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SYSTEMATIC REVIEW

Probiotic Supplementation for Prevention of Atopic Dermatitis in Infants and Children: A Systematic Review and Meta-analysis

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Abstract

Background Probiotic supplementation in early life may be effective in preventing atopic dermatitis (AD); however, results regarding efficacy have been controversial.

Objective The aim of our study was to investigate the effect of probiotic supplementation on the risk of AD.

Methods We systematically searched PubMed, EBSCO, Embase and Web of Science databases up to 8 March 2018 for potentially relevant studies regarding probiotic supplementation and AD. Included infants and children were those with probiotic exposure in utero and/or after birth who were not previously diagnosed with AD. We calculated the odds ratios (ORs) and 95% confidence intervals (CIs) and used the Jadad and Newcastle–Ottawa scales to assess methodologic quality.

Results A total of 28 studies met the inclusion criteria. Compared with controls, probiotic treatment was associated with a reduced risk of AD (OR 0.69; 95% CI 0.58–0.82, $P < 0.0001$). The use of probiotics during both the prenatal and the postnatal period significantly reduced the incidence of AD (OR 0.67; 95% CI 0.54–0.82); however, analysis of studies of probiotics given prenatally only or postnatally only did not reach statistical significance.

Conclusions Our meta-analysis showed that probiotic supplementation during both the prenatal and the postnatal period reduced the incidence of AD in infants and children. Our findings suggest that starting probiotic treatment during gestation and continuing through the first 6 months of the infant's life may be of benefit in the prevention of AD.

Key Points

Probiotic treatment begun in gestation and continued through the first 6 months of life was shown to have benefit in preventing atopic dermatitis (AD).

Probiotic supplementation was beneficial in both high-risk and unselected subjects.

Mixtures of probiotics, including *Lactobacillus*, *Bifidobacterium* and *Propionibacterium* strains, significantly decreased the risk of AD.

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1 Introduction

In recent decades, the prevalence of atopic dermatitis (AD) has rapidly increased worldwide, with a prevalence of 10–20% in children and 1–3% in adults [1]. It commonly presents during early infancy and childhood [2] and is associated with several key factors, such as diet, environmental exposures and food allergens. Exposure to these factors in early life is critical, and prenatal exposure may provide the greatest protection [3].

Increasing numbers of studies [4, 5] have focused on the use of probiotic supplementation early in life for the prevention of atopic diseases.

Recently, several clinical trials suggested that administration of specific probiotic supplementation in early life could reduce the risk of AD [6–8]. The probiotic strains studied were *Lactobacillus*, *Bifidobacterium* and *Propionibacterium*. However, other studies failed to show a significant decrease in the risk of AD [9, 10]. One meta-analysis [11] showed that probiotic treatment beginning in gestation through the first 6 months of life was beneficial and that strains of *Bifidobacterium* and *Lactobacillus* were efficacious in protecting

against AD. Overall, whether probiotic supplementation in early life is of interest as a potential treatment for AD prevention remains a matter of controversy.

We conducted a systematic review and meta-analysis to investigate the effect of probiotic supplementation during gestation and/or infancy on the risk of AD in infants and young children and to discuss the issues regarding the selection of probiotic strains and the time of exposure.

2 Materials and Methods

2.1 Data Sources

Two independent investigators (LL and ZH) systematically identified studies in the PubMed, EBSCO, Embase and Web of Science databases (inception through 8 March 2018) for all potentially relevant articles regarding the efficacy of prenatal and/or postnatal probiotic supplementation on AD prevention using the following medical subject heading (MeSH) terms: probiotics AND atopic dermatitis or atopic eczema or atopy. Finally, we also conducted a Google Scholar search and examined the reference list of each selected paper for additional relevant articles.

2.2 Inclusion Criteria

Articles had to meet the following criteria to be included in our meta-analysis: (1) studies must be randomized controlled or controlled observational clinical trials, (2) participants enrolled in the studies must be the infants and children who were exposed to probiotics in utero and/or after birth and who were not diagnosed with AD previously, (3) reports must refer to investigating the efficacy of prenatal and/or postnatal probiotic supplementation on the prevention of AD, (4) studies must report the number of treated and control participants with and without AD, (5) studies or their abstract must be published in English.

2.3 Exclusion Criteria

Studies were excluded if they (1) were reviews, duplicate publications or commentaries, (2) did not include a placebo arm, (3) did not provide essential information on treatment and control subjects, (4) included infants who had already been diagnosed with either AD or any form of eczema before beginning supplementation.

2.4 Quality of Included Studies

Two authors (LL and ZH) independently assessed the quality of the included randomized controlled trials (RCTs) using three parameters of the Jadad scale [12]: randomization, double blinding and reported dropout. If randomization and double blinding were mentioned (+1) and appropriate (+1), 2 points were allocated. A dropout was scored (+1) if the fate of the patients and the reason for the dropout were reported. The highest possible score for study quality was 5 points, with total scores of 3–5 corresponding to good trials and total scores of 0–2 corresponding to poor trials.

The quality of nonrandomized trials was evaluated with the Newcastle–Ottawa scale (NOS) [13], which assesses the quality of studies according to selection, comparability and exposure (case–control studies) or outcome (cohort studies). The highest possible study quality was 9 points, with a maximum of 4 points for selection, 2 points for comparability and 3 points for exposure/outcome, with total scores of 0–3, 4–5 and 6–8 corresponding to low, moderate and high quality, respectively.

2.5 Data Extraction

As per the inclusion criteria, data were carefully extracted independently by two observers (LL and ZH), including first author, year of publication, country, study type (RCT or non-RCT), probiotic strains, time of exposure to probiotics in pregnancy, time of exposure to probiotics after birth, diagnosis of AD and participant age at final evaluation, source of participants (average- or high-risk patients), and the incidence of AD in treated and control subjects. Where evaluations conflicted, agreement was reached by consensus with another reviewer (CYH) after referring to the original papers.

2.6 Statistical Analysis

The primary endpoint of this study was the efficacy of prenatal and/or postnatal probiotic supplementation on the prevention of AD. This was evaluated using the pooled odds ratio (OR) with its corresponding 95% confidence interval (CI). Post hoc subgroup analyses were used to explore heterogeneity of results. Subgroups were explored as followed: region (Asia, North America, Europe or Oceania), publication period (2006–2010, 2011–2015 or 2016–2018), time of exposure to probiotics (prepartum, postpartum or pre- and postpartum), design of trials (RCTs or non-RCTs), quality of studies (high or low quality), probiotic strains (mixtures including *Lactobacillus*, *L. rhamnosus* alone, *L. reuteri* alone, *L. paracasei* alone, *L. acidophilus* alone; mixtures including *Bifidobacterium*, *B. lactis* alone, mixtures including *B. lactis*, mixtures including *B. longum*, mixtures including *B. bifidum*, mixtures including *B. breve*, mixtures including *Propionibacterium*), and source of participants (average or high risk).

Heterogeneity was measured using the Chi-squared-based Q statistic test and the I^2 test and was considered significant

when the result of the Q test was $P < 0.10$ or that of the I^2 test was > 50%. ORs were pooled according to the fixed-effects model (Mantel–Haenszel) if heterogeneity was not significant among the studies; otherwise, the random-effects model (DerSimonian and Laird) was used [14–16].

Publication bias was assessed by visually inspecting funnel plots [17], with an asymmetric plot indicating a possible publication bias. We also assessed publication bias using the Begg and Mazumdar [18] adjusted rank correlation test and the Egger regression asymmetry test [19].

All statistical analyses were conducted using Review Manager meta-analysis software version 5.2 (The Cochrane Collaboration; Oxford, UK) and STATA statistical software package version 12.0 (2000; STATA Corp.; College Station, TX, USA). All the reported P values were two-sided, and values < 0.05 were considered statistically significant. The significance of the pooled OR was determined by Z test.

3 Results

3.1 Literature Search

As shown in Fig. 1, the systematic literature review identified 327 potentially relevant references. In total, 191 irrelevant papers were excluded after screening the titles, as were 78 duplicate papers or commentaries. After reviewing the abstracts or full texts, 17 studies were excluded, including 15 reviews and meta-analyses and two articles without controls. From the remaining 41 publications, 13 were excluded because data were insufficient. Thus, 28 studies, including 27 RCTs and 1 controlled cohort article (C-C) containing 6907 subjects (3595 receiving probiotics and 3312 controls), met the inclusion criteria and were eventually selected for review and analysis [5–7, 9, 10, 20–41].

3.2 Characteristics of Included Studies

Table 1 shows the basic characteristics of the included studies. According to the inclusion criteria, nine trials [6, 26, 27, 32, 34–36, 38] defined AD using the UK Working Party's

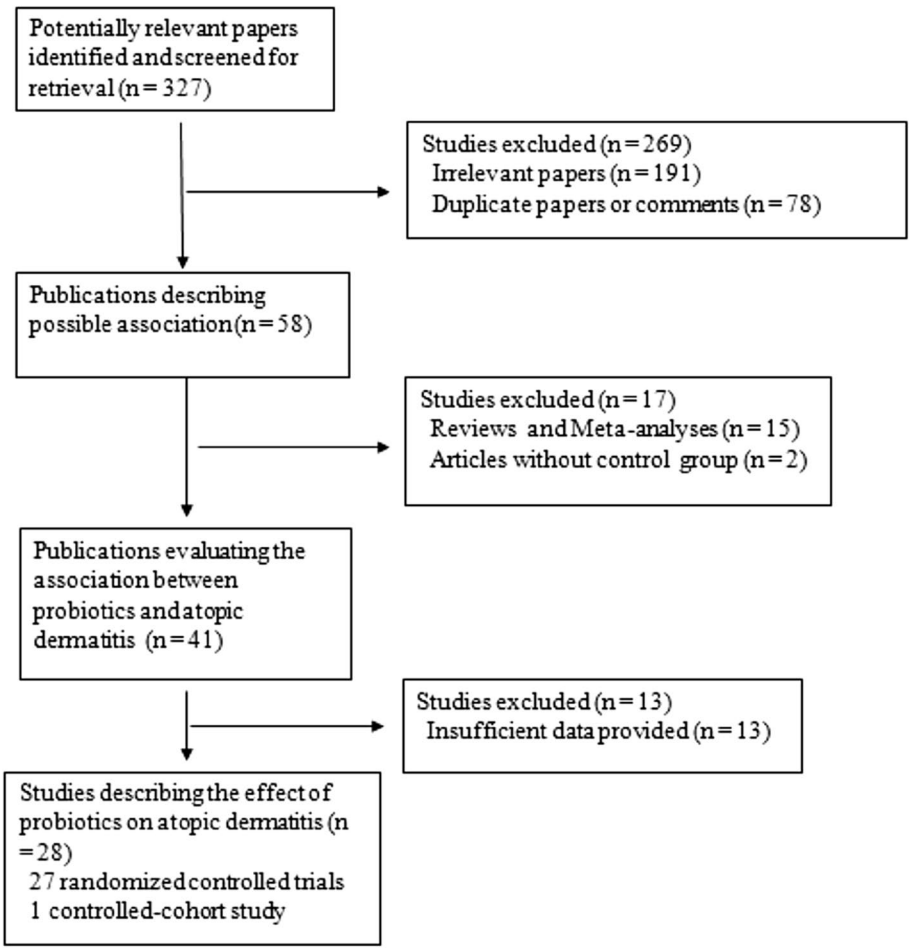

Fig. 1 Flow chart of the literature search for evaluating the effect of probiotics on preventing atopic dermatitis

Table 1 Characteristics of included studies on the incidence of atopic dermatitis in treatment and control groups

Study, country	Study type	Treated/control[a] (*N*)	Time of exposure (before/after birth)	Probiotic treatment	Definition of AD	Age at final evaluation	Sources of participants	Incidence of AD in treated/control (*n*)	Jadad scores/NOS scores[b]
Rautava et al. [41] Finland	RCT	32/40	NA/12 mo	LGG + *B. breve* 12	Hanifin and Rajka criteria	1 y	Average risk	4/8	3
Kukkone et al. [34] Finland	RCT	461/464	2–4 wk/6 mo	LGG + *L. rhamnosus* LC705 + *B. breve* Bb99 + PFS	UK Working Party criteria	2 y	High risk	120/150	5
Kalliomaki et al. [33] Finland	RCT	53/62	4 wk/6 mo	LGG	Hanifin and Rajka criteria	7 y	High risk	23/41	2
Abrahamsson et al. [5] Sweden	RCT	94/94	4 wk/12 mo	*L. reuteri* ATCC 55730	Hanifin and Rajka criteria	2 y	High risk	34/32	3
Kopp et al. [36] Germany	RCT	50/44	4–6 wk/6 mo	LGG	UK Working Party criteria	2 y	High risk	14/12	4
Huurre et al. [7] 2008 Finland	RCT	72/68	7 mo/6 mo	LGG + *B. breve* 12	Hanifin and Rajka criteria	1 y	High risk	7/12	2
Wickens et al. [32] NZ	RCT	157/159	5 wk/6 mo	*L. rhamnosus* HN001	UK Working Party criteria	2 y	High risk	23/43	5
Wickens et al. [32] NZ	RCT	157/159	5 wk/6 mo	*B. lactis* HN019	UK Working Party criteria	2 y	High risk	38/43	5
Soh et al. [31] Singapore	RCT	124/121	NA/6 mo	*B. longum* 999 + *L. rhamnosus*	Hanifin and Rajka criteria	1 y	High risk	27/30	4
West et al. [30] Sweden	RCT	84/87	NA/4–13 mo	*L. paracasei* F19	Hanifin and Rajka criteria	13 mo	Average risk	9/19	4
Niers et al. [29] 2009 Netherlands	RCT	50/48	6 wk/3 mo	*B. bifidum* + *B. lactis* + *L. lactis*	Hanifin and Rajka criteria	2 y	High risk	27/33	4
Kuitunen et al. [6] Finland	RCT	445/446	4 wk/6 mo	LGG + *L. rhamnosus* LC705 + *B. breve* Bb99 + PFS	UK Working Party criteria	5 y	High risk	175/193	3
Kim et al. [28] Korea	RCT	33/35	4–8 wk/6 mo	*B. bifidum* BGN4 + *B. lactis* AD011 + *L. acidophilus* AD031	Hanifin and Rajka criteria	1 y	High risk	12/22	4
Dotterud et al. [35] Norway	RCT	138/140	4 wk/3 mo	LGG + *L. acidophilus* + *B. breve* 12	UK Working Party criteria	2 y	Average risk	29/48	4

Table 1 (continued)

Study, country	Study type	Treated/control[a] (*N*)	Time of exposure (before/after birth)	Probiotic treatment	Definition of AD	Age at final evaluation	Sources of participants	Incidence of AD in treated/control (*n*)	Jadad scores/NOS scores[b]
Boyle et al. [27] Australia	RCT	108/102	4 wk/NA	LGG	UK Working Party criteria	1 y	High risk	35/43	5
Kukkonen et al. [39] Finland	RCT	64/67	4 wk/6 mo	LGG + *L. rhamnosus* LC705 + *B. breve* Bb99 + PFS	SPT positive	5 y	High risk	30/35	4
Wickens et al. [26] NZ	RCT	315/159	5 wk/6 mo	*L. rhamnosus* HN001 + *B. lactis* HN019	UK Working Party criteria	4 y	High risk	115/79	3
Jensen et al. [25] Australia	RCT	62/56	NA/6 mo	*L. acidophilus*	Hanifin and Rajka criteria	5 y	High risk	19/9	2
Rautava et al. [24] Finland	RCT	143/62	6 wk/2 mo	*L. rhamnosus* + *B. longum* 999 + *L. paracasei* ST11	Hanifin and Rajka criteria	2 y	High risk	41/44	5
Rozé et al. [38] France	RCT	39/45	NA/6 mo	*L. rhamnosus* LCS-742 and *B. longum* M63	UK Working Party criteria	6 mo	Average risk	1/8	5
Ou et al. [40] Taiwan	RCT	65/64	4 mo/6 mo	LGG	Hanifin and Rajka criteria	3 y	High risk	16/16	4
Allen et al. [37] UK	RCT	171/173	4 wk/12 mo	Two strains of Lactobacilli + 2 of B. (genus NS)	SPT positive	2 y	Average risk	58/56	2
West et al. [23] Sweden	RCT	48/58	NA/4–13 mo	*L. paracasei* F19	Hanifin and Rajka criteria	8–9 y	Average risk	7/11	3
Abrahamsson et al. [22] Sweden	RCT	94/90	4 wk/12 mo	*L. reuteri* ATCC 55730	Hanifin and Rajka criteria	7 y	Average risk	20/17	4
Loo et al. [21] Singapore	RCT	124/121	NA/6 mo	*B. longum* 999 + *L. rhamnosus*	Hanifin and Rajka criteria	5 y	High risk	31/38	3
Allen et al. [10] UK	RCT	214/222	4 wk/6 mo	*L. salivarius* CUL61 + *L. paracasei* CUL08 + *B. lactis* CUL34 + *B. bifidum* CUL20	SPT positive	2 y	High risk	73/72	5
Enomoto et al. [20] Japan	C-C	94/31	4 wk/6 mo	*B. breve* M-16V + *B. longum* BB536	Hanifin and Rajka criteria	18 mo	Average risk	9/8	9[b]

Table 1 (continued)

Study, country	Study type	Treated/control[a] (*N*)	Time of exposure (before/after birth)	Probiotic treatment	Definition of AD	Age at final evaluation	Sources of participants	Incidence of AD in treated/control (*n*)	Jadad scores/NOS scores[b]
Cabana et al. [9] USA	RCT	92/92	NA/6 mo	LGG	Hanifin and Rajka criteria	2 y	High risk	26/28	5

Though data are provided as AD, the definition of each dataset of AD defines it as eczema. Author uses AD and eczema interchangeably

AD atopic dermatitis, B *Bifidobacterium, C-C* controlled-cohort trial, *L Lactobacillus*, *LGG Lactobacillus rhamnosus* GG, *mo* month, *NA* none, *NOS* Newcastle-Ottawa scale, *NS* not specified, *PFS Propionibacterium freudenreichii ssp . shermanii JS*, *RCT* randomized controlled trial, *SPT* skin prick test, *wk* week, *y* year

[a]Compared with the probiotic group, the controls received placebo and not prebiotic or synbiotic preparations

[b]The quality of nonrandomized trials was evaluated with the NOS; the quality of remaining RCTs were assessed using the Jadad scale

criteria (an itchy skin condition plus three or more of the following: history of atopic disease in the family, dry skin during the last year, history of eczema, or visible eczema involving typical sites) [42]. However, 16 studies [5, 7, 9, 20–25, 28–31, 33, 40, 41] defined AD using the criteria of Hanifin and Rajka [43] (a pruritic, chronic, or chronically relapsing noninfectious dermatitis with typical features and distribution).

Of the 28 articles, five were performed in Asia, 17 in Europe, five in Oceania and one in North America (Table 2); 14 studies were carried out between 2006 and 2010, 13 were conducted between 2011 and 2015 and one was conducted

Table 2 Subgroup analysis of the atopic dermatitis occurrence in treatment vs. control groups

Subgroup	Studies (*N*)	AD in treated	AD in controls	OR (95% CI)	*P*	*Z*	Tests of heterogeneity			
							Chi^2	*df*	*P*	I^2 (%)
Region[a]										
Asia	5	95/440	114/372	0.68 (0.49–0.94)	0.02	2.32	5.52	4	0.24	28
North America	1	26/92	28/92	0.90 (0.48–1.70)	0.32	0.75	–	–	–	–
Europe	17	672/2263	791/2213	0.67 (0.53–0.85)	0.001	3.25	41.27	16	0.0005	61
Oceania	5	230/800	217/635	0.74 (0.49–1.09)	0.13	1.52	10.37	4	0.03	61
Year										
2006–2010	14	542/1951	686/1967	0.71 (0.62–0.81)	< 0.0001	4.86	15.89	13	0.26	18
2011–2015	13	455/1552	436/1253	0.71 (0.50–0.99)	0.04	2.02	41.66	12	< 0.0001	71
2016–2018	1	26/92	28/92	0.90 (0.48–1.70)	0.75	0.32	–	–	–	–
Time of exposure										
Prepartum	1	35/108	43/102	0.66 (0.37–1.15)	0.14	1.46	–	–	–	–
Postpartum	8	124/616	151/623	0.77 (0.59–1.01)	0.06	1.87	11.21	7	0.13	38
Pre and postpartum	19	864/2871	956/2587	0.67 (0.54–0.82)	0.0002	3.79	46.56	18	0.0002	61
Source of participants										
Average risk	8	137/771	175/667	0.69 (0.53–0.89)	0.005	2.84	13.07	7	0.07	46
High risk	20	886/2884	975/2645	0.71 (0.58–0.86)	0.0005	3.48	44.99	19	0.0007	58
Design of trial										
RCT	27	1014/3501	1142/3281	0.70 (0.59, 0.83)	< 0.0001	4.03	55.54	26	0.0006	53
Non-RCT	1	9/94	8/31	0.30 (0.11, 0.88)	0.03	2.20	-	-	-	-
Quality of studies										
High	24	916/3237	1032/2953	0.71 (0.63–0.79)	< 0.00001	6.15	45.68	23	0.003	50
Low	4	107/358	118/359	0.85 (0.42–1.71)	0.64	0.47	10.77	3	0.01	72
All studies	28	1023/3595	1150/3312	0.69 (0.58–0.82)	< 0.0001	4.22	58.18	27	< 0.0001	53.6

AD atopic dermatitis, *CI* confidence interval, *df* degrees of freedom, *OR* odds ratio, *RCT* randomized controlled trial

[a]Singapore, Japan and Korea were grouped in Asia; California was grouped in North America; and UK, Sweden, Finland and Netherlands were grouped in Europe; Australia and New Zealand were grouped in Oceania according to similarities in geographic position and racial traits

between 2016 and 2018 (Table 2). Probiotic strain mixtures, including *Lactobacillus*, *Bifidobacterium* and *Propionibacterium* were investigated in 15, 16, and 3 studies, respectively (Table 3). Probiotics were given prenatally in one study, postnatally in eight studies, and during both the prenatal and the postnatal period in 19 studies (Table 2). In total, 20 studies included only subjects at high risk for AD, such as pregnant women with atopic sensitization and either a history of or active allergic disease, and infants with a first-degree relative with either asthma or eczema; however, the remaining eight studies [20, 22, 23, 30, 35, 37, 38, 41] included unselected participants (Table 2).

Only two studies [27, 34] reported adverse events, such as gastrointestinal symptoms, vomiting and excessive crying. These adverse events were not notable, and the adverse event rate was not significantly different between treatment and control groups.

3.3 Quality of Included Studies

Table 1 presents the quality of the 27 RCTs and one nonrandomized study, according to the Jadad scale and the NOS, respectively. In total, 23 RCTs were assessed as being high-quality trials and four RCTs were assessed as low quality. On the other hand, one nonrandomized paper [20] was evaluated as high quality. We also compared high- and low-quality studies (Table 2).

3.4 Overall Results

In total, 28 studies met the inclusion criteria and were eventually selected for analysis. Heterogeneity among these studies was significant ($I^2 = 53.6\%$), so we calculated the pooled estimates using the random-effects model. As shown in Fig. 2 and Table 2, AD occurred in 1023 of 3595 patients (28.5%) in the experimental group versus 1150 of 3312 patients (34.7%) in the control group (OR 0.69; 95% CI 0.58–0.82; $P < 0.0001$).

3.5 Subgroup Analysis

To determine the influencing factors that might have affected the overall results, we conducted subgroup analyses. As shown in Table 2, prenatal and/or postnatal probiotic supplementation was effective for preventing AD in infants and children in Asia (OR 0.68; 95% CI 0.49–0.94) and Europe (OR 0.67; 95% CI 0.53–0.85). The risk of AD was decreased in studies conducted during the periods 2006–2010 (OR 0.71; 95% CI 0.62–0.81) and 2011–2015 (OR 0.71; 95% CI 0.50–0.99). The use of probiotics during both the prenatal and the postnatal period reduced the incidence of AD (OR 0.67; 95% CI 0.54–0.82); however, studies without a prenatal component (OR 0.77; 95% CI 0.59–1.01) or a postnatal component (OR 0.66; 95% CI 0.37–1.15) failed to show a statistically significant decrease in the risk of AD. The incidence of AD was decreased in both average-risk (OR 0.69; 95% CI 0.53–0.89) and high-risk (OR 0.71; 95% CI 0.58–0.86) cohorts as well as in RCTs (OR 0.70; 95% CI 0.59–0.83) and non-RCTs (OR 0.30; 95% CI 0.11–0.88). According to the Jadad scale and the NOS, we found that the risk of AD was significantly reduced in the high-quality studies (OR 0.71; 95% CI 0.63–0.79) but not in the low-quality studies (OR 0.85; 95% CI 0.42–1.71).

Table 3 Subgroup analysis of the probiotic strains in treatment group vs. control group

Subgroup	Studies (*N*)	AD in treated	AD in controls	OR (95% CI)	*P*	*Z*	Tests of heterogeneity			
							Chi^2	*df*	*P*	I^2 (%)
Probiotic strains										
L. rhamnosus	6	137/525	183/523	0.65 (0.50–0.86)	0.002	3.07	6.14	5	0.29	19
L. reuteri	2	54/188	49/184	1.12 (0.71–1.78)	0.62	0.49	0.01	1	0.91	0
L. paracasei	2	16/143	30/148	0.50 (0.26–0.96)	0.04	2.10	0.27	1	0.60	0
L. acidophilus	1	19/62	9/56	2.31 (0.94–5.64)	0.07	1.83	–	–	–	–
Mixtures including *Lactobacillus*	15	750/2425	828/2211	0.64 (0.51–0.81)	0.0002	3.70	37.07	14	0.0007	62
B. lactis	1	38/158	43/159	0.85 (0.52–1.42)	0.54	0.61	–	–	–	–
Mixtures including *B. lactis*	4	227/612	206/464	0.65 (0.41–1.03)	0.07	1.82	7.88	3	0.05	62
Mixtures including *B. longum*	5	109/524	128/380	0.39 (0.18–0.83)	0.01	2.44	18.11	4	0.001	78
Mixtures including *B. bifidum*	3	112/297	127/305	0.65 (0.32–1.32)	0.23	1.20	5.95	2	0.05	66
Mixtures including *B. breve*	7	374/1306	454/1256	0.73 (0.62–0.86)	0.0003	3.64	6.33	6	0.39	5
Mixtures including *Bifidobacterium*	16	759/2519	836/2242	0.63 (0.50–0.79)	< 0.0001	3.95	39.55	15	0.0005	62
Mixtures including PFS	3	325/970	378/977	0.80 (0.66–0.96)	0.02	2.39	0.51	2	0.77	0

AD atopic dermatitis, *B Bifidobacterium*, *CI* confidence interval, *L Lactobacillus*, *OR* odds ratio, *PFS Propionibacterium freudenreichii ssp. shermanii JS*

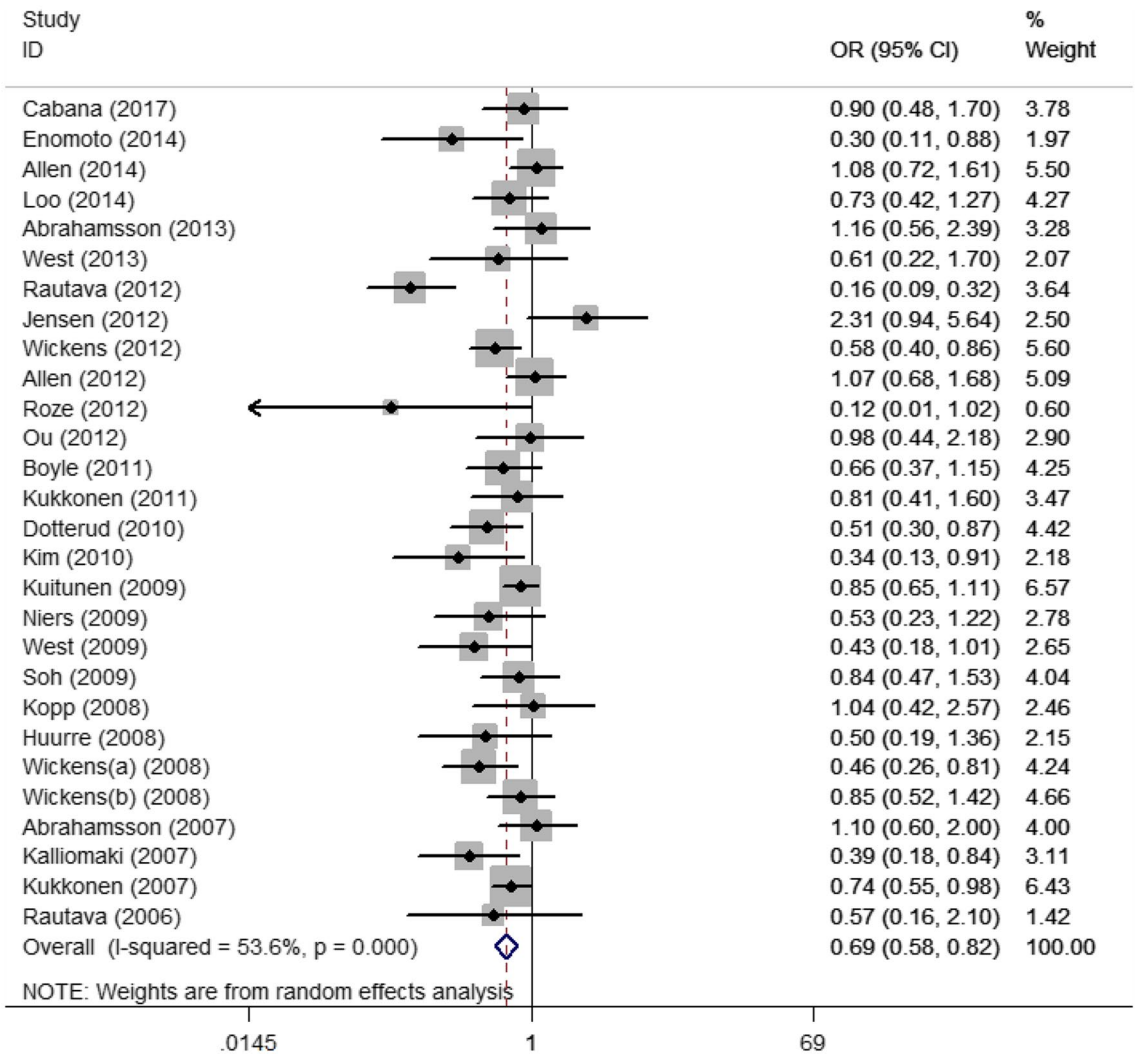

Fig. 2 Meta-analysis for the effect of probiotics on atopic dermatitis. *CI* confidence interval, *OR* odds ratio

Taking into the account the probiotic strains, the use of mixtures including strains of *Lactobacillus* (OR 0.64; 95% CI 0.51–0.81), *Bifidobacterium* (OR 0.63; 95% CI 0.50–0.79) and *Propionibacterium* (OR 0.80; 95% CI 0.66–0.96) all appeared to reduce the incidence of AD (Table 3). Furthermore, for *Lactobacillus* strains, *L. rhamnosus* alone, with a pooled OR of 0.65 (95% CI 0.50–0.86), and *L. paracasei* alone, with a pooled OR of 0.50 (95% CI 0.26–0.96), seemed more protective than *L. reuteri* alone (OR 1.12; 95% CI 0.71–1.78) or *L. acidophilus* alone (OR 2.31; 95% CI 0.94–5.64). However, mixtures containing *B. longum* (OR 0.39; 95% CI 0.18–0.83) or *B. breve* (OR 0.73; 95% CI 0.62–0.86) achieved statistical significance.

Based on these differences, we found that exclusive supplementation of *L. rhamnosus* and *L. paracasei* seemed more effective than supplementation with *L. reuteri* and *L. acidophilus* at preventing AD in infants and children.

Based on results indicating that probiotic supplementation during both the prenatal and the postnatal period was effective for AD prevention in infants and children, we conducted a subgroup analysis to evaluate the issue in terms of duration of postpartum exposure. Besides the time of prenatal exposure, we found that, compared with controls, infants receiving probiotics after birth for no more than 6 months (OR 0.61; 95% CI 0.48–0.76) had a significantly lower incidence of AD. However, administration of probiotics for >12 months after birth was not effective in preventing AD compared with controls (OR 1.10; 95% CI 0.80–1.51) (Table 4).

3.6 Bias Diagnostics

Begg's test was created to assess possible publication bias (Fig. 3). The p-values for the Begg's and Egger's tests were 0.079 and 0.116, respectively, indicating that the results of

Table 4 Subgroup analysis of evaluating the effect of duration of postpartum exposure on preventing atopic dermatitis in subjects given both pre- and postpartum exposure to probiotics

Subgroup	Studies (*N*)	AD in treated	AD in controls	OR (95% CI)	*P*	*Z*	Tests of heterogeneity			
							Chi^2	*df*	*P*	I^2 (%)
Time of postpartum exposure										
≤ 3 Months	3	97/331	125/250	0.35 (0.16–0.76)	0.008	2.67	7.94	2	0.02	75
> 3 Months, ≤ 6 months	13	655/2181	726/1980	0.74 (0.64–0.84)	< 0.0001	4.52	18.38	12	0.10	35
≥ 12 Months	3	112/359	105/357	1.10 (0.80–1.51)	0.57	0.56	0.03	2	0.98	0
Studies of pre and postpartum exposure	19	864/2871	956/2587	0.67 (0.54–0.82)	0.0002	3.79	46.56	18	0.0002	71

AD atopic dermatitis, *CI* confidence interval, *df* degrees of freedom, *OR* odds ratio

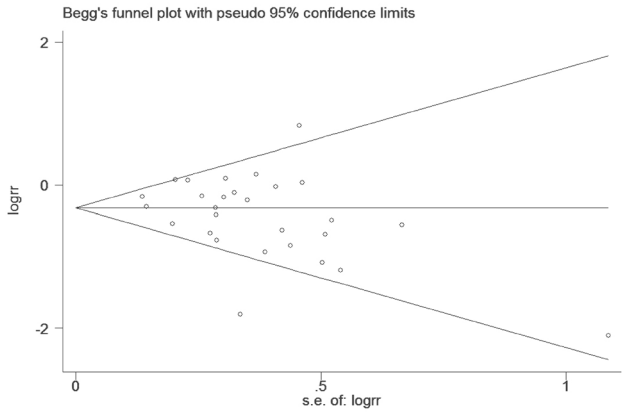

Fig. 3 Funnel plot assessing for publication bias. No significant publication bias was noted. *rr* risk ratio, *se* standard error

the present meta-analysis were relatively stable and the publication bias might have little influence on the overall results.

4 Discussion

Our systematic review and meta-analysis showed that prenatal and postnatal probiotic supplementation significantly reduced the incidence of AD in infants and children. Probiotic supplementation was beneficial in both high-risk participants and unselected subjects. Mixtures of probiotic supplementation including *Lactobacillus* strains, *Bifidobacterium* strains or *Propionibacterium* strains significantly decreased the risk of AD.

Our overall result was in line with those of another meta-analysis [11]. Our meta-analysis contained 28 articles, including 27 RCTs and one non-RCT, which added 16 new studies and was markedly larger than the previous study.

Our study suggests that probiotic treatment might be effective, although there is significant heterogeneity between study findings ($I^2 = 53.6\%$). Such heterogeneity may be explained by differences in regions, timing of probiotic supplementation and probiotic strains selected. The risk of AD differed significantly between Asia, Europe, North America and Oceania, suggesting that regional factors influenced overall results. This may be explained by ethnicity, and the host immune mechanisms may be a key to differing responses to probiotics according to population and geographic area. The published meta-analysis [11] demonstrated that the use of probiotic supplementation beginning in gestation through the first 6 months of life decreased the incidence of AD in infants. One of our findings confirmed that result: Table 4 shows that compared with controls, participants with postpartum exposure for no more than 6 months had a lower risk of AD; however, participants exposed to probiotics for > 12 months seemed to receive no benefit in terms of AD prevention. Thus, we recommend that starting probiotic treatment in gestation and continuing through the first 6 months of life may have a more powerful benefit on the prevention of AD. We speculate that a longer use of probiotics during the postnatal period did not lead to a lower prevalence of AD in infants and children.

Unlike our study, the previous meta-analysis [11] showed that mixtures including *Bifidobacterium* or *Lactobacillus* strains were efficacious in protecting against AD; however, mixtures including *Propionibacterium* strains did not reach statistical significance. Our meta-analysis suggested that the use of mixtures of probiotic supplementation including *Lactobacillus* strains, *Bifidobacterium* strains or *Propionibacterium* strains, decreased the risk of AD. Further, for *Lactobacillus* strains, exclusive supplementation of *L. rhamnosus* and *L. paracasei* seemed more efficacious than that of *L. reuteri* and *L. acidophilus* in preventing AD in infants and children.

However, the mechanism of action of probiotics in preventing AD has not been completely described and is an evolving area of research. There is evidence that strains of *Lactobacillus* and *Bifidobacterium* can influence immune function through toll-like receptors (TLRs), which have been identified as critical to reducing the risk of immunologically mediated disease, such as allergic diseases

[44]. Niers et al. [29] found that the prevention of atopic eczema by perinatal administration of probiotic bacteria was indeed through TLRs, which might contribute to maintaining mucosal and intestinal homeostasis. As reported [45], in allergic children, functional modifications consisted of the decreased adhesion to intestinal mucosa of *Bifidobacterium* species, decreased levels of interleukin-10 and increased levels of pro-inflammatory cytokine. Another human study [46] suggested that prenatal/postnatal administration of *L. rhamnosus* HN001 reduced the rate of eczema and increased the level of cord blood interferon-γ. Thus, we speculate that the use of probiotic supplements might change the composition of the intestinal flora of children, subsequently modulating the reactivity of the immune system and possibly play an important role in AD prevention. In the future, more research is required to fully understand how this relates to the development of allergic diseases.

4.1 Study Limitations

Several limitations should be addressed. First, as the articles in our study were limited to those published until 8 March 2018, it is possible that several relevant published or not yet published articles were missed. Second, our study focused only on papers published in the English language, which might exclude some eligible articles published in other languages. Lastly, our meta-analysis has moderate to significant heterogeneity according to Q or I^2; however, the results of our meta-analysis are similar when using a random-effects model.

5 Conclusions

Probiotic supplementation during the prenatal and postnatal period reduced the incidence of AD in infants and children in both high-risk and unselected subjects, especially beginning in gestation through the first 6 months of life. More rigorous, double-blind and larger, well-designed RCTs are required to conclusively evaluate the efficacy of probiotics for preventing AD and to explore the essential mechanisms.

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Compliance with Ethical Standards

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