


Probiotics supplementation during pregnancy or infancy on multiple food allergies and gut microbiota: a systematic review and meta-analysis

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Context: Probiotics show promise in preventing and managing food allergies, but the impact of supplementation during pregnancy or infancy on children's allergies and gut microbiota remains unclear. **Objective:** This study aimed to assess the effects of maternal or infant probiotic supplementation on food allergy risk and explore the role of gut microbiota. **Data Sources:** A systematic search of databases (PubMed, Cochrane Library, Embase, and Medline) identified 37 relevant studies until May 20, 2023. **Data Extraction:** Two independent reviewers extracted data, including probiotics intervention details, gut microbiota analysis, and food allergy information. **Data Analysis:** Probiotics supplementation during pregnancy and infancy reduced the risk of total food allergy (relative risk [RR], 0.79; 95% CI, 0.63–0.99), cow-milk allergy (RR, 0.51; 95% CI, 0.29–0.88), and egg allergy (RR, 0.57; 95% CI, 0.39–0.84). Infancy-only supplementation lowered cow-milk allergy risk (RR, 0.69; 95% CI, 0.49–0.96), while pregnancy-only had no discernible effect. Benefits were observed with over 2 probiotic species, and a daily increase of 1.8×10^9 colony-forming units during pregnancy and infancy correlated with a 4% reduction in food allergy risk. Children with food allergies had distinct gut microbiota profiles, evolving with age. **Conclusions:** Probiotics supplementation during pregnancy and infancy reduces food allergy risk and correlates with age-related changes in gut microbial composition in children.

Systematic Review Registration: PROSPERO registration no. CRD42023425988.

Key words: children, food allergy, gut microbiota, meta-analysis, probiotics supplementation.

INTRODUCTION

Food allergies are on the rise and have affected millions of people worldwide.^{1,2} The global incidence of food allergies is approximately 10% in infants and 4% to 5% in older children and young adolescents.³ The Wayne County Health, Environment, Allergy, and Asthma

Longitudinal Study (WHEALS) birth cohort study indicated that the main immunoglobulin (Ig) E-mediated food allergens in adolescents are milk, eggs, and peanuts.⁴ IgE-mediated food allergy refers to the production of food allergen-specific IgE on first exposure, and upon re-exposure to the allergen, specific IgE binds to Fc-epsilon receptor I (FcεRI) on mast cells, releasing

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<https://doi.org/10.1093/nutrit/nuae024>

Nutrition Reviews® Vol. 00(0):1–17

mediators and causing acute symptoms.⁵ Food-allergic symptoms range from skin irritation to life-threatening anaphylaxis.⁶ Hence, food allergies have become a global public health concern.

Avoidance of allergic foods, food-processing desensitization, and oral immunotherapy are the major treatment strategies for food allergies. However, relevant dietary exposures, such as probiotics supplementation during pregnancy or after birth, can influence the development of food allergies.⁷ The potential role of probiotics in influencing the immune system as an innovative strategy to combat food allergies has attracted a high degree of attention. One randomized controlled trial (RCT) indicated that maternal probiotics supplementation during pregnancy can prevent egg allergy.⁷ However, another study suggested that no benefit of probiotics supplementation during infancy has been shown.⁸ Factors such as the period (during pregnancy or infancy), duration (short or long term), dose, and type of probiotics may impact the effectiveness of probiotics supplementation. However, no relevant analyses have been reported. Additionally, variations in the microbial environment may affect the risk of food allergies in offspring receiving probiotics support during pregnancy or infancy.

The development of the fetal immune system depends on the environmental exposures, ranging from the prenatal placental environment to postnatal conditions, especially during the first trimester of life.^{9,10} The gut microbiota, skin, and vasculature play an important role in the development of the immune system during early life.⁹ Gut microbiota undergo changes and maturation as individuals age. Gut microbial maturation in healthy infants undergoes a transition from *Escherichia coli* dominated, to *Bifidobacterium bifidum* dominated, eventually to Bacteroidetes dominated.¹¹ However, the gut microbiota of children with food allergies differ from those of healthy children.¹² Meanwhile, the spectrum of microbial colonization with age in children with food allergies is not clear. If the delay in maturation of the immune system is partly due to microbiota imbalance, it is then particularly important to understand age-specific microbial alterations in food-allergic infants, providing insights for early precision prevention and treatment of food allergies.

Recent reviews provided summaries of probiotics' effects on allergic diseases; however, they did not include food allergies and did not separately address differences in supplementation during pregnancy or infancy.¹³ The objective of this meta-analysis and systematic review was to evaluate the effects of probiotics supplementation during pregnancy or infancy on overall food, cow-milk, egg, and peanut allergies in children, and to synthesize the specific microbial profiles of children during each period with food allergies.

METHODS

Data sources and searches

PubMed, Cochrane Library, Embase, and Medline were searched for studies related to food allergies, probiotics, and gut microbiota published until May 20, 2023. The details of the search strategy used for all databases are available in [Material S1 \(please see the Supporting Information online\)](#). The study protocol was registered prospectively in PROSPERO (<https://www.crd.york.ac.uk/prosperto/>) with the registration number CRD42023425988. This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (see [Table S4 in the Supporting Information online](#)).

Eligibility criteria

The inclusion criteria for this meta-analysis were based on the Participants, Interventions, Comparisons, Outcomes, and Study design (PICOS) framework ([Tables 1 and 2](#)).

Study selection and data extraction

Records obtained from the searches were downloaded and exported to EndNote X9 (Clarivate Analytics, London, UK) for de-duplication. Two independent reviewers performed 2-round screening (titles and abstracts in round 1 and full-text eligibility in round 2). Extracted data consisted of publication details, study design characteristics, probiotics intervention details, stool collection, and gut microbiota analysis. Primary outcomes of interest included the occurrence and

Table 1 PICOS criteria for inclusion of studies of probiotics supplementation on food allergies

Parameter	Inclusion criterion
Participants	Human studies
Interventions	Probiotics supplementation during pregnancy or infancy
Comparisons	With or without probiotics supplementation
Outcomes	Occurrence or tolerance of food allergies
Study design	Randomized controlled trial

Table 2 PICOS criteria for inclusion of studies of gut microbiota

Parameter	Inclusion criterion
Participants	Human studies
Interventions	Gut microbiota analysis
Comparisons	Food allergic children or healthy children
Outcomes	Gut microbial diversity
Study design	Case-control study

tolerance of food allergy during pregnancy or infancy, composition of gut microbiota (alpha and beta diversity), and relative abundance at the phylum, order, family, and genus levels. Discrepancies regarding study inclusion and data interpretation were resolved by consensus through group discussions.

Quality assessment

Randomized controlled trials of probiotics supplementation on food allergy were evaluated for risk of bias using modified versions of the Cochrane Collaboration Risk of Bias tool.¹⁴ The Risk of Bias tool was used to assess the randomization process, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting bias, and other biases. The Newcastle–Ottawa Quality Assessment Scale (NOS) was used to evaluate case-control studies of gut microbiota.¹⁵ The NOS was assessed in 3 categories: selection, comparability, and exposure. No studies were excluded based on quality concerns. The detailed assessment is available in [Tables S2 and S3](#) (please see the [Supporting Information online](#)).

Statistical analysis

The main effect data were analyzed using Stata (version 11; StataCorp, College Station, TX, USA) and RevMan (version 5). Heterogeneity of the studies was quantified using I^2 statistics. The fixed-effects model was adopted with low heterogeneity ($I^2 < 50\%$). Otherwise, a random-effects model was used.

Studies on food allergies were categorized based on probiotics supplementation during pregnancy or infancy. Subgroup analysis was performed based on follow-up duration, region, and probiotics type. Sensitivity analysis was performed to investigate the influence of each study on the overall analysis. The potential nonlinear effects of probiotics dosage and follow-up duration were examined using a restricted cubic spline model.

Funnel plots and Begg's and Egger's tests were utilized to assess potential publication bias. A heatmap of the gut microbiota was generated using the R package pheatmap (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < 0.05$.

RESULTS

Study characteristics

A total of 37 studies were included after screening, with 17 trials for probiotics supplementation on food allergy including 4 trials also for probiotics supplementation on gut microbiota, 3 trials for probiotics

supplementation on tolerance towards food, and 17 case-control studies for gut microbiota ([Fig. 1](#)). The 20 RCTs captured 4597 participants in the probiotics supplementation group and 4470 participants in the control group. Seven studies^{7,16–21} for probiotics supplementation on food allergy were conducted during pregnancy and infancy, 1 study²² on pregnancy alone, and 9 studies^{8,23–30} on infants alone after birth; 3 studies were conducted for probiotics supplementation during infancy on tolerance towards food.^{31–33} Twelve (60.0%), 6 (30.0%), and 2 (10.0%) studies were conducted in Europe, Oceania, and Asia, respectively. The 17 trials on the risk food allergy included 15 studies on total food allergy, 10 studies on cow-milk allergy, 8 studies on egg allergy, and 6 studies on peanut allergy ([Table 3](#)).

Seventeen studies on gut microbiota included 706 patients with food allergies and 913 healthy controls.^{34–50} They included 7 studies in Asia, 7 in America, 2 in Europe, and 1 in Oceania. No difference in sex was found between the food allergy and control groups. The ages of the participants ranged from 0 to 18 years ([Table 4](#)). The collection, preservation, and extraction of intestinal samples and the methods of β -diversity analysis are shown in [Table S1](#) (please see the [Supporting Information online](#)).

Sensitivity analyses did not reveal any change in the main effects of probiotics on food allergies and gut microbiota diversity. Funnel plots showed a slight publication bias, but not all effects were significant according to Egger's parametric or Begg's nonparametric distribution tests.

Probiotics supplementation on multiple food allergies

Seven studies assessed the effects of probiotics supplementation during pregnancy and infancy on food allergies in children.^{7,16–21} The number of studies associated with food allergies,^{16–19,21} cow-milk allergy,^{7,16,19,20} egg allergy,^{7,16,19} and peanut allergy^{19,20} were 5, 4, 3, and 2, respectively. Probiotics were provided in capsule or powder forms and at a dose of 0.1 to 24.2 billion colony-forming units (CFUs) per day. Probiotics supplementation during pregnancy and infancy can reduce the risk of total food allergy (relative risk [RR], 0.79; 95% CI, 0.63–0.99; $I^2 = 0\%$), cow-milk allergy (RR, 0.51; 95% CI, 0.29–0.88; $I^2 = 5\%$), and egg allergy (RR, 0.57; 95% CI, 0.39–0.84; $I^2 = 10\%$) ([Fig. 2](#)). No significant associations with peanut allergies were observed. Subgroup analysis ([Table 5](#)) showed that probiotics supplementation significantly decreased the risk of cow-milk and egg allergies in Europe but not in Oceania and Asia. The use of more than 2 types of probiotics had a beneficial effect on cow-milk allergy (RR, 0.45; 95% CI, 0.23–0.86; $I^2 = 51.8\%$) and egg allergy (RR, 0.55; 95% CI, 0.34–0.89; $I^2 = 40.3\%$). Based on the dose–response

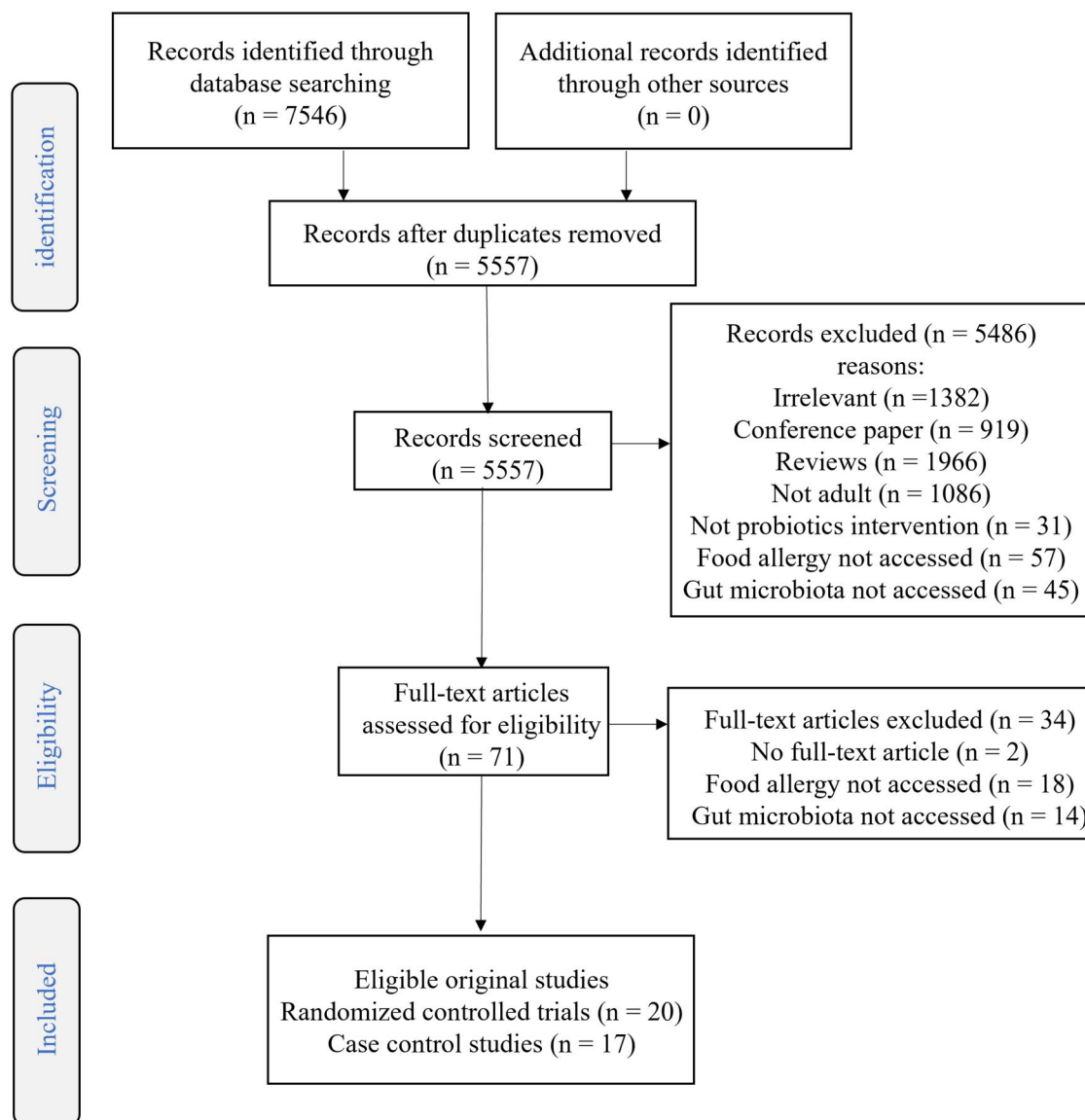


Figure 1 Flow diagram of the literature search process.

data, probiotics supplementation during pregnancy and infancy decreased the risk of food allergy in a nonlinear fashion ($R^2 = 0.15$, P -nonlinearity = 0.23), with stronger effects at doses of approximately $3\text{--}12 \times 10^9$ CFUs per day (see Fig. S1 in the Supporting Information online). The summary RR (95% CI) for a 1.8×10^9 -CFU per day increment was 0.96 (0.93–0.99) for food allergy risk.

Only 1 study has assessed the effect of probiotics supplementation during pregnancy on food allergies in children.²² Probiotics were administered in capsule form at a dose of 1.8×10^9 CFUs per day. There was no significant effect of probiotics supplementation on total food, cow-milk, egg, or peanut allergies.

The effects of probiotics supplementation on infants were evaluated in 9 intervention trials,^{8,23–30}

which included 9 for total food allergy,^{8,23–30} 5 for cow-milk allergy,^{8,24–26,29} 4 for egg allergy,^{8,25,26,28} and 3 for peanut allergy.^{8,25,26} Probiotics were provided in powder form or as part of formula milk at a dose of $9\text{--}305 \times 10^7$ CFUs per day. Supplementation of probiotics in infants significantly decreased the risk of cow-milk allergy (RR, 0.69; 95% CI, 0.49–0.96; $I^2 = 0\%$) (Fig. 3). There were no significant effects on total food, egg, or peanut allergies. Subgroup analysis (Table 5) showed a significant difference among regions and probiotics types in cow-milk allergies. A significant reduction in risk was observed in the European subgroup (RR, 0.68; 95% CI, 0.48–0.98; $I^2 = 0\%$) and in those taking more than 2 types of probiotics (RR, 0.68; 95% CI, 0.48–0.98; $I^2 = 0\%$). No association was found in the subgroups of

Table 3 Characteristics of included studies for probiotics supplementation during pregnancy and infancy on food allergy and tolerance to foods in children

Reference	Study type	Study region	Food allergy types	Intervention period	Probiotics	Types of probiotics	Dosage
Allen (2014) ⁷	RCT	UK	Egg and cow milk	Pregnant women: gestation 36 wk to delivery; infants: birth to age 6 mo (follow-up duration: 6 mo, 24 mo)	<i>Lactobacillus salivarius</i> , <i>Lactobacillus paracasei</i> , <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> , and <i>Bifidobacterium bifidum</i>	4	<i>Lactobacillus salivarius</i> 6.25 × 10 ⁹ CFU, <i>Lactobacillus paracasei</i> 1.25 × 10 ⁹ CFU, <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> 1.25 × 10 ⁹ CFU and <i>Bifidobacterium bifidum</i> 1.25 × 10 ⁹ CFU
Kallio (2019) ²¹	RCT	Finland	All food	Pregnant women: gestation 36 wk to delivery; infants: birth to age 6 mo (follow-up duration: 13 y)	<i>Lactobacillus rhamnosus</i> GG and LC705, <i>Bifidobacterium breve</i> Bb99 and <i>Propionibacterium freudenreichii</i>	4	One capsule contains <i>Lactobacillus rhamnosus</i> GG: 5 × 10 ⁹ CFU, <i>Lactobacillus rhamnosus</i> LC705: 5 × 10 ⁹ CFU, <i>Bifidobacterium breve</i> Bb99: 2 × 10 ⁸ CFU, <i>Propionibacterium freudenreichii</i> : 2 × 10 ⁹ CFU; pregnant women: 2 capsules; infants: 1 capsule
Abrahamsson (2007) ¹⁶	RCT	Sweden	All food, cow milk, and egg	Pregnant women: gestation 36 wk to delivery; infants: birth to age 12 mo (follow-up duration: 24 mo)	<i>Lactobacillus reuteri</i>	1	1 × 10 ⁸ CFU
Wickens (2008) ¹⁷	RCT	New Zealand	All food	Pregnant women: gestation 35 wk to breastfeeding within 6 mo postpartum; infants: birth to age 24 mo (follow-up duration: 24 mo)	<i>Lactobacillus rhamnosus</i> , <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> strain	1	<i>Lactobacillus rhamnosus</i> : 6 × 10 ⁹ CFU, <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> strain: 9 × 10 ⁹ CFU
Niers (2009) ¹⁸	RCT	Netherlands	All food	Pregnant women: 6 wk before delivery; infants: birth to age 12 mo (follow-up duration: 24 mo)	<i>Bifidobacterium bifidum</i> , <i>Bifidobacterium lactis</i> , and <i>Lactococcus lactis</i>	3	3 × 10 ⁹ CFU
Kim (2010) ¹⁹	RCT	Korea	All food, cow milk, egg, and peanut	Pregnant women: 8 wk before delivery to 3 mo after delivery; infants: birth to age 4–6 months (follow-up duration: 12 mo)	<i>Bifidobacterium bifidum</i> , <i>Bifidobacterium lactis</i> , and <i>Lactobacillus acidophilus</i>	3	<i>Bifidobacterium bifidum</i> : 1.6 × 10 ⁹ CFU; <i>Bifidobacterium lactis</i> : 1.6 × 10 ⁹ CFU; <i>Lactobacillus acidophilus</i> : 1.6 × 10 ⁹ CFU
Boyle (2011) ²²	RCT	Australia	All food, cow milk, egg, and peanut	Pregnant women: gestation 36 wk to delivery (follow-up duration: 12 mo)	<i>Lactobacillus rhamnosus</i> GG	1	1.8 × 10 ¹⁰ CFU

(continued)

Table 3 Continued

Reference	Study type	Study region	Food allergy types	Intervention period	Probiotics	Types of probiotics	Dosage
Kalliomäki (2003) ²⁰	RCT	Finland	Cow milk and peanut	Pregnant women: 4 wk before delivery to 6 mo after delivery (the mother or the infant consumed the preparation) Infants: very preterm infants from soon after birth until discharge from hospital or term corrected age	<i>Lactobacillus rhamnosus</i> GG	2	1×10^{10} CFU
Plummer (2019) ²³	RCT	Australia	All food		<i>Bifidobacterium infantis</i> , <i>Streptococcus thermophilus</i> , and <i>Bifidobacterium lactis</i>	3	<i>Bifidobacterium infantis</i> : 3×10^8 ; <i>Streptococcus thermophilus</i> : 3.5×10^8 ; <i>Bifidobacterium lactis</i> : 3.5×10^8 per 1.5 g base powder
Morisset (2008) ²⁴	RCT	France	All food and cow milk	Infants: birth to age 12 mo (follow-up duration: 4, 12, and 24 mo)	Heat-killed <i>Bifidobacterium breve</i> C50 and <i>Streptococcus thermophilus</i> 065	2	<i>Bifidobacterium breve</i> C50: 4.2×10^9 bacteria per 100 g of powder formula; <i>Streptococcus thermophilus</i> 065: 3.84×10^7 bacteria per 100 g of powder formula
Taylor (2007) ²⁵	RCT	Australia	All food, cow milk, egg, and peanut	Infants: birth to age 6 mo (follow-up duration: 12 mo)	<i>Lactobacillus acidophilus</i>	1	3×10^9 CFU
Prescott (2008) ²⁶	RCT	Australia	All food, cow milk, egg, and peanut	Infants: birth to age 6 mo (follow-up duration: 30 mo)	<i>Lactobacillus acidophilus</i>	1	3×10^9 CFU
Jensen (2012) ⁸	RCT	Australia	All food, cow milk, egg, and peanut	Infants: birth to age 6 mo (follow-up duration: 5 y)	<i>Lactobacillus acidophilus</i>	1	3×10^9 CFU
West (2013) ²⁷	RCT	Sweden	All food	Infants: 4 to 13 mo (follow-up duration: 8–9 y)	<i>Lactobacillus paracasei</i> ssp. <i>paracasei</i> F19	1	1×10^8 CFU
Soh (2009) ²⁸	RCT	Singapore	All food and egg	Infants: birth to age 6 mo (follow-up duration: 12 mo)	<i>Bifidobacterium longum</i> and <i>Lactobacillus rhamnosus</i>	2	At least 2.8×10^8 CFU
Rautava (2006) ²⁹	RCT	Finland	All food and cow milk	Infants: 2 to 12 mo (follow-up duration: 12 mo)	<i>Lactobacillus rhamnosus</i> and <i>Bifidobacterium lactis</i> Bb-12	2	1×10^{10} CFU
Lau (2012) ³⁰	RCT	Germany	All food	Infants: 5 to 31 wk (follow-up duration: 36 mo)	Heat-killed nonpathogenic gram-negative <i>Escherichia coli</i> <i>Symbio</i> and nonpathogenic gram-positive <i>E. faecalis</i> <i>Symbio</i>	2	$3.15\text{--}9.45 \times 10^7$ bacteria
Hol (2008) ³¹	RCT	Netherlands	Cow milk	Infants: 6 and 12 mo after initial cow-milk allergy diagnosis	<i>Lactobacillus casei</i> CRL431 and <i>Bifidobacterium lactis</i> Bb-12	2	1×10^7 CFU/g formula
Berni Canani (2012) ³²	RCT	Italy	Cow milk	Infants: 6 and 12 mo after initial cow-milk allergy diagnosis	<i>Lactobacillus rhamnosus</i> GG	1	6.5×10^7 CFU/g formula
Berni Canani (2013) ³³	RCT	Italy	Cow milk	Infants: 12 mo after initial cow-milk allergy diagnosis	<i>Lactobacillus rhamnosus</i> GG	1	Not indicated

Abbreviations: CFU, colony-forming unit; RCT, randomized controlled trial.

Table 4 Characteristics of included studies for perturbations of gut microbiota composition in children with food allergy

Reference	Study type	Study region	No. of patients	Age	Female, %	Food allergy types
Bao (2021) ³⁴	Case control	USA	34	39.4 ± 4.1 y (M ± SEM)	64.7%	Food allergy
Bunyavanich (2016) ³⁵	Case control	USA	226	3.6–16.9 mo (range)	51.7%	Milk
Schink (2018) ³⁶	Case-control	Germany	31	38.1 ± 15.1 y (M ± SD)	83.9%	—
Du (2020) ³⁷	Case-control	China	50	33.0 ± 11.7 y (M ± SD)	48.0%	Wheat-dependent, exercise-induced anaphylaxis
Fazlollahi (2018) ³⁸	Case control	USA	141	9.5 (7.1–12.3) mo (IQR)	32.6%	Egg
Goldberg (2020) ³⁹	Case-control	USA	291	Allergic: 77 (63.0–114.5) mo Control: 78 (48.0–125.3) mo (M, IQR)	40.9%	Milk, peanut, sesame, tree nuts
Kourosh (2018) ⁴⁰	Case-control	USA	42	0–18 y (range)	52.4%	Peanut/tree nuts, fish, milk, egg, sesame, soy, wheat, chick pea, lentil, avocado, green pea
Lee (2021) ⁴¹	Case-control	Australia	60	1–7 y (range)	60.7%	Nuts, egg, and mixed allergies
Savage (2018) ⁴⁴	Case-control	USA	216	Allergic: 153 (115–208) d Control: 142 (78–206) d (M, range)	49.1%	Milk, egg, peanut, soy, wheat, walnut
Dong (2018) ⁴⁵	Case-control	China	120	2.9 ± 1 mo (M ± SD)	46.7%	Milk
Ling (2014) ⁴⁶	Case-control	China	79	5.4 ± 2.1 mo (M ± SD)	50.6%	Milk, eggs, wheat, nut, peanuts, fish, shrimp, and soybeans
Łoś-Rycharska (2021) ⁴⁷	Case-control	Poland	44	15.1 ± 6.6 wk (M ± SD)	40.9%	Milk
Yamagishi (2021) ⁴⁸	Case-control	Japan	40	Allergic: 3.1 (1.5–5.5) ys Control: 4.0 (2.9–6.1) y (M, IQR)	NA	Egg
Azad (2015) ⁴⁹	Case-control	Canada	166	3 mo or 1 y	48.8%	—
Tanaka (2017) ⁵⁰	Case-control	Japan	41	1 y	34.1%	Egg, milk, wheat, soybean
Dong (2018) ⁴²	Case-control	China	14	5–8 y (range)	Sex-matched	Milk
Guo (2016) ⁴³	Case-control	China	24	5–8 y (range)	50.0%	Milk

Abbreviations: IQR, interquartile range; M, mean; NA, not applicable; SD, standard deviation; SEM, standard error of mean.

other regions or in 1 type of probiotic. Probiotics dosage ($R^2 = 0.183$, P -nonlinearity = 0.1084) and follow-up duration ($R^2 = 0.183$, P -nonlinearity = 0.1084) did not show any nonlinear relationship with the risk of food allergy (see Fig. S1 in the Supporting Information online).

Three studies assessed the effects of probiotics supplementation during infancy on tolerance towards cow milk.^{31–33} The results indicated that probiotics supplementation did not accelerate cow-milk tolerance in infants with cow-milk allergy (RR, 1.39; 95% CI, 0.97–1.99; $I^2 = 81\%$) (Fig. 2).

Perturbations of gut microbiota in food-allergic children with age progression

Alpha diversity. Data from 11 studies were included in this meta-analysis (308 patients and 655 controls).^{34,36,38,40,41,44–49} Four indices were used to assess alpha diversity, including estimates of diversity, richness, and evenness (Shannon, Simpson, Chao1, and observed operational taxonomic units [OTUs]).

Eleven studies reported the Shannon index in patients ($n = 308$) vs controls ($n = 655$).^{34,36,38,40,41,44–49} No difference was observed between the groups (standardized mean difference [SMD], -0.13 ; 95% CI, -0.42 to 0.17 ; $I^2 = 81.1\%$) (see Fig. S2 in the Supporting Information online). Within the follow-up duration categories, there was a significant decrease, with a small effect size in the 0–6-month group (SMD, -0.36 ; 95% CI, -0.70 , -0.03 ; $I^2 = 55\%$) and an increase in the 6–12-month group (SMD, 0.5 ; 95% CI, 0.21 to 0.80 ; $I^2 = 0\%$). Three studies provided data on the Simpson index in patients ($n = 73$) and controls ($n = 77$).^{36,46,48} The pooled estimate did not show any difference between the groups (SMD, -0.18 ; 95% CI, -0.74 to 0.38 ; $I^2 = 60.8\%$), except for the 12–48-month subgroup, which showed a decrease (SMD, -0.74 ; 95% CI, -1.38 , -0.09) (see Fig. S2 in the Supporting Information online).

With regard to richness, 4 studies provided data on Chao1 in patients ($n = 125$) vs controls ($n = 458$).^{38,41,44,49} There was no significant difference between the groups (SMD, 0.44 ; 95% CI, -0.48 to 1.36 ;

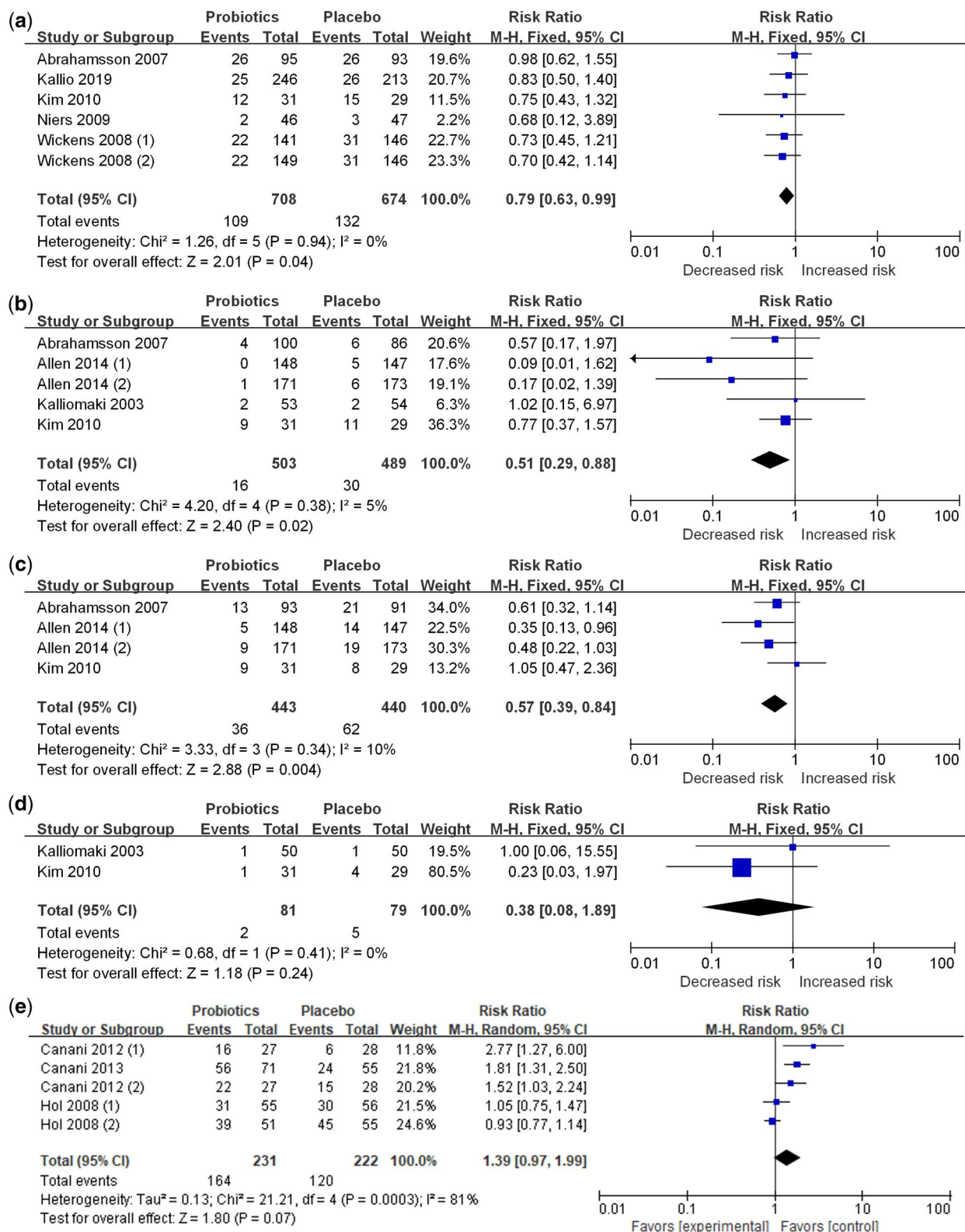


Figure 2 Forest plots of randomized controlled trials for probiotic supplementation during pregnancy and infancy on (a) total food allergy, (b) cow-milk allergy, (c) egg allergy, and (d) peanut allergy and (e) forest plot of randomized controlled trials for probiotic supplementation on tolerance towards food. Abbreviation: M-H, Mantel-Haenszel.

Table 5 Subgroup analysis of probiotics supplementation during pregnancy and infancy on food allergy in children

Subgroup	Food allergy				Cow-milk allergy				Egg allergy				Peanut allergy			
	n	Pooled RRs (95% CI)	I ²	P	n	Pooled RRs (95% CI)	I ²	P	n	Pooled RRs (95% CI)	I ²	P	n	Pooled RRs (95% CI)	I ²	P
Probiotics supplementation during pregnancy and infancy																
Follow-up duration																
1~12 mo	1	0.748 (0.425, 1.317)	—	—	2	0.545 (0.273, 1.088)	57.3%	0.126	2	0.613 (0.331, 1.136)	65.3%	0.089	1	0.234 (0.028, 1.972)	—	—
13~24 mo	4	0.790 (0.600, 1.041)	0.0%	0.755	2	0.379 (0.134, 1.069)	0.2%	0.317	2	0.546 (0.336, 0.888)	0.0%	0.642	—	—	—	—
25~36 mo	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
>36 mo	1	0.833 (0.496, 1.397)	—	—	1	1.019 (0.149, 6.970)	—	—	—	—	—	—	1	1.000 (0.064, 15.548)	—	—
Country																
Europe	3	0.892 (0.635, 1.253)	0.0%	0.854	4	0.363 (0.157, 0.837)	1.3%	0.386	3	0.497 (0.321, 0.768)	0.0%	0.660	1	1.000 (0.064, 15.548)	—	—
Oceania	2	0.715 (0.504, 1.015)	0.0%	0.877	—	—	—	—	—	—	—	—	—	—	—	—
Asia	1	0.748 (0.425, 1.317)	—	—	1	0.765 (0.372, 1.574)	—	—	1	1.158 (0.708, 1.896)	—	—	1	0.234 (0.028, 1.972)	—	—
Probiotics type																
1	3	0.794 (0.600, 1.049)	0.0%	0.561	2	0.678 (0.242, 1.896)	0.0%	0.622	1	0.606 (0.323, 1.136)	—	—	1	1.000 (0.064, 15.548)	—	—
>2	3	0.795 (0.542, 1.164)	0.0%	0.949	3	0.447 (0.231, 0.862)	51.8%	0.126	3	0.552 (0.341, 0.892)	40.3%	0.187	1	0.234 (0.028, 1.972)	—	—
Probiotics supplementation during infancy																
Follow-up duration																
1~12 mo	5	1.246 (0.941, 1.652)	0.0%	0.790	4	0.746 (0.478, 1.163)	8.5%	0.351	3	1.291 (0.829, 2.011)	0.0%	0.726	1	1.412 (0.637, 3.130)	—	—
13~24 mo	2	1.192 (0.771, 1.841)	0.0%	0.342	1	0.726 (0.411, 1.284)	—	—	—	—	—	—	—	—	—	—
25~36 mo	2	0.960 (0.791, 1.164)	0.0%	0.615	1	0.194 (0.023, 1.621)	—	—	1	1.336 (0.572, 3.121)	—	—	1	1.601 (0.625, 4.103)	—	—
>36 mo	2	1.294 (0.712, 2.352)	0.0%	0.383	1	0.592 (0.140, 2.512)	—	—	1	1.579 (0.418, 5.968)	—	—	1	2.171 (0.741, 6.365)	—	—
Country																
Europe	6	0.991 (0.843, 1.164)	0.0%	0.969	4	0.681 (0.475, 0.976)	0.0%	0.815	—	—	—	—	—	—	—	—
Oceania	4	1.500 (1.057, 2.128)	0.0%	0.782	3	0.719 (0.290, 1.783)	48.3%	0.145	3	1.443 (0.948, 2.197)	0.0%	0.974	3	1.642 (0.969, 2.784)	0.0%	0.819
Asia	1	1.138 (0.394, 3.290)	—	—	—	—	—	—	2	0.976 (0.414, 2.301)	0.0%	1.000	—	—	—	—
Probiotics type																
1	4	1.366 (0.985, 1.895)	0.0%	0.708	3	0.719 (0.290, 1.783)	48.3%	0.145	3	1.443 (0.948, 2.197)	0.0%	0.974	3	1.642 (0.969, 2.784)	0.0%	0.819
>2	7	1.009 (0.858, 1.187)	0.0%	0.907	4	0.681 (0.475, 0.976)	0.0%	0.815	2	0.976 (0.414, 2.301)	0.0%	1.000	—	—	—	—

P values for heterogeneity.

Abbreviation: RR, relative risk.

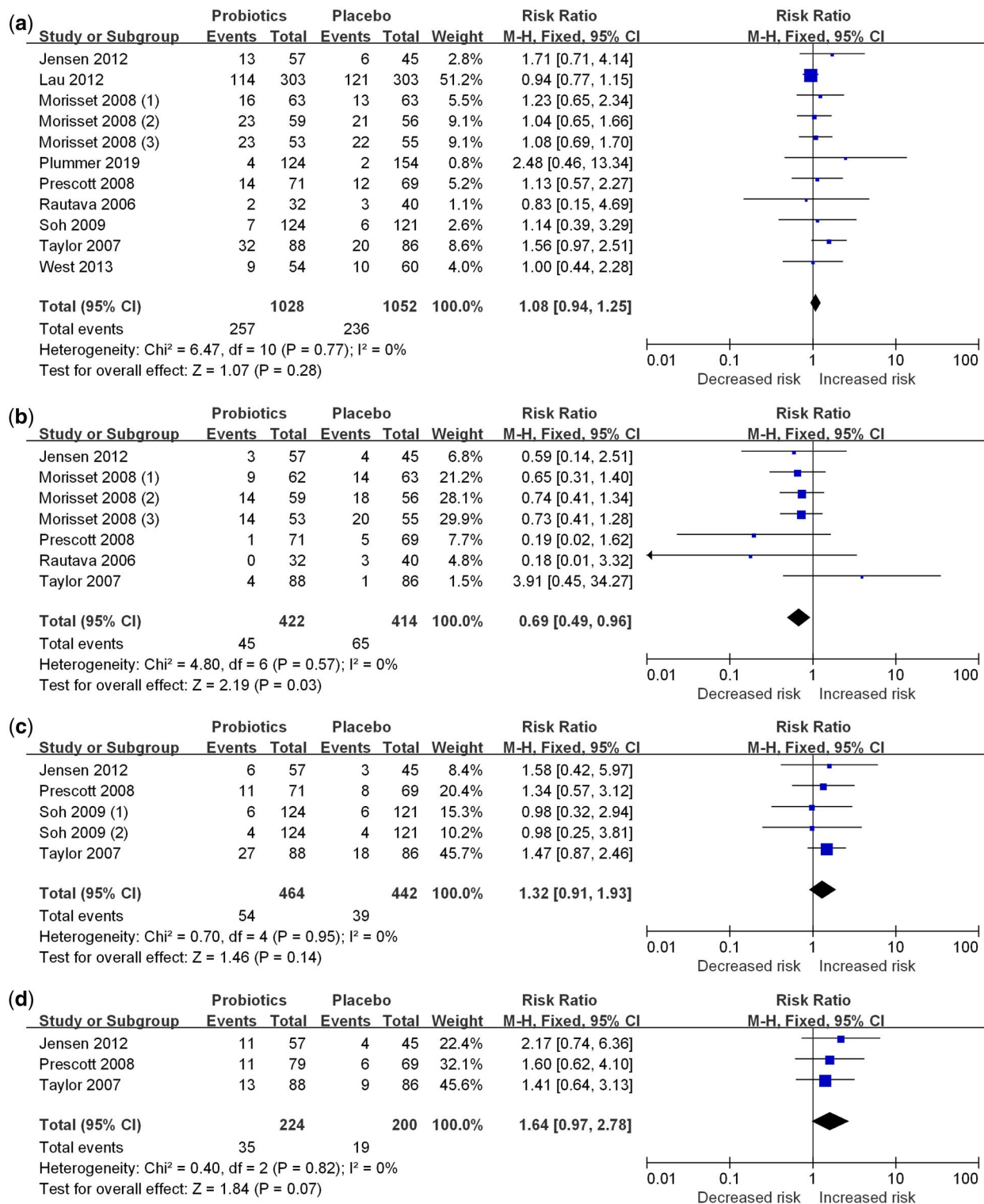


Figure 3 Forest plots of randomized controlled trials for probiotic supplementation during infancy on (a) total food allergy, (b) cow-milk allergy, (c) egg allergy, and (d) peanut allergy. Abbreviation: M-H, Mantel-Haenszel.

$I^2 = 41.8\%$) (see Fig. S2 in the Supporting Information online). With regard to evenness, observed OTU data were provided in 4 studies ($n = 89$ patients, $n = 97$

controls).^{40,41,47,48} No difference was observed between the groups (SMD, -0.24 ; 95% CI, -0.93 to 0.45 ;

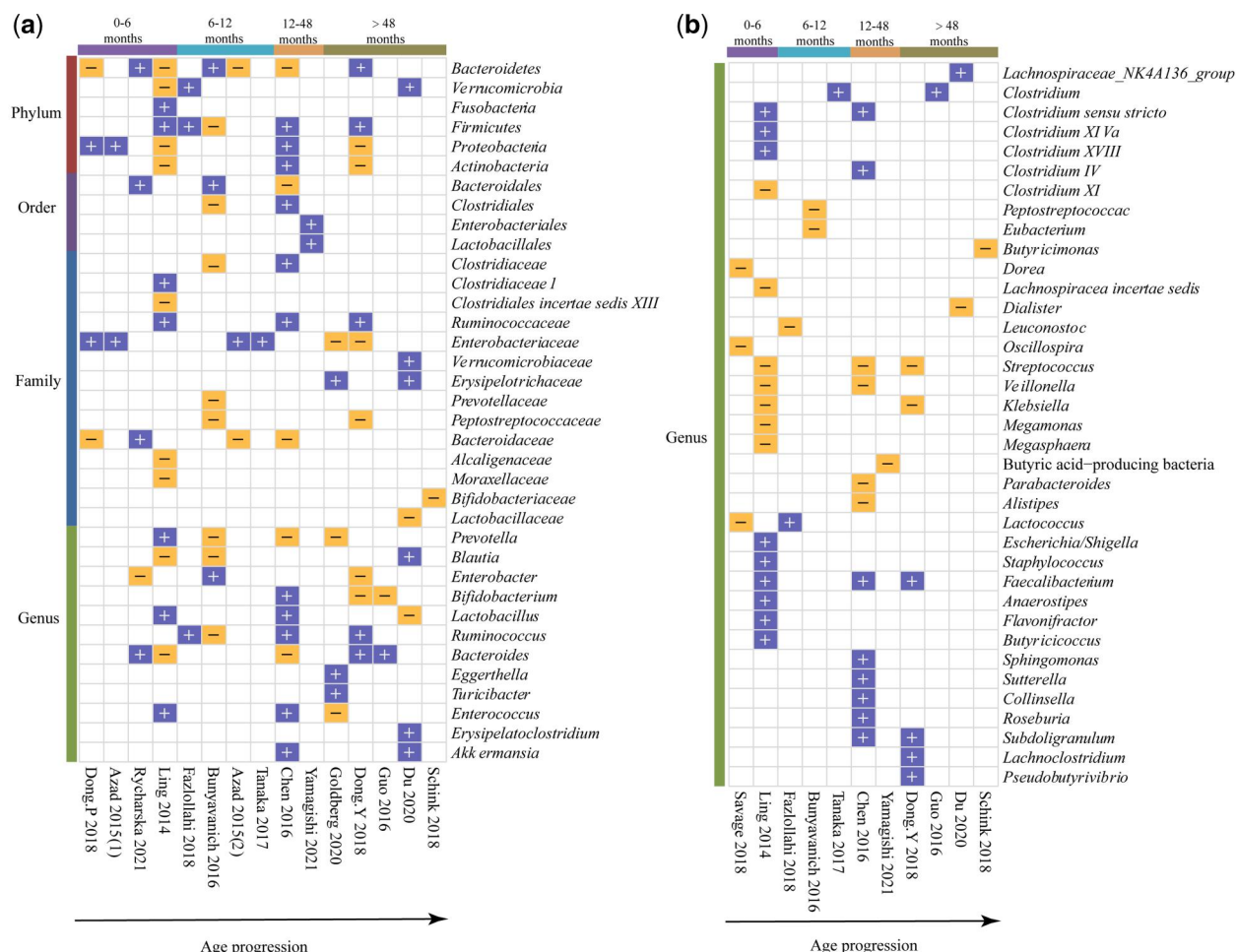


Figure 4 Differentially abundant microbial taxa in children with age progression. Blue cells indicate increases and orange cells indicate decreases.

$I^2 = 0\%$) (see Fig. S2 in the Supporting Information online).

Beta diversity. Beta-diversity comparisons between patients with food allergies and healthy controls were reported in 13 studies. Seven studies reported significant differences, whereas 5 studies reported no differences. The remaining study demonstrated a significant difference in infants aged 3–6 months and 13–16 months and a nonsignificant difference in infants aged 7–12 months. These findings provide reliable evidence for differences in the gut microbiota composition of food-allergic children compared with that in the controls. However, this difference appears to be dependent on the age of children.

Differentially abundant microbial taxa in children with age progression. Fifteen studies were included to assess the relative abundance of gut microbiota and to identify significant differences between patients with food allergy and healthy controls at the phylum, order,

family, or genus levels. The differences spanned 6 phyla, 4 orders, 14 families, and 49 genera. Figure 4 shows the changes in gut microbiota abundance with age progression in children with food allergies.

At the phylum level, the gut microbiota abundance differed across all age groups. Verrucomicrobia, Fusobacteria, Firmicutes, and Proteobacteria were elevated, and Actinobacteria was decreased in allergic children. Six families, including Clostridiaceae, Ruminococcaceae, Verrucomicrobiaceae, and Erysipelotrichaceae, increased, and 8 families, including Prevotellaceae, Bacteroidales, Peptostreptococcaceae, Bifidobacteriaceae, and Lactobacillaceae, decreased in the stools of children with allergies. At the genus level, the results showed an upward trend for Prevotella in allergic infants aged 0–6 months and a downward trend in infants more than 6 months old. The abundances of Blautia and Bacteroides first decreased and then increased with age. The abundance of probiotics in the intestine, including Lactobacillus, Bifidobacterium, and Enterococcus, decreases after age 48 months in children. Twenty-four genera, including Ruminococcus,

Clostridium, *Eggerthella*, *Flavonifractor*, *Anaerostipes*, and *Faecalibacterium*, were elevated. The other 17 genera, including *Butyricoccus*, *Butyricimonas*, *Leuconostoc*, *Veillonella*, and butyric acid-producing bacteria (eg, *Eubacterium*, *Dialister*), decreased with food allergy.

Probiotics supplementation on gut microbiota

Two studies on the effect of probiotics supplementation during pregnancy and infancy on gut microbiota composition were included.^{17,18} Wickens et al¹⁷ suggested that bacteria from the environment can be inoculated into the digestive tract at birth, such as *Bifidobacterium animalis* subsp. *lactis* and *Lactobacillus rhamnosus*. However, children in the probiotics group had significantly higher detection rates of probiotics in feces at 3, 12, and 24 months than those in the placebo group.¹⁷ *L. rhamnosus* was more likely to be present in feces at 3 months (71.5%) than *B. animalis* subsp. *lactis* (22.6%), but the detection rate was similar at 24 months.¹⁷ Niers et al¹⁸ showed that, within the first 3 months of life, *Lactococcus lactis* colonization was significantly more frequent and more numerous in the probiotics group than in the placebo group; all children in the probiotics group and 85% of children in the placebo group had bifidobacteria colonization.

Two studies on the effect of probiotics supplementation during infancy on the gut microbiota composition were included.^{25,27} Taylor et al²⁵ suggested that, at 6 months of age, the rate of *Lactobacillus* colonization was significantly higher in the probiotics group (36%) than in the placebo group (21.6%); however, *Lactobacillus* colonization was associated with an increased risk of milk sensitization. West et al²⁷ concluded that *Lactobacillus paracasei* ssp. *paracasei* F19 (LF19) is a transient colonizer because LF19 was not detected in fecal samples from children aged 8–9 years.

DISCUSSION

Proactive approaches are required to reduce the global burden of food allergies. The findings from this current meta-analysis and review suggested that probiotics supplementation during pregnancy and infancy could reduce the risk of total food, cow-milk, and egg allergy, and probiotics supplementation during infancy reduced the risk of milk allergy in children. Dose–response analysis indicated that more than 2 types of probiotics species had beneficial effects, and an increase of 1.8×10^9 CFUs of probiotics during pregnancy and infancy per day could reduce the risk of food allergy by 4%. The age-related microbiota composition can partly account for the varied effects of probiotics on food allergies. In this study, we explored for the first time the

different effects of probiotics during pregnancy or infancy on various food allergies and probed the influencing factors, first revealing the role played by age-dependent microbiota perturbations.

The decreased risk of cow-milk allergy associated with probiotics in the meta-analysis is in concordance with findings from a systematic review of observational studies.¹⁴ Nevertheless, no meta-analysis has differentiated the effects of probiotics supplementation during pregnancy or infancy on distinct types of food allergies in children. Additionally, while the majority of studies in this meta-analysis indicated no significant impact of probiotics supplementation on food allergies, the overall results of the meta-analysis demonstrated a reduction in the risk of total food allergy, cow-milk allergy, and egg allergy associated with probiotics supplementation during pregnancy and infancy. One potential explanation could be that the meta-analysis expanded the sample size by aggregating multiple studies to make the protective effect of probiotics more apparent.

Probiotics supplementation during both pregnancy and infancy had a more favorable effect on food allergies compared with supplementation during either pregnancy or infancy alone. In this meta-analysis and review, the supplementation of probiotics during both pregnancy and infancy was associated with a decreased risk of total food allergy, cow-milk allergy, and egg allergy. Meanwhile, probiotics supplementation during infancy alone was linked to a reduced risk of milk allergy, while supplementation during pregnancy alone showed no effect on food allergy. Although direct oral supplementation of probiotics during infancy may affect immune development through allergen-specific mechanisms, concurrent probiotics supplementation during pregnancy and infancy may have broader effects on the developing immune system.¹⁴ First, it may be related to the development of the infant immune system, which is influenced by maternal cells, pathogens, and commensal microorganisms (Fig. 5). Probiotics supplementation in pregnant mothers, which may directly modulate intestinal microorganisms, can affect the number of induced cells in the fetal lymphoid tissue and the development of secondary lymphoid organs.⁵¹ Probiotics colonize the intestine and ferment dietary fibers into short-chain fatty acids (SCFAs), which, in turn, can foster immune maturation in offspring by activating G protein-coupled receptors (GPRs) on the surface of the immune cells.⁵¹ Previous studies have shown that probiotics fermentation of dietary fiber during pregnancy and lactation can induce the differentiation of regulatory T cells in the offspring.⁵² Second, maternal gut microbes can influence the composition and function of offspring gut microbes, thus promoting maturation of the body's immune system (Fig. 5). A prospective birth cohort

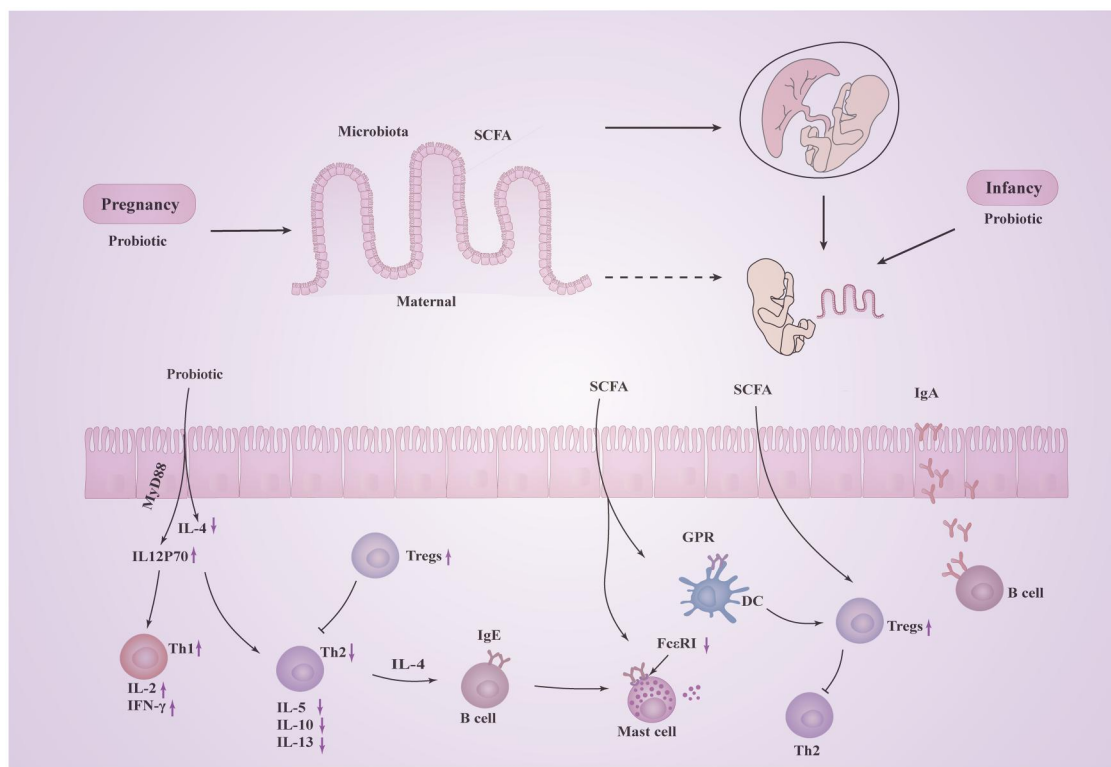


Figure 5 Schematic mechanisms by which probiotic and gut bacteria modulate food allergy in children. Abbreviations: DC, dendritic cell; FcεRI, Fc-epsilon receptor 1; GPR, G protein-coupled receptor; IFN-γ, interferon-γ; IgA, immunoglobulin A; IgE, immunoglobulin E; IL, interleukin; SCFA, short-chain fatty acid; Th, T-helper; Tregs, regulatory T cells.

study including 70 mother–infant pairs suggested that maternal gut microbiota share genes with infant gut microbiota from the perinatal period until a few weeks after birth and can shape the infant gut microbiota through horizontal gene transfer.⁵³ Newborns are born in symbiosis with microorganisms before birth and have access to oral and body surface microorganisms through birth to promote the growth and maturation of the immune system.⁵¹ Third, prolonged and higher-dose probiotic supplementation during both pregnancy and infancy is more conducive to the colonization of beneficial bacteria in the intestinal tract.

The present study demonstrated that supplementing with more than 2 types of probiotics had a preventive effect on egg and milk allergies, whereas a single type did not. Combining more than 2 types of probiotics helps colonize the intestine more easily than a single type of probiotic. The synergistic effects of multiple probiotics can also modulate the immune responses.⁵⁴ The combined use of several types of probiotics in fish significantly enhanced beneficial intestinal bacterial counts and mucosal immune responses, and altered the expression of interleukin (IL)-1β, tumor necrosis factor α (TNF-α), and IL-10 cytokines.⁵⁴ The combination of *Bifidobacterium*, *Lactobacillus*, and *Enterococcus*

significantly increases the richness and evenness of the gut microbiota in mice,⁵⁵ which may contribute to the reduction in food allergies.⁴⁵ The approach of colonization of bacteria from a healthy population without food allergies is more advantageous than using a single strain. Another study found that the colonization of healthy infants by gut bacteria can protect against cow-milk allergy in germ-free mice.⁵⁶ Therefore, targeting underlying microbiota dysbiosis could be an option for reducing food allergies in the future.

The current discourse on the impact of probiotics supplementation on allergic disease symptoms remains contentious. While probiotics supplementation did not accelerate cow-milk tolerance in infants with cow-milk allergy in this work, another study involving *Lactobacillus rhamnosus* GG (LGG) supplementation in mothers of breastfed infants with cow-milk allergy significantly improved Scoring Atopic Dermatitis (SCORAD) scores.^{57,58} Previous research suggests that probiotic supplementation can alleviate eczema and atopic dermatitis (AD) symptoms, resulting in reduced SCORAD scores and shorter eczema treatment duration.⁵⁹ In a 12-week clinical trial involving 50 children with moderate AD, the administered probiotic mixture effectively lowered the SCORAD scores and reduced

topical steroid use.⁶⁰ However, not all clinical studies support a clear role for probiotics in alleviating allergic disease symptoms. A 6-week probiotic mixture supplementation study in 100 children with mild-to-moderate AD did not reveal additional therapeutic or immunomodulatory effects of probiotics on AD treatment.⁶¹ Some studies reported side effects linked to specific opportunistic bacterial pathogens that should be avoided.^{58,59} The differential impact of probiotics is associated with the type or strain, dosage, and equilibrium of the patient's gut microbiota.⁵⁹ Additionally, an RCT with 49 participants revealed variations in the consumption of probiotic *Bifidobacterium lactis* V9 among subjects with differing gut microbiota.⁶² Therefore, individual differences emerge as a pivotal factor influencing outcomes, underscoring the need for larger studies to validate these results in the future.

The balance of gut microbiota is closely related to food allergies, and the intestinal microbiota composition differs across age groups in infants and children. As infants grow and develop, the gut microbial composition in individuals tends to be distributed toward an adult-like microbiota with a higher richness.^{63,64} In the early months of life, infants are exposed to a variety of microbial species, some of which colonize the intestines.⁶⁵ Breast milk can provide infants with more probiotics, such as bifidobacteria and lactobacilli, and prebiotics, such as oligosaccharides, making it easier to form a bifidobacteria-dominated microbiota.^{66,67} Upon the introduction of solid foods, the intestinal microbiota undergoes a transition from infancy to adulthood, gradually adopting a microbiota dominated by *Bacteroides* and *Firmicutes* genera.⁶⁸ The abundances of intestinal *Bacteroides* in food-allergic infants were inconsistent compared with healthy controls, suggesting that the intestinal flora composition of food-allergic children differed from that of normal children but tended to resemble that of adults. The abundance of 3 probiotics—*Lactobacillus*, *Bifidobacterium*, and *Enterococcus*—decreased after 48 months of age in children with food allergies compared with healthy controls. The elevated abundance of probiotics plays an essential role in regulating gut microbiota. Probiotics colonize the intestine and interact with intestinal epithelial cells or produce active substances to alleviate food-allergic diseases.^{69,70} *Prevotella copri* is a major species of the *Prevotella* genus in the human intestinal microbiome.⁷¹ It is responsible for the production of succinate, which stimulates dendritic cell (DC) function and migration.⁷² The establishment of a fetal DC network provides protection against allergic diseases. The decreased abundance of *Veillonella* in saliva and stool samples is significantly related to peanut allergy.^{73,74} *Veillonella* can reduce

inflammatory responses by degrading amylase-trypsin inhibitor variants and alleviating the symptoms of wheat food allergy.⁷⁵

Continuous probiotics supplementation in infants during the critical period of microbiota and immune system maturation may offer benefits. Two mechanisms of action for probiotics supplementation have been proposed (Fig. 5). First, probiotics supplementation may improve food-allergic diseases by rebalancing the T-helper (Th) 1/Th2 immune response.⁷⁶ Enhanced Th2 immune responses are associated with food allergies,⁷⁷ with IL-4 directing Th2 cell development. Additionally, Th2 cell differentiation induces the production of various cytokines, including IL-5, IL-10, and IL-13.⁷⁸ IL-12p70 is a major cell-mediated Th1 immune cytokine promoting the production of interferon- γ (IFN- γ) and IL-2.^{79,80} Intervention with *Bifidobacterium breve* M-16V may enhance Th1-related cytokine IL-12p70 production by activating MyD88 expression and decreasing Th2 cell proportion.⁸¹ *Lactobacillus reuteri* Fn041 regulates adaptive immune responses, leading to increases in the levels of IFN- γ and IL-12 associated with Th1, as well as reducing the IL-4 and IgE levels associated with Th2 to suppress the inflammatory infiltration of eosinophils and mast cells.⁸² *L. reuteri* Fn041 can improve early atopic immune responses by regulating the balance between Th1 and Th2 immune responses.⁸²

Second, the intestinal microbiota, engaged in complex metabolic activities, generates numerous metabolites in the body (Fig. 5). The abundances of *Prevotella* and *Veillonella* were significantly correlated with the production of SCFAs in the oral and intestinal microbiota.⁷⁴ Butyric acid-producing bacteria, including *Faecalibacterium*, *Anaerostipes*, and *Eubacterium* (effective SCFA producers),^{83–85} were decreased in this study. SCFAs binding to GPRs can activate diverse signaling cascades.⁸⁶ SCFA receptors are expressed on the surface of DCs and regulatory T cells (Tregs). SCFAs enhance the function of intestinal CD103⁺ DCs by stimulating GPR109a cell surface receptor.⁸⁷ The DC subpopulation can trigger the proliferation and expansion of Tregs in mesenteric lymph nodes, thereby promoting tolerance in the intestine.⁸⁷ SCFAs increased the number of IgA-secreting lamina propria plasma cells and B cells in Peyer's patches to protect against food allergy.^{88,89} SCFAs also directly inhibit mast cell degranulation and histamine release, regulating Fc ϵ RI-mediated signaling molecules to alleviate allergic responses.⁹⁰

A strength of our meta-analysis is the novel exploration of the distinct effects of probiotics during pregnancy or infancy on various food allergies, probing the

influencing factors and, foremost, revealing the role played by age-dependent microbiota perturbations.

However, our study had several limitations. There is a paucity of experimental evidence regarding the effect of probiotics supplementation on food allergies, especially peanut allergies. Differences in probiotics and their mixtures used in these studies could introduce bias into the results.

CONCLUSION

Probiotics supplementation during both pregnancy and infancy demonstrated greater effectiveness against food allergies compared with supplementation during either pregnancy or infancy alone, with enhanced benefits observed at higher doses. Children with food allergies exhibited age-related changes in microbial profiles, offering insight into the varying effects of probiotics on food allergies. This study introduces a novel perspective to the prevention and treatment of food allergies in children.

Despite numerous conducted studies, additional trials with larger sample sizes are required to assess the effects of diverse probiotic strains, dosages, and intervention durations on food allergies. This systematic review and meta-analysis suggested that probiotics supplementation may offer significant benefits to children with food allergies. The potential mechanism might involve modifying the composition of gut microbiota. In future research, it is crucial to further explore the factors influencing gut microbiota stabilization. Additionally, conducting gut microbiota testing before probiotic intervention could enhance its effectiveness.

Acknowledgments

Author contributions. The authors' responsibilities were as follows: L.J., V.R., and J.W. designed the study; L.J., L.Z., J.X., L.C., G.C., and J.W. conducted the research; L.J. analyzed the data and prepared the figures and tables; L.J., G.C., and J.W. wrote the paper; L.J., L.Z., J.X., L.C., G.C., and J.W. revised the paper; J.W. had primary responsibility for the final content; all authors read and approved the final manuscript.

Funding. This work was supported by the National Natural Science Foundation of China (32102093), Natural Science Foundation of Jiangsu Province (BK20210226), and Natural Sciences and Engineering Research Council of Canada (NSERC).

Declaration of interest. The authors have no relevant interests to declare.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Material S1 Search strategy

Figure S1 Nonlinear dose-responses between (a) probiotic supplementation during pregnancy and infancy, (b) probiotic supplementation during infancy and the risk ratio in food allergy, and (c) nonlinear dose-response between follow-up duration of probiotic supplementation during infancy and the risk ratio in food allergy. Shaded regions represented the 95% CIs

Figure S2 Forest plots of case-control studies for gut microbiota of alpha diversity in children with food allergy. Diversity including (a) Shannon index and (b) Simpson index, and richness including (c) Chao 1 and (d) evenness including observed OTUs

Table S1 The measures of collection, preservation, and extraction of intestinal samples and the methods of beta-diversity analysis

Table S2 Quality assessment of studies investigating probiotics supplementation during pregnancy and infancy on food allergy

Table S3 Quality assessment of studies investigating perturbations of gut microbiota composition with food allergy in children

Table S4 PRISMA 2020 checklist

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