

Probiotics for Prevention of Atopy and Food Hypersensitivity in Early Childhood

A PRISMA-Compliant Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract: Most studies investigated probiotics on food hypersensitivity, not on oral food challenge confirmed food allergy in children. The authors systematically reviewed the literature to investigate whether probiotic supplementation prenatally and/or postnatally could reduce the risk of atopy and food hypersensitivity in young children.

PubMed, Embase, the Cochrane Central Register of Controlled Trials, and 4 main Chinese literature databases (Wan Fang, VIP, China National Knowledge Infrastructure, and SinoMed) were searched for randomized controlled trials regarding the effect of probiotics on the prevention of allergy in children. The last search was conducted on July 11, 2015.

Seventeen trials involving 2947 infants were included. The first follow-up studies were analyzed. Pooled analysis indicated that probiotics administered prenatally and postnatally could reduce the risk of atopy (relative risk [RR] 0.78; 95% confidence interval [CI] 0.66–0.92; $I^2 = 0\%$), especially when administered prenatally to pregnant mother and postnatally to child (RR 0.71; 95% CI 0.57–0.89; $I^2 = 0\%$), and the risk of food hypersensitivity (RR 0.77; 95% CI 0.61–0.98; $I^2 = 0\%$). When probiotics were administered either only prenatally or only postnatally, no effects of probiotics on atopy and food hypersensitivity were observed.

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Probiotics administered prenatally and postnatally appears to be a feasible way to prevent atopy and food hypersensitivity in young children. The long-term effects of probiotics, however, remain to be defined in the follow-up of existing trials. Still, studies on probiotics and confirmed food allergy, rather than surrogate measure of food hypersensitivity, are warranted.

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Abbreviations: CI = confidence interval, Ig = immunoglobulin, IL = interleukin, RCT = randomized controlled trial, RR = relative risk, SPT = skin prick test, Th1 = lymphocyte T helper 1, Th2 = lymphocyte T helper 2.

INTRODUCTION

Over the last few decades, there has been a sharp rise in the global prevalence of allergic diseases, such as asthma, eczema, and allergic rhinitis.^{1,2} At present, it is estimated that 1 in 5 persons worldwide would be affected by some form of allergic diseases.³ Atopic disorders can have significant effects on morbidity and quality of life and can be costly in terms of medical visits and treatments, which therefore prompts considerable interest in generating efficient approaches for the prevention of allergic disorders.

The hygiene hypothesis proposed by Strachan in 1989,⁴ suggested that increased cleanliness, reduced family size, and decreased childhood infections could explain the increasing prevalence of allergic diseases.⁵ In the light of such a conception, a gut flora hypothesis has been formulated,⁶ suggesting that alterations in the gut microbiota, the most massive source of microbial exposure and a critical source of early immune stimulation, may underlie the atopic epidemic. In this perspective, supplementing microbes using probiotics, defined as “live microorganisms which, when administered in adequate amounts, confer a health benefit to the host” by the World Health Organization,⁷ seems an attractive way to prevent allergic disorders. Several experimental and observational studies have emphasized in the maintenance of normal gut microbes and development of atopic disorders.^{8–11} Biologic mechanisms with respect to the protective role of probiotics in atopy remain unclear, but are plausible through reduced exposure to allergens by improved epithelial barrier function and immunoregulation to prevent immunoglobulin (Ig) E sensitization.¹²

Several studies were designed to examine the efficacy of probiotics in the prevention of allergic disorders in the last decade. Studies on atopic sensitization and food hypersensitivity, however, conveyed conflicting results. Moreover, because

of small sample sizes, these reports were underpowered to detect the effect of probiotics on atopy or food hypersensitivity. Thus, to provide the latest and most convincing evidence, we performed a meta-analysis of randomized controlled trials (RCTs) to assess whether probiotic supplementation during pregnancy and/or infancy could reduce the risk of atopy or food hypersensitivity in young children.

METHODS

This systematic review and meta-analysis was conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement,¹³ and the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.¹⁴ Because our study was a review of previous published studies, ethical approval or patient consent was not required.

Literature Search and Selection Criteria

In July 2015, we performed a systematic literature search in PubMed, Embase, and the Cochrane Central Register of Controlled Trials for RCTs evaluating the effects of probiotic supplementation on allergic diseases in children. We also searched ClinicalTrials.gov (<https://clinicaltrials.gov/>), European Union Clinical Trials Register (<https://www.clinicaltrials-register.eu/>), and 4 main Chinese literature databases, that is, Wan Fang, VIP, China National Knowledge Infrastructure, and SinoMed. The last search was conducted on July 11, 2015. In all databases, we used the following keywords: “probiotic”, “probiotics”, “food allergy”, “food hypersensitivity”, “atopy”, “allergy”, “immunoglobulin”, “IgE”, “sensitization”, or “eczema”. The search was restricted to clinical trials conducted in humans. No language restriction was imposed. The search strategy is shown in Table 1. We also manually checked the references of the retrieved articles and previous reviews to identify additional eligible studies. Two review team members (G-QZ and H-JH) independently conducted the initial search, deleted duplicate records, screened the titles and abstracts for relevance, checked the reference lists of all records of interest for other pertinent publication, and identified as excluded or requiring further assessment. Then, we reviewed the full-text articles for inclusion. Abstracts and unpublished studies were not included.

We developed a PICOS (Patient, Intervention, Comparators, Outcome, and Study design) approach as the eligibility criteria: 1) Population: children in whom outcome assessment performed during infancy or childhood (ie, up to 12 years of age), without atopic diseases at the time of probiotic administration; 2) Intervention: any species/strains/doses regimen of live probiotics administered prenatally and/or postnatally within the first year of life; 3) Comparators: placebo or no probiotics;

4) Outcome: the primary outcome was atopic sensitization, and the secondary outcome was food sensitization. Sensitization was defined as a positive result on a skin prick test (SPT) and/or elevated specific IgE (>0.35 kU/L) to any allergen, food allergens, or aeroallergens; 5) Study design: only RCTs. We excluded interventions other than live probiotics, administration of probiotics with prebiotics, and those focused on treatment of atopic diseases. When studies used the same population, the earliest publication was included in the meta-analysis, because of lower dropout rates and an end point more similar to other studies. Discrepancies regarding study inclusion between review team members were resolved through discussion with a third reviewer (Z-YL), as required.

Data Extraction and Quality Assessment

Data extraction was performed by H-JH and confirmed independently by G-QZ. The following information were extracted from each study: source (first author), intervention period (prenatal and/or postnatal), number of participants in the intervention and control groups, strains/doses/duration of probiotics administered, control group, outcomes (atopic sensitization or food sensitization), definition of sensitization, and end of follow-up. When data were separately reported on positive SPT and elevated IgE, data on positive SPT were selected. Extracted data were entered into a standardized Word file. Disagreement was further checked on the original articles, and was resolved. The Cochrane Risk of Bias Tool was adopted to assess the risk of bias for each RCT.¹⁵

Statistical Analysis

To evaluate the effects of probiotics, we calculated relative risks (RRs) for the development of sensitization between intervention and control groups. When trials investigated 2 separate probiotic groups versus placebo, data on the 2 probiotic groups were combined into a single RR, which we included in the meta-analysis. Heterogeneity across studies was tested by using the I^2 statistic. Studies with an I^2 value greater than 50% were considered to have significant heterogeneity.¹⁶ The Mantel-Haenszel method with random effects model was used to calculate pooled RRs and 95% confidence intervals (CIs). Subgroup analyses were conducted according to intervention subject, duration of intervention, probiotic dose, probiotic organism, end of follow-up, risk of allergic diseases, caesarean delivery rate, geographical area, and risk of bias. An assessment of publication bias was performed by visually inspecting funnel plot and by using the Begg's and Egger's tests.^{17,18} A P value less than 0.05 was considered as statistically significant, except where otherwise specified. All the statistical analyses were performed using the Stata 12.0 (Stata Corporation, College Station, TX) and RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Figure 1 shows a flow diagram for selection of articles. A total of 1352 articles were identified by the initial databases search. Total 235 articles were excluded for duplicates. By examining the titles and abstracts, an additional 1091 articles were excluded as irrelevant (reviews, letters, animal studies, or treatment of atopic diseases). The remaining 26 full-text articles were retained for further consideration, and 9 studies^{19–27} were excluded because they were extended follow-up publications. Finally, the remaining 17 trials were included in the meta-analysis.^{28–44}

TABLE 1. Search Strategy

Search terms
1. Probiotic or probiotics
2. Food allergy, or food hypersensitivity, or atopy, or allergy, or immunoglobulin, or IgE, or sensitization, or eczema
3. Human
4. Child: birth-18 years
5. 1, 2, 3, and 4

IgE = immunoglobulin E.

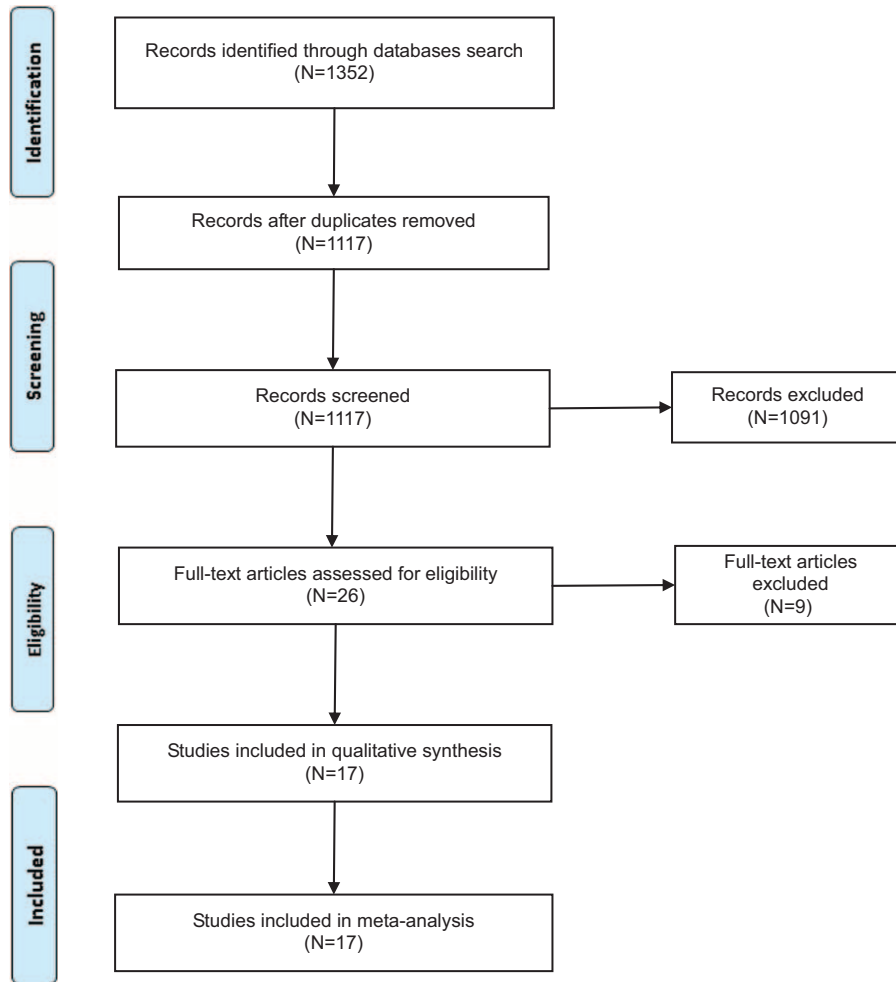


FIGURE 1. Selection process for the studies included in the meta-analysis.

Characteristics of Included Studies

The main characteristics of included studies are described in Table 2. Studies that were included were published between 2001 and 2014. All trials were randomized, double-blinded, and placebo-controlled. Ten trials were conducted in Europe,^{28,30–33,36,37,39,42,43} 4 in Asia,^{35,38,41,44} 2 in Australia,^{34,40} and 1 in New Zealand.²⁹ Based on family history, 12 trials enrolled participants at high risk for allergy,^{29–32,34–41} and the remaining 5 were conducted in unselected populations. Probiotics were administered prenatally in 1 trial,³⁴ prenatally to pregnant mothers and postnatally to mothers or directly to children in 12 trials,^{28–32,35–37,39,41,42,44} and only postnatally to infants in 4 trials.^{33,38,40,43} Seven trials used *Lactobacillus*,^{30,34,36,39–41,43} 1 trial used *Bifidobacterium*,⁴⁴ and 8 trials used probiotic mixtures.^{28,31–33,35,37,38,42} Wickens et al²⁹ used separate *Lactobacillus* and *Bifidobacterium* arms compared with 1 placebo group. All the included studies reported data on probiotics for the prevention of atopic sensitization, and 9 studies for food sensitization.^{29,33–35,37–40,44} Atopic sensitization was defined as positive SPT and/or elevated IgE to any allergen in all included studies, except that 2 trials^{33,35} tested only for food allergens and 1³⁶ tested only for inhalant allergens. The end of follow-up varied from 1 year of age,^{32–35,38,40,43} to

2 years of age,^{28–31,36,37,39,42,44} to 3 years of age.⁴¹ Eight trials were adjudicated to be of unclear risk of bias,^{28,30,32–35,38,44} 5 at high risk of bias,^{37,39–42} and 4 trials were considered to have low risk of bias across all domains,^{29,31,36,43} shown in Table 3.

Atopic Sensitization

Seventeen trials including 2947 children contributed atopic sensitization data for meta-analysis, shown in Figure 2. Overall, there was no significant effect of probiotic supplementation on the risk of atopic sensitization (RR 0.89, 95% CI 0.77–1.03, $I^2 = 9\%$). Significantly beneficial effects were observed when probiotics were administered both prenatally and postnatally (RR 0.78, 95% CI 0.66–0.92, $I^2 = 0\%$), but not when administered only prenatally to pregnant mother (RR 1.00, 95% CI 0.68–1.48) or only postnatally to infant (RR 1.36, 95% CI 1.00–1.86, $I^2 = 0\%$). There was no evidence of significant publication bias by inspection of the funnel plot and formal statistical tests (Egger’s test, $P = 0.988$; Begg’s test, $P = 0.773$; Figure 3).

Subgroup Analysis

Table 4 reports the pooled RRs for probiotic supplementation prenatally and postnatally in the prevention of atopic

TABLE 2. Characteristics of Included Studies

Source	Intervention Period	Experimental/Control	Probiotics Group*			Outcomes	Definition of Sensitization	End of Follow-up
			Strains, Doses, and Duration	Control Group	Strains, Doses, and Duration			
Allen ²⁸	Prenatal and postnatal	220/234 (mixed)	A mixture of <i>L. salivarius</i> , <i>L. paracasei</i> , <i>B. animalis</i> , and <i>B. bifidum</i> , 1 × 10 ¹⁰ CFU/d, from 36 wk gestation to delivery (mother), then from birth to age 6 mo (child)	Placebo	Atopy	Positive SPT	2 y of age	
Wickens ²⁹	Prenatal and postnatal	170/171/171 (high risk)	<i>L. rhamnosus</i> 6 × 10 ⁹ CFU/d, or <i>B. animalis</i> 9 × 10 ⁹ CFU/d, from 35 wk gestation to 6 mo if breastfeeding (mother), then from birth to 2 y (child)	Placebo	Atopy and food sensitization	Positive SPT	2 y of age	
Kalliomaeki ³⁰	Prenatal and postnatal	77/82 (high risk)	<i>L. rhamnosus</i> GG, 2 × 10 ¹⁰ CFU/d, from 2 to 4 wk before expected delivery (mother) to 6 mo of children through breastfeeding or directly to child	Placebo	Atopy	Positive SPT	2 y of age	
Rautava ³¹	Prenatal and postnatal	81/82/78 (high risk)	A mixture of <i>L. rhamnosus</i> and <i>B. longum</i> or a mixture of <i>L. paracasei</i> and <i>B. longum</i> , 2 × 10 ⁹ CFU/d, starting 2 mo before delivery and during the first 2 mo of breastfeeding (mother)	Placebo	Atopy	Positive SPT	2 y of age	
Huurre ³²	Prenatal and postnatal	72/68 (high risk)	A mixture of <i>L. rhamnosus</i> GG and <i>B. lactis</i> , 2 × 10 ¹⁰ CFU/d, from the first trimester of pregnancy to the end of exclusive breastfeeding (mother)	Placebo	Atopy	Positive SPT	1 y of age	
Rautava ³³	Postnatal	38/43 (mixed)	A mixture of <i>L. rhamnosus</i> GG and <i>B. lactis</i> , 2 × 10 ¹⁰ CFU/d, from starting artificial feeding to 12 mo	Placebo	Atopy	Positive SPT	1 y of age	
Boyle ³⁴	Prenatal	125/125 (high risk)	<i>L. rhamnosus</i> GG, 1.8 × 10 ¹⁰ CFU/d, from 36 wk gestation to delivery	Placebo	Atopy and food sensitization	Positive SPT	1 y of age	
Kim ³⁵	Prenatal and postnatal	57/55 (high risk)	A mixture of <i>B. bifidum</i> , <i>B. lactis</i> , and <i>L. acidophilus</i> , 4.8 × 10 ⁹ CFU/d, from 8 wk before delivery to 3 mo after delivery (mother), then from 4 to 6 mo of age (child)	Placebo	Atopy	Circulating IgE ≥ 0.35 kU/L	1 y of age	
Kopp ³⁶	Prenatal and postnatal	54/51 (high risk)	<i>L. rhamnosus</i> GG, 1 × 10 ¹⁰ CFU/d, from 4 to 6 wk before delivery to 3 mo after delivery (mother), then from 4 to 6 mo of age (child)	Placebo	Atopy	Inhalant allergen-specific IgE	2 y of age	
Niers ³⁷	Prenatal and postnatal	78/78 (high risk)	A mixture of <i>B. bifidum</i> , <i>B. lactis</i> , and <i>Lactococcus lactis</i> , 3 × 10 ⁹ CFU/d, from 6 wk before term to delivery (mother), then from birth to 12 mo of age (child)	Placebo	Atopy and food sensitization	Positive SPT	2 y of age	
Soh ³⁸	Postnatal	127/126 (high risk)	A mixture of <i>B. longum</i> and <i>L. rhamnosus</i> , at least 2.8 × 10 ⁸ CFU/d, from birth to 6 mo of life (child)	Placebo	Atopy and food sensitization	Positive SPT	1 y of age	
Abrahamsson ³⁹	Prenatal and postnatal	117/115 (high risk)	<i>L. reuteri</i> , 1 × 10 ⁹ CFU/d, from 4 wk before term to delivery (mother), then from birth to 12 mo of age (child)	Placebo	Atopy and food sensitization	Positive SPT, circulating IgE > 0.35 kU/L	2 y of age	
Taylor ⁴⁰	Postnatal	115/111 (high risk)	<i>L. acidophilus</i> , 3 × 10 ⁹ CFU/d, from birth to 6 mo of age (child)	Placebo	Atopy and food sensitization	Positive SPT	1 y of age	
Ou ⁴¹	Prenatal and postnatal	95/96 (high risk)	<i>L. rhamnosus</i> GG, 1 × 10 ¹⁰ CFU/d, from second trimester of pregnancy (mother) to 6 mo of children, through breastfeeding or directly to child	Placebo	Atopy	Circulating IgE > 0.7 kU/L	3 y of age	
Dotterud ⁴²	Prenatal and postnatal	211/204 (mixed)	A mixture of <i>L. rhamnosus</i> GG, <i>L. acidophilus</i> , and <i>B. animalis</i> , 1.05 × 10 ¹¹ CFU/d, from 36 wk of gestation to 3 mo postnatally during breastfeeding (mother)	Placebo	Atopy	Positive SPT	2 y of age	
West ⁴³	Postnatal	89/90 (mixed)	<i>L. paracasei</i> , 1 × 10 ⁸ CFU/d, from 4 to 13 mo (child)	Placebo	Atopy	Circulating IgE > 0.35 kU/L	13 mo of age	
Wu ⁴⁴	Prenatal and postnatal	36/36 (mixed)	<i>B. bifidum</i> , 1.5 × 10 ⁸ CFU/d, from 36 wk of gestation to the end of exclusive breastfeeding (mother)	Placebo	Atopy and food sensitization	Circulating IgE	2 y of age	

CFU = colony-forming unit, IgE = immunoglobulin E, SPT = skin prick test.
* *L* = *Lactobacillus*, *B* = *Bifidobacterium*.

TABLE 3. Risk-of-Bias Assessment of the Included Randomized Controlled Trials*

Study	Adequate Sequence Generation?	Allocation Concealment?	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data?	Selective Reporting?	Other Bias?	Overall Risk of Bias
Allen ²⁸	Yes	Yes	Yes	Yes	Unclear	No	No	Unclear
Wickens ²⁹	Yes	Yes	Yes	Yes	No	No	No	Low
Kalliomaki ³⁰	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Unclear
Rautava ³¹	Yes	Yes	Yes	Yes	No	No	No	Low
Huurre ³²	Yes	Unclear	Yes	Yes	No	No	No	Unclear
Rautava ³³	Yes	Unclear	Unclear	Yes	No	Unclear	Unclear	Unclear
Boyle ³⁴	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Unclear
Kim ³⁵	Yes	Unclear	Yes	Yes	No	No	No	Unclear
Kopp ³⁶	Yes	Yes	Yes	Yes	No	No	No	Low
Niers ³⁷	Unclear	Yes	Yes	Yes	Yes	No	No	High
Soh ³⁸	Yes	Unclear	Yes	Yes	No	No	No	Unclear
Abrahamsson ³⁹	Yes	Yes	Yes	Yes	Yes	No	No	High
Taylor ⁴⁰	Yes	Yes	Yes	Yes	Yes	No	No	High
Ou ⁴¹	Unclear	Yes	Yes	Yes	Yes	Unclear	No	High
Dotterud ⁴²	Yes	Yes	Yes	Yes	Yes	No	No	High
West ⁴³	Yes	Yes	Yes	Yes	No	No	No	Low
Wu ⁴⁴	Yes	Unclear	Yes	Yes	No	Unclear	Unclear	Unclear

* Risk of bias was assessed with use of the Cochrane risk-of-bias tool.

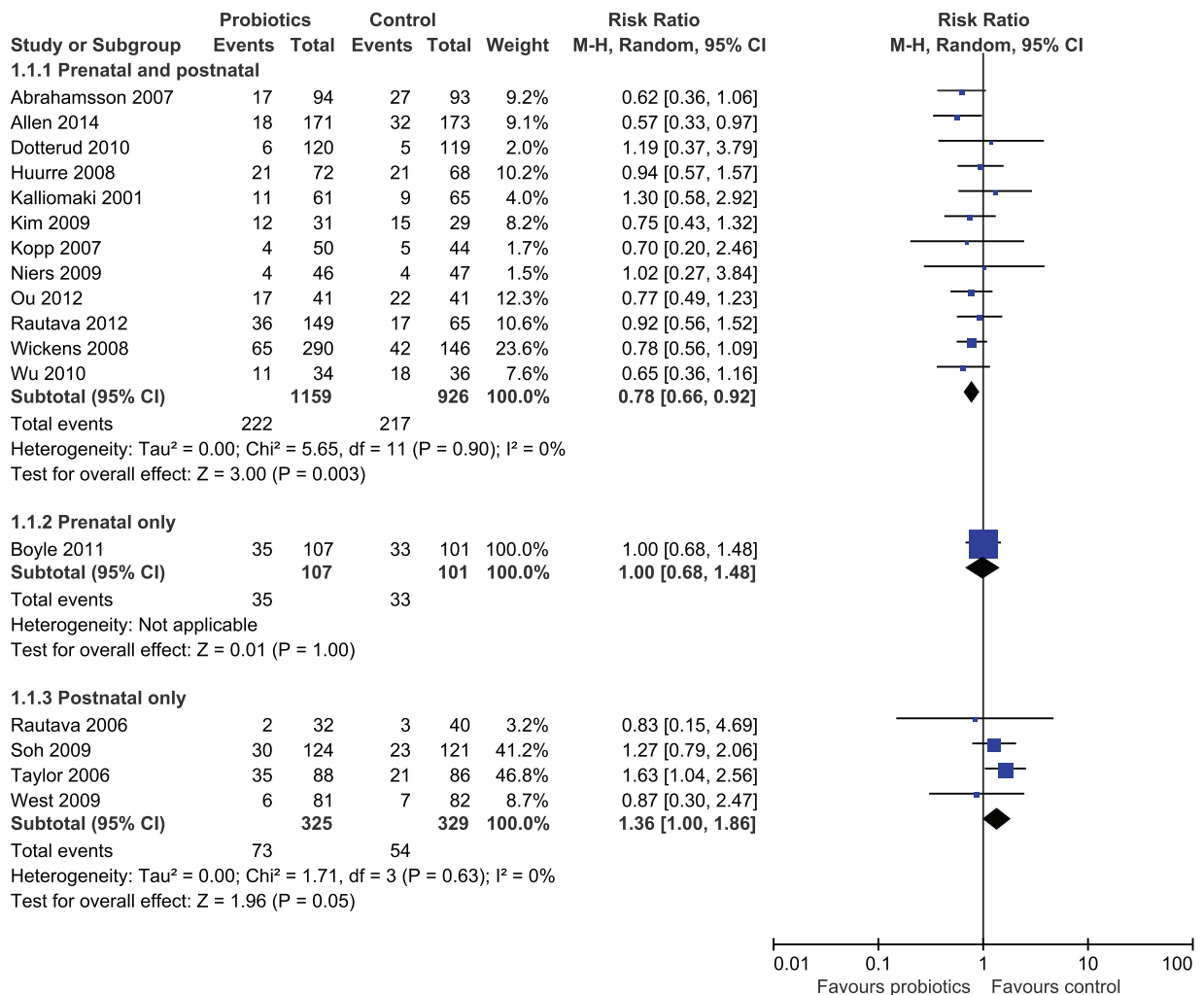


FIGURE 2. Effect of probiotic supplementation on atopic sensitization.

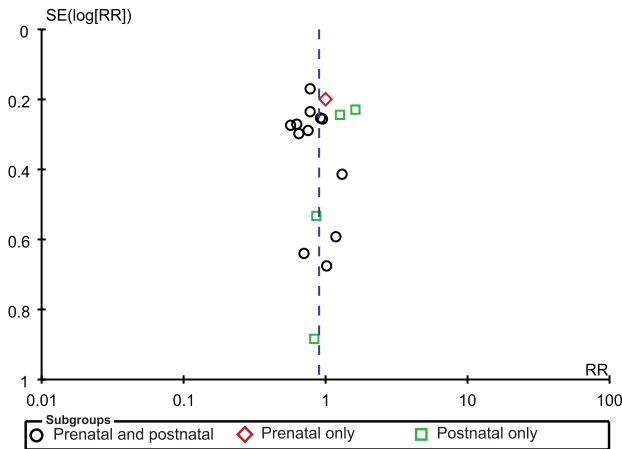


FIGURE 3. Funnel plot of trials on probiotics and prevention of atopic sensitization.

sensitization in predefined subgroups. The results were consistent in most subgroups. Significant differences were observed according to intervention subject (mother only, or mother and child), duration of intervention (≤ 6 or > 6 months), and caesarean delivery rate ($\leq 19\%$ or $> 19\%$).

Food Sensitization

Nine trials including 1506 children contributed food sensitization data for meta-analysis, shown in Figure 4. Overall, there was no significant effect of probiotics on the risk of food sensitization (RR 0.92, 95% CI 0.75–1.12, $I^2 = 7\%$). Significantly beneficial effects were observed when probiotics were administered both prenatally and postnatally (RR 0.77, 95% CI 0.61–0.98, $I^2 = 0\%$), but not when administered only prenatally to pregnant mother (RR 1.01, 95% CI 0.66–1.55) or only postnatally to infant (RR 1.43, 95% CI 0.94–2.18, $I^2 = 0\%$). There was no evidence of significant publication bias by inspection of the funnel plot and formal statistical tests (Egger’s test, $P = 0.806$; Begg’s test, $P = 0.917$; Figure 5).

DISCUSSION

The results of our meta-analysis indicate that probiotics administered prenatally and postnatally is effective in reducing the risk of atopy, particularly in families at high risk for allergy, and the risk of food hypersensitivity in young children. According to subgroup analyses, probiotics administered to both mother and child, or longer duration of intervention may be more effective in preventing atopy. In addition, cesarean-delivered children might particularly benefit from probiotic administration.

Several mechanisms might explain such an effect. First, colonizing the mother prenatally by supplementing probiotics, favorable bacteria could be transferred to the infant during birth. In addition, immunomodulation of the mother and changes in her breast milk composition could benefit the infant with respect to allergy development.⁴⁵ Second, the gut is the most massive source of postnatal microbial exposure and a critical source of early immune stimulation,⁴⁶ and probiotic supplementation early in life may modulate the maturation of the immune response.^{12,47} Differences in the gut microbiota composition have been observed before the development of allergic symptoms in several studies.⁴⁶ The underlying mechanisms whereby probiotics prevent atopy might include producing a shift of the lymphocyte T helper 1 (Th1)/lymphocyte T helper 2

TABLE 4. Subgroup Analyses for Probiotic Supplementation Prenatally and Postnatally in the Prevention of Atopic Sensitization

Subgroup	Number of Studies	RR (95% CI)	I^2 (%)
All studies	12	0.78 (0.66, 0.92)	0
Intervention subject*			
Mother only	4	0.86 (0.64, 1.16)	0
Mother and child	6	0.71 (0.57, 0.89)	0
Duration of intervention, mo			
≤ 6	3	0.83 (0.58, 1.19)	0
> 6	9	0.77 (0.64, 0.92)	0
Probiotic dose			
$< 1 \times 10^{10}$	6	0.76 (0.62, 0.93)	0
$\geq 1 \times 10^{10}$	6	0.81 (0.63, 1.05)	0
Probiotic organism†			
<i>Lactobacillus</i> species	5	0.76 (0.59, 0.97)	0
<i>Bifidobacterium</i> species	2	0.76 (0.55, 1.05)	0
Mixture	6	0.81 (0.63, 1.05)	0
End of follow-up, mo			
Children ≤ 12	2	0.85 (0.58, 1.24)	0
Children > 12	10	0.76 (0.64, 0.92)	0
Risk of allergic diseases‡			
High	10	0.80 (0.67, 0.95)	0
Unselected	3	0.65 (0.45, 0.94)	0
Caesarean delivery rate			
\leq Median (19%)	4	0.83 (0.62, 1.11)	0
$>$ Median	4	0.72 (0.56, 0.92)	0
Not reported	4	0.82 (0.60, 1.13)	0
Geographic area			
Europe/Oceania	9	0.80 (0.66, 0.97)	0
Asia	3	0.73 (0.54, 0.99)	0
Risk of bias			
Low or unclear	8	0.79 (0.66, 0.95)	0
High	4	0.75 (0.54, 1.04)	0

All RRs were calculated using random-effects models.

CI = confidence interval, RR = relative risk.

* Two studies (Kalliomaki 2001 and Ou 2012) were excluded because it included 2 subgroups (ie, after delivery, breastfeeding mothers could decide to take probiotic/placebo themselves or to give it to the child), but did not provide their separate data.

† One trial (Wickens 2008) compared *Lactobacillus* with *Bifidobacterium* in separate groups.

‡ Nine studies enrolled only subjects with family history of allergic diseases, 1 trial (Allen 2014) had subjects of both subgroups and provided separate information, and 1 trial (Dotterud 2010) had subjects of both subgroups, but did not provide separate information.

(Th2) balance toward a Th1 response and a consequent decreased secretion of Th2 cytokines, such as interleukin (IL)-4, IL-5, and IL-13, as well as decreased IgE, and increased production of C-reactive protein and IgA.⁴⁵

In our study, no effects of postnatal probiotic supplementation (direct to child), however, were observed, which implied that prenatal supplementation may be a more important factor in conferring these benefits. Only 1 study³⁴ used solely prenatal supplementation, and no significant effect was observed between groups. Therefore, whether antenatal supplementation alone could account for such significant differences, or still needs to be further followed by stimulation of the infant’s gut immune system (probiotics administered preferably directly to

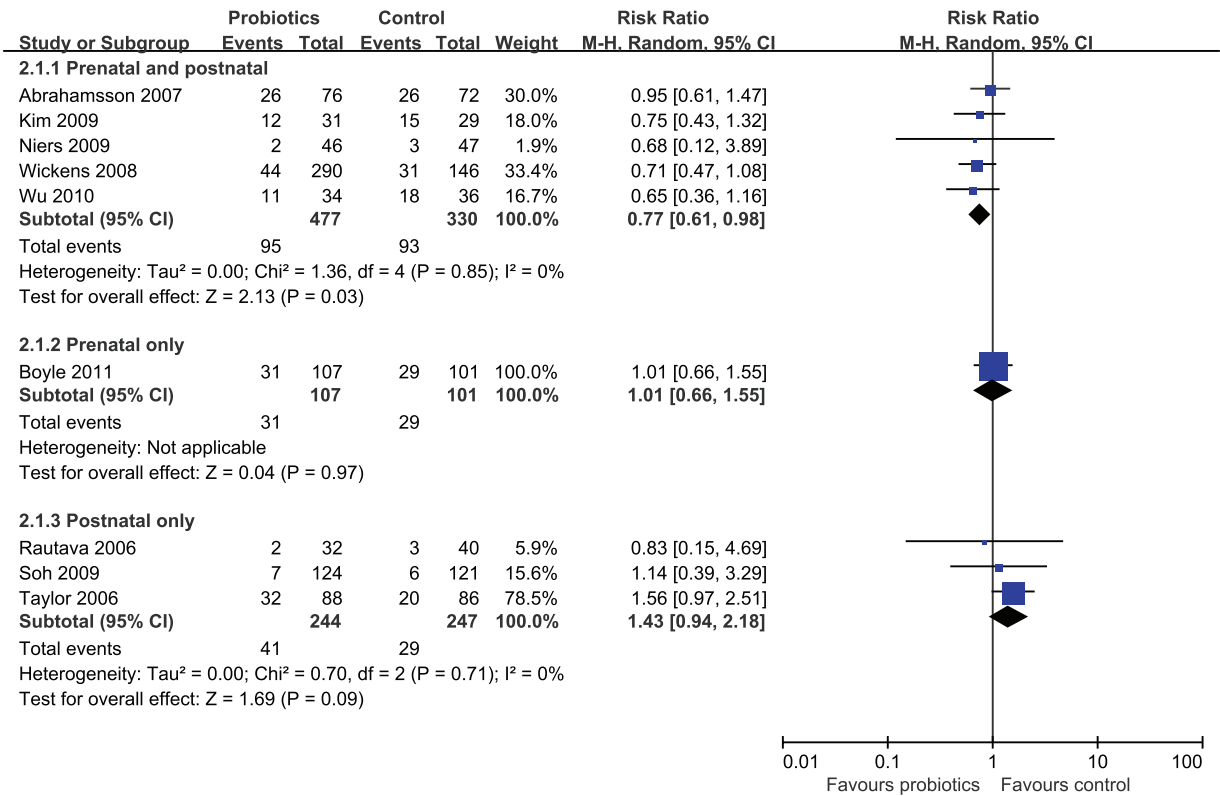


FIGURE 4. Effect of probiotic supplementation on food hypersensitivity.

the child), remains to be explored.⁴⁸ Of note, the potential mechanisms behind the allergy-preventive effects afforded by probiotics remain a highly live issue, and what exactly constitutes a “healthy gut microbiome” that promotes tolerance is far from understood.⁴⁶ Although the new World Allergy Organization guidelines suggested that probiotics should be recommended in mothers of high-risk infants and in infants at high risk of allergic disease, the recommendations are conditional and based on very low quality evidence, with no specific recommendation regarding strains, dose, treatment duration, etc.⁴⁹ Hence, more work still needs to be done in this field.

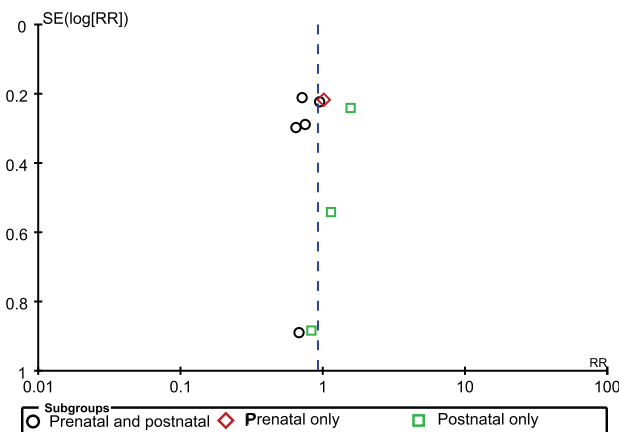


FIGURE 5. Funnel plot of trials on probiotics and prevention of food hypersensitivity.

We found that higher cesarean delivery rate group, compared with lower cesarean delivery rate, was associated with a lower risk of atopy when administered probiotics. Our result was consistent with the study by Kuitunen et al,⁵⁰ which concluded that probiotic and prebiotic supplementation during pregnancy and infancy conferred protection preferably to cesarean-delivered children. It has been suggested that children born by means of cesarean section were colonized with beneficial microflora later than vaginally delivered children,^{51,52} and have higher risk of developing allergic disorders.^{53–55} We could speculate that cesarean-delivered children, who are deprived of massive microbial load from vaginal delivery, might particularly benefit from probiotic administration.

One of our aims was to summarize the data on probiotic use and food hypersensitivity. Guidelines published in 2014 by the European Academy of Allergy and Clinical Immunology’s Taskforce on the prevention of food allergy suggested that there was still no evidence to support the use of probiotics for food allergy prevention, which was primarily based on studies of probiotics and food hypersensitivity.⁵⁶ Our pooled result indicated that probiotics administered prenatally and postnatally could reduce the risk of food hypersensitivity, with all included studies reporting results in the same direction. Our result was also consistent with previous reviews.^{45,57} Therefore, we speculate that probiotic supplementation prenatally and postnatally maybe a feasible way to prevent IgE-related food allergy in early life. Of note, our result was based on data from positive SPT and/or elevated specific IgE to food allergens rather than confirmed food allergy. And, food hypersensitivity is not always associated with clinical reactions and food allergy, although infants with food sensitization may be more prone

to develop food allergy.⁵⁸ To our knowledge, studies exploring the effects of probiotics on confirmed food allergy are surprisingly scant. Two trials^{28,40} considered food allergy as outcome, either confirmed by allergic symptoms or reported by parents, reported totally opposite effects of probiotics but not statistically significant. Another 2 trials^{33,59} considered cow's milk allergy as outcome, confirmed by cow's milk challenge, and consistently suggested a preventative effect of probiotics but not statistically significant. Thus, although our study strongly suggested that probiotics administered prenatally and postnatally were effective in reducing the risk of food hypersensitivity, studies investigating the effects of probiotics on oral food challenge confirmed food allergy are still warranted.

During the last few decades, the nexus between allergic disorders and autoimmune diseases (such as multiple sclerosis, rheumatoid arthritis, and type I diabetes mellitus, etc.) has prompted considerable interest. One generally accepted concept, postulated by Sornasse et al in 1996,⁶⁰ was that autoimmune and allergic disease was Th1- and Th2 mediated, respectively, which occurred in mutually exclusive populations of patients. Until recently, several observations have challenged this paradigm that the presence of allergic and autoimmune diseases are mutually exclusive states, and provided additional insight into the roles of mast cells, B cells, and some other subsets of T cells (such as, Th17 and regulatory T cells) as a common link between atopy and autoimmunity.⁶¹ There is growing body of evidence indicating that probiotics could modulate the immune response, such as the balance of Th1/Th2 cells,⁶² and prevent autoimmune and allergic diseases.^{5,12,63} Still, the exact mechanisms up to now are far from understood, and further clinical and experimental studies are needed to fully clarify such an effect.

Comparison With Previous Studies

Differences between the current meta-analysis and previous meta-analyses should be noted. A meta-analysis by Elazab et al⁶⁴ evaluated the effect of probiotic supplementation during pregnancy or infancy on the prevention of atopy in young children. The authors included 15 RCTs involving 2797 children and concluded that probiotics administered prenatally and postnatally was associated with reduced risk of atopy (RR 0.88, 95% CI 0.78–0.99). Notably, the control groups of 2 included trials were double counted.^{22,31} Moreover, studies with the longest follow-up time were included, which resulted in big variation across included studies, that is, 12 studies with follow-up of 1 to 2 years and the other 3 studies with follow-up of 4 to 7 years.^{19,22,25} In another 2 meta-analyses focusing on food hypersensitivity, Osborn et al⁶⁵ included 2 RCTs involving 247 children and found a lack of effect of probiotics on food hypersensitivity, and the recent meta-analysis conducted by Kong et al⁶⁶ included 10 RCTs and yielded a similar nonsignificant result. Of note, 2 included RCTs^{23,40} were based on the same population, and 3 RCTs should be excluded because of ineligible intervention (probiotics administered with prebiotics)^{50,67} and ineligible participants (children with highly suspected cow's milk allergy).⁶⁸ Overall, the 3 previous meta-analyses had obvious flaws that might threaten the authenticity of their findings. After the 3 meta-analyses, several studies investigating probiotics for the prevention of atopy or food hypersensitivity were published. Our updated meta-analysis included 17 studies with a total of 2947 children and data were from studies with similar follow-up time. In contrast with the previous meta-analyses, the current 1 suggested that combined prenatal and postnatal supplementation of probiotics may

reduce the risk of atopy and food hypersensitivity. Moreover, low heterogeneity, the consistency of findings in most subgroups, and lack of publication bias or other major biases added robustness to our main findings.

Several potential limitations should be taken into consideration when interpreting the results. First, although no statistical heterogeneity was found for the outcomes of interest, population characteristics, probiotic regimens (various organisms, daily doses, and length of intervention), and follow-up time differed across the included studies. We adopted random effects models to try to account for such variability. Second, to further examine the influence of these clinical factors on the pooled results and verify the robustness of our findings, subgroup analyses were conducted and the results were consistent in most selected subgroups. We, however, can only analyze factors that are available to us from the original articles. Also, subgroup analyses were susceptible to type II errors because of relatively small sample sizes. Third, because all the included studies were followed up to 1 to 3 years of age, the long-term effects of probiotics on atopy and food hypersensitivity cannot be defined in our study. Hence, follow-up of existing trials are warranted.

CONCLUSIONS

The current systematic review and meta-analysis suggested that probiotics administered prenatally and postnatally could reduce the risk of atopy and food hypersensitivity in young children. Future studies should consider the optimal probiotic strains, dosing, duration of therapy, and longer follow-up times. Researches assessing the effects of probiotics on confirmed food allergy rather than surrogate measure of food sensitization are warranted.

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