Original Article

The effect of probiotics in the prevention of atopic dermatitis in children: a systematic review and meta-analysis

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Background: Probiotics have anti-inflammatory effects and can alleviate clinical symptoms of atopic dermatitis (AD) in children. However, the effects of probiotics on AD in children were controversial. This study aimed to evaluate the clinical efficacy of probiotics in the prevention of AD in children by a meta-analysis method.

Methods: Randomized controlled trials (RCTs) on probiotics in the prevention of AD in children performed at home and abroad were searched in the PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang databases using a combination of subject terms and free terms. The retrieval time was from the establishment of the database to November 2022. Meta-analysis was performed by using Stata 14.0 software. The inclusion criteria were based on the Population, Intervention, Comparison, Outcomes and Study (PICOS) framework. (I) Participants: age ≤18; (II) Intervention: the intervention group received probiotics; (III) Control: the control group received placebo; (IV) Outcomes: AD; (V) the type of study: randomized control group. We collected the number of two groups and the number of AD in the included literatures. The I^2 statistic was employed to evaluate heterogeneity.

Results: Thirty-seven RCTs were eventually included, including 2,986 in the experimental group and 3,145 in the control group. The meta-analysis showed that probiotics were superior to placebo in the prevention of AD [risk ratio (RR) (95% confidence interval): 0.83 (0.73, 0.94), I^2=65.2%]. The sub-group meta-analysis showed that the clinical efficacy of probiotics in the prevention of AD was more significant in the following groups: mothers and infants, before and after childbirth, *Lactobacillus rhamnosus* or mixed probiotics, follow-up time ≤2 years, and conducted in Europe.

Conclusions: Probiotic intervention may provide an effective means of preventing AD in children. However, due to the heterogeneity of the results of this study, the results need confirmation in follow-up studies.

Keywords: Probiotics; atopic dermatitis; prevention; meta-analysis

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Introduction

Atopic dermatitis (AD) is a relapsing, chronic, non-infectious, inflammatory skin disease characterized by persistent itching of the skin, with an incidence of up to 20% in children (1,2). In recent decades, the incidence of pediatric AD has been increasing every year in both developed and developing countries (3). The clinical manifestations of AD in children include eczema-like rashes, such as erythema, papules, and exudative lesions at specific sites (4). As a non-fatal skin disease, pediatric AD imposes a significant psychosocial burden on patients and their families. A previous study reported that children with AD are more likely to have allergies, asthma, and mental health problems (5). Infants and children with AD are often treated with topical corticosteroids, antihistamines, and even antibiotics (6). However, these drugs have some side effects, and AD symptoms may recur quickly after the treatment is stopped. Therefore, it is necessary to carry out relevant research on the prevention and treatment of AD in children.

A previous study found that the gut microbiota is closely related to the occurrence and development of various human diseases. The gut microbiota of newborns comes from customized meconium, which is the result of maternal intestinal translocation. The gut microbiota in the early stages of the body's life may play an important role in the occurrence of allergic diseases in the subsequent life cycle (7). Changing the microbiome of the body can effectively prevent and treat allergic diseases. According to the definition of the World Health Organization, probiotics are living microorganisms that have a beneficial effect on the host organism and help protect the host from harmful bacteria (7). When given in sufficient amounts, probiotics can exert beneficial effects not only in the gastrointestinal tract but also in the gut-brain-skin axis (8-10). Previous studies have reported that probiotics exert anti-inflammatory effects and can alleviate gastrointestinal inflammation and the clinical symptoms of AD (11). The levels of bifidobacteria and lactobacilli in the intestines of AD patients decreased, while the levels of Clostridium increased (11). However, previous research on probiotics for preventing AD has not yielded consistent results. Ou *et al.* found in a study of 191 pregnant women and newborns that oral probiotics can reduce the risk of AD in pregnant women, but there is no significant correlation with the risk of AD in newborns (12). However, Schmidt *et al.* conducted a randomized controlled experiment on 290 study subjects and found that oral probiotics can reduce the risk of AD in newborns (13). The heterogeneity of different research results may be related to differences in oral probiotic strains, probiotic combinations, study population, and treatment duration. In this study, we performed a meta-analysis to evaluate the efficacy of probiotics at home and abroad compared with placebo in the prevention of AD in children, aiming to provide a certain theoretical basis for the prevention of AD in children. We present the following article in accordance with the PRISMA reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-200/rc).

Highlight box

Key findings

- In this study, the meta-analysis showed that probiotics can effectively prevent the occurrence of atopic dermatitis (AD). Further subgroup analysis showed that taking rhamnose-lactobacillus probiotics and mixed bacteria before and after delivery could significantly prevent the incidence of AD.

What is known and what is new?

- When given in adequate amounts, probiotics can exert beneficial effects not only in the gastrointestinal tract but also in the gut-brain-skin axis. Previous studies have reported that probiotics have anti-inflammatory effects and may reduce gastrointestinal inflammation and the clinical symptoms of AD;
- The prevention effect of *Lactobacillus rhamnosus* and probiotics with mixed flora on AD is superior, which may be related to the reduction of intestinal microorganisms such as *bifidobacterium* and *Lactobacillus* in the intestines of children with AD.

What is the implication, and what should change now?

- AD in children can be prevented in clinical practice using probiotics, especially when given pre- and postnatally;
- Further subgroup analysis of probiotic dosage and supplementation time was not performed in this study, which can be explored later.

Methods

Literature search strategy and inclusion and exclusion criteria

The search terms were based on the objectives of this study. The English and Chinese search terms were as follows: "infant", "children", "Atopic dermatitis", and "Probiotic". Based on the above search terms, a systematic search was carried out in the China National Knowledge Infrastructure (CNKI), Wanfang database, PubMed, and Web of Science databases, and the retrieval time was from the establishment

of the database to November 10, 2022. A manual search was also performed of all relevant literature, including published reviews and meta-analyses.

The inclusion criteria were based on the Population, Intervention, Comparison, Outcomes and Study (PICOS) principle: (I) Study: the article is clearly indicated as a randomized controlled trial (RCT); (II) Participants: the age of the observation object is ≤18 years old; the observation object is clinically diagnosed with AD; (III) Intervention: the experimental group was treated with probiotics (including *Lactobacillus*, *Bifidobacterium*, *Lactobacillus rhamnosus*, or mixed microbial communities).; (IV) Comparison: the control group was treated with a placebo. (V) Outcome: the clinical diagnosis is AD. However, if multiple reports assessed the same group of patients, we only selected the latest complete report.

The exclusion criteria were as follows: (I) the subject of the study was not probiotics and pediatric AD; (II) there was no control group, the baseline balance of the components was poor, or the two groups were not comparable; (III) outcome: the evaluation indicators were not clear; (IV) duplicate or incomplete literature, such as literature with only an abstract but no full text and no contact with the author, or literature with missing specific data (the number of people in both groups and the occurrence of AD were not reported); (V) reviews or case reports.

Data extraction and quality assessment

Two researchers independently conducted a quality assessment and extracted the data, and any disagreements were resolved through third-party discussion. The following data were extracted from the studies included in this article: author, year, recipients of intervention, the timing of probiotic intervention, duration of probiotic intervention, type of probiotic, follow-up time, study region, and other information.

The risk of bias in the included studies was assessed using the Cochrane systematic review methods tool (Cochrane ROB Tool v1). The assessments included sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias (14). Each quality item was categorized as low risk of bias, high risk of bias, or unclear risk of bias. The evaluation for each entry involved assessing the risk of bias as 'Yes' (low risk), 'No' (high risk), or 'Not available' (unclear risk) (15). Differences were resolved by consensus.

Statistical analysis

In this study, statistical analysis was performed using STATA 14.0 (Computer Resource Center, USA). Each effect size was represented by the risk ratio (RR) and its 95% confidence interval (95% CI). Heterogeneity testing was evaluated using I^2 (the proportion of heterogeneity variation to overall variation). When I^2=0, it indicates homogeneity and no heterogeneity between studies; I^2<50%, with low heterogeneity. For cases where heterogeneity does not exist or is low, a fixed effects model is used for meta-analysis; I^2≥50%, with significant heterogeneity between studies, a random effects model was used for meta-analysis. Conduct subgroup analysis on the intervention target (mother and/or infant), intervention timing (pre/post-natal), type of probiotics (*Lactobacillus/Bifidobacterium*, or *Lactobacillus rhamnosus* and mixed microbiota), intervention duration (<2 years/≥2 years), and experimental region (Europe, Oceania, or Asia). The Harbor method is based on the statistics and variance of integral tests to correct linear regression, which can avoid the risk of adding Class 1 errors to the traditional publication bias detection method Egger test. The Harbord method was used to determine whether there was publication bias among the included studies. Heterogeneity was assessed using Rabe plots. If the circles on the Rabe diagram are distributed in a straight line, it indicates that the heterogeneity in meta-analysis is relatively small. Statistical analysis with P<0.05 indicates statistical significance.

Results

Literature search results and the basic characteristics of the included articles

A total of 786 studies were initially obtained, including 341 articles retrieved from PubMed, 258 from Web of Science, 18 from CNKI, and 169 from the Wanfang database. Of these, 118 studies were excluded by eliminating duplicate articles; 423 studies that do not align with the research topic were excluded by reading the titles, abstracts, and full texts and 128 studies, including comments, reviews, and case reports, were excluded. After reading the full texts and re-screening, excluding 31 studies that did not find the full text and 49 studies with incomplete clinical data (without

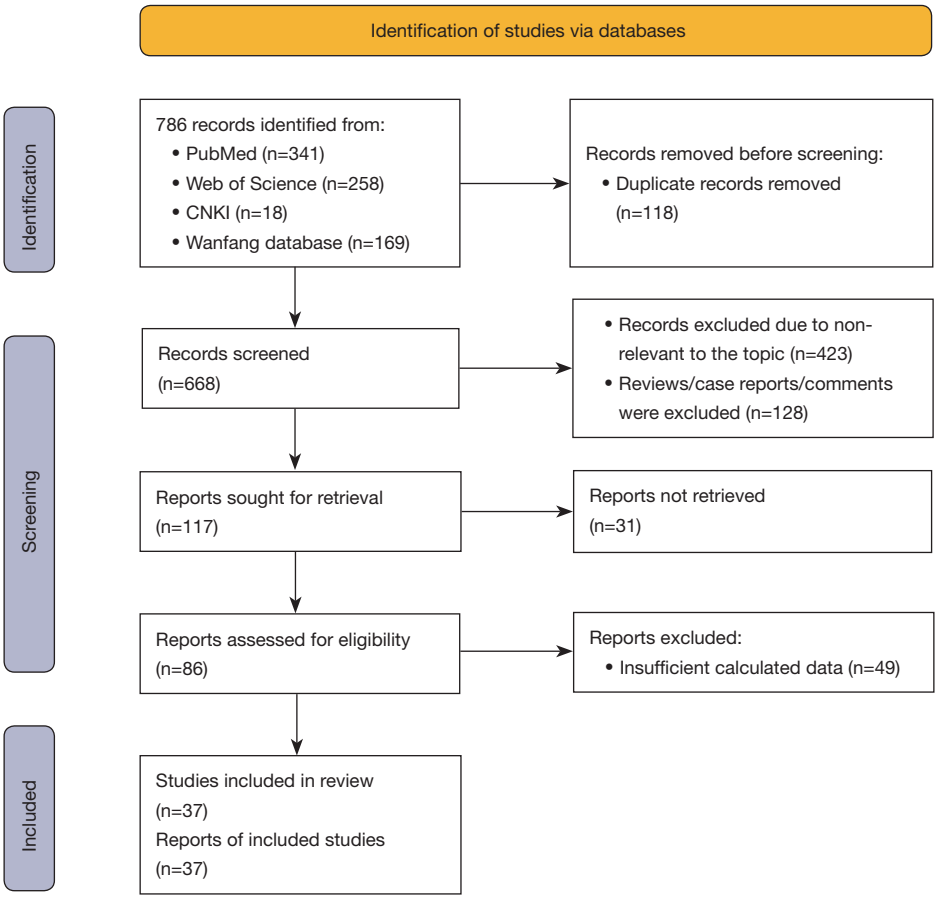

Figure 1 Literature screening flow chart. CNKI, China National Knowledge Infrastructure.

reporting the occurrence of AD in both groups). Finally, 37 articles were included in this meta-analysis, with 2,986 patients in the experimental group receiving probiotics and 3,145 patients in the control group. The literature screening process and results are shown in *Figure 1*.

The basic characteristics of the included studies are listed in *Table 1*. Among them, there were 19 studies involving mothers and infants as the intervention objects, seven studies with mothers as the intervention objects, and 11 studies with infants as the intervention objects. The intervention time was prenatal in one study, postpartum in 11 studies, and prenatal and postpartum in 25 studies. Moreover, 12 studies used *Lactobacillus rhamnosus* alone, eight studies used *Lactobacillus* alone, one study used *Bifidobacterium* as probiotics, and 16 studies utilized mixed probiotics. The study area included 24 studies in Europe, six studies in Asia, and seven studies in Oceania. The research conducted by Kalliomäki [2003] (25) and Kalliomäki [2007] (26) were follow-up studies of Kalliomäki [2001] (24); studies by Kuitunen [2009] (29) and Peldan [2017] (33) were follow-up studies of Kukkonen [2007] (30); studies by Wickens [2012] (46), Wickens [2013] (48), and Wickens [2018] (44) were follow-up studies of Wickens [2008] (47). Therefore, Kalliomäki [2003] (25), Kalliomäki [2007] (26), Kuitunen [2009] (29), Peldan [2017] (33), Wickens [2012] (46), Wickens [2013] (48), and Wickens [2018] (44) were excluded. Thirty studies were finally included in further analysis.

Quality assessment of the included studies

Table 2 shows that all of the studies had a low risk of bias in terms of the blinding of investigators and patients, and 23 studies had a low risk of bias in terms of the blinding of outcome measures. Only one of the 30 studies was unclear about the random method bias; the remaining 29 studies had a low risk of random method bias. Additionally, 17 studies had low risk of bias in terms of

Table 1 Characteristics of the included studies

First author	Year	Intervention participants	Intervention timing	Intervention duration	Types of probiotics	Follow-up period	Region	Remarks
Abrahammson (16)	2013	Mothers and their infants	Prenatal and postpartum	From 4 weeks before the expected date of delivery to 12 months after delivery	*Lactobacillus*	7 years	Europe	–
Allen (17)	2014	Mothers and their infants	Prenatal and postpartum	From 4 weeks before the expected date of delivery to 6 months after delivery	Mixed probiotics: *Lactobacillus salivarius, Lactobacillus paracasei, Bifidobacterium animalis subsp Lactobacillus and Bifidobacterium bifidum*	2 years	Europe	–
Böttcher (18)	2008	Mothers and their infants	Prenatal and postpartum	From 4 weeks before the expected date of delivery to 12 months after delivery	*Lactobacillus*	2 years	Europe	–
Boyle (19)	2011	Mothers	Prenatal	From 4 weeks before the expected date of delivery to the delivery	*Lactobacillus rhamnosus*	1 years	Europe	–
Cabana (20)	2017	Infants	Postpartum	From birth to 6 months	*Lactobacillus rhamnosus*	2 years	Europe	–
Dotterud (21)	2010	Mothers	Prenatal and postpartum	From 4 weeks before the expected date of delivery to 3 months after delivery	Mixed probiotics	2 years	Europe	–
Huurre (22)	2008	Mothers and their infants	Prenatal and postpartum	From 3 months before the expected date of delivery to the end of breastfeeding	Mixed probiotics	1 year	Europe	–
Jensen (23)	2012	Infants	Postpartum	From birth to 6 months	*Lactobacillus*	1 years	Asia	–
Kalliomaki (24)	2001	Mothers and their infants	Prenatal and postpartum	From 2–4 weeks before the expected date of delivery to 6 months after delivery	*Lactobacillus rhamnosus*	2 years	Europe	–
Kalliomäki (25)	2003	Mothers and their infants	Prenatal and postpartum	From 2–4 weeks before the expected date of delivery to 6 months after delivery	*Lactobacillus rhamnosus*	4 years	Europe	A follow-up study by Kalliomaki [2001]
Kalliomäki (26)	2007	Mothers and their infants	Prenatal and postpartum	From 2–4 weeks before the expected date of delivery to 6 months after delivery	*Lactobacillus rhamnosus*	7 years	Europe	A follow-up study by Kalliomaki [2001]
Kim (27)	2010	Mothers and their infants	Prenatal and postpartum	From 8 weeks before the expected date of delivery to 6 months after delivery	Mixed probiotics	1 year	Asia	–

Table 1 (*continued*)

Table 1 (*continued*)

First author	Year	Intervention participants	Intervention timing	Intervention duration	Types of probiotics	Follow-up period	Region	Remarks
Kopp (28)	2008	Mothers and their infants	Prenatal and postpartum	From 6 weeks before the expected date of delivery to 6 months after delivery	*Lactobacillus*	2 years	Europe	–
Kuitunen (29)	2009	Mothers and their infants	Prenatal and postpartum	From 4 weeks before the expected date of delivery to 6 months after delivery	*Lactobacillus rhamnosus*	5 years	Europe	A follow-up study by Kukkonen [2007]
Kukkonen (30)	2007	Mothers and their infants	Prenatal and postpartum	From 2–4 weeks before the expected date of delivery to 6 months after delivery	*Lactobacillus rhamnosus*	2 years	Europe	–
Loo (31)	2014	Infants	Postpartum	From birth to 6 months	Mixed probiotics	5 years	Asia	–
Niers (32)	2009	Mothers and their infants	Prenatal and postpartum	From 6 weeks before the expected date of delivery to 12 months after delivery	Mixed probiotics	2 years	Europe	–
Ou (12)	2012	Mothers and their infants	Prenatal and postpartum	From 16 weeks before the expected date of delivery to 6 months after delivery	*Lactobacillus rhamnosus*	18 months	Asia	–
Peldan (33)	2017	Mothers and their infants	Prenatal and postpartum	From 2–4 weeks before the expected date of delivery to 6 months after delivery	*Lactobacillus rhamnosus*	10 years	Europe	A follow-up study by Kukkonen [2007]
Plummer (34)	2020	Infants	Postpartum	From birth to 1months after delivery	Mixed probiotics: *Lactobacillus rhamnosus*, *Lactobacillus, Streptococcus thermophilus*	1 years	Oceania	–
Prescott (35)	2008	Infants	Postpartum	From birth to 6 months	Lactobacillus	2.5 years	Oceania	–
Rautava (36)	2012	Mothers	Prenatal and postpartum	From 8 weeks before the expected date of delivery to 2 months after delivery	*Lactobacillus rhamnosus*	2 years	Europe	–
Rautava (37)	2002	Mothers and their infants	Prenatal and postpartum	From 2–4 weeks before the expected date of delivery to 6 months after delivery	*Lactobacillus rhamnosus*	2 years	Europe	–
Rø (38)	2017	Mothers	Prenatal and postpartum	From 4 weeks before the expected date of delivery to 3 months after delivery	Mixed probiotics: *Lactobacillus rhamnosus* and *Bifidobacterium*	2 years	Europe	–

Table 1 (*continued*)

Table 1 (*continued*)

First author	Year	Intervention participants	Intervention timing	Intervention duration	Types of probiotics	Follow-up period	Region	Remarks
Rozé (39)	2012	Infants	Postpartum	From birth to 6 months	Mixed probiotics: *Lactobacillus* rhamnosus and *Bifidobacterium*	6 months	Europe	–
Schmidt (13)	2019	Infants	Postpartum	8–14 months	Mixed probiotics: *Lactobacillus* rhamnosus and *Bifidobacterium*	6 months	Europe	–
Simpson (40)	2015	Mothers	Prenatal and postpartum	From 4 weeks before the expected date of delivery to 3 months after delivery	Mixed probiotics: *Lactobacillus rhamnosus*, *Lactobacillus acidophilus* and *Bifidobacterium animalis*	6 years	Europe	–
Taylor (41)	2007	Infants	Postpartum	From birth to 6 months	*Lactobacillus*	5 years	Europe	–
West (42)	2009	Infants	Postpartum	4–13 months	*Lactobacillus*	4–13 months	Europe	–
West (43)	2013	Infants	Postpartum	4–13 months	*Lactobacillus*	9 years	Europe	–
Wickens (44)	2018	Mothers and their infants	Prenatal and postpartum	From 4 weeks before the expected date of delivery to 2 years after delivery	Mixed probiotics: *Lactobacillus rhamnosus* and *Bifidobacterium*	11 years	Oceania	A follow-up study by Wickens [2008]
Wickens (45)	2018	Mothers	Prenatal and postpartum	From 24 weeks before the expected date of delivery to 6 months after delivery	*Lactobacillus rhamnosus*	1 years	Oceania	–
Wickens (46)	2012	Mothers and their infants	Prenatal and postpartum	From 4 weeks before the expected date of delivery to 2 years after delivery	Mixed probiotics: *Lactobacillus rhamnosus* and *Bifidobacterium animalis*	4 years	Oceania	A follow-up study by Wickens [2008]
Wickens (47)	2008	Mothers and their infants	Prenatal and postpartum	From 4 weeks before the expected date of delivery to 2 years after delivery	Mixed probiotics: *Lactobacillus rhamnosus* and *Bifidobacterium animalis*	2 years	Oceania	–
Wickens (48)	2013	Mothers and their infants	Prenatal and postpartum	From 4 weeks before the expected date of delivery to 2 years after delivery	Mixed probiotics: *Lactobacillus rhamnosus* and *Bifidobacterium animalis*	6 years	Oceania	A follow-up study by Wickens [2008]
Han (49)	2019	Infants	Postpartum	3 days to 10 days after birth	Mixed probiotics: *Bifidobacterium*, *Lactobacillus*, *Streptococcus thermophilus*	1 months	Asia	–
Wu (50)	2010	Mothers	Prenatal and postpartum	From 4 weeks before the expected date of delivery to the end of breastfeeding	*Bifidobacterium*	2 years	Asia	–

Table 2 Risk of bias assessment of the included studies

First author	Year	Sequence generation	Allocation sequence concealment	Blinding methods		Incomplete outcome data	Selective outcome reporting	Other potential sources of bias
				Researchers and patients	Outcome measurers			
Kalliomaki	2001	Yes	Not available	Yes	Yes	No	Yes	Yes
Rautava	2002	Yes	Not available	Yes	Yes	No	Yes	Yes
Kukkonen	2007	Yes	Not available	Yes	Yes	No	Yes	Yes
Taylor	2007	Yes	Yes	Yes	Yes	Not available	No	Not available
Böttcher	2008	Yes	Yes	Yes	Not available	Yes	No	Not available
Huurre	2008	Yes	Not available	Yes	Yes	No	Yes	Yes
Kopp	2008	Yes	Not available	Yes	Yes	Yes	Yes	Yes
Prescott	2008	Yes	Yes	Yes	Yes	Yes	No	Not available
Wickens	2008	Yes	Not available	Yes	Yes	No	Yes	Yes
Niers	2009	Not available	Yes	Yes	Yes	Not available	No	Not available
West	2009	Yes	Yes	Yes	Yes	Yes	No	Not available
Dotterud	2010	Yes	Not available	Yes	Yes	No	Yes	Yes
Kim	2010	Yes	Yes	Yes	Yes	Yes	No	Not available
Wu	2010	Yes	Yes	Yes	Not available	Yes	No	Not available
Boyle	2011	Yes	Yes	Yes	Yes	Yes	No	Not available
Jensen	2012	Yes	Yes	Yes	Not available	Not available	No	Not available
Ou	2012	Yes	Not available	Yes	Not available	No	Yes	Yes
Rautava	2012	Yes	Not available	Yes	Yes	No	Yes	Yes
Roze	2012	Yes	Yes	Yes	Yes	Yes	No	Not available
Abrahammson	2013	Yes	Yes	Yes	Not available	Not available	No	Not available
West	2013	Yes	Yes	Yes	Not available	Yes	No	Not available
Allen	2014	Yes	Yes	Yes	Yes	Yes	No	Not available
Loo	2014	Yes	Not available	Yes	Not available	Yes	No	Not available
Simpson	2015	Yes	Not available	Yes	Yes	No	Yes	No
Cabana	2017	Yes	Not available	Yes	Yes	Yes	No	Not available
Rø	2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wickens	2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schmidt	2019	Yes	Yes	Yes	Yes	Yes	Yes	Not available
Han	2019	Yes	Not available	Yes	Yes	Yes	Yes	Not available
Plummer	2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes

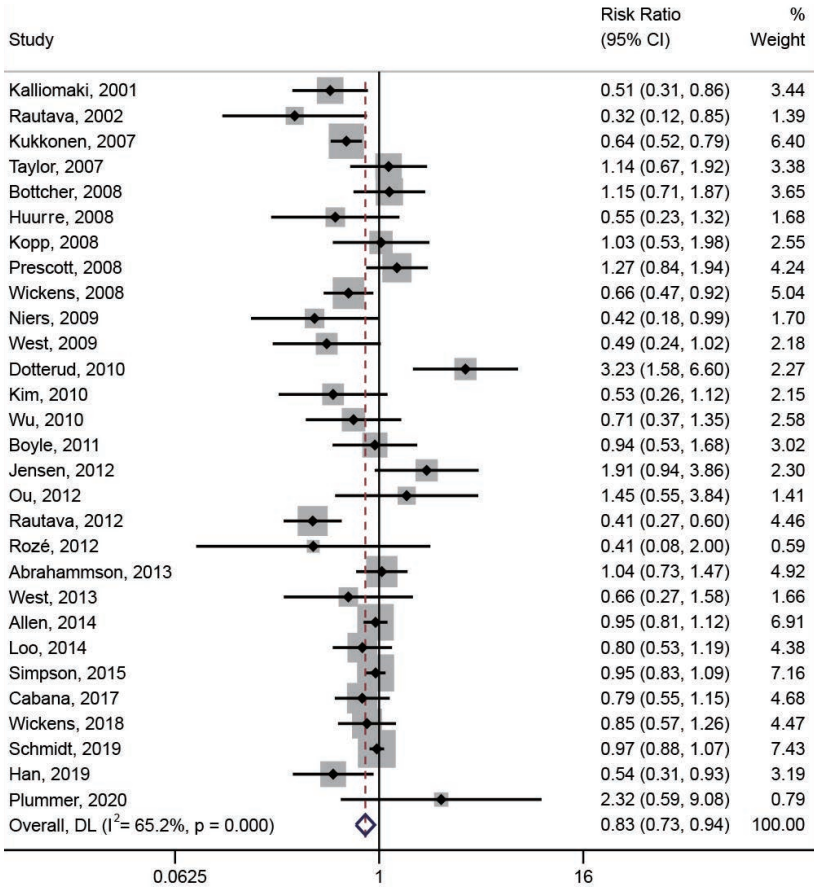

Figure 2 Forest plot of probiotic interventions for the prevention of pediatric atopic dermatitis. CI, confidence interval; DL, deep learning.

allocation concealment, 17 studies had a low risk of bias for completeness of outcome data, 15 studies had a low risk of bias in terms of the reported outcomes of selective studies, and 12 studies had a low risk of other bias.

Effect of probiotics on AD prevention

As shown in *Figure 2*, the heterogeneity test results showed that P<0.001, I^2=65.2% and $P_{heterogeneity}$<0.001, indicating that there is heterogeneity among these studies, which may originate from 49 studies with different intervention subjects, intervention timing, and probiotic dosage. Using the random effect model, the pooled effect size results showed that probiotic intervention has a significant effect on the prevention of AD [RR (95% CI) =0.83 (0.73, 0.94)].

Subgroup analysis

Subgroup analysis was carried out for the intervention object, follow-up time, intervention probiotic species, intervention duration and trial region.

In the subgroup analysis on the intervention objects (shown in *Figure 3*), probiotic intervention had a significant effect on the prevention of AD [RR (95% CI) =0.65 (0.49, 0.86), I^2=49.3%, $P_{heterogeneity}$=0.027] when the intervention recipients were mothers and infants. When the patients were mothers or infants, probiotic intervention had no significant effect on preventing AD [RR (95% CI) =0.69 (0.38, 1.26), I^2=79.7%, $P_{heterogeneity}$<0.001; RR (95% CI) =0.85 (0.62, 1.17), I^2=44.7%, $P_{heterogeneity}$=0.054].

In the subgroup analysis on the timing of the intervention (shown in *Figure 4*), the effect of probiotic intervention on

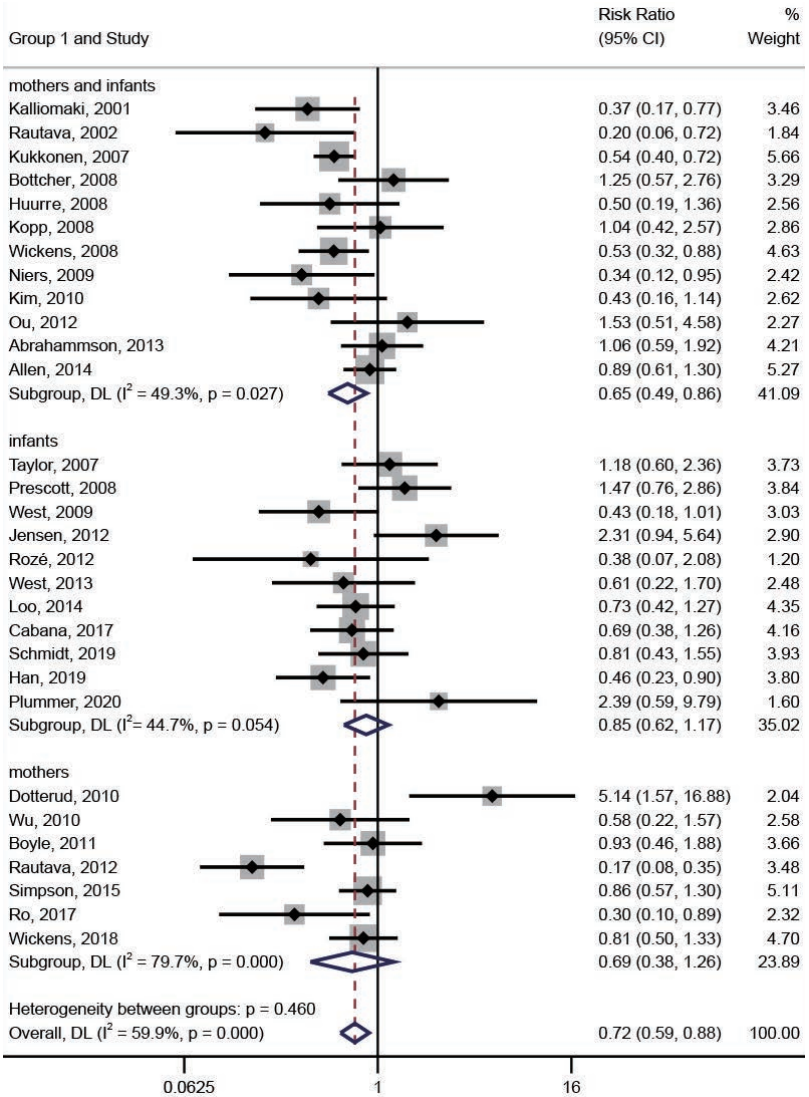

Figure 3 Subgroup analysis of probiotic interventions for the prevention of atopic dermatitis in children (grouped by intervention subject). CI, confidence interval; DL, deep learning.

the prevention of AD was significant [RR (95% CI) =0.64 (0.49, 0.85), I^2=66.6%, $P_{heterogeneity}$<0.001] when the timing of the intervention was prenatal and postpartum. However, when it was prenatal or postpartum, probiotic intervention had no significant effect on the prevention of AD [RR (95% CI) =0.93 (0.46, 1.88), I^2=0.0%; RR (95% CI) =0.85 (0.62, 1.17), I^2=44.7%, $P_{heterogeneity}$=0.054].

In subgroup analysis on the types of probiotics (shown in *Figure 5*), the effect of probiotic intervention on the prevention of AD was significant [RR (95% CI) =0.54 (0.36, 0.80), I^2=68.2%, $P_{heterogeneity}$=0.003; RR (95% CI) =0.70 (0.52, 0.93), I^2=52.4%, $P_{heterogeneity}$=0.014] when the types of probiotics were *Lactobacillus rhamnosus* and mixed flora; however, when the probiotics were *Lactobacillus* or *Bifidobacterium*, the effect of probiotic intervention on the prevention of AD was not significant [RR (95% CI) =1.09 (0.79, 1.49), I^2=25.7%, $P_{heterogeneity}$=0.224; RR (95% CI) =0.58 (0.22, 1.57), I^2=0.0%].

In subgroup analysis on the trial region (shown in *Figure 6*), probiotic intervention had a significant effect on the prevention of AD [RR (95% CI) =0.66 (0.51, 0.86), I^2=63.2%, $P_{heterogeneity}$<0.001] when the trial region was

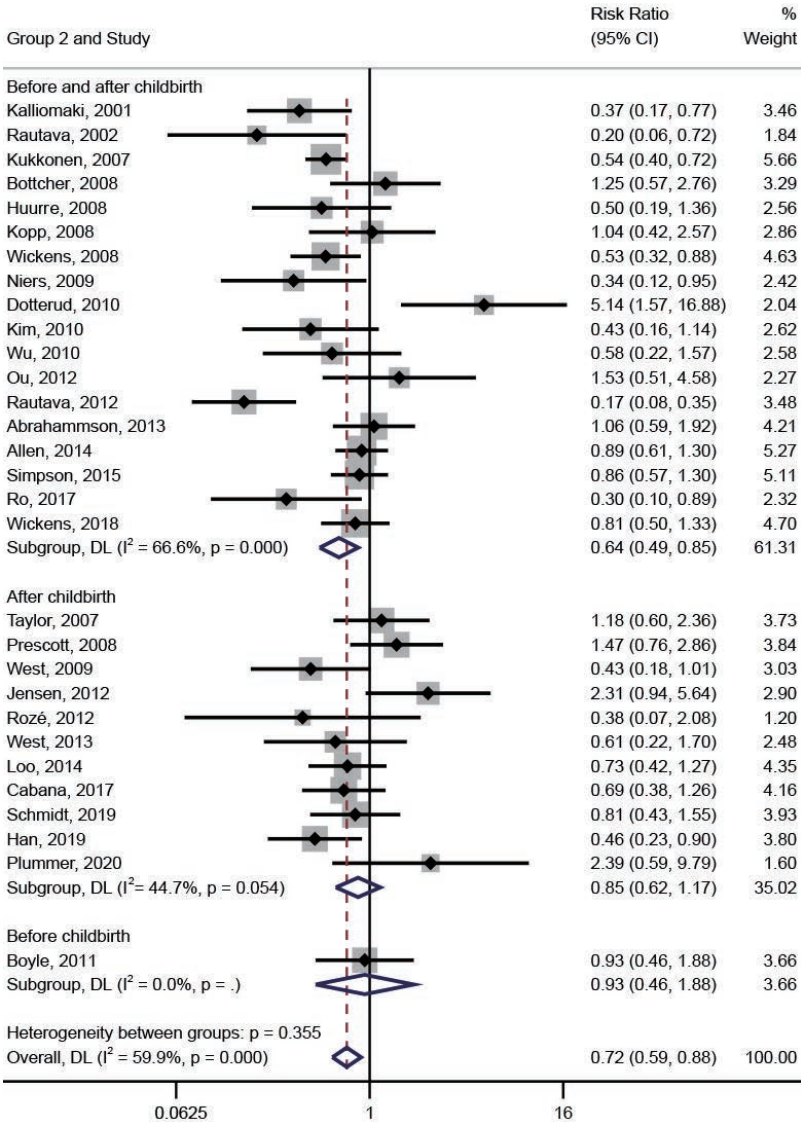

Figure 4 Subgroup analysis of probiotic interventions for the prevention of atopic dermatitis in children (grouped by timing of the intervention). CI, confidence interval; DL, deep learning.

Europe; meanwhile, when the trial region were Oceania and Asia, the effect of probiotic intervention on the prevention of AD was not significant [RR (95% CI) =0.94 (0.54, 1.61), I^2=62.6%, $P_{heterogeneity}$=0.046; RR (95% CI) =0.78 (0.47, 1.31), I^2=55.7%, $P_{heterogeneity}$=0.046].

In subgroup analysis on the follow-up time (shown in *Figure 7*), probiotic intervention had a significant effect on the prevention of AD [RR (95% CI) =0.66 (0.51, 0.85)] when the follow-up time was less than 2 years; meanwhile, when the follow-up time was longer than 2 years, the effect of probiotic intervention on the prevention of AD was not significant [RR (95% CI) =0.95 (0.75, 1.20), I^2=0.0%, $P_{heterogeneity}$=0.552].

Evaluation of publication bias and heterogeneity

As shown in *Figure 8*, the publication bias analysis results indicated that the included studies had no obvious publication bias (P=0.433). A Rabe diagram was used to evaluate the heterogeneity of the literature included in

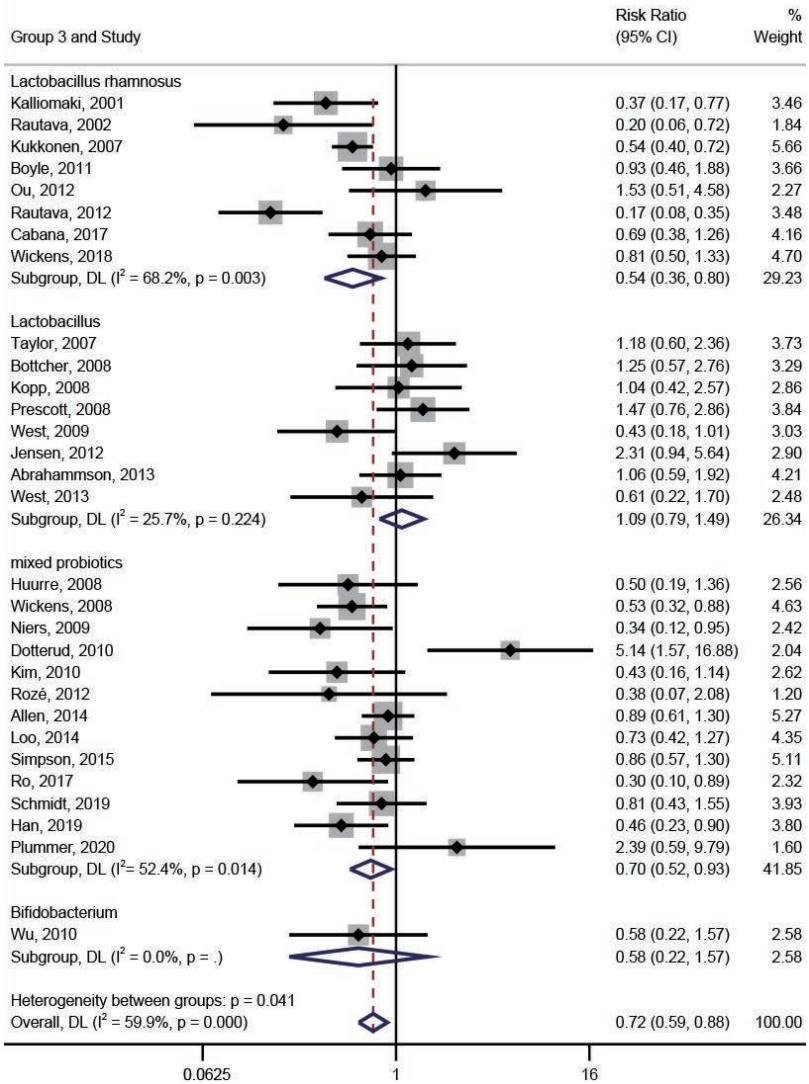

Figure 5 Subgroup analysis of probiotic interventions for the prevention of atopic dermatitis in children (grouped by probiotic species). CI, confidence interval; DL, deep learning.

the analysis, and the results are shown in *Figure 9*. The literature was basically distributed according to a straight line, indicating that the heterogeneity was small. However, it is also important to note that there may be errors in the intuitive evaluation through the use of a Rabe diagram. The results of this meta-analysis are generally reliable.

Discussion

In this meta-analysis, we systematically reviewed 37 double-blind RCTs on the preventive effects of oral probiotics in pregnant women and/or their infants on AD. The results of the analysis showed that probiotics could effectively prevent the incidence of AD. Furthermore, the subgroup analysis results showed that the occurrence of AD could be significantly prevented when mothers and infants took *Lactobacillus rhamnosus* and mixed flora probiotics before and after delivery. Also, studies with follow-up times of less than 2 years and those conducted in Europe found that probiotics were more effective in preventing AD. These findings provide evidence for the efficacy of probiotics in preventing AD in children.

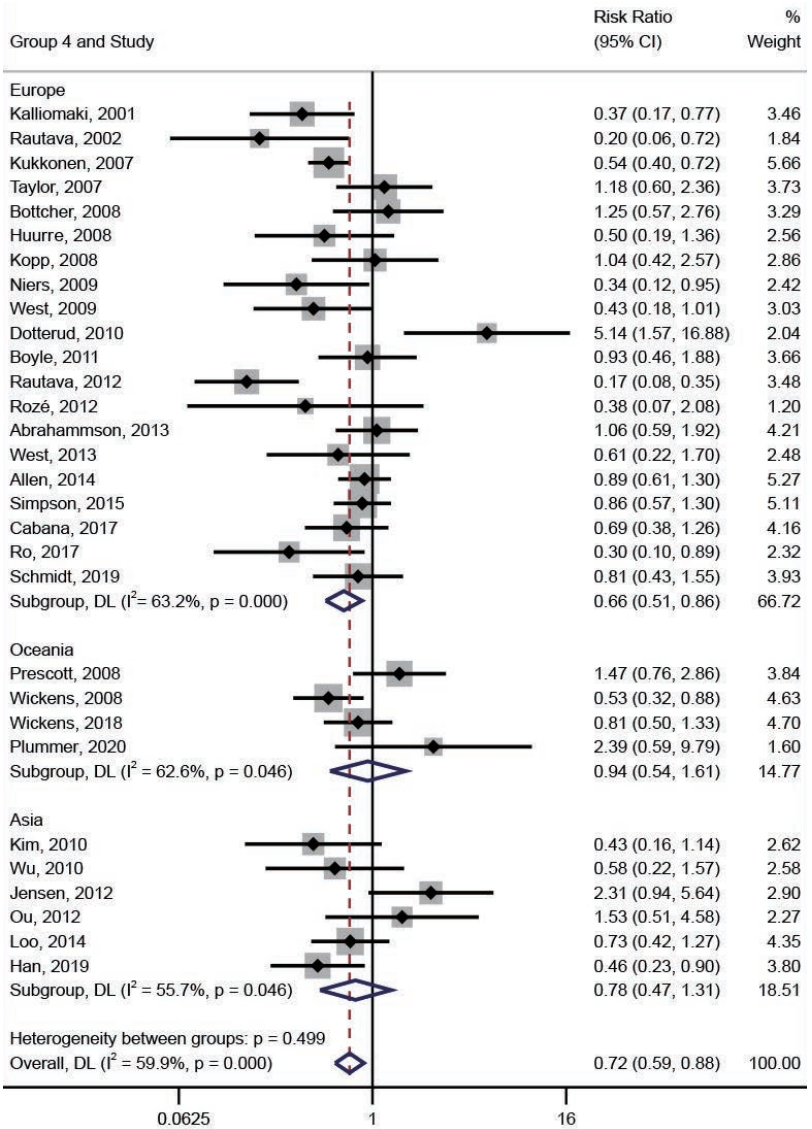

Figure 6 Subgroup analysis of probiotic interventions for the prevention of atopic dermatitis in children (grouped by trial region). CI, confidence interval; DL, deep learning.

In recent years, researchers have gained a better understanding of the physiological functions of human gut microbiota, and gut microbiota have become a research hotspot (51,52). Newborns' first exposure to microbes is provided by the maternal microbiota, and the newborn's gut microbes are influenced by the mode of delivery, type of feeding, and use of antibiotics (53). Colonized gut microbiota is indispensable for intestinal physiological regulation and immune function, and changes in their types and levels may affect the risk of related diseases.

According to the definition by the World Health Organization, probiotics are a type of living microorganism, and a certain amount of probiotics can provide benefits to the health of the host (54,55). Probiotics can promote and regulate immune maturation and prevent allergic diseases by regulating the structure of the intestinal microbiota as well as the function of immune cells (56). However, there is still no consensus on the efficacy of probiotics for the clinical prevention and treatment of allergic diseases, and further research is needed. Previous studies have analyzed

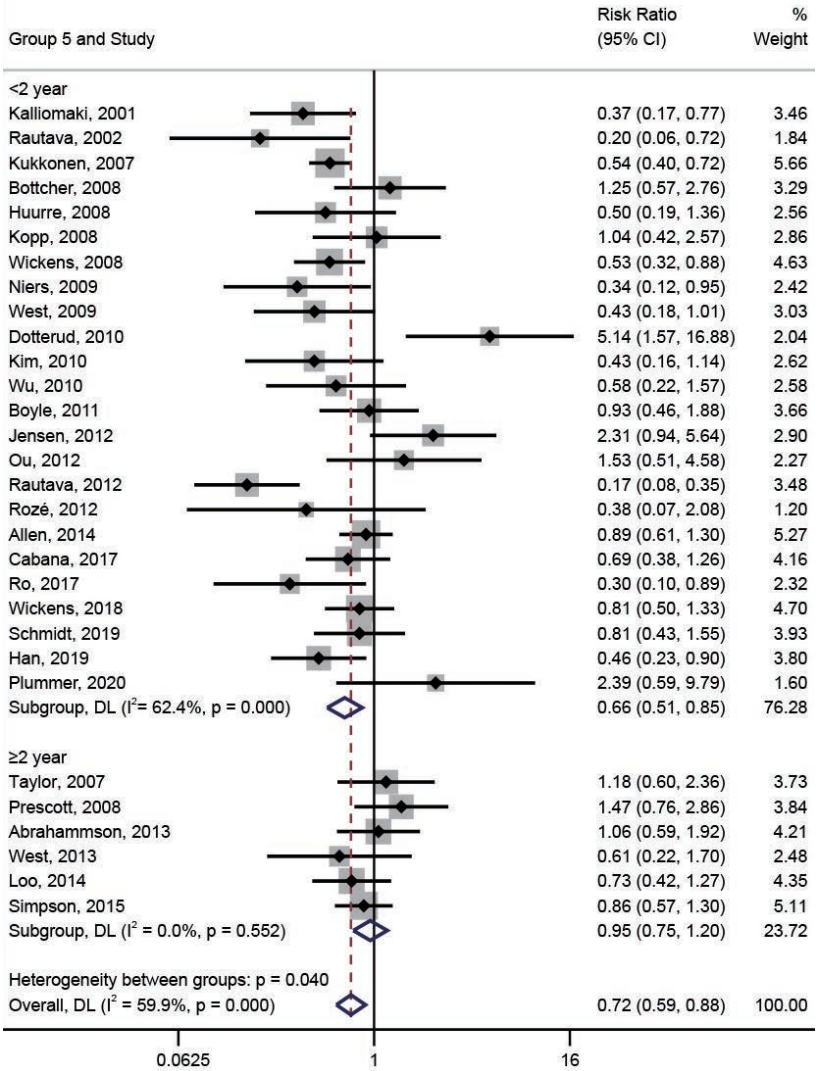

Figure 7 Subgroup analysis of probiotic intervention for the prevention of atopic dermatitis in children (grouped by follow-up time). CI, confidence interval; DL, deep learning.

the efficacy of probiotic intervention in the prevention of AD (1,38,45). However, the sample size of a single study is limited, and confounding factors such as intervention objects, types of probiotics, and appropriate intervention timing were not adjusted. Therefore, this study conducted a meta-analysis of previous studies on the prevention of AD with probiotics, aiming to provide evidence for probiotic intervention in the prevention of AD.

This study found that probiotics could effectively prevent AD [RR (95% CI) =0.83 (0.73, 0.94)], which was basically consistent with previous research results both at home and abroad. Sun *et al.* conducted a meta-analysis of 17 RCTs involving a total of 4,011 children and found that probiotic intervention had a significant benefit in preventing eczema in children [RR (95% CI) =0.59 (0.45, 0.78)] (57). Pan *et al.* conducted a meta-analysis of eight RCTs involving a total of 2,575 newborns and found that probiotics can effectively prevent AD [RR (95% CI) =0.86 (0.78, 0.95)] (58). Probiotics can stimulate intestinal immunoglobulin A (IgA), reduce the adhesion of pathogenic bacteria, and form tight junctions with intestinal epithelial cells to decrease intestinal permeability (59). On the other hand, probiotics can mediate allergic skin inflammation by promoting T helper type 1 (Th1) cytokines, reducing the

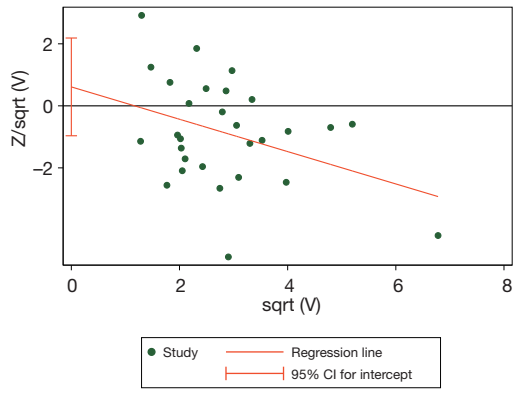

Figure 8 Assessment of publication bias. CI, confidence interval.

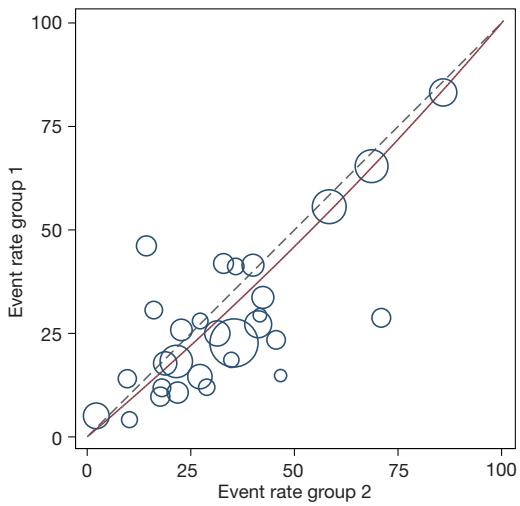

Figure 9 Rabe plot for heterogeneity assessment.

production of IgE, and decreasing the secretion of Th2 cytokines such as interleukin (IL)-5 and IL-10 (60).

Our subgroup analysis found that probiotic interventions for both mothers and infants had a significant effect on AD prevention when taken at the prenatal and postpartum stages; however, probiotic interventions only for mothers or infants, and only prenatal or postnatal interventions had no significant effect. Maternal microbes are transferred to offspring during pregnancy and can affect immune development and susceptibility to allergic diseases in the offspring (61). Prenatal and postnatal probiotic interventions are beneficial for the prevention of AD in infants. *Lactobacillus rhamnosus* and probiotics with mixed flora have better preventive effects on AD, which may be related to the reduction of intestinal microorganisms such as *Bifidobacterium* and *Lactobacillus* in the intestines of children with AD.

This meta-analysis accounted for the differences in intervention objects, intervention timing, types of probiotics, follow-up time, and trial regions, and carried out subgroup analyses to ensure that the results were detailed and reliable. Yet, there were still some limitations that should be noted. Firstly, we cannot confirm whether there are unpublished relevant data, and there may be some bias in the selection of literature and data extraction. Second, there may be differences in the criteria for AD diagnosis in different studies. In addition, this study did not conduct further subgroup analyses on the dosage of probiotics and the duration of supplementing probiotics.

In conclusion, our study found that probiotics can be an effective means of preventing AD and provide a basis for the clinical prevention of AD. Finally, it cannot be ignored that there is heterogeneity in this study, which may stem from differences in the general characteristics (age, gender, family factors, etc.) of different research subjects, as well as differences in the dosage of probiotics used. Therefore, further research is needed to explore the preventive effect of probiotic intervention on pediatric specific dermatitis in the future.

Conclusions

This study found through meta-analysis that probiotics may be an effective means of preventing AD, and this study can provide a certain degree of basis for the prevention of AD in clinical practice.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-200/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-200/coif). The authors

have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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