

CHINESE MEDICAL SCIENCES JOURNAL

ORIGINAL ARTICLE

Probiotics' Preventive Effect on Pediatric Food Allergy: A Meta-analysis of Randomized Controlled Trials

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Key words: probiotics; food allergy; preventive effect; meta-analysis

Objective To investigate the preventive effect of probiotics on pediatric food allergy.

Methods From MEDLINE bibliographical database, we searched and reviewed all randomized controlled trials on the preventive effects of probiotics on pediatric food allergies up to September 2013 and excluded the studies that do not meet inclusion criteria and extracted the data. Meta-analysis for the results of homogenous studies was performed using RevMan 5.0 and the co-effect was pooled by using fixed-effects model of relative risk (*RR*) ratios.

Results Ten trials published between 2007 and 2012 including 2701 cases were included. Meta-analysis based on included data showed that the preventive effect of prenatal and postnatal probiotic supplementation on food allergies was not significant with the $RR=0.88$ (95% *CI*: 0.76-1.03).

Conclusion Present evidences cannot show in unequivocal terms that prenatal and postnatal probiotic supplementation will prevent food allergic diseases.

Chin Med Sci J 2014; 29(3):144-147

FOOD allergy is one of the most common diseases in Children. Decrease of early exposure to micro-organisms may increase the incidence of food allergies.¹ Aseptic animal models have already proved that normal flora play an important role in gut immunity and systemic immune development.² The amount of bacillus acidi lactici and enterococcus in the stool of children with allergies decreases significantly, which suggests that intestinal flora imbalance is associated with the occurrence of allergic diseases.³ Probiotics, as a kind of live non-pathogenic microorganisms, mainly include bifidobacterium and lactobacillus.⁴ At present, there have been

lots of randomized controlled trials about probiotics in preventing food allergic diseases in children, but most of their sample sizes are too small, and not all the research conclusions are consistent with each other. Under the light of the above, the present meta-analysis aims to examine whether probiotics are associated with food allergy's prevention in infants or children.

MATERIALS AND METHODS

Trial identification

Eligible articles were identified by a search of MEDLINE bibliographical database for the period up to October 2013 (last search: September 30, 2013) using combinations of the following key words: "food hypersensitivity", "food allergy", "polymorphism", "probiotic", "Bifidobacterium", "Lactobacillus".

Received for publication March 3, 2014.

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In addition, we checked all the references of relevant reviews and eligible articles that our search retrieved. Language restrictions were not used. Data were independently abstracted from each trial by 2 researchers independently, before which, the information of these studies which may affect researchers' selecting predispositions was hid. Disagreement was resolved by consensus. Then we did quality evaluation and bias analysis according to the quality evaluation standard raised in Cochrane Reviewer's Handbook 5.0

Inclusion and exclusion criteria

(1) Study design: All randomized controlled studies published with any sample size whose original data is complete examining the association between food allergies and probiotics were considered eligible for this meta-analysis. (2) Patients' type: Infants and their mothers whose at least 1 first-degree relatives (father, mother, brother or sister) have a history of allergic disease (asthma, allergic nose inflammation, allergic conjunctivitis, allergic eczema, food allergies, etc.). (3) Interventions: Experimental group of probiotics + placebo, the control group for placebo alone. Probiotics may be of single or multiple mixed bacteria type whose treatment course and dose are not limited. Other treatment should be consistent between the experimental groups and control groups. (4) The ending index: All randomized controlled studies taking the cumulative incidence of food allergy diseases as the judgment index for curative effect are incorporated into the analysis.

Data extraction

Data were extracted with a pre-designed review form. Data to be extracted were as follows: journal name, year of publication, inclusion and exclusion criteria, demographic characteristics of the population being studied, severity in the experimental group and control group.

Statistical analysis

Meta-analysis was performed based on the collected literatures with RevMan 5.0. Based on whether food allergies happened or not in the experimental group and control group, relative risks (RRs) and 95% confidence interval (CIs) were calculated. To judge the rationality of analyzing all the studies together, we did a heterogeneity test at first. The fixed-effects model (Mantel-Haenszel method), as well as the random effects (DerSimonian Laird) model were used to calculate the pooled odd ratio (OR). Between-study heterogeneity and between-study inconsistency were assessed by using Cochran Q statistic and by estimating I^2 , respectively. In case no significant heterogeneity was detected, the fixed effects model was chosen. Evidence of publication bias was determined using Egger's formal statistical test and by visual inspection of the funnel plot. For the interpretation of Egger's test, statistical significance was defined as $P > 0.05$.

In addition, meta-regression was performed to assess whether RR was associated with publication year, which were conducted using RevMan 5.0.

RESULTS

Literature retrieval results

A total of 621 literatures were retrieved, most of which are not standard randomized controlled trials that directly examined the association between food allergies and probiotics, and some of which are blank control trials without a placebo. The judgment indexes or patients' types of some studies do not conform to the certain standards set before. At last, a total of 10 randomized controlled trials including 2701 cases were meta-analyzed. All of them were published in English. The most recent literature was published in September 2012 (Table 1).

Table 1. Quality evaluation and their general conditions of 10 included studies

Study	Publishing year	Random method	Case number (experimental/control)	Allocation concealment	Lose visit rate (%)
Abrahamsson <i>et al</i> ⁵	2007	Unclear	95/93	Enough	18.9
Taylor <i>et al</i> ⁶	2007	Computer	88/87	Enough	18.3
Kuitunen <i>et al</i> ⁷	2009	Unclear	443/445	Enough	37.1
Niers <i>et al</i> ⁸	2009	Computer	50/48	Enough	37.1
Soh <i>et al</i> ⁹	2009	Computer	124/121	Unclear	4.1
Kim <i>et al</i> ¹⁰	2010	Computer	31/29	Enough	39.3
Boyle <i>et al</i> ¹¹	2011	Computer	108/102	Enough	15.2
Kukkonen <i>et al</i> ¹²	2011	Computer	342/346	Enough	12.5
Jensen <i>et al</i> ¹³	2012	Unclear	51/64	Enough	6.5
Berni Canani <i>et al</i> ¹⁴	2012	Unclear	37/36	Enough	8.8

All documents are double-blind studies, and their baselines are consistent.

Publication bias

Publication bias analysis of these 10 literatures was conducted through the type of funnel plot with the result of symmetric distribution (Fig. 1). Begg's test and Egger's test were also done. And both the *P* values were greater than 0.05 suggesting there is no publication bias of the literatures included.

Effect of probiotic supplementation on incidence of food allergy diseases

All these 10 articles including a total of 2701 cases investigated the relationship between the prenatal and postnatal probiotic supplementation and the incidence of food allergies. Through the meta-analysis, the final *P*=0.88 (95% *CI*: 0.76-1.03), suggesting the preventative effect of probiotic supplementation on food allergies may be not significant (Fig. 2).

DISCUSSION

Food allergy is one of the most important issues that affect infant health today. Epidemiological study showed that the improvement of human living environment especially hygienic status may be related to the increase of the incidence of food allergy. And thus hygiene hypothesis speculates that early life exposure to infectious pathogens, as well as normal gut microbiota, may influence the development of the immune system away from a Th2 response.¹⁵ Better hygiene, resulting in less microbial exposure, may lead to an increase in atopic disease. The microbial environment of the gut (microbiota) provides a major stimulus to the gut immune system. Specific patterns of microbiota colonization, such as colonization in large number by probiotics or greater microbial diversity, may favor tolerance, possibly through increased production of IgA and interleukin 10.^{16, 17}

Treatment with probiotics during the last month of pre-

gnancy and first six months of infancy may decrease IgE-associated allergic disease, particularly eczema, and sensitization to food allergens in children at high risk for atopic disease born by caesarean delivery.⁷

However, what is of vital importance is that the results of the present meta-analysis are not totally in accordance with other reports^{7,14} concerning food allergies. Although Cox *et al*¹⁸ once stated that the (positive association) "daily supplements of *Lactobacillus GG* given to infants induce an increase in a large number of taxa previously associated with a decreased risk for the development of allergy and atopy", the present meta-analysis does not strongly support this observation with the *RR* value as 0.88 (95%*CI*: 0.76-1.03), suggesting prenatal and postnatal probiotic supplementation may have some preventive effects on food allergic diseases in some degree, but not significant.

According to our data, the results in prebiotics and probiotics for prevention of food allergic diseases were inconsistent, pointing to opposite directions. At any case, the negative correlation between prebiotics or probiotics and food allergy risk essentially remains an open field.

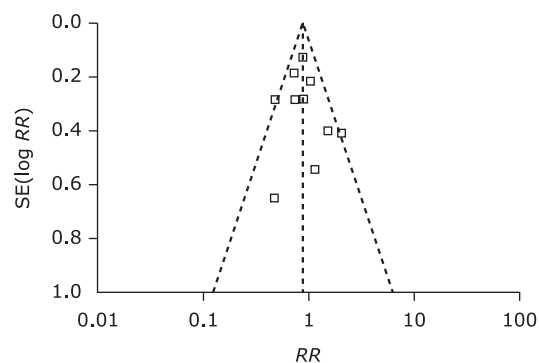


Figure 1. Funnel plot for the meta analysis of effect of probiotics on pediatric food allergy.

RR: relative risk; *SE*: standard error.

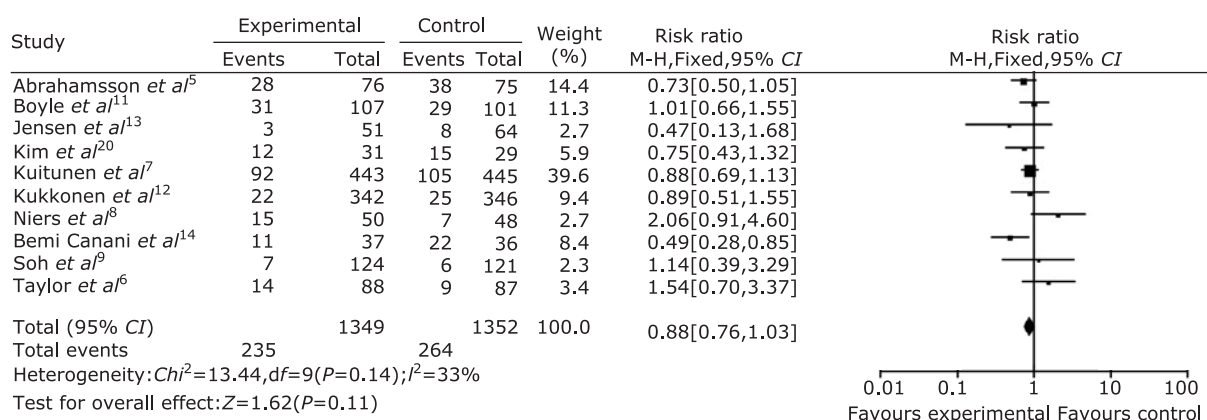


Figure 2. Results of meta analysis of the effect of the prenatal and postnatal probiotic supplementation on the incidence of food allergies.

Limitations of our study: (1) Ending time of all these 10 incorporated literatures is inconsistent, the longest 7 years old, the shortest 12 months. However, food allergic diseases mostly occurred in infants or young children less than 1 year old, and as infants or young children grow, their immune systems gradually developed, so many food allergies can heal themselves. Therefore, the difference of the ending points may cause these results between original literatures are not comparable. (2) Difference is relatively big between the case numbers of different literatures, which may affect the final result of this meta-analysis. (3) Flora types of probiotic bacteria used in these trials were not completely consistent. And their dose and concentration were also different. In addition, interference factors as whether the mothers smoke, environmental factors, artificial feeding, the use of antibiotics, etc. all can lead to different clinical research results. (4) Randomized controlled trials are from different countries, for different races, under different environment, so the children analyzed here may have different sensitivity and response differently to the same dose and concentration of probiotics, which may also affect the final results.

In conclusion, present evidences can not show in unequivocal terms that prenatal and postnatal probiotic supplementation will prevent food allergic diseases ($RR=0.88$, $95\%CI$: $0.76-1.03$). The underlying mechanism, if existing, by which probiotics improves food allergy still remains to be investigated. The need for additional studies on probiotics for food allergy seems warranted, as the results remain inconclusive.

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