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Effectiveness of Probiotics in Treating Food and Cow's Milk Allergies among Pediatric Age Group: A Meta-analysis of Randomized Controlled Trials

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ABSTRACT

The global prevalence of allergies is on the rise. Food allergies are of special concern among children under 5 years of age, leading to morbidity and mortality. Though the standard management is avoidance, probiotics are being used widely to prevent and treat food allergies.

We aimed to determine the effect of probiotics as a therapeutic option for controlling food and cow's milk allergy among children under 5 years of age. A systematic search of electronic medical literature databases was conducted. We included all eligible randomized controlled trials available from inception until May 2021. The primary outcome of interest was the relief of allergic symptoms, while the secondary outcome was the induction of tolerance. Two investigators undertook the literature search, screening, data extraction, and quality appraisal independently. Data analysis and synthesis were performed using STATA 14 software. Subgroup analysis was performed for the duration of use and follow-up, and the age category of children included in the outcome were done.

Twenty trials involving 4043 pediatric patients with food allergies were included in the review. Subgroup analysis also revealed that probiotics were effective in treating food allergies across the various subgroups included in the model. Around 15 trials reported our primary outcome, relief of symptoms, as a binary variable, which was pooled to obtain a risk ratio of 0.86 (95% confidence interval [CI], 0.77–0.95), with very low heterogeneity (I^2 7.7%). Six trials were included for the secondary outcome of interest, which gave an imprecise pooled estimate of 1.29 (95% CI, 0.98–1.70) with significant heterogeneity (I^2 77%).

Thus, we conclude that probiotics can serve as a vital therapeutic option in tackling food allergies among children less than 5 years of age. Further larger studies exploring the effectiveness of individual strains and their safety pattern are essential.

Keywords: Food allergy; Meta-analysis; Milk hypersensitivity; Probiotics; Randomized control trials

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INTRODUCTION

Recently, the global prevalence of allergic diseases including allergic rhinitis, food allergies, and eczema are

on the rise.[1] It is now estimated that the global prevalence of food allergy has reached 10%.[2] Food allergy is often termed as any adverse health effect that occurs due to a specific immune response that usually repeats every time after a specific food exposure." Food allergens are specific factors recognized by our immune system, causing specific allergic symptoms.[3] Symptomatology can range from common gastrointestinal symptoms, such as vomiting, gastroesophageal reflux, abdominal pain, diarrhea, blood in stools, and growth retardation; cutaneous manifestations like urticaria, pruritus, and eczema; and respiratory complaints such as wheezing, sneezing, and rhinorrhea. Sometimes these reactions could also be life-threatening, leading to angioedema and anaphylaxis.[4]

The pattern and determinants of food allergies vary considerably across age groups and according to geographical distribution. Asians are more prone to shellfish allergy, while peanut allergy is more frequently encountered in the western world. Allergies to cow's milk, wheat, eggs and maize are the other frequent types.[5] Food allergies, mainly cow's milk, are of important concern among children younger than 5 years of age. They can have significant effects on the growth and nutrition of the child, affecting their quality of life and resulting in severe morbidity. Treatment options for such allergies, though available, are limited and often costly.

The Food and Agriculture Organization of the United Nations has defined probiotics as "live microorganisms that, when administered in adequate amounts, confer health benefits to the host".[6] Probiotics are widely explored as a therapeutic option for treating food allergies. The commonly studied probiotic strains include *Lactobacillus* species (*L rhamnosus*, *L acidophilus*, *L reuteri*), *Bifidobacterium* species, *Escherichia coli Nissle 1917*, and *Enterococcus faecium SF68*. They primarily act by activating local macrophages, altering inflammatory cytokines, and modulating local and systemic IgA production as a response to food allergens.[7] Several studies have examined the effect of probiotics in treating allergies in recent years. Given the burden of this condition among children, a comprehensive systematic review and meta-analysis is necessary to support the use of probiotics in treating common food allergies. Thus, we aimed to determine the effectiveness of administering probiotics as a supplement to treat food and cow's milk allergies among children less than 5 years old as compared to placebo.

Research Question

Among children with food and cow's milk allergies, what is the effect of using probiotics as a therapeutic option for relief compared to a placebo for the control of allergic symptoms?

MATERIALS AND METHODS

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework was used for conducting and reporting our current meta-analysis.[8] Ethics approval was not required since this study involved a secondary data analysis.

Inclusion Criteria

We included all parallel-arm randomized (RCT) or cluster-randomized controlled trials (CRCT) for our review. We conducted a search for free full-text articles in the English language from the following databases: Medline, Google Scholar, ScienceDirect, EMBASE, and Cochrane Central from inception to May 2021.

Exclusion Criteria

Studies that were available as full text only were included, while studies with only abstract or unpublished data and languages other than English, involving more than five-year-old individuals and reporting diseases other than food allergies were excluded. Also, studies reporting surrogate outcomes such as lymphocyte counts, immunoglobin estimation, or other biochemical markers were not included.

Type of Participants

We included all RCTs involving pediatric patients (<5 years) with any type of food allergies (cow's milk allergy, peanut allergy, allergy to egg, fish, and shellfish, wheat allergy, and soy allergy). We include only studies reporting children with confirmed or suspected food allergies (clinical diagnosis) for our analysis.

Type of Intervention

Studies in which probiotics were orally administered, of any strain, duration, or dose, were included in our meta-analysis. This intervention was compared with a placebo control group.

Type of Outcome Measure

Primary Outcome

The primary outcome of interest was relief from allergic symptoms (e.g., wheezing, itching, hives, and swelling of the lips and nose) reported as the presence or absence of allergic manifestations after the intervention.

Secondary Outcome

Induction of tolerance: tolerance was defined as a state of healthy unresponsiveness to food allergens. Tolerance was observed to have set in if the patients no longer experienced allergic symptoms despite consumption of a particular allergen or food or after an oral food challenge. It was also noted as the presence or absence of tolerance after a specified time.

Search Strategy

We conducted an extensive electronic search on Medline, Google Scholar, EMBASE, ScienceDirect, Cochrane Central, and ClinicalTrials.gov. Medical subject headings (MeSH) were used for our literature search. The following MeSH terms were used: "probiotics" and "food allergy," “milk allergy” or "food hypersensitivity," or "food anaphylaxis," “randomized controlled trial,” “controlled trial” or “clinical trial” along with the filter of free text terms. The search was done from inception up to 31 May 2021.

Searching Other Resources

After a preliminary search, efforts were made to check the references of primary trials, and relevant articles were included for further review. Wherever possible, the authors were contacted in case of clarification or the requirement of any additional information for the methodological evaluation of the included studies.

Data Collection and Analysis

Selection of Studies

Two independent authors (HF and YW) performed the literature search independently, where the title, abstract, and keywords of all the identified studies were scrutinized for possible inclusion. For the second screening, free full-texts of the relevant articles were screened and retrieved. In case free full texts were unavailable and the article was found to fit our review, efforts were made to contact the author to get the necessary information. Any disagreements during the above process were resolved through mutual consensus.

Data Extraction and Management

The primary investigator extracted the following information from the included studies:

1. General information: study title, year of publication, and authors’ names
2. In the Methods section: study design, study participants, and setting
3. In the Participants section: number of participants in each arm, type of food allergy
4. In the Interventions section: details of the intervention group, probiotic strain, and dose
5. In the Outcome section: primary and secondary outcomes reported in the study and time of outcome assessment;

The first and second authors (HF and YW) independently extracted relevant data from the included studies. Data entry was double-checked for correctness, and in case of disagreement, it was mutually consulted among the investigators to arrive at a consensus. Only relevant arms were included when studies reported multiple arms in a single trial.

Risk of Bias Assessment

Two independent investigators (HF and YW) appraised the risk of bias for included studies using the Cochrane risk of bias tool for RCTs.[9] The following domains were assessed: random sequence generation, blinding of the participants, outcome assessment, allocation concealment, data completeness, and selective reporting of the outcome. For each of the domains mentioned above, the risk of bias was graded as low (if adequate information is provided), high (if the information is inadequate or not performed), and unclear (if the information is missing).

Statistical Analysis

Data was transferred into Stata version 14.2. (StataCorp. 2015. College Station, TX: StataCorp LP) We pooled the effect across studies for the relief of food allergy symptoms using the inverse variance method using risk ratios (RR) with a 95% confidence interval (CI) for binary outcomes (for both primary and secondary objectives) using the Mantel-Haenszel method. The analysis was performed appropriately based on the level at which the randomization was performed (either individual or clustered RCTs). Meta-analysis was performed using Stata version 14.2.

Assessment of Heterogeneity

The chi-square test of heterogeneity and I^2 statistic (to quantify heterogeneity) were used to assess the between-study variance due to heterogeneity. I^2 less than 25% was considered mild, 25-75% moderate, and more than 75% substantial heterogeneity. Study details and pooled estimates were graphically represented through forest plots. When no significant heterogeneity was observed, the fixed-effects model was used, whereas the random-effects model was used in the case of significant heterogeneity. Subgroup analysis was also performed to explore the source of heterogeneity. Publication bias was assessed and graphically represented using a funnel plot.

Sensitivity Analysis

A sensitivity analysis was performed to assess the impact of the high risk of bias among the included studies. Therefore, separate pooled estimates were obtained by analyzing studies with low and high risks of bias.

RESULTS

Study Selection

A total of 871 articles were identified through our systematic search, of which around 234 were duplicate records. After the abstract screening, 603 records did not meet our inclusion criteria and were therefore excluded. We could retrieve 34 articles as full text from the remaining articles, of which only 20 were included for the final review and meta-analysis for both objectives. The PRISMA flow diagram is shown in Figure 1. The detailed search strategy is mentioned in Supplementary Figure 6.

Characteristics of the Included Studies

Table 1 explains the characteristics of the included studies in the review. Of the 20 studies that were included[10-29], 15 (n=3491) corresponded to objective 1 to assess the effectiveness of probiotics in reducing food allergy. The remaining 5 were included (n=552) for objective 2 (rate of induction of tolerance). All studies included only children younger than 5 years old, with a follow-up ranging from 12 months to 5 years. All the included studies were randomized, placebo-controlled trials and had assessed the effectiveness of various probiotics in treating food allergies. The common food allergies were egg white, cow's milk, wheat, peanut, soybean, and buckwheat. All studies reported effectiveness as a binary outcome.

Ten studies[11-13,15,17,18,21,23,24] used *L rhamnosus* GG (LGG) as the probiotic, while 3 studies used *B bifidum* as the probiotic strain.[14,16,18] Other strains included *L casei CRL431, B lactis Bb-12, B breve Bb99 (DSM 13692),* and *B longum and B infantis*.

Excluded Studies

Of the 34 full-text articles, 14 were excluded as they failed to meet the inclusion criteria. Five articles were excluded as they involved children younger than 10 years old, 4 were excluded as they had a different probiotic as a comparator group (not a placebo), 3 had combined food and other forms of allergic children as study participants, 1 article was excluded as they reported outcomes as hypo-allergenicity of milk formula, and 1 article evaluated symbiotic, where a cointervention of immunotherapy was added.

Risk of Bias in Included Studies

The risk of bias statement and summary are represented in Table 2. We followed the Cochrane Risk of Bias tool for assessing the risk of bias among the included studies. All trials used randomization for the allocation of study participants into intervention and control arms. In most trials, information regarding allocation concealment was not provided adequately or was unclear. Despite efforts to contact the authors via email, we could not retrieve any information on the procedure. Four of the included studies failed to provide any information on the extent of blinding and thus were considered having a high risk of bias. Nine of the 20 included studies had a low risk of bias. In contrast, for the rest, the risk of bias was unclear (studies failed to provide necessary information on allocation concealment and random sequence generation).

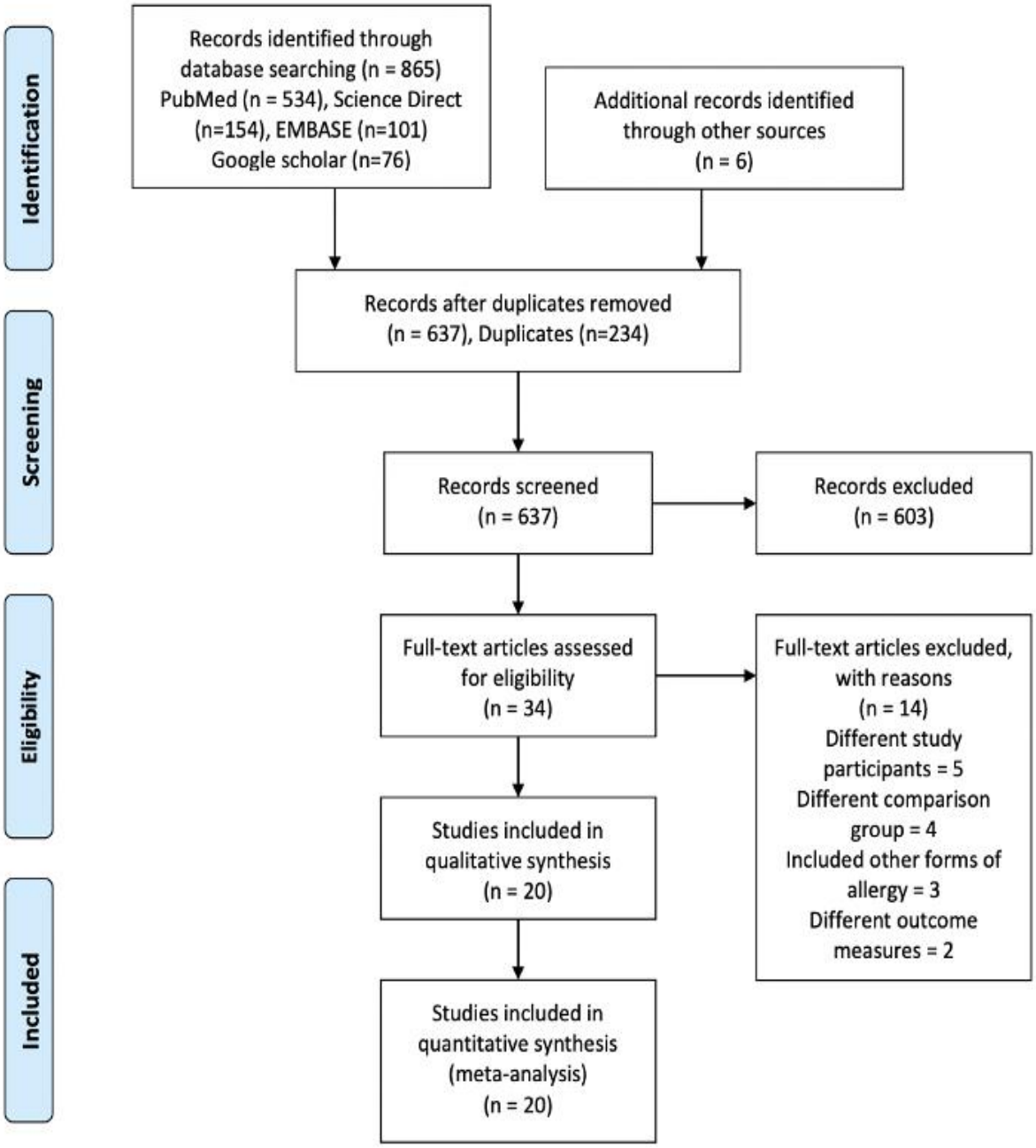

Figure 1. PRISMA flow diagram explaining the search flow

Effects of Interventions

Effectiveness of Probiotics in Treating Food Allergy

In total, 15 studies reported the association between the use of probiotics and the treatment of food allergies. (10-24) The pooled RR was 0.86 (95% CI, 0.77–0.95), indicating that probiotics effectively treat food allergies among children under 5 (Figure 2). We found very low heterogeneity between the studies reporting this outcome (I^2 7.7%, p=0.367).

Subgroup analysis based on the type of participants revealed that probiotics use significantly reduced food allergy among children under 2 years of age (pooled RR, 0.85; 95% CI, 0.74–0.99) (Supplementary Figure 1). Analysis based on the probiotic use duration revealed that probiotics remained protective against food allergy not only for durations less than 12 months (pooled RR, 0.86; 95% CI, 0.75–0.98) but also for a longer duration of administration (pooled RR, 0.75; 95%CI, 0584–0.98) (Supplementary Figure 2). Analysis taking the duration of follow-up into consideration revealed that probiotics remained effective in treating food allergy even after 12 months and 24 months of follow-up (pooled RR, 0.73; 95%CI, 0.57–0.94) and (pooled RR, 0.85; 95%CI, 0.74–0.99) respectively (Supplementary Figure 3). Subgroup analysis based on the risk of bias among the included studies showed that the pooled estimate did not vary between the low- and high-risk studies. (Supplementary Figure 4). Univariable meta-regression analysis was not done as there was not much heterogeneity. Publication bias was verified graphically using a funnel plot (Figure 3). Funnel plot showed signs of asymmetry, and it was also statistically confirmed by Egger's test (p=0.057).

Effect of Probiotic Administration on Tolerance

Development of tolerance to the administered probiotics was our secondary outcome of interest. We found that it was reported by 6 studies.[20,25-29] We considered the number of children who acquired tolerance as the event of interest. Thus, the pooled estimate of these studies was found to be an RR of 1.29 (95% CI, 0.98–1.70). This point estimate favors the use of probiotics in inducing tolerance among children with food allergies; however, it was not statistically significant as the 95% CI line included the null value. In addition, we also found that the included studies had a high degree of heterogeneity, with an I^2 of 77%. Figure 4 explains the forest plot showing the summary of the results.

We also did subgroup analysis taking the time period of tolerance measurement (Supplementary Figure 5). Two studies[25,26] were pooled at 6 months, 5 studies at 12 months,[20,25-28] and 2 more studies were pooled at ≥24 months.[20,29] At 6 months, the RR was 1.60 (95% CI, 0.62–4.90); at 12 months, it was found to be an RR of 1.24 (95% CI, 0.82–1.88); while at 24 months, we estimated the pooled estimate to be RR of 1.13 (95% CI, 0.47–2.70). Although point estimates at all follow-up durations favored probiotic use for tolerance induction, the CI was not precise or statistically significant. Moreover, significant heterogeneity (an I^2 of 79%, 84%, and 63% were observed at 6 months, 12 months, and 24 months, respectively.

Table 1. Study characteristics and effect of probiotics on Food allergy among children less than 5 years compared to placebo (n=16)

Study	Probiotics (Events/ Total)	Placebo (Events/ Total)	Sample size	Duration of intervention	Duration of follow up	Type of Allergy	Participants	Conflict of interest	Source of funding	Assessment of allergies	Strain
Abrahamsson 2007	26/76	26/72	188	12	24	Food (Both respiratory and skin manifestations)	Under 2 years	Yes	Food industry	Doctors and research nurses	Freeze-dried L reuteri (strain American Type Culture Collection 55730)*(1x10^{8} colony forming units)*
Kukkonen 2007	145/461	163/464	925	6	24	Food (Skin and respiratory manifestations)	Under 2 years	Yes	Food industry and public money	Pediatrician	*Lactobacillus rhamnosus GG(ATCC 53103), 5x10^{9} colony-forming units (cfu); L rhamnosus LC705 (DSM 7061), 5x 10^{9} cfu; Bifidobacterium breve Bb99(DSM 13692), 2x10^{8} cfu; and Propionibacterium freudenreichii ssp. shermanii JS(DSM 7076), 2x10^{9} cfu.*
Rautava 2006	2/32	3/40	72	12	12	Food (Skin manifestations)	Infant	Unclear	Food industry	Not available	*1x10 ^{10} CFU of both Lactobacillus rhamnosus* (*Lactobacillus* GG, American type culture collection 53103) *and Bifidobacterium lactis Bb-12*
Wickens 2008	44/290	31/146	474	24	24	Food (Skin and respiratory manifestations)	Under 2 years	Yes	Public money	Pediatrician	*Lactobacillus rhamnosus HN001 (L rhamnosus)* (6x10^{9} colony-forming units/d) *Bifidobacterium animalis subsp lactis strain HN019* (9x10^{9} colony-forming units/d
Kim 2010	12/31	15/29	68	6	12	Food (Skin manifestations)	Infant	Unclear	Public money	Pediatric allergist	*Mixture of B. bifidum BGN4 (*1.6 x 10^{9} colony forming units (CFU)) *B. lactis AD01 (*1.6 x 10^{9} CFU), *and L. acidophilus AD031 (*1.6 x 10^{9} CFU)
Kuitunen 2012	234/445	245/446	891	6	60	Food (Skin and respiratory manifestations)	Under 5 years	Unclear	Public money	Pediatrician	*LGG (American Type Culture Collection 53103; 5x10^{9} colony-forming units [cfu]), L rhamnosus LC705 (DSM 7061; 5x10^{9} cfu), Bifidobacterium breve Bb99 (DSM 13692; 2x10^{8} cfu), and Propionibacterium freudenreichii ssp. shermanii JS (DSM 7076; 2x10^{9} cfu)*

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Niers 2009	2/46	3/47	102	12	24	Food (Skin manifestations)	Under 2 years	No	Public money	Pediatrician	*3x10^9 colony forming units (CFU) (1x10^9 CFU of each strain: B. bifidum W23, Bifidobacterium lactis W52 (previously classified as Bifidobacterium infantis), and Lactobacillus lactis W58)*- Freeze-dried powder of the probiotic mixture
Soh 2009	7/124	6/121	253	6	12	Food (Skin manifestations)	Infant	No	Public money and food allergy	Pediatrician	*Bifidobacterium longum (BL999) 1x10^7 colony forming unit (CFU)/g and Lactobacillus rhamnosus (LPR) 2x10^7 CFU/g*
Baldassarre 2010	0/12	9/14	30	1	12	Food (Skin manifestations and GI manifestations)	Unclear	No	Public money and food industry	Pediatrician	2.50x10^7 to 5x10^8 colony-forming units (CFU)/g, and the guaranteed level of *Lactobacillus rhamnosus GG (LGG)* is 1.46x10^7 CFU/100 mL (~1x10^6 CFU/g
Wu 2010	11/34	18/36	36	6	24	Food (Skin manifestations)	Under 2 years	No	Public money	Physician	*B. bifidum, 1.5x10^8 CFU/d*
Canani 2017	15/98	26/95	110	12	36	Food (Skin and respiratory manifestations)	Under 5 years	Yes	Public money and food industry	Physician	*Lactobacillus rhamnosus GG (LGG)*
Basturk 2020	19/48	33/52	106	1	12	Food (Skin and respiratory manifestations)	Infant	Yes	Pharma industry	Pediatrician	*LGG 1x10^9 CFU and corn oil*
Plummer 2020	4/124	2/154	281	-	12	Food (Skin and respiratory manifestations)	Infant	Yes	Public money	Pediatrician	*Bifidobacterium infantis (BB-02; 300 × 10^6), Streptococcus thermophilus (TH-4; 350 × 10^6), and Bifidobacterium lactis (BB-12 350 × 10^6) once daily (total of 1 × 10^9 organisms per 1.5 g in a maltodextrin base powder)*
Nocerino 2019	18/110	23/110	330	3	12	Food (Skin and respiratory manifestations)	Under 5 years	No	Public money	Pediatric gastroenterologist	*LGG 1.46x10^7 CFU/ 100 mL (1x10^6 CFU/g).*
Cukrowska 2021	11/66	14/68	134	3	12	Food (Skin manifestations)	Under 2 years	Yes	Public money	Not available	*Lactobacillus rhamnosus ŁOCK 0900, Lactobacillus rhamnosus ŁOCK 0908, and Lactobacillus casei ŁOCK 0918*
Hol 2008	45/59	48/60	119	6	12	Food (Skin manifestations)	Under 1 year	Yes	Public money	Not available	(*Lactobacillus casei CRL431 and Bifidobacterium lactis Bb-12)*

Table 2. Risk of bias statement for the included studies using Cochrane Risk of Bias tool (n=16)

Study	Random sequence generation	Allocation concealment	Blinding of the participants and personal	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall risk of bias
Abrahamsson 2007	×	Unclear	×	×	✓	×	×	Low
Kukkonen 2007	×	✓	×	×	✓	×	×	Unclear
Rautava 2006	✓	✓	✓	✓	×	×	×	High
Wickens 2008	×	×	×	×	×	×	Unclear	Unclear
Kim 2010	×	×	×	×	×	×	×	Low
Kuitunen 2012	Unclear	Unclear	×	×	✓	×	✓	Unclear
Niers 2009	Unclear	✓	✓	✓	✓	×	×	High
Soh 2009	✓	Unclear	×	×	×	×	×	Unclear
Baldassarre 2010	×	✓	×	×	×	×	Unclear	Unclear
Wu 2010	✓	Unclear	✓	✓	×	Unclear	Unclear	High
Canani 2017	×	×	×	×	✓	✓	Unclear	Low
Basturk 2020	✓	✓	×	×	✓	×	×	Unclear
Plummer 2020	✓	✓	×	×	✓	Unclear	×	Unclear
Nocerino 2019	✓	✓	×	×	✓	Unclear	✓	Unclear
Cukrowska 2021	×	×	×	×	×	×	✓	Low
Hol 2008	×	Unclear	×	×	✓	×	×	Low

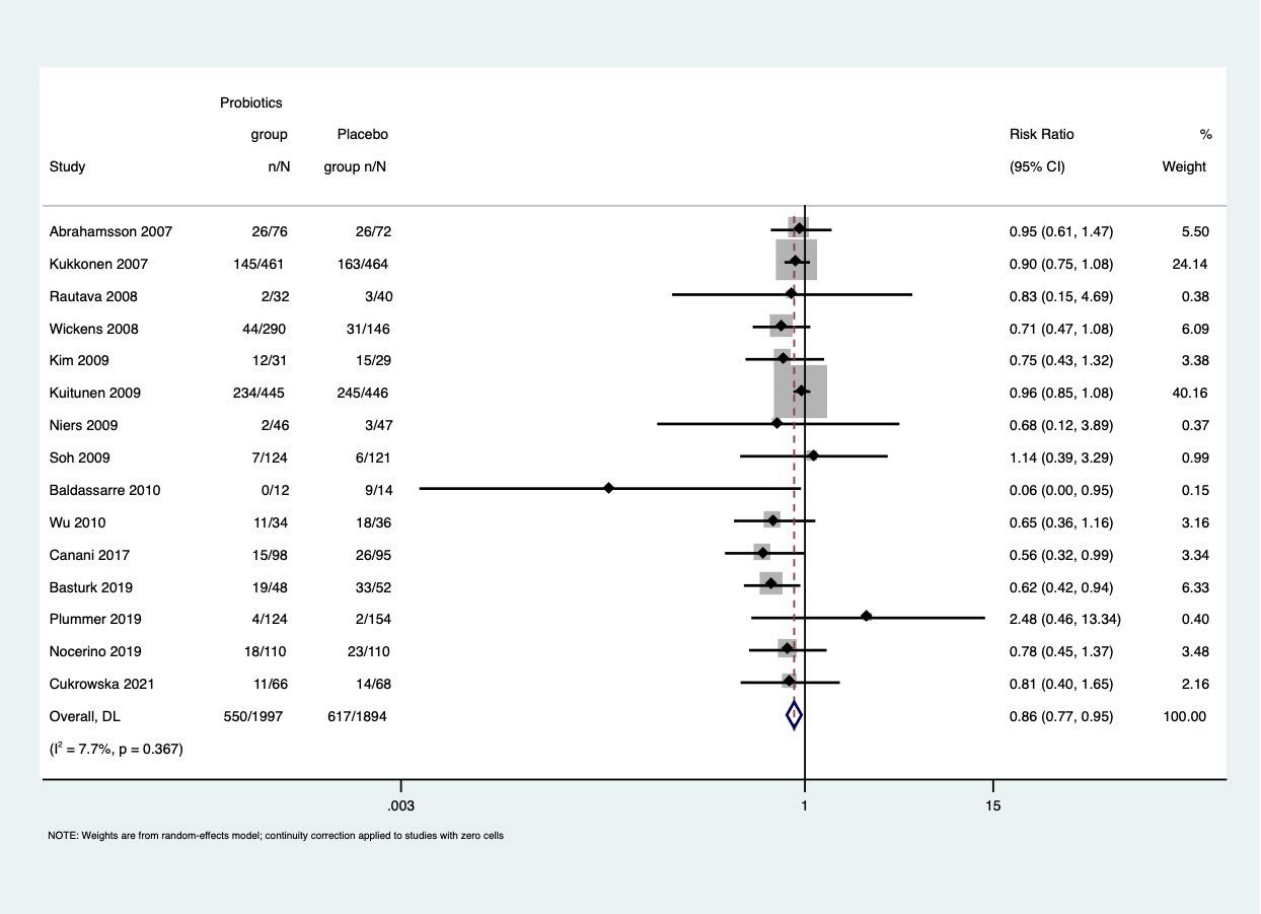

Figure 2. Forest plot showing the effectiveness of probiotics in treating food allergies among children of less than 5 years of age

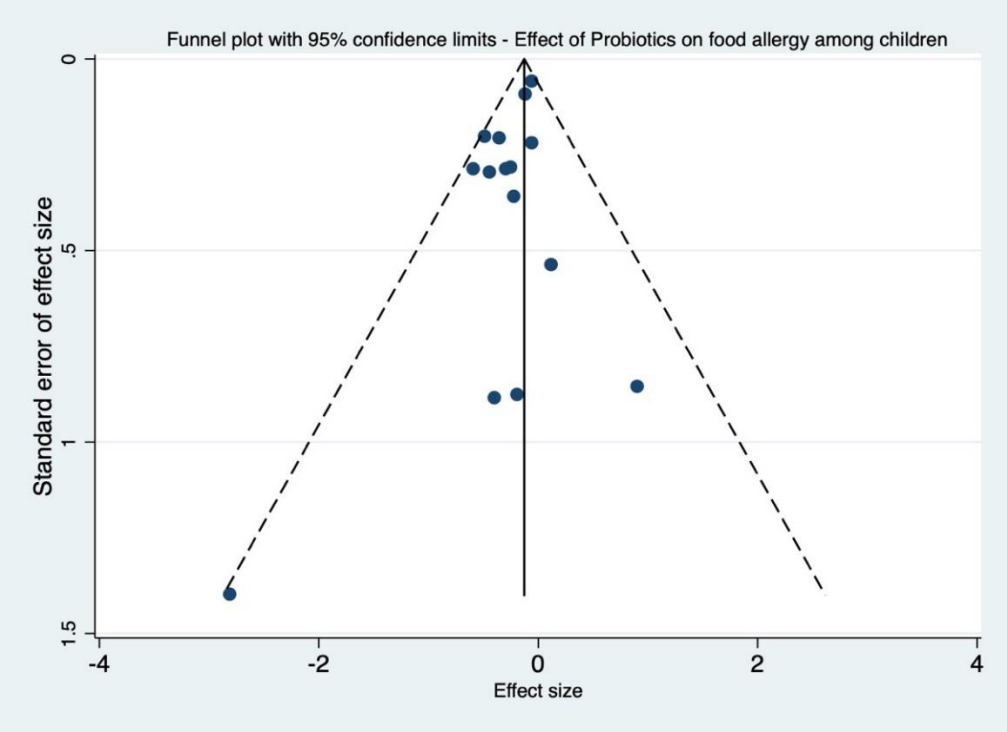

Figure 3. Funnel plot showing publication bias

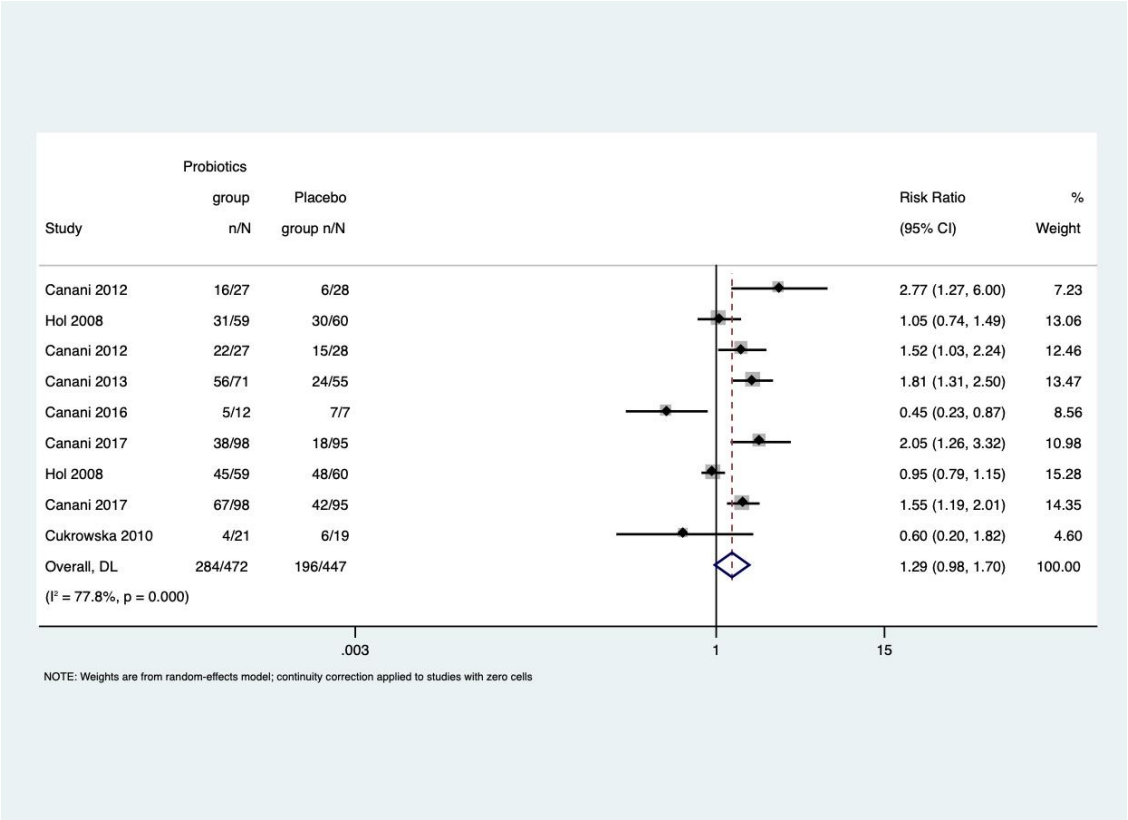

Figure 4. Forest plot showing the effectiveness of probiotics in preventing food tolerance

DISCUSSION

Our meta-analysis summarizes all available evidence to support the use of probiotics for the treatment of food allergies among children less than 5 years old with food allergies. Our study showed that probiotic supplementation significantly improved food allergy symptoms when compared to a placebo. Furthermore, subgroup analysis also revealed that the effect remained favorable in all subgroups.

Other studies and RCTs further support this finding from various study settings.[30-31] Current evidence shows that the interactions between genetic, personal, disease-related, and other environmental factors largely influence most food allergies. Gut microbiota and epigenetic mechanisms, such as DNA methylation, play a crucial role in facilitating the immune response against allergic diseases.[32]

Several mechanisms underplay this effect; firstly, the gut of newborn children serves as an immense reservoir of microbes that act as a source of immune stimulation. Secondly, supplementation of probiotics early in life might facilitate immune response. Third, the addition of favorable probiotics during the prenatal periods to pregnant women has also shown high efficacy in the immunomodulation of children's response to food allergies in the later part of life. Meanwhile, despite the World Health Organization's (WHO) suggestion for considering the use of probiotics for mothers of high-risk children and in infants having food allergies, this evidence is largely based on individual studies, and it lacks evidence exploring the effectiveness of individual strains and the duration of treatment and follow-up.[33,34] Our study is one such attempt to fill this gap, thereby speculating clinicians to experiment with the use of probiotics in treating food allergies.

Comparison with Previous Studies

Our study had findings similar to the previous reviews and meta-analyses that assess the effectiveness of probiotics in treating food allergies.[35,36] Previous studies have underscored the effect of antenatal administration of probiotics on mothers and its effect on treating food allergies among children during infancy. Previous attempts have also evaluated the effectiveness for different age groups of children, a combination of probiotic strains, and longer durations of follow-up. However, they had a few methodological flaws, as mentioned elsewhere.[36] Our updated meta-analysis has almost 20 studies with a total sample size of 4043, much higher than the previously published evidence. Subgroup analysis in our study among the various age categories of children, duration of follow-up, and duration of administration of probiotics, have also highlighted the protective nature of probiotics in children with allergies, which is in line with previous reviews.[37]

Generalizability and Applicability of Evidence

We included studies from various parts of the world involving children less than 5 years of age with any form of food allergy. The majority of studies were done in European counties (Sweden, Italy, Netherlands), Australia, and other Asian countries (Korea, Singapore), thus making the synthesized evidence to be generalizable to similar study settings. Generalizing the findings to other countries is complex due to variations in commercially available probiotic strains and protocols in place for treating food allergies. We also noted that the majority of the studies included in our review were funded by pharmacological industries and companies, thus, limiting their generalizability.

Quality of Evidence

Most of the studies included in the review had low or unclear risk of bias, according to the risk of bias tool by Cochrane that considered study participant selection, performance, outcome ascertainment, attrition, and reporting other biases for assessing the quality.

Potential Biases in the Review Process

We tried to minimize the selection bias in our review by using proper inclusion and exclusion criteria and including only RCTs in our study. All the included studies were reviewed independently by 2 authors for their applicability, and any disagreement was resolved through mutual consensus. We tried to minimize publication bias by contacting the authors to obtain the necessary information. We have used articles published in English; thus, the possibility of Language bias adds to the potential bias.

Our current systematic review and meta-analysis have suggested that probiotics may be useful in reducing food allergies among children under 5. Future research is warranted to evaluate the effectiveness of individual probiotic strains with a special focus on commercially available ones and the dose administered. More systematic reviews assessing the safety pattern of these probiotics and assess their side effects pattern, need to be encouraged.

STATEMENT OF ETHICS

An ethics statement was not required for our review since we performed a secondary data analysis of published research.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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