	5	Infant	High (family history)	Postnatal	<i>L. rhamnosus</i> LPR, 1×10^7 /g, daily and <i>B. longum</i> BL999, 2×10^7 /g, daily ($n = 124$) <i>L. rhamnosus</i> GG, 1×10^{10} , daily ($n = 95$)	Placebo ($n = 121$)	No	6	Yes	NA
Ou et al. [28], 2012 (Taiwan)	3	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. acidophilus</i> LAVRI-A, 3×10^9 , daily ($n = 89$)	Placebo ($n = 96$)	No	12	NA	Yes
Taylor et al. [29], 2007 (Australia)	0.5~1	Infant	High (family history)	Postnatal	<i>L. acidophilus</i> LAVRI-A, 3×10^9 , daily ($n = 76$)	Placebo ($n = 89$)	No	6	NA	Yes
Prescott et al. [40] ^a , 2008 (Australia)	2.5	Infant	High (family history)	Postnatal	<i>L. acidophilus</i> LAVRI-A, 3×10^9 , daily ($n = 66$)	Placebo ($n = 74$)	No	6	NA	Yes
Jensen et al. [41] ^a , 2012 (Australia)	5	Infant	High (family history)	Postnatal	<i>L. acidophilus</i> LAVRI-A, 3×10^9 , daily ($n = 36$)	Placebo ($n = 57$)	No	6	Yes	Yes
van der Aa et al. [30], 2011 (Netherlands)	1	Infant	High (atopic dermatitis)	Postnatal	<i>B. breve</i> M-16V, 1.3×10^9 /100 ml, daily ($n = 36$)	Placebo ($n = 39$)	Yes	3	NA	Yes
West et al. [31], 2009 (Sweden)	1	Infant	High (family history)	Postnatal	<i>L. paracasei</i> F19, 1×10^8 , daily ($n = 84$)	Placebo ($n = 87$)	No	7	Yes	Yes
West et al. [42] ^a , 2013 (Sweden)	8	Infant	Unselected	Postnatal	<i>L. paracasei</i> F19, 1×10^8 , daily ($n = 59$)	Placebo ($n = 62$)	No	7	Yes	Yes
Wickens et al. [32], 2008 (New Zealand)	2	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. rhamnosus</i> HN001, 6×10^9 , daily ($n = 144$); <i>B. lactis</i> HN019, 9×10^9 , daily ($n = 152$)	Placebo ($n = 150$)	No	24	NA	NA
Wickens et al. [43] ^a , 2012 (New Zealand)	4	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. rhamnosus</i> HN001, 6×10^9 , daily ($n = 136$); <i>B. lactis</i> HN019, 9×10^9 , daily ($n = 146$)	Placebo ($n = 143$)	No	24	NA	NA
Wickens et al. [44] ^a , 2013 (New Zealand)	6	Mother and infant	High (family history)	Prenatal and postnatal	<i>L. rhamnosus</i> HN001, 6×10^9 , daily ($n = 134$); <i>B. lactis</i> HN019, 9×10^9 , daily ($n = 144$)	Placebo ($n = 144$)	No	24	Yes	Yes
Wickens et al. [33], 2018 (New Zealand)	1	Mother	High (family history)	Prenatal and postnatal	<i>L. rhamnosus</i> HN001, 6×10^9 , daily ($n = 206$)	Placebo ($n = 201$)	No	12	NA	Yes

^aIncluded trials represented in italics: extended follow-up trials.*B.*, *Bifidobacterium*; *L.*, *Lactobacillus*; CMA, Cow's milk allergy; NA, not available.

(A)		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
Abrahamsson 2007		+	+	+	+	?	+	?
Berni Canani 2017		+	?	+	?	?	+	+
Boyle 2011		+	+	+	+	+	+	?
Cabana 2017		+	?	+	+	+	+	+
Dotterud 2010		+	+	+	+	+	+	?
Gore 2012		+	?	+	+	+	+	+
Hol 2008		+	+	+	+	?	?	+
Kalliomäki 2001		+	+	+	+	+	+	?
Kauppi 2014		?	?	+	?	?	+	+
Kopp 2008		+	+	+	+	?	+	?
Kuitunen 2007		+	+	+	+	+	+	+
Loo 2014		+	?	+	?	+	+	+
Niers 2009		?	+	+	+	?	+	+
Ou 2012		?	+	+	+	+	+	?
Taylor 2007		+	+	+	+	?	+	+
van der Aa 2011		+	+	+	+	+	+	?
West 2009		+	+	+	+	+	+	+
Wickens 2008		+	+	+	+	+	+	?
Wickens 2018		+	+	+	+	+	+	?

(B)		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
Abrahamsson 2013		+	+	-	-	?	+	?
Gorissen 2014		?	+	-	+	?	+	+
Jensen 2012		+	+	+	+	?	+	+
Kalliomäki 2003		+	+	+	+	+	+	?
Kalliomäki 2007		+	+	+	+	+	+	?
Kuitunen 2009		+	+	+	+	+	+	+
Prescott 2008		+	+	+	+	?	+	+
Simpson 2015		+	+	-	+	+	+	+
West 2013		+	+	+	+	+	+	+
Wickens 2012		+	+	-	+	+	+	?
Wickens 2013		+	+	-	+	+	+	?

Figure 2. Risk of bias summary with the following: (A) primary studies; (B) extended follow-up studies. Green dots (+), red dots (-), and yellow dots (?), respectively, indicate the items that were low risk of bias, high risk of bias, and unclear the risk of bias.

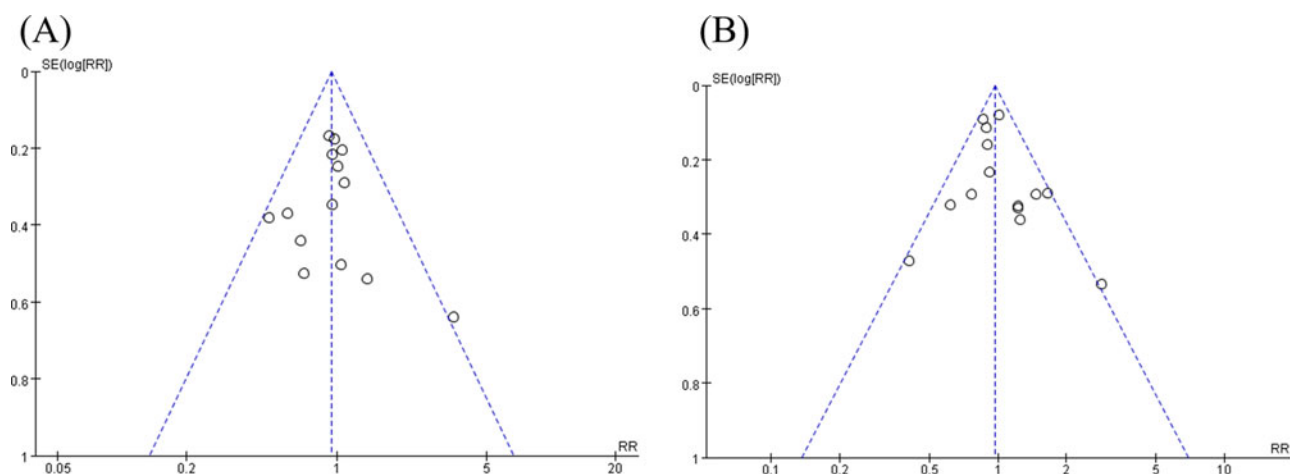


Figure 3. Funnel plots of the meta-analysis of probiotics with the following: (A) asthma; (B) wheeze.

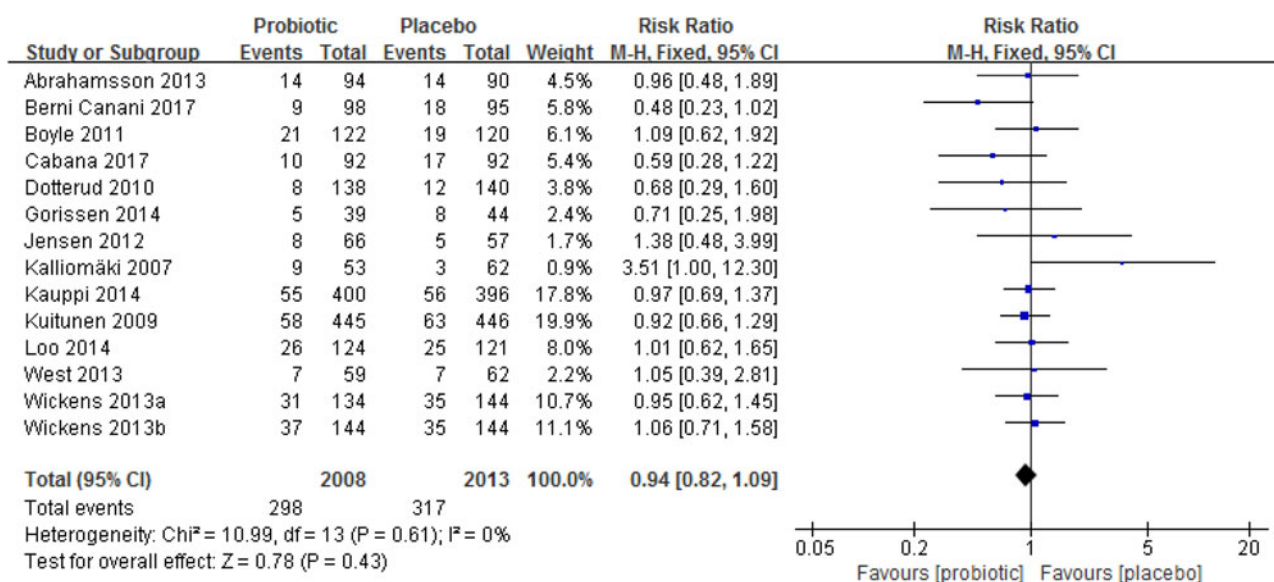


Figure 4. Meta-analysis results of probiotic supplementation for the incidence of asthma.

Discussion

Results of this meta-analysis showed that probiotic supplementation during pregnancy or early life was not significantly associated with a lower incidence of asthma or wheeze in infants. These results were consistent with the systematic review and meta-analysis performed by Azad MB et al. in 2013 [45], although our analysis evaluated updated long-term findings from these five original trials [34–36,42,44], and adds results from five new trials reporting on probiotic supplements for asthma or wheeze prevention [16,18,24,27,33]. In addition, there were no differences based on the participant receiving the intervention, timing of intervention, asthma risk (family history or CMA), prevention regimen, probiotic organism, duration of intervention or duration of follow-up, but the decrease in the risk of wheeze was significant only

when probiotic supplements were administered among infants with atopy disease.

Most of the previous clinical trials reported investigating the prevention of asthma/wheeze with probiotic supplementation focused on high-risk infants with allergic parents or siblings, while few clinical trials paid close attention to high-risk infants with atopy disease. In our meta-analysis, there were only two trials [20,30] performing the research on the preventive efficacy of probiotic supplements in infants with atopy disease. One trial [20] investigated the preventive effects of the probiotics *Lactobacillus paracasei* or *Bifidobacterium lactis* on infants with eczema at age 3–6 months. The other trial [30] assessed the effects of early intervention with synbiotics (*Bifidobacterium breve* M-16V and fructooligosaccharide) on infants with atopic dermatitis at age <7 months.

Table 2. Subgroup analysis of association between probiotic supplementation and asthma/wheeze in infants.

Subgroup		No. studies ^a	No. participants		RR (95% CI)	I ² (%)
			Events	Total		
Asthma (primary outcome)						
Participant receiving intervention						
Mother + infant		6 [24, 34, 36, 38, 39, 44]	423	2635	0.99 (0.83–1.18)	0
Mother		2 [17, 19]	60	520	0.93 (0.58–1.49)	0
Infant		5 [16, 18, 27, 41, 42]	132	866	0.81 (0.59–1.11)	13
Timing of intervention						
Prenatal and postnatal		7 [19, 24, 34, 36, 38, 39, 44]	443	2913	0.97 (0.82–1.15)	0
Prenatal		1 [17]	40	242	1.09 (0.62–1.92)	-
Postnatal		5 [16, 18, 27, 41, 42]	132	866	0.81 (0.59–1.11)	13
Asthma risk						
High (family history)		11 [17, 18, 24, 27, 31, 34, 36, 38, 39, 41, 44]	561	3537	0.97 (0.84–1.13)	0
High (infants with CMA)		1 [16]	27	193	0.48 (0.23–1.02)	-
Unselected		1 [19]	20	278	0.68 (0.29–1.60)	0
Prevention regimen						
Probiotic alone		11 [16–19, 27, 34, 36, 38, 41, 42, 44]	383	2334	0.94 (0.79–1.13)	0
Probiotic + prebiotic		2 [24, 39]	232	1687	0.95 (0.74–1.20)	0
Probiotic organism						
Lactobacillus species		8 [16–18, 34, 38, 41, 42, 44]	227	1440	0.93 (0.74–1.19)	28
Bifidobacterium species		1 [44]	72	288	1.06 (0.71–1.58)	-
Combination		5 [19, 24, 27, 36, 39]	316	2293	0.93 (0.76–1.14)	0
Duration of intervention						
≤6 mo		5 [17–19, 27, 41]	151	1072	0.91 (0.68–1.23)	0
>6 mo		7 [24, 34, 36, 38, 39, 42, 44]	437	2756	0.99 (0.84–1.18)	0
Not reported		1 [16]	27	193	0.48 (0.23–1.02)	-
Follow-up duration ^b						
≤5 yr		8 [15–17, 19, 31, 37, 39, 41]	249	2193	0.86 (0.68–1.09)	0
>5 yr		9 [18, 24, 27, 34–36, 38, 42, 44]	398	2575	0.99 (0.83–1.19)	0
Wheeze (secondary outcome)						
Participant receiving intervention						
Mother + infant		4 [25, 28, 34, 44]	467	1028	1.02 (0.83–1.25)	45
Mother		3 [17, 33, 35]	329	918	0.90 (0.76–1.06)	0
Infant		5 [20, 22, 30, 41, 42]	174	575	0.96 (0.64–1.43)	58
Timing of intervention						
Prenatal and postnatal		6 [25, 28, 33–35, 44]	740	1704	0.95 (0.84–1.08)	21
Prenatal		1 [17]	56	242	0.92 (0.58–1.45)	-
Postnatal		5 [20, 22, 30, 41, 42]	174	575	0.96 (0.64–1.43)	58
Asthma risk						
High (family history)		7 [17, 25, 28, 33, 34, 41, 44]	724	1795	0.98 (0.88–1.08)	14
High (infants with atopic disease)		2 [20, 30]	76	225	0.61 (0.42–0.90)*	0
High (infants with CMA)		1 [22]	33	106	1.46 (0.82–2.60)	-
Unselected		2 [35, 42]	137	395	1.16 (0.64–2.09)	71
Prevention regimen						
Probiotic alone		11 [17, 20, 22, 25, 28, 33–35, 41, 42, 44]	952	2447	0.98 (0.89–1.08)	27
Probiotic + prebiotic		1 [30]	18	74	0.41 (0.16–1.02)	-
Probiotic organism						
Lactobacillus species		9 [17, 20, 25, 28, 33, 34, 41, 42, 44]	586	1680	1.01 (0.84–1.21)	34
Bifidobacterium species		3 [20, 30, 44]	250	461	0.72 (0.41–1.24)	67
Combination		2 [22, 35]	134	380	1.08 (0.68–1.71)	53
Duration of intervention						
≤6 mo		6 [17, 20, 22, 30, 35, 41]	295	970	0.89 (0.74–1.08)	26
>6 mo		6 [25, 28, 33, 34, 42, 44]	675	1551	1.00 (0.90–1.11)	46
Follow-up duration ^b						
≤5 yr		9 [15, 17, 20, 22, 25, 28, 30, 33, 41]	440	1509	0.96 (0.82–1.12)	35
>5 yr		4 [34, 35, 42, 44]	562	1200	0.98 (0.87–1.09)	33

^aBoth Refs. 20 and 44 had two intervention groups, we divided them into separate comparison groups.

^bWith regard to subgroup analysis of follow-up duration, based on the number and duration of follow-up assessments, some trials contributed data to more than one predefined subgroup. For all other subgroup analyses, the longest available follow-up data from each trial were used.

* $p < 0.05$.

CMA, cow's milk allergy.

Unfortunately, there was the only incidence of wheeze data reported in the two trials [20,30], while no incidence of asthma data. Therefore, we pooled the wheeze data and then found the positive result that early-life administration of probiotics may protect against wheeze in infants with atopy disease. In view of the small sample size in this subgroup analysis, the

result should be interpreted with caution. Future powerful trials are needed to confirm if infants with atopy disease could be most likely to benefit from probiotics.

In addition, note that properties of different probiotic species vary and can be strain-specific [46]. For example, Lyons et al. [47] found probiotic

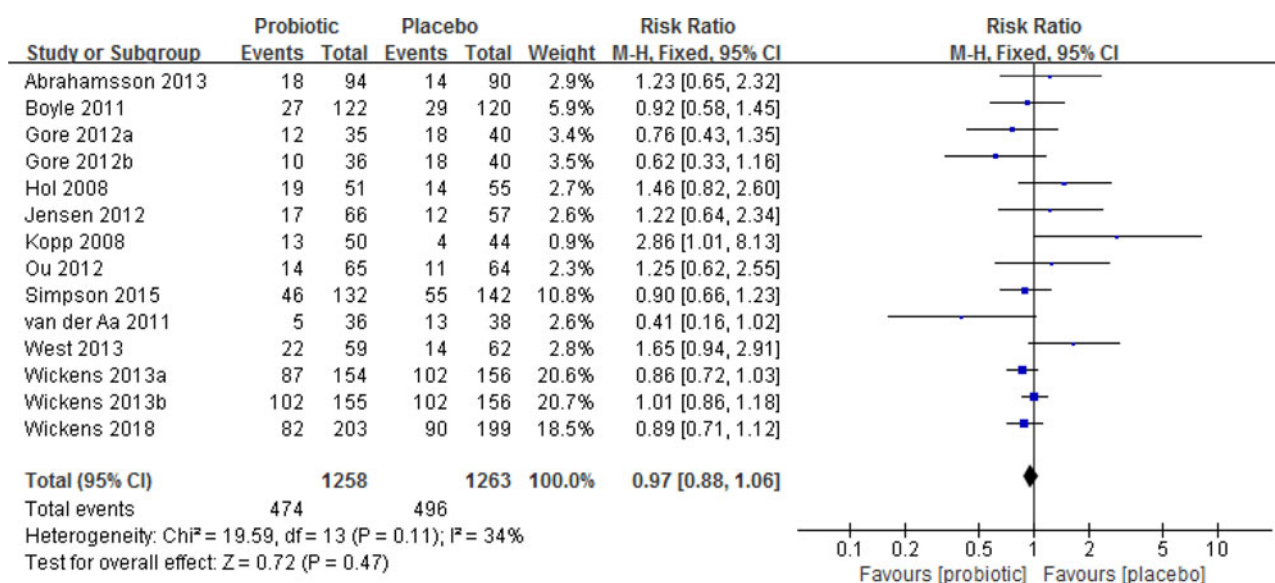


Figure 5. Meta-analysis results of probiotic supplementation for the incidence of wheeze.

strain-specific induction of Foxp3+ T regulatory cells in murine allergy models. Lee et al. [48] reported that four *Lactobacillus* species had markedly different immunomodulatory effects in animal experiments. Moreover, strain-specific effects have been observed in clinical studies. For example, *Lactobacillus salivarius* and *Lactobacillus fermentum* were effective, while *Lactobacillus plantarum* had no effect against allergy [49]. Therefore, it should be important to confirm which strains were most likely effective in preventing asthma and wheeze. However, because of the large variety of strains, combinations, and doses administered, the efficacy of specific probiotic strains was difficult to evaluate. Our subgroup analyses based on probiotic organisms did not find any valuable results. We speculated that the lack of efficacy of probiotics in reducing the risk of asthma and wheeze might be due to clinical diversity in the use of strains. A recent allergic asthma animal study indicated that the preventive treatment with *Lactobacillus rhamnosus* GG, but not *Lactobacillus rhamnosus* GR-1, resulted in a significant decrease in bronchoalveolar lavage eosinophil counts, lung interleukin-13 and interleukin-5 levels, and airway hyperreactivity [50]. Similarly, another animal study showed that *Lactobacillus reuteri*, but not *Lactobacillus salivarius*, was able to attenuate antigen-induced airway eosinophil influx, local cytokine responses, and hyperresponsiveness to methacholine [51]. In addition, Hougee et al. reported *Bifidobacterium breve* M-16V has strain-dependent immunomodulatory effects and was more effective than several other *Bifidobacterium* and *Lactobacillus* strains [52]. Therefore, further study should be needed

to optimize the selection of probiotic species and the design of intervention regimens.

There are several potential limitations to our study. First, population characteristics, probiotic regimens, and duration of follow-up were variable in each included study, which may produce confound bias for the evaluation of probiotics benefits in preventing asthma and wheeze in early-life children. Second, significant heterogeneity, which may decrease the strength of our estimates, was observed in some subgroup analyses of wheeze. Third, subgroup analyses were susceptible to type II errors due to relatively small sample sizes. Fourth, some RCTs were of poor quality and, for example, assessed unblinding of study participants at extended follow-up, which may lead to high risk of performance bias.

Conclusions

In this meta-analysis of randomized clinical trials, the use of probiotic supplements during pregnancy or infancy compared with placebo was not associated with a lower risk of asthma in infants. These findings do not support recommendation to use probiotics in the prevention of asthma in infants.

Funding

No funding was received for this study.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Tesse R, Borrelli G, Mongelli G, Mastroiilli V, Cardinale F. Treating pediatric asthma according guidelines. *Front Pediatr* 2018;6:234.
2. Akinbami LJ, Simon AE, Schoendorf KC. Trends in allergy prevalence among children aged 0-17 years by asthma status, United States, 2001-2013. *J Asthma* 2016;53:356-362. doi:10.3109/02770903.2015.1126848
3. Bryant-Stephens T. Asthma disparities in urban environments. *J Allergy Clin Immunol* 2009;123:1199-1206.
4. Johnson CC, Ownby DR. The infant gut bacterial microbiota and risk of pediatric asthma and allergic diseases. *Transl Res* 2017;179:60-70.
5. Moonie SA, Sterling DA, Figgs L, Castro M. Asthma status and severity affects missed school days. *J Sch Health* 2006;76:18-24.
6. Clarke SA, Calam R. The effectiveness of psychosocial interventions designed to improve health related quality of life (HRQOL) amongst asthmatic children and their families: a systematic review. *Qual Life Res* 2012;21:747-764. doi:10.1007/s11136-011-9996-2
7. Rautava S, Ruuskanen O, Ouwehand A, Salminen S, Isolauri E. The hygiene hypothesis of atopic disease-an extended version. *J Pediatr Gastroenterol Nutr* 2004;38:378-388. doi:10.1097/00005176-200404000-00004
8. Wold AE. The hygiene hypothesis revised: is the rising frequency of allergy due to changes in the intestinal flora? *Allergy* 1998;53:20-25.
9. Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach J-F, La Vecchia C, et al. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. *Epidemiology* 2012;23:402-414.
10. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 2014;11:506-514.
11. Noverr MC, Huffnagle GB. The 'microflora hypothesis' of allergic diseases. *Clin Exp Allergy* 2005;35:1511-1520.
12. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions*, version 5.1.0 (updated March 2011). Cochrane Collaboration website. Available from: <http://training.cochrane.org/handbook>. 2011.
13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, Clarke M, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700. doi:10.1136/bmj.b2700
14. Herzog R, Cunningham-Rundles S. Pediatric asthma: natural history, assessment, and treatment. *Mt Sinai J Med* 2011;78:645-660.
15. Abrahamsson TR, Jakobsson T, Böttcher MF, Fredrikson M, Jenmalm MC, Björkstén B, Oldaeus G, et al. Probiotics in prevention of IgE-associated eczema: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2007;119:1174-1180. doi:10.1016/j.jaci.2007.01.007
16. Berni Canani R, Di Costanzo M, Bedogni G, Amoroso A, Cosenza L, Di Scala C, Granata V, et al. Extensively hydrolyzed casein formula containing *Lactobacillus rhamnosus* GG reduces the occurrence of other allergic manifestations in children with cow's milk allergy: 3-year randomized controlled trial. *J Allergy Clin Immunol* 2017;139:1906-1913.
17. Boyle RJ, Ismail IH, Kivivuori S, Licciardi PV, Robins-Browne RM, Mah L-J, Axelrad C, et al. *Lactobacillus* GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial. *Allergy* 2011;66:509-516.
18. Cabana MD, McKean M, Caughey AB, Fong L, Lynch S, Wong A, et al. Early probiotic supplementation for eczema and asthma prevention: a randomized controlled trial. *Pediatrics* 2017;140:1-9.
19. Dotterud CK, Storror O, Johnsen R, Oien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. *Br J Dermatol* 2010;163:616-623. doi:10.1111/j.1365-2133.2010.09889.x
20. Gore C, Custovic A, Tannock GW, Munro K, Kerry G, Johnson K, Peterson C, et al. Treatment and secondary prevention effects of the probiotics *Lactobacillus paracasei* or *Bifidobacterium lactis* on early infant eczema: randomized controlled trial with follow-up until age 3 years. *Clin Exp Allergy* 2012;42:112-122.
21. Niers L, Martín R, Rijkers G, Sengers F, Timmerman H, van Uden N, Smidt H, et al. The effects of selected probiotic strains on the development of eczema (the PandA study). *Allergy* 2009;64:1349-1358.
22. Hol J, van Leer EHG, Elink Schuurman BEE, de Ruiter LF, Samsom JN, Hop W, Neijens HJ, et al. The acquisition of tolerance toward cow's milk through probiotic supplementation: a randomized, controlled trial. *J Allergy Clin Immunol* 2008;121:1448-1454. doi:10.1016/j.jaci.2008.03.018
23. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;357:1076-1079. doi:10.1016/S0140-6736(00)04259-8
24. Kauppi PK, Kuokkanen MK, Kukkonen KK, Laitinen TH, Kuitunen MK. Interaction of NPSR1 genotypes and probiotics in the manifestation of atopic eczema in early childhood. *Allergol Immunopathol (Madr)* 2014;42:560-567.
25. Kopp MV, Hennemuth I, Heinzmann A, Urbanek R. Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of *Lactobacillus* GG supplementation. *Pediatrics* 2008;121:e850-e856.
26. Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2007;119:192-198. doi:10.1016/j.jaci.2006.09.009
27. Loo EX, Llanora GV, Lu Q, Aw MM, Lee BW, Shek LP. Supplementation with probiotics in the first 6 months of life did not protect against eczema and allergy in at-risk Asian infants: a 5-year follow-up. *Int Arch Allergy Immunol* 2014;163:25-28.

28. Ou C-Y, Kuo H-C, Wang L, Hsu T-Y, Chuang H, Liu C-A, Chang J-C, et al. Prenatal and postnatal probiotics reduces maternal but not childhood allergic diseases: a randomized, double-blind, placebo-controlled trial. *Clin Exp Allergy* 2012;42:1386–1396. doi:[10.1111/j.1365-2222.2012.04037.x](https://doi.org/10.1111/j.1365-2222.2012.04037.x)
29. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2007;119:184–191. doi:[10.1016/j.jaci.2006.08.036](https://doi.org/10.1016/j.jaci.2006.08.036)
30. van der Aa LB, van Aalderen WMC, Heymans HSA, Henk Sillevius Smitt J, Nauta AJ, Knippels LMJ, Ben Amor K, et al. Synbiotics prevent asthma-like symptoms in infants with atopic dermatitis. *Allergy* 2011;66:170–177.
31. West CE, Hammarström ML, Hernell O. Probiotics during weaning reduce the incidence of eczema. *Pediatr Allergy Immunol* 2009;20:430–437. doi:[10.1111/j.1399-3038.2009.00745.x](https://doi.org/10.1111/j.1399-3038.2009.00745.x)
32. Wickens K, Black PN, Stanley TV, Mitchell E, Fitzharris P, Tannock GW, Purdie G, et al. A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2008;122:788–794. doi:[10.1016/j.jaci.2008.07.011](https://doi.org/10.1016/j.jaci.2008.07.011)
33. Wickens K, Barthow C, Mitchell EA, Stanley TV, Purdie G, Rowden J, Kang J, et al. Maternal supplementation alone with *Lactobacillus rhamnosus* HN001 during pregnancy and breastfeeding does not reduce infant eczema. *Pediatr Allergy Immunol* 2018;29:296–302.
34. Abrahamsson TR, Jakobsson T, Björkstén B, Oldaeus G, Jenmalm MC. No effect of probiotics on respiratory allergies: a seven-year follow-up of a randomized controlled trial in infancy. *Pediatr Allergy Immunol* 2013;24:556–561. doi:[10.1111/pai.12104](https://doi.org/10.1111/pai.12104)
35. Simpson MR, Dotterud CK, Storø O, Johnsen R, Øien T. Perinatal probiotic supplementation in the prevention of allergy related disease: 6 year follow up of a randomised controlled trial. *BMC Dermatol* 2015;15:13.
36. Gorissen DMW, Rutten NBMM, Oostermeijer CMJ, Niers LEM, Hoekstra MO, Rijkers GT, van der Ent CK, et al. Preventive effects of selected probiotic strains on the development of asthma and allergic rhinitis in childhood. The Panda study. *Clin Exp Allergy* 2014;44:1431–1433. doi:[10.1111/cea.12413](https://doi.org/10.1111/cea.12413)
37. Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003;361:1869–1871. doi:[10.1016/S0140-6736\(03\)13490-3](https://doi.org/10.1016/S0140-6736(03)13490-3)
38. Kalliomäki M, Salminen S, Poussa T, Isolauri E. Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in a randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2007;119:1019–1021. doi:[10.1016/j.jaci.2006.12.608](https://doi.org/10.1016/j.jaci.2006.12.608)
39. Kuitunen M, Kukkonen K, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Haahtela T, et al. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *J Allergy Clin Immunol* 2009;123:335–341.
40. Prescott SL, Wiltschut J, Taylor A, Westcott L, Jung W, Currie H, Dunstan JA, et al. Early markers of allergic disease in a primary prevention study using probiotics: 2.5-year follow-up phase. *Allergy* 2008;63:1481–1490. doi:[10.1111/j.1398-9995.2008.01778.x](https://doi.org/10.1111/j.1398-9995.2008.01778.x)
41. Jensen MP, Meldrum S, Taylor AL, Dunstan JA, Prescott SL. Early probiotic supplementation for allergy prevention: long-term outcomes. *J Allergy Clin Immunol* 2012;130:1209–1211. doi:[10.1016/j.jaci.2012.07.018](https://doi.org/10.1016/j.jaci.2012.07.018)
42. West CE, Hammarström ML, Hernell O. Probiotics in primary prevention of allergic disease—follow-up at 8–9 years of age. *Allergy* 2013;68:1015–1020.
43. Wickens K, Black P, Stanley TV, Mitchell E, Barthow C, Fitzharris P, Purdie G, et al. A protective effect of *Lactobacillus rhamnosus* HN001 against eczema in the first 2 years of life persists to age 4 years. *Clin Exp Allergy* 2012;42:1071–1079. doi:[10.1111/j.1365-2222.2012.03975.x](https://doi.org/10.1111/j.1365-2222.2012.03975.x)
44. Wickens K, Stanley TV, Mitchell EA, Barthow C, Fitzharris P, Purdie G, Siebers R, et al. Early supplementation with *Lactobacillus rhamnosus* HN001 reduces eczema prevalence to 6 years: does it also reduce atopic sensitization? *Clin Exp Allergy* 2013;43:1048–1057.
45. Azad MB, Coneys JG, Kozyrskyj AL, Field CJ, Ramsey CD, Becker AB, Friesen C, et al. Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: systematic review and meta-analysis. *BMJ* 2013;347:f6471.
46. Boyle RJ, Robins-Browne RM, Tang ML. Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr* 2006;83:1256–1264.
47. Lyons A, O'Mahony D, O'Brien F, MacSharry J, Sheil B, Ceddia M, et al. Bacterial strain-specific induction of Foxp3+ T regulatory cells is protective in murine allergy models. *Clin Exp Allergy* 2010;40:811–819.
48. Lee J, Bang J, Woo HJ. Immunomodulatory and anti-allergic effects of orally administered *Lactobacillus* species in ovalbumin-sensitized mice. *J Microbiol Biotechnol* 2013;23:724–730. doi:[10.4014/jmb.1211.11079](https://doi.org/10.4014/jmb.1211.11079)
49. Huang R, Ning H, Shen M, Li J, Zhang J, Chen X. Probiotics for the treatment of atopic dermatitis in children: a systematic review and meta-analysis of randomized controlled trials. *Front Cell Infect Microbiol* 2017;7:392.
50. Spacova I, Petrova MI, Fremau A, Pollaris L, Vanoirbeek J, Ceuppens JL, et al. Intranasal administration of probiotic *Lactobacillus rhamnosus* GG prevents birch pollen-induced allergic asthma in a murine model. *Allergy* 2018. [Epub ahead of print]. doi:[10.1111/all.13502](https://doi.org/10.1111/all.13502)
51. Forsythe P, Inman MD, Bienenstock J. Oral treatment with live *Lactobacillus reuteri* inhibits the allergic airway response in mice. *Am J Respir Crit Care Med* 2007;175:561–569. doi:[10.1164/rccm.200606-821OC](https://doi.org/10.1164/rccm.200606-821OC)
52. Hougee S, Vriesema AJM, Wijering SC, Knippels LMJ, Folkerts G, Nijkamp FP, Knol J, et al. Oral treatment with probiotics reduces allergic symptoms in ovalbumin-sensitized mice: a bacterial strain comparative study. *Int Arch Allergy Immunol* 2010;151:107–117. doi:[10.1159/000236000](https://doi.org/10.1159/000236000)