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Postnatal probiotics administration does not prevent asthma in children, but using prebiotics or synbiotics may be the effective potential strategies to decrease the frequency of asthma in high-risk children - a meta-analysis of clinical trials

Ewelina Wawryk-Gawda*, Ewa Markut-Miotła, Andrzej Emeryk

Department of Paediatric Pulmonology and Rheumatology, Medical University of Lublin, Lublin, Poland

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Abstract

Background: The role of probiotics, prebiotics, and synbiotics in preventing asthma and other allergic diseases has been widely explored via many randomized controlled trials. However, the results on the effect of their supplementation during infancy to the incidence of allergic rhinitis or asthma, are conflicting.

The study was designed to bring to light the potential effects of pro-, pre-, and synbiotics supplementation in early childhood with regard to the future occurrence of allergic diseases.

Method: The results of randomized controlled trials were searched for in several medical data bases. The study protocol was prepared in accordance with PRISMA guidelines and applied a Revised Cochrane risk-of-bias tool for randomized trials. Two writers were designed to perform studies selection.

Results: Eleven randomized controlled trials, among 1659 children (525 in the probiotic group, 342 in prebiotic group, 128 in synbiotic group and 833 in control groups) were analyzed. There was no difference in asthma risk development between the groups that received probiotics or placebo. We observed lower risk of asthma in children receiving prebiotic and synbiotic than in control groups.

Conclusion: The current study indicates that probiotics supplementation in the first months after birth does not decrease the risk of asthma development in the first years of life in high-risk children, although prebiotics and synbiotics may be the potential preventive factors that reduce the incidence of asthma in children.

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*Corresponding author: Ewelina Wawryk-Gawda, Lung Disease and Child Rheumatology Clinic, Medical University of Lublin, University Children's Hospital, Prof. A. Gębali Street 6, 20-093 Lublin, Poland. *Email address:* ewelina.wawryk-gawda@umlub.pl

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Introduction

Asthma is a heterogeneous and potentially serious chronic inflammatory disease of the respiratory system. It is one of the most common airway disorders and affects people in all ages, but usually begins in childhood. It has impact upon an average of 10% of all children in the European Union and North America.^{1,3} The risk factors of asthma are congenital and acquired. A positive family history of asthma or allergy is a high predictive risk value, but cesarean birth, using antibiotics in utero or in perinatal period, short-time breastfeeding, exposure to environmental pollutants and allergens, respiratory tract infections, and allergic rhinitis and dermatitis are the factors that increase the risk of asthma development.^{2,4} The symptoms characteristic for asthma are wheezing, breathlessness, chest tightness, cough and shortness of breath and may be triggered or worsened by viral infections, allergens, tobacco smoke, exercise, and stress.^{2,3,5} Children with high risk of asthma should be protected from asthma development, to prevent the consequences of impairment of life quality that children suffering from asthma must endure, as well as the severe adverse effects caused by medicaments used for asthma treatment.^{1,5} Protection of asthma development is also exigent in terms of socio-economic reasons because medicaments used for asthma treatment and their consequences are a high-cost burden for families and the society as a whole.¹

Recent data suggest that children suffering from allergies and asthma and also neonates at high-risk for asthma have altered gut and lung microbiota, reduced bacterial diversity and they are depleted for a range of anti-inflammatory fecal lipids, therefore, modulation of microbiome may be a protecting factor against asthma development.^{3,6,7} In breastfed children, oligosaccharides, and microbiota present in human milk partially regulate infant's microbiota, and these children have lower risk of asthma than those fed infant formula.^{6,8} When mother's milk is not available or reduced, supplementation of probiotics and prebiotics may have promising clinical implications.^{9,12} Probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host"; the prebiotics are selectively fermented food ingredients that result in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefits upon host health.^{13,14} A synbiotic is a mixture of both probiotics and prebiotics. It improves the host's health condition via enhancing the survival rate of the probiotic and implantation of useful intestinal microbes.¹⁵

In the last years, the role of probiotics in preventing asthma and other allergic diseases has been investigated by way of many randomized controlled trials, but the results are conflicting.¹⁶ Moreover, the safety of using viable bacteria in humans has been questioned, therefore other products regulating gut microbiota are under test.¹⁷⁻¹⁹

In this study, we performed a meta-analysis of randomized controlled trials to assess whether probiotic, prebiotic, or synbiotic administration to infants with high-risk of asthma development decreases the incidence of asthma in young children.

Material and methods

The study protocol was designed in accordance with PRISMA guidelines²⁰ and applied Revised Cochrane risk-of-bias tools for randomized trials.^{21,32}

Literature search

We searched the PubMed database (<https://www.ncbi.nlm.nih.gov/pubmed/>), Web of Science Core Collection (<https://apps.webofknowledge.com/>), Cochrane Library database (<https://www.cochranelibrary.com/view/0/index.html>), and Scopus database (<https://www.scopus.com/>) for randomized trials evaluating the effect of pro-, pre-, and synbiotics supplementation for asthma in children. In all the databases, we used the following keywords: (infant OR infants OR neonate OR neonates OR newborn OR newborns OR toddler OR toddlers OR child* OR children) AND (asthma OR asthma* OR wheeze OR wheeze*) AND (probiotic OR probiotics OR probiotic OR probiotics OR probio*) for probiotics; (infant OR infants OR neonate OR neonates OR newborn OR newborns OR toddler OR toddlers OR child* OR children) AND (asthma OR asthma* OR wheeze OR wheeze*) AND (prebiotic OR prebiotics OR pre-biotic OR prebiotics OR prebio*) for prebiotics and (infant OR infants OR neonate OR neonates OR newborn OR newborns OR toddler OR toddlers OR child* OR children) AND (asthma OR asthma* OR wheeze OR wheeze*) AND (synbiotic OR synbiotics OR syn-biotic OR synbiotics OR synbio*) for synbiotics. Search limits were set for studies written in English, involving only human subjects and published as of 2009 and up to May 2019. In addition, we manually screened references in the selected articles for additional relevant studies.

The search strategies are reported in the flow chart in [Figure 1](#). The search was conducted by authors (EWG and EMM), all the relevant studies were identified through title and abstracts reading. Duplicated articles were initially excluded. A careful analysis of full texts was done. Studies were precluded if probiotics, prebiotics or synbiotics were administered prenatally in pregnant women, if the study design was ineligible (nonrandomized, placebo-noncontrolled trials, observation studies), if it did not meet population eligibility (animal studies, studies including adults aged over 18 years), was intervention (administration of products other than probiotics, prebiotics, or synbiotics or associated with other products) or included outcomes other than asthma (diagnosis of other allergic diseases without asthma). Authors of trials were contacted for additional information. Studies on pro-, pre-, and synbiotics that met the following predefined criteria were included in the meta-analysis. Clinical diagnosis of asthma and wheezing was made according to international guidelines. Asthma herein was defined as "a chronic inflammatory disorder of the airways, usually associated with airway hyper-responsiveness and variable airflow obstruction, that is often reversible spontaneously or under treatment." Wheezing was defined as "an episode with obstructive airway symptoms."¹⁶

Study design

Double-blinded, randomized, placebo controlled trials published in English were included. Randomization was

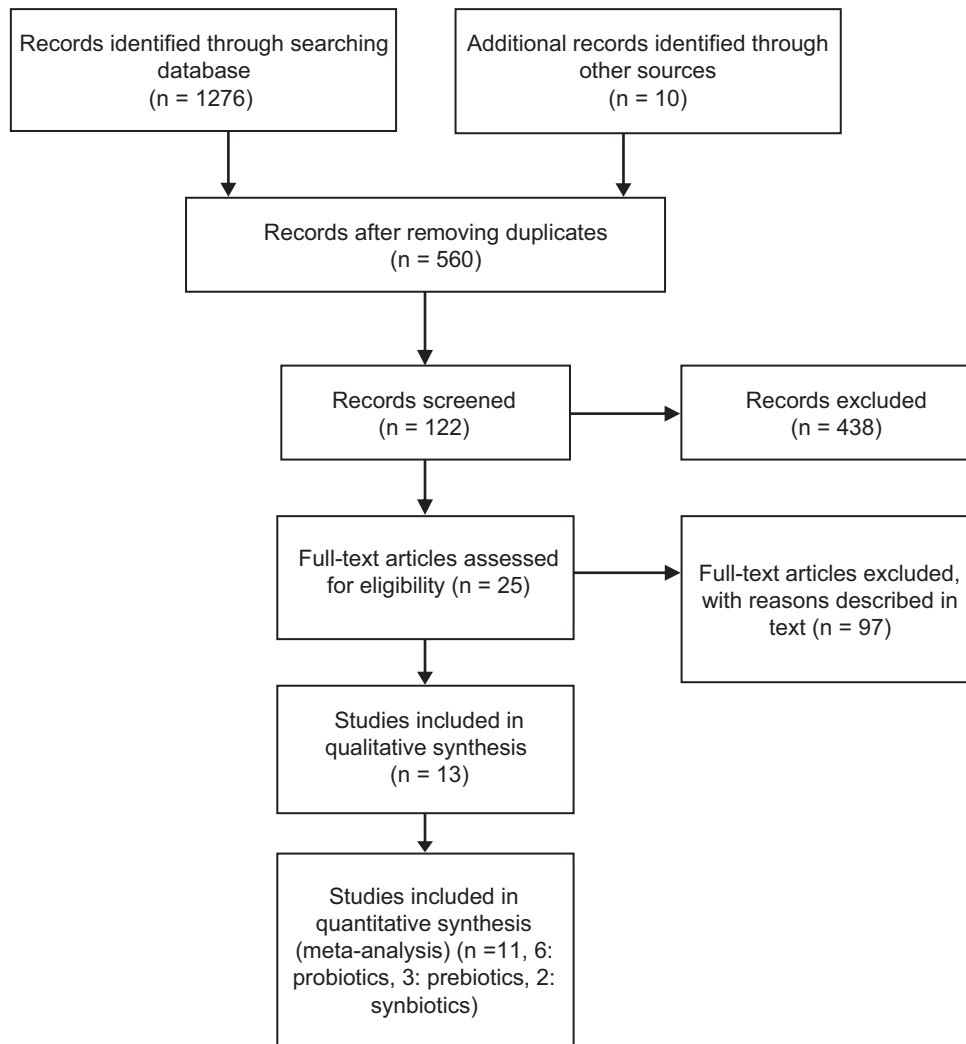


Figure 1 The search strategies.

considered adequate when a study was described as randomized and if the precise randomization method was reported. Trials were included if supplementation was directed toward children between the neonatal period and the age 18 years.

Intervention

Bacterial probiotics (single strain or mixture), prebiotics (galacto/fructooligosaccharide mixture), or synbiotics (mixture of probiotics and prebiotics) administered postnatally within the first year of life for the prevention of asthma were assessed.

Control

Control subjects were children who received a placebo or in one study, inulin.

Outcomes

Asthma or ≥ 2 wheeze was diagnosed by physicians participating in the trials.

Study quality

The quality of the included studies was evaluated by EWG and EMM according to the risk of bias as proposed by the Cochrane collaboration (Figure 2).^{16,21} The association between probiotics, prebiotics, or synbiotics use and asthma was evaluated by estimation of relative risks (RR) and 95% confidence interval (CI) for dichotomous outcomes as conducted by using the Medical Set of Statistica 13.0 StatSoft. Results of meta-analyses were presented using forest plots, while funnel plots were used for asymmetry and investigating publication bias. Random-effect models were employed for the all analyses. The Q statistic and I^2 test for inconsistency and heterogeneity was performed with a p value of 0.05 or less as a suggestion of important

statistical of significant heterogeneity. Finally, an a priori plan was made to explain inconsistency based on the differences in study populations, probiotics and prebiotics dosage, type and form of administration.

Results

Literature search

A total of 1276 articles were identified: 260 in the PubMed database (probiotics: 183, prebiotics: 57, and synbiotics: 20); 524 articles were found in the Scopus database (probiotics: 362, prebiotics: 135, synbiotics: 27); 312 in Web of Science Core Collection (probiotics: 233, prebiotics: 63, synbiotics: 16); and 180 in the Cochrane Library (probiotics: 131, prebiotics: 34, synbiotics: 15). Duplicated articles were excluded after analysis of titles (Figure 1). After a careful analysis of abstracts or full texts, studies were also excluded if probiotics were administered in animal, in pregnant women, or adults aged over 18 years. Further, 11 articles were judged as suitable for inclusion in the meta-analyses, six concern probiotics, three concern prebiotic, and two concern synbiotics.^{9,10,22-31} The characteristics of the included studies are described in Table 1.

Probiotics, prebiotics, or synbiotics and asthma

In 10 of the studies, infants were in majority considered as “high risk” if they had one or more family members with allergic dermatitis (AD), asthma, allergic rhinitis, or conjunctivitis. In one study, the family history was not specified. Infants with diagnosed AD were in two studies. Commercially available cow’s milk-based infant formula or breastfeeding was used in seven studies, while partially hydrolyzed whey-formula was used in two studies and extensively hydrolyzed whey-formula was administered in two studies. Time of supplementation varied from 3 to 7 or 8 months; age at which intervention was started varied from 0 to 10.1 months. Strains supplemented were rather heterogenous, the studies used: *Lactobacillus paracasei*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus LPR and GG*, *Bifidobacterium lactis*, *Bifidobacterium longum*, *Bifidobacterium animalis*, and *Bifidobacterium breve*. Prebiotics used in the studies were in a majority, a mixture of 90% short chain galactooligosaccharides (GOS) and 10% long chain fructo-oligosaccharides (FOS). Asthma or wheezing diagnosis required a recurrence of symptoms with a clinical diagnosis according to the international guidelines.

Data from 1659 children (525 in the probiotic group, 342 in prebiotic group, 128 in synbiotic group, and 833 in control groups) were analyzed. There was no difference in asthma risk development between groups received probiotics or placebo. The risk of asthma development was lower in the prebiotic and synbiotic groups than in the control group (Figure 2).

In the study of West et al., all infants with diagnosed asthma had a family history of allergy.²⁶

No major adverse effects were observed in the assessed studies. However, Gore et al. reported that at the 4-week visit 30.7% of all parents observed digestive

problems (green loose stools, increased vomiting, colic, and feed-refusal), so 17.5% of all children enrolled in their study stopped taking the study’s extensively hydrolyzed formula.⁹

The study populations of the included studies in this study varied to race (Caucasian, African American, American Indian, Asian, Pacific Islander, and others). However, there is no assessment of the correlation between factors of high risk of asthma and supplementation used in studies as allocated to race.

Although Figure 3 suggests the shape of funnel plot to be seemingly asymmetric (Figure 3), the applied Egger test showed no publication bias for probiotic ($p = 0.08$) and for prebiotic data ($p = 0.44$). The Egger test could not be used to analyse the synbiotics data (too small a number of studies). The L’Abby’s charts show heterogeneity (Figure 4).

Risk of bias in included studies

We used the Cochrane Risk of Bias Tool²¹ for establishing the quality of the chosen publications. Thus, we investigated the publication bias of the 11 studies in this meta-analysis. This tool assessed six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each domain was judged in the degree of low, unclear, or high risk of bias. All the studies fall to the unclear risk of bias due to reporting bias because of insufficient information to permit judgement. We found no studies at high and overall high risk of bias (Figure 5).

The Q statistic and I^2 test for inconsistency and heterogeneity was performed with a p value of 0.05 or less as a suggestion of important statistics of significant heterogeneity (Table 2).

Discussion

The results of the current study have indicated that probiotics supplementation in the first months after birth does not decrease the risk of asthma development in the first years of life. Moreover, while the assessed population was in the mostly high-risk of allergy development, the relevant data, however, regarding the effects of prebiotics and synbiotic administration is not sufficient and enough evidence supplied to unambiguously prove the beneficial effect on children’s asthma. Still, the analysis of the few trials in this study suggests that prebiotics or synbiotics added to infant formula decrease the risk of recurrent wheezing and asthma.^{10,22-25}

These results are consistent with previous studies.^{2,7,33,34} Wei et al., as with Elazab et al., report that the risk of wheezing and asthma was similar in probiotic supplemented infants with high-risk of atopy disease and as in the non-supplemented.^{2,34} In this study, the group of children also mostly consisted of children at high-risk of asthma development because of familiar history. Indeed, in one study, all the children had diagnosed AD.²³ Positive familiar history is a factor that increases the risk of asthma development in children, and eczema or food allergy might be a first manifestation of allergy. According to current data, 40% of all children with AD develop asthma eventually - this

Table 1 Characteristics of the included studies.

Authors	Strain	No. of participants that completed study	Population	Baseline age (months)	Daily Dose ($\times 10^8$)	Duration (months)	Follow-up (months)	Outcomes	Results
West 2009	<i>Lactobacillus paracasei</i> ssp F19	171	Ca 70% of children were high-risk (at least one parent with allergy)	4	10^8	6	108	Spirometry, doctor-diagnosed asthma	No statistically significant differences in diagnosed asthma between probiotic (2%) and placebo (6%) groups
Gore 2011	<i>Lactobacillus paracasei</i> CNCM I-2116 or <i>Bifidobacterium lactis</i> CNCM I-3446	133	High-risk (with diagnosed AD)	3-6	10^9	3	12,18,36	Doctor-diagnosed asthma	No statistically significant differences in diagnosed asthma between probiotic (31%) and placebo (45%) groups
Jensen 2012	<i>Lactobacillus acidophilus</i>	123	High-risk (atopic mother)	0	3×10^9	6	60	Doctor-diagnosed asthma	No statistically significant differences in diagnosed asthma between probiotic (12%) and placebo (9%) groups
West 2013	<i>Lactobacillus paracasei</i> ssp F19	121	Ca 60% of children were high-risk (at least 1 parents with allergy)	4	10^8	6	108	Spirometry, doctor-diagnosed asthma	No statistically significant differences between probiotic (20.3%) and placebo (19.4%) groups in diagnosed asthma
Loo 2014	<i>Lactobacillus rhamnosus</i> LPR and <i>Bifidobacteria longum</i> BL999	245	High-risk (a first-degree relative with asthma, AR or AD)	0	2.8×10^8	6	60	Doctor-diagnosed asthma	No statistically significant differences in diagnosed asthma between probiotic and placebo groups
Schmidt 2018	<i>Lactobacillus rhamnosus</i> GG with <i>Bifidobacterium animalis</i> subsp <i>lactis</i> (BB-12)	263	Ca 50% high-risk (First-degree relative with asthma, AR, AD or conjunctivitis)	8-14 mean 10.1	10^9 (of each)	6	6	Doctor-diagnosed asthma	Lower risk of AD in the probiotic group compared with placebo during the intervention, but asthma risk and food sensitization or food reactions was at the same level in both groups.
Arslanoglu 2008	Mixture of 90% short chain galactooligosaccharides (scGOS) and 10% long chain fructo-oligosaccharides (lcFOS)	134	High-risk (a parent with asthma, AR or AD)	0	8 g/ L hypoallergenic formula	6	24	Recurrent wheezing (≥ 3 physician-diagnosed wheezing episodes during each follow-up period)	Recurrent wheezing was more frequently in placebo group

(continues)

Authors	Strain	No. of participants that completed study	Population	Baseline age (months)	Daily Dose (x10 ⁸)	Duration (months)	Follow-up (months)	Outcomes	Results
Arslanoglu 2012	Mixture 9:1 of scGOS and lcfOS	95	High-risk (a parent with asthma, AR or AD)	0	8 g/L hypoallergenic formula	6	60	Recurrent wheezing (≥3 physician-diagnosed wheezing episodes during each follow-up period)	No statistically significant difference between groups/Wheezing was observed in 4.8% children in the scGOS/lcfOS group and in 14 % in the placebo group
Ivankhnenko 2013	Mixture 9:1 of scGOS and lcfOS;	115	Healthy	0	8 g/L a standard infant formula	ca 8,7	18	Recurrent wheezing defined ≥3 physician-diagnosed wheezing	Children fed with formula enhanced with prebiotics had rarer recurrent wheezing and allergic reactions to food and the saliva sIgA level, concentration of lysozyme in feces, saliva α-1- defensin concentration and gut microbiocenosis was similar to the breast-feeding group
van der Aa 2011	<i>Bifidobacterium breve</i> M-16V and mixture 9:1 of scGOS and lcfOS	75	High-risk (with diagnosed AD)	<7	0.8 g/100 ml hydrolyzed whey-based formula	3	12	>3 episodes of wheezing	Synbiotics significantly reduced frequent wheezing, noisy (rattly) breathing apart from colds, total IgE level, the use of asthma medications and the numbers of new asthma medication users
Cabana 2017	<i>Lactobacillus rhamnosus GG with inulin</i>	184	High-risk (at least 1 parent with asthma)	0	10 ⁹ CFU 225mg	6	60	Doctor-diagnosed asthma	No statistically significant differences between synbiotic (9.7%) and placebo (17.4%) groups in diagnosed asthma

AR: allergic rhinitis, AD: allergic dermatitis.

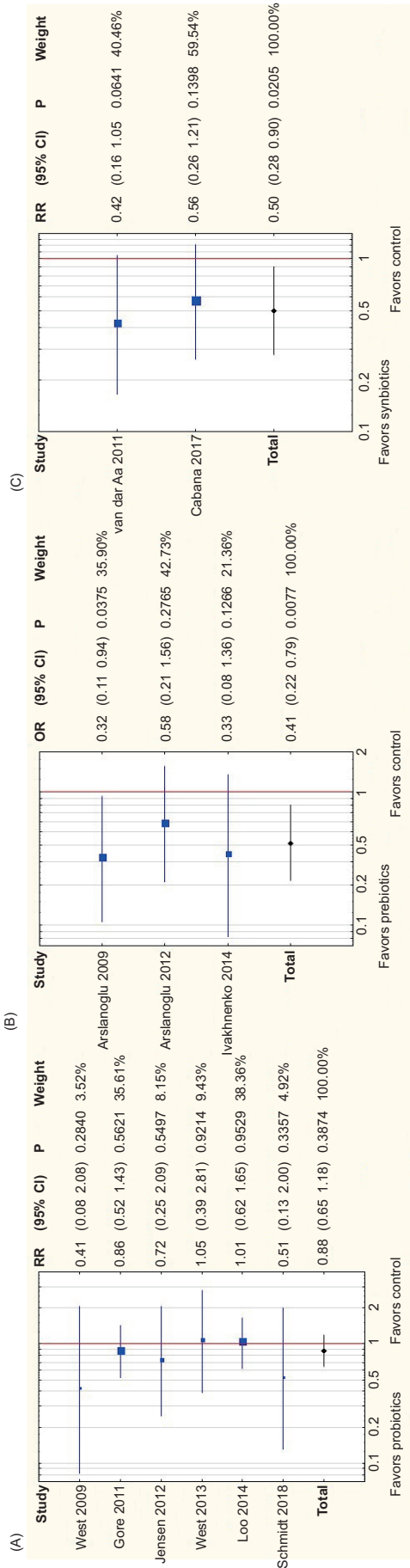


Figure 2 Forest plots for the effects of probiotic (A), prebiotic (B), and synbiotic (C) supplementation vs placebo on asthma.

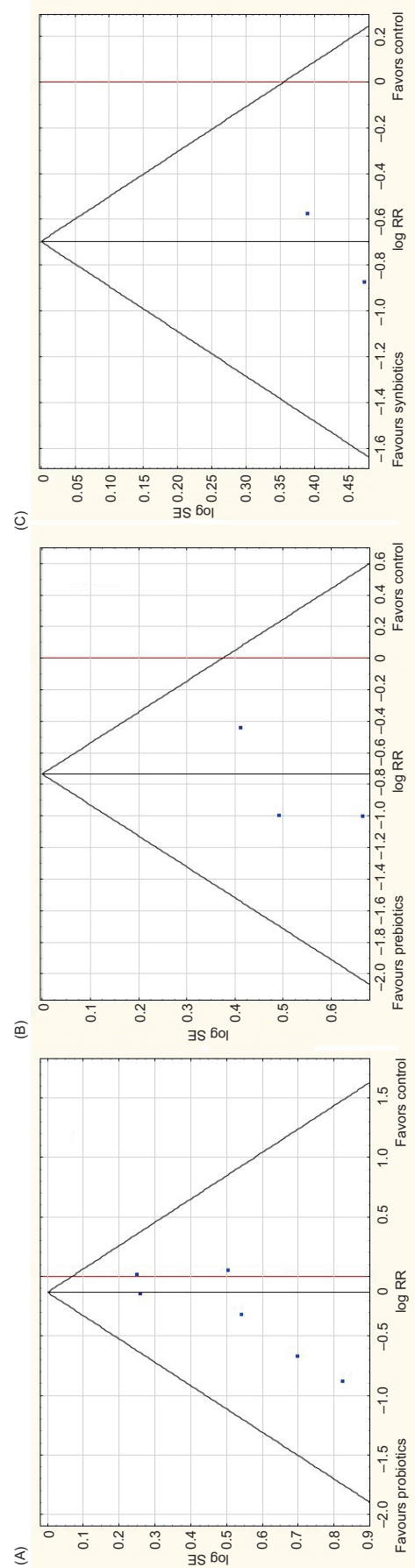


Figure 3 Funnel plots on the included studies reporting on probiotic (A), prebiotic (B), and synbiotic (C).

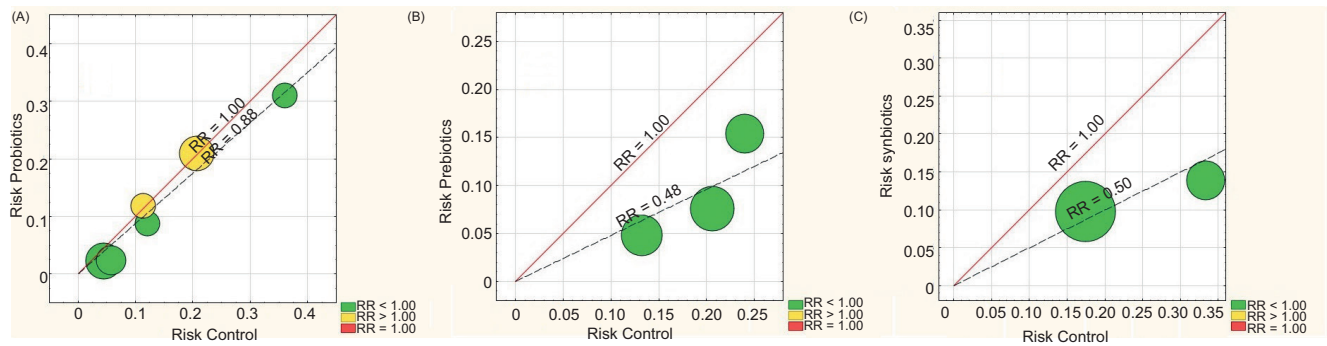


Figure 4 L'Abby's heterogeneity analysis of the included studies reporting on probiotic (A), prebiotic (B) and synbiotic (C).

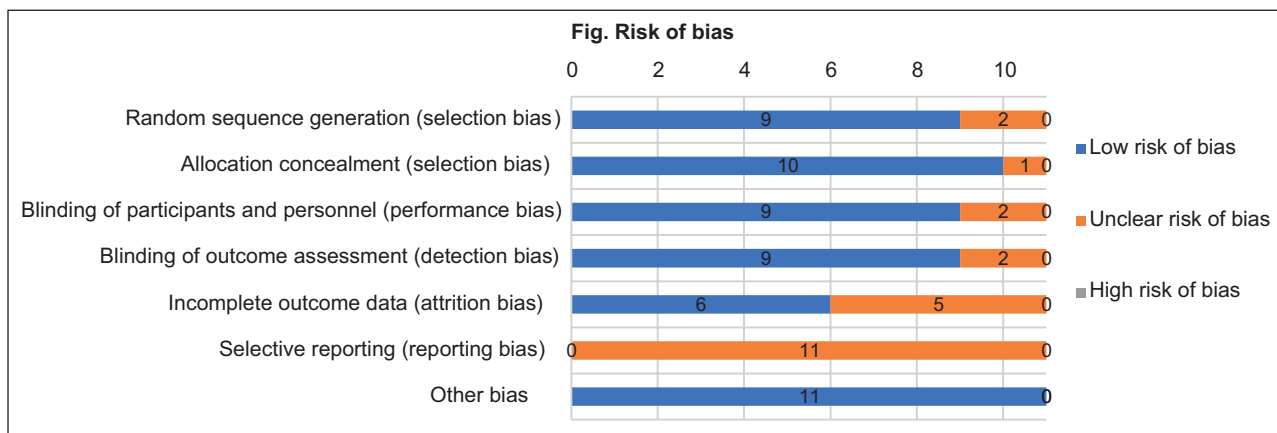


Figure 5 The assessment of the risk of bias in 11 extended follow-up studies.

Table 2 The Q statistic and I² test for inconsistency and heterogeneity.

Product	Q	p	I ² (%)	Lower border PU95%	Upper border PU95%
Prebiotics	2.03	0.84	0	0	39.43
Probiotics	0.95	0.62	0	0	92.62
Synbiotics	0.24	0.62	0	0	0

phenomenon is called the atopic march.^{9,10} Children with high-risk of atopy therefore constitute a group that should be intensively observed and protected from development of typical full symptomatologic disease. There are theories that supplementation with probiotics could decrease the risk of asthma in these children.^{3,6}

The data we obtained also indicate that children who were breastfed have lower risk of asthma development than do infants fed unfortified formula, and children with atopy have microbiomes different to that of healthy children.^{2,6,7} Human milk is a source of probiotics and prebiotics (human milk oligosaccharides, HMOs) that establish infant gut microbiota, and regulate their changes with age.^{8,35} The mechanism of action of the microbiome is associated with stimulation of the infant's naive and immature immune system, cytokine production, maintenance of the

Th1/Th2 cytokines balance and lymphocytes B maturation that are important factors of induction of immunological tolerance to food components, commensal microbiota and auto-antigens, as well as in the acquisition of the capacity to appropriately respond to pathogenic microbes.^{8,36} Human studies have indicated that pathogenic bacteria such as *Clostridium difficile* and *Staphylococcus aureus* are more frequently observed in children with atopy.³⁷ Furthermore, the proportions of coliform presence is higher in allergic children and bacteroides lower than in non-allergic children (38). Moreover, lower gut microbiota diversity in infants is associated with higher risk of asthma.⁸⁻¹⁰

Alteration of gut microbiota in consequence of cesarean birth, antibiotic administration, or mother's dysbiosis may be the factor contributing to increased incidences of autoimmune reaction. Hence, modification of the intestinal flora by supplements with viable bacteria or other products is one of the possibilities of atopy prevention.⁸ While the results of studies are conflicting, Taylor et al., have shown that children supplemented with probiotics had significantly higher colonization of *Lactobacillus*, but *Bifidobacterium* colonization was similar in probiotic and placebo groups at the sixth month of study.³⁵ Accordingly, *Lactobacillus rhamnosus* (LGG) and *Bifidobacterium animalis* subsp *lactis* (BB-12) were detected in 91% and 95%, respectively, of all the fecal samples from the probiotic group, and in 2% and 31%, respectively, of the fecal samples from all the placebo group at sixth month follow-up.³¹ However, another

study has indicated that 6 months *Lactobacillus rhamnosus* GG supplementation effect is lost at 12 months of age.⁶ Although the microbiome temporarily changes, the studies have not suggested that using probiotics in early life could prevent asthma development.^{9,29,36,37,39} In addition, Taylor et al. reported that children who received probiotics have more episodes of wheezing, are more likely develop a positive skin prick test (SPT) to milk, and have more frequent ear infections and prescribed antibiotics compared with placebo groups.³⁶ Finally, the *European Academy of Allergy and Clinical Immunology* (EAACI), in their guidelines, does not support the use of probiotics in the prevention of allergy.⁴⁰

The more hopeful group of supplements are the prebiotics.^{19,22,23} They are synthesized based on the data concerning HMOs that are the substrates for gut bacteria. These are in majority metabolized by the infant's gut microbes or excreted intact with the infant's feces, but approximately 1% of HMOs are absorbed and achieve systemic circulation. In the blood, they reach many organs other than the gut, including the liver, the brain, the respiratory tract, and the urinary tract. HMOs alter epithelial and immune cell responses with the potential to affect the infant's risk to develop allergies, asthma, and other disorders.³⁵ HMOs serve as anti-adhesives and prevent the attachment of various pathogens to the infant's epithelial surfaces, reducing infectious diseases in the gut, and potentially also the same in the respiratory and the urinary tract.³⁵ The available treatment consists of a prebiotic mixture of GOS/FOS that mimics the modulatory function of HMOs and reduces the incidence of infections and atopy.¹⁰

A combination of probiotics and prebiotics (synbiotics) may be a more effective approach to atopy prevention, and it will be active for a longer period. There are just few studies describing the results of synbiotic use to decrease the atopy development risk. Van der Aa et al. have demonstrated the statistically significant and clinically relevant benefits of synbiotics supplementation in high-risk infants, on the asthma-like symptoms and asthma medication use.²⁴ Cabana et al., in contrast, have not reported a decrease of asthma incidence in children after synbiotics supplementation.²⁵

In summary, the result of this meta-analysis have indicated that supplementation with probiotics does not have preventive effects to asthma, in high-risk infants, but prebiotic and synbiotic may be potential preventive factors that reduce the incidence of asthma in children. Still, there is a need for more studies to assess the effectiveness and safety of their use in infants. New products such as postbiotics (the fragments of bacteria or metabolites; 19) or fermented milk¹¹ could also be potential strategies of allergy and asthma prevention, because they have similar properties to probiotics, without adverse effects such as translocation of bacteria, translocation of genes anti-antibiotics or pathogenicity, because they are not viable organisms. However, this group of supplements is not yet been sufficiently tested.

Conclusions

The result of this meta-analysis have indicated that supplementation with probiotics does not have preventive

effects against asthma in high-risk infants, but prebiotics and synbiotics may be potential preventive factors that reduce the incidence of asthma in children. In view of the small sample size of the prebiotics and synbiotics groups in this study, the result should be interpreted with caution. Future powerful trials are needed to confirm if infants with atopy disease or a family history of atopy could likely benefit from prebiotics or synbiotic administration.

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Declaration of interest

The authors report no conflicts of interest.

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