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Therapeutic effectiveness of probiotics for atopic dermatitis: A systematic review and meta-analysis of randomized controlled trials with subgroup analysis

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Abstract

Background: The effect of probiotics in the treatment of atopic dermatitis (AD) is inconclusive, partially due to the heterogeneities of AD.

Objective: The aim of the present study was to investigate the efficacy of probiotics in the treatment of AD with a subgroup analysis according to country, severity of AD, duration of supplementation, and probiotic strain.

Methods: Original articles reporting the therapeutic efficacy of probiotics for AD were identified by searching PubMed, Cochrane Library databases, and Embase from inception to September 30, 2022.

Results: This meta-analysis included 1,382 patients with AD from 25 randomized controlled trials randomized controlled trials. Probiotic supplementation was effective for the treatment of AD, reflected in a significant decrease in the SCORing Atopic Dermatitis (SCORAD) index (SMD, −4.0; 95%CI, −7.3 to −0.7). The subgroup analysis showed a significant therapeutic effect for AD among patients with mild or moderate AD (SMD, −1.4; 95%CIs −2.2 to −0.7), in those supplemented for more than three months (SMD, −5.1; 95%CIs −9.7 to −0.4), and in those supplemented with a probiotic that contained *Lactobacillus* spp. strains combined with or without other strains (SMD, −4.4; 95%CIs −8.0 to −0.8). In addition, the therapeutic effects of probiotics showed differences according to country and geographic region.

Conclusion: Probiotics can be beneficial for the treatment of AD, and their therapeutic effect may be individually tailored to improve it based on the severity of AD, strain of probiotics, duration of supplementation, and geographic region.

Key words: atopic dermatitis; meta-analysis; randomized controlled trials; probiotics; treatment

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Introduction

Atopic dermatitis (AD) is a chronic and relapsing skin inflammatory disease that results from the complex interactions between skin barrier dysfunction, immune dysregulation, and genetic susceptibility.[1] Due to its high prevalence and impacts on short- and long-term quality of life, the global disease burden of AD has been substantial.[2-4] Therefore, a need for the development and establishment of therapeutic strategies for AD has been recognized. However, AD is a heterogeneous disease in terms of its severity, longitudinal course, onset age, and burden of symptoms, and characteristic features underlying each AD phenotype,[5,6] leading to the development of personalized and targeted therapy for AD.[7]

Alterations of the gut microbiome can affect the development and exacerbation of AD via modulation of skin and systemic immune responses.[8,9] Previous studies have reported that supplementation of probiotics can be effective for the treatment of AD by modulating the immune system and improving skin barrier dysfunction.[9,10] However, previous studies on the therapeutic effect of probiotic supplementation for AD showed inconclusive results, partially due to heterogeneities in the study populations, probiotic strains, duration and dosage of probiotic supplementation, and history of antibiotic exposure in early life.[11,12] In addition, the disease burden of AD shows significant geographic variations,[3] suggesting that differences in diet habits and antibiotic prescription rates might indirectly affect the therapeutic effect of probiotics through alteration of the gut microbiota.

To identify the therapeutic effect of probiotic supplementation for AD, consideration of the probiotic strain, geographic region, severity of AD, and duration of probiotic supplementation is required. However, meta-analyses considering these factors are lacking. Therefore, we performed the present meta-analysis to investigate the therapeutic effect of probiotic supplementation for AD. Furthermore, we elucidated the therapeutic effect of probiotics for AD according to the severity of AD, duration of probiotic supplementation, geographic region, and probiotic strain.

Methods

Literature search strategy

This systematic review and meta-analysis was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] A literature search of PubMed, Cochrane Library, Embase, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials databases was conducted to identify articles published up to September 30, 2022, using the following keywords: (atopic dermatitis OR eczema OR dermatitis) and (probiotics OR probiotic OR synbiotics OR prebiotics). The search was restricted to English-language publications. No ethical approval was required for the analysis of publicly available anonymized data. This systematic review was not registered.

Selection criteria and study selection

The inclusion criteria for study selection were as follows: (1) studies that investigated the therapeutic effect of probiotics in patients with AD; (2) randomized controlled trials (RCTs); (3) studies that clearly reported on the administered probiotic strains, duration of probiotic administration, and severity of AD; and (4) studies that included a control arm of patients who received a placebo. The exclusion criteria were as follows: (1) abstracts, case reports, editorials, letters, review articles, and publications that included overlapping study populations; (2) studies that included single-arm cross-over designs; and (3) studies that did not include sufficient information on clinical data. Patients with AD of all ages were included.

Study selection and data extraction

Four authors (E.L., K.H.K., I.S.S., and T.K.M.) independently screened titles/abstracts, and any disagreements were resolved by consensus. The full literature search strategies are presented in **Figure 1**.

The following data were extracted by the four authors (E.L., K.H.K., I.S.S., and T.K.M.): study author, year of publication, study design, number of study subjects in both the control and intervention groups, country, intervention period, probiotic strains, SCORing Atopic Dermatitis (SCORAD) index, and age of included study population.

Definitions of subgroups

The severity of AD was classified based on the SCORAD index (< 15, mild; 15 ≤ moderate < 40; ≥ 40, severe).[14] Subgroup analyses of the therapeutic effects of probiotic supplementation for AD were performed according to disease severity (mild, moderate, or severe), country, World Health Organization (WHO) geographical region (European Region [EUR], Eastern Mediterranean Region [EMR], Region of the Americas [AMR], and Western Pacific Region [WPR]), duration (< 3 months vs. ≥ 3 months) of probiotic supplementation, and probiotic strain. Probiotics containing *Lactobacillus* spp. with or without other strains were defined as those containing one or more strains of *Lactobacillus* spp. with or without other genera. Probiotics containing only *Lactobacillus* spp. were defined as those containing the *Lactobacillus* genus. The same definition was used for *Bifidobacterium*.

Quality assessment

The quality of evidence was assessed using the Cochrane risk of bias tool. All studies were included in the present systematic review and meta-analysis regardless of the levels of quality (**Supplementary Figure 1**).[15]

Statistical analysis

Heterogeneity among studies was expressed as I^2 (values over 50% are commonly considered to represent significant heterogeneity).[16] Review Manager (Rev Man 5.3; Cochrane Collaboration, London, UK) was used to perform the meta-analyses. The meta-analyses were conducted using

random-effects models. The effect size was calculated with standardized mean differences (SMDs) with 95% confidence intervals (95% CIs). *P* values < 0.05 were considered statistically significant. The statistical analyses were conducted using R version 4.1.0 (R Foundation for Statistical Computing).

Results

Literature search

A total of 834 articles were initially identified through the literature search. After removing 437 duplicates, screening of the titles and abstracts was performed, and a total of 357 articles were excluded (**Figure 1**). Finally, a total of 25 RCTs including 1,382 patients with AD were included in this systematic review and meta-analysis.

Study characteristics

The baseline characteristics of the included studies are summarized in **Table 1**. All of the studies were RCTs, and the studies were performed in 16 countries and four WHO geographic regions. Nineteen studies were conducted in children, and the remaining six studies were conducted in adults. Probiotics were taken for less than three months in 10 studies, whereas probiotics were administered for more than three months in 15 studies. In 23 studies, probiotics containing *Lactobacillus* spp. with or without other strains were used, whereas 19 studies used probiotics containing only *Lactobacillus* spp. Six studies used probiotics containing *Bifidobacterium* spp. with or without other strains, whereas two studies used probiotics containing only *Bifidobacterium* spp.

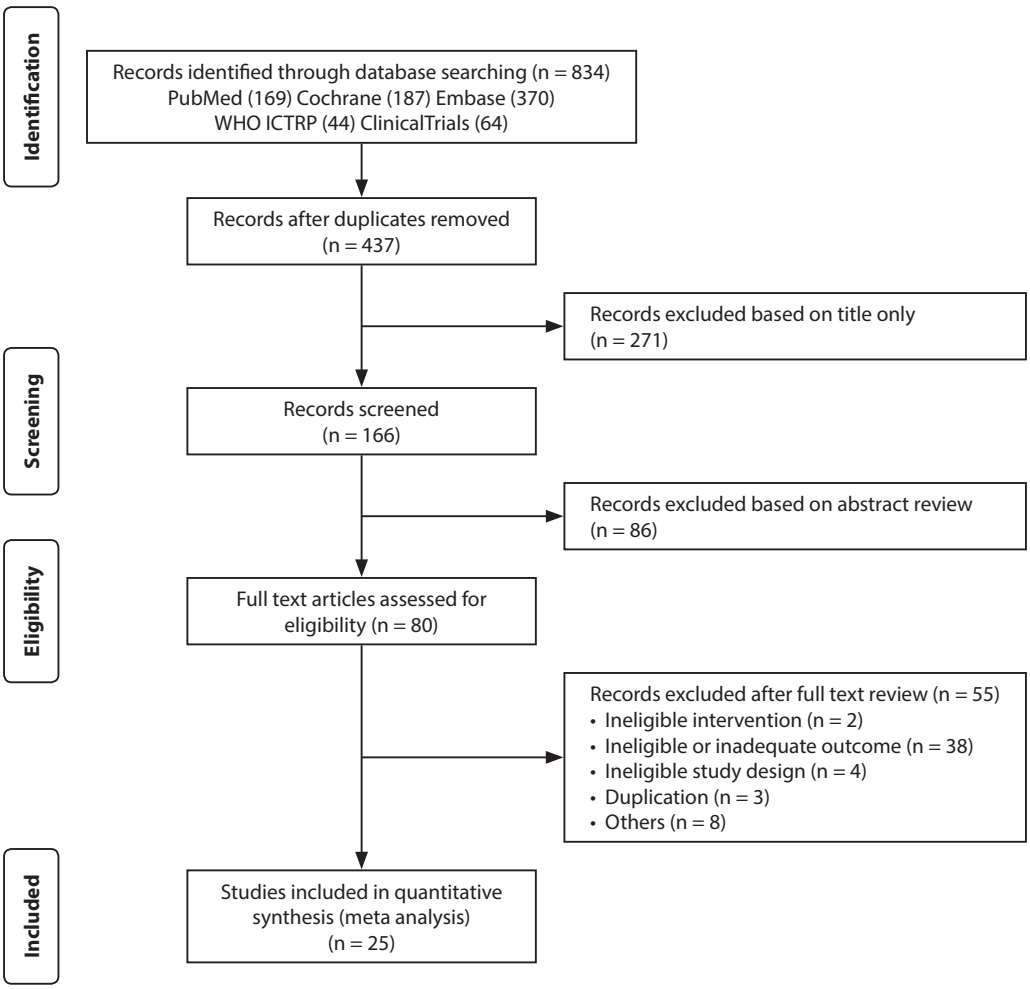

Figure 1. PRISMA flow diagram.

Table 1. Characteristics of the included studies.

Study	Country	State	Design	Papulation	AD severity	Intervention	n	Control	n	Duration (weeks)
Weston 2005	Australia	WPR	RCT	Children	Moderate, severe	*Lactobacillus fermentum*	28	Placebo	28	8
Folster-Holst 2006	Germany	EUR	RCT	Children	Moderate, severe	*Lactobacillus rhamnosus*	22	Placebo	25	8
Passeron 2006	France	EUR	RCT	Children	Moderate, severe	*Lactobacillus rhamnosus*	17	Placebo	22	12
Kaur 2008	Estonia	EUR	RCT	Adults	Mild	*Lactobacillus fermentum*	10	Placebo	6	12
Chernyshov 2009	Ukraine	EUR	RCT	Children	Moderate, severe	*Lactobacillus rhamnosus*, *Lactobacillus helveticus*	30	Placebo	28	4
Gerasimov 2010	Ukraine	EUR	RCT	Children	Moderate, severe	*Lactobacillus acidophilus*, *Bifidobacterium lactis*	43	Placebo	47	8
van der Aa 2010	Netherlands	EUR	RCT	Children	Moderate, severe	*Bifidobacterium breve*	42	Placebo	43	12
Woo, 2010	Korea	WPR	RCT	Children	Moderate	*Lactobacillus sakei*	41	Placebo	34	12
Drago 2011	Italy	EUR	RCT	Adults	Moderate	*Lactobacillus salivarius*	19	Placebo	19	16
Farid 2011	Iran	EMR	RCT	Adults	Not described	*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium infantis*, *Lactobacillus bulgaricus*	19	Placebo	21	8
Drago 2012	Italy	EUR	RCT	Adults	Moderate, severe	*Lactobacillus salivarius*	19	Placebo	19	16
Han 2012	Korea	WPR	RCT	Children	Moderate, severe	*Lactobacillus plantarum*	44	Placebo	39	12

Table 1. (Continued)

Study	Country	State	Design	Papulation	AD severity	Intervention	n	Control	n	Duration (weeks)
Iemoli 2012	Italy	EUR	RCT	Adults	Moderate, severe	*Lactobacillus salivarius*, *Bifidobacterium breve*	31	Placebo	15	12
Wu 2012	Taiwan	WPR	RCT	Children	Moderate, severe	*Lactobacillus salivarius*	27	Placebo	27	8
Lin 2015	China	WPR	RCT	Children	Mild, moderate	*Bifidobacterium bifidum*	20	Placebo	20	4
Prakoeswa 2017	Indonesia	AMR	RCT	Children	Mild, moderate	*Lactobacillus plantarum*	12	Placebo	10	12
Wu 2017	Taiwan	WPR	RCT	Children	Moderate	*Lactobacillus rhamnosus*	30	Placebo	32	8
Navarro-López 2018	Spain	EUR	RCT	Children	Moderate	*Bifidobacterium lactis*, *Bifidobacterium longum*, *Lactobacillus casei*	23	Placebo	24	12
Nakata 2019	Japan	WPR	RCT	Children	Mild, moderate, severe	*Lactobacillus acidophilus*	25	Placebo	20	24
Ahn 2020	Korea	WPR	RCT	Children	Moderate	*Lactobacillus pentosus*	41	Placebo	41	12
Jeong 2020	Korea	WPR	RCT	Children	Moderate, severe	*Lactobacillus rhamnosus*	33	Placebo	33	12
Cukrowska 2021	Poland	EUR	RCT	Children	Moderate, severe	*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus rhamnosus*	66	Placebo	68	12
DAuria 2021	Italy	EUR	RCT	Children	Moderate, severe	*Lactobacillus paracasei*	26	Placebo	27	12
Rather 2021	Korea	WPR	RCT	Children	Mild, moderate	*Lactobacillus sakei*	16	Placebo	20	12
Prakoeswa 2022	Indonesia	AMR	RCT	Adults	Mild, moderate	*Lactobacillus plantarum*	15	Placebo	15	8

AD: Atopic dermatitis, AMR: Region of the Americas, CI: Confidence Interval, EMR: Eastern Mediterranean Region, EUR: European Region, RCT: Randomized controlled trial, SMD: Standardized Mean Difference, WPR: Western Pacific Region

Outcomes

Probiotic supplementation significantly decreased the SCORAD index in patients with AD (SMD, −4.0; 95%CI, −7.3 to −0.7) (**Figure 2**). When the studies were classified according to the country where the RCTs were conducted, those performed in China (SMD, −1.6; 95%CI, −2.3 to −0.9), Iran (SMD, −1.1; 95%CI, −1.7 to −0.4), Poland (SMD, −1.7; 95%CI, −2.1 to −1.3), and Spain (SMD, −31.5; 95%CI, −38.1 to −24.8) reported a statistically significant decrease in the SCORAD index in the probiotic supplementation group. In contrast, in studies performed in Germany (SMD, 1.4; 95%CI, 0.8 to 2.1) and the Netherlands (SMD, 0.9; 95%CI, 0.5 to 1.4), an increased SCORAD index was found in the probiotic supplementation group (**Supplementary Table 1**). When the country where the RCTs were conducted were classified according to the WHO geographical regions, one study that was performed in the EMR showed significant reductions in the SCORAD index in the probiotic supplementation group (SMD, −1.1; 95%CI, −1.7 to −0.4) (**Supplementary Table 1**).

When analyzing the therapeutic effect of probiotics according to the severity of AD, studies that included both mild and moderate AD indicated statistically significant decreases in the SCORAD indexes in the probiotic supplementation groups (SMD, −1.4; 95%CI, −2.2 to −0.7) (**Table 2**). In addition, in the subgroup analysis according to the duration of probiotic supplementation, significant decreases in the SCORAD index were identified in RCTs in which patients received probiotic supplementation for more than three months (SMD, −5.1; 95%CIs, −9.7 to −0.4) (**Table 2**).

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	SMD	95%CI	Weight
Children									
Weston 2005	28	-17.1	11.3	28	-8.8	19.5	-0.5	[-1.0; 0.0]	4.1%
Folster-Holst 2006	22	-8.0	1.8	25	-9.8	0.0	1.4	[0.8; 2.1]	4.1%
Passeron 2006	17	-16.3	10.0	22	-15.4	4.4	-0.1	[-0.7; 0.5]	4.1%
Chernyshov 2009	30	-14.4	1.6	28	-18.1	0.7	2.9	[2.2; 3.7]	4.0%
Gerasimov 2010	43	-14.2	9.9	47	-7.8	7.7	-0.7	[-1.1; -0.3]	4.1%
Van der Aa 2010	42	-12.7	0.2	43	-14.5	2.8	0.9	[0.5; 1.4]	4.1%
Woo 2010	41	-13.8	0.5	34	-4.2	0.3	-21.1	[-24.6; -17.6]	3.9%
Han 2012	44	-7.6	12.0	39	-2.6	10.1	-0.4	[-0.9; -0.0]	4.1%
Wu 2012	27	-32.8	0.7	27	-17.9	0.4	-25.8	[-30.8; -20.7]	3.7%
Lin 2015	20	-8.9	5.8	20	-2.3	0.8	-1.6	[-2.3; -0.9]	4.1%
Prakoeswa 2017	12	-36.8	1.1	10	-26.9	5.0	-2.8	[-4.0; -1.5]	4.0%
Wu 2017	30	-23.2	15.2	32	-12.3	12.8	-0.8	[-1.3; -0.2]	4.1%
Navarro-Lopez 2018	23	-27.0	0.6	24	-7.8	0.6	-31.5	[-38.1; -24.8]	3.5%
Nakata 2019	25	-8.1	18.5	20	-2.5	25.6	-0.3	[-0.8; 0.3]	4.1%
Ahn 2020	41	-6.8	2.4	41	-11.2	1.4	2.2	[1.7; 2.8]	4.1%
Jeong 2020	33	-13.9	10.1	33	-8.4	9.9	-0.5	[-1.0; -0.1]	4.1%
Cukrowska 2021	66	-22.8	5.2	68	-16.4	0.2	-1.7	[-2.1; -1.3]	4.1%
DAuria 2021	26	-23.8	4.4	27	-19.7	4.1	-1.0	[-1.5; -0.4]	4.1%
Rather 2021	16	-6.8	2.2	20	-4.4	1.9	-1.1	[-1.9; -0.4]	4.1%
	586			**588**			**-4.1**	**[-8.2; 0.1]**	**75.9%**
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 85.6367$, $p < 0.01$									
Adults									
Kaur 2008	10	-2.9	2.1	6	-2.5	1.9	-0.2	[-1.2; 0.8]	4.0%
Drago 2011	19	-14.4	3.1	19	-4.1	1.9	-3.9	[-5.0; -2.8]	4.0%
Farid 2011	19	-39.2	24.2	21	-20.1	8.6	-1.1	[-1.7; -0.4]	4.1%
Drago 2012	19	-14.4	3.1	19	-4.1	3.3	-3.1	[-4.1; -2.2]	4.0%
Lemoli 2012	31	-23.6	0.9	15	-6.6	1.2	-16.6	[-20.2; -13.0]	3.9%
Prakorswa 2022	15	-25.2	9.9	15	-18.4	7.7	-0.7	[-1.5; 0.0]	4.0%
	113			**95**			**-4.1**	**[-8.8; 0.6]**	**24.1%**
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 34.0325$, $p < 0.01$									
Overall	**699**			**683**			**-4.0**	**[-7.3; -0.7]**	**100.0%**
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 69.9163$, $p < 0.01$									

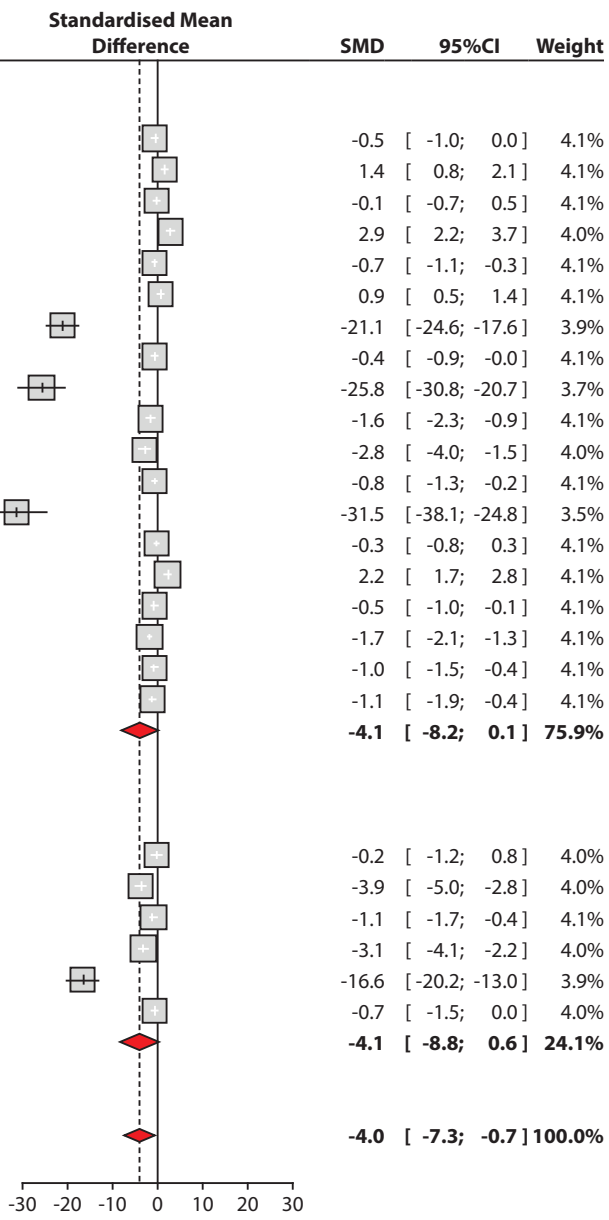

Figure 2. Meta-analysis of the effects of probiotics in reducing AD symptoms.

Table 2. Analysis of RCTs of probiotics for the treatment of AD based on the severity of AD and duration of probiotic supplementation.

	Number of studies	Number of observations	SMD	95%CIs	*P* value	I^2	*P* value Subgroup differences
AD severity							0.03
Mild	1	16	-0.2	(-1.2, 0.8)	0.72	-	
Moderate	5	304	-10.7	(-23.3, 1.8)	0.09	98.8%	
Mild, moderate	4	128	-1.4	(-2.2, -0.7)	< 0.01	64.3%	
Moderate, severe	13	849	-3.3	(-7.4, 0.93)	0.13	96.9%	
Mild, moderate, severe	1	45	-0.3	(-0.8, 0.3)	0.41	-	
Duration							0.45
≥ 3 months	15	869	-5.1	(-9.7, -0.4)	0.03	97.4%	
< 3 months	10	513	-2.5	(-7.2, 2.1)	0.28	96.0%	

AD: Atopic dermatitis, CI: Confidence Interval, SMD: Standardized Mean Difference

Subgroup analysis based on age group

After classifying RCTs according to age group (children vs. adults), the therapeutic effect of probiotic supplementation for AD was investigated based on the severity of AD and duration of probiotic supplementation (**Table 3**). In children with AD, RCTs that included mild and moderate AD showed a statistically significant decrease in the SCORAD index in the probiotic supplementation group (SMD, −1.7; 95%CI, −2.5 to −0.9). In children with AD, there was no significant therapeutic effect for AD according to the duration of probiotic supplementation. In RCTs that involved adults, probiotic supplementation showed a significant therapeutic effect for moderate AD (SMD, −3.9; 95%CI, −5.0 to −2.8). In addition, probiotic supplementation for more than three months showed a significant reduction in the SCORAD index in adults with AD (SMD, −0.9; 95%CI, −1.4 to −0.4).

Subgroup analysis based on probiotic strain

Twenty-three RCTs investigated the therapeutic effects of probiotics that included *Lactobacillus* spp. with or without other strains for AD; the overall results showed a significant decrease in the SCORAD index in the probiotic supplementation group (SMD, −4.4; 95%CI, −8.0 to −0.8) (**Figure 3A**). On the other hand, 19 RCTs that used probiotics containing only *Lactobacillus* spp. showed no significant therapeutic effect of probiotics for AD (**Figure 3B**).

Supplementation of probiotics that contained *Bifidobacterium* spp. strains with or without other strains had no significant therapeutic effect for AD (**Supplementary Table 2**). In addition, probiotics containing only *Bifidobacterium* spp. also had no significant therapeutic effect for AD. In addition, there was no significant difference in the therapeutic effect of probiotics in AD between probiotics containing only *Lactobacillus* strain and those containing only *Bifidobacterium* strain (**Supplementary Table 3**).

Table 3. Subgroup analysis based on age groups including children and adults.

Variables	Number of studies	Number of observations	SMD	95%CIs	*P* value	I^2	*P* value Subgroup differences
Children							
AD severity							0.02
Moderate	4	226	-12.5	(-28.3, 3.2)	0.12	99.0%	
Mild, moderate	3	98	-1.7	(-2.5, -0.9)	< 0.01	60.4%	
Moderate, severe	11	765	-2.1	(-6.3, 2.1)	0.34	96.5%	
Mild, moderate, severe	1	45	-0.3	(-0.8, 0.3)	0.41	-	
Duration							0.68
≥ 3 months	11	731	-4.8	(-10.9, 1.2)	0.12	97.5%	
< 3 months	8	443	-3.0	(-9.0, 3.0)	0.32	96.8%	

Table 3. (Continued)

Variables	Number of studies	Number of observations	SMD	95%CIs	*P* value	I^2	*P* value Subgroup differences
Adults							
AD severity							<0.01
Mild	1	16	-0.2	(-1.2, 0.8)	0.72	-	
Moderate	1	38	-3.9	(-5.0, -2.8)	< 0.01	-	
Mild, moderate	1	30	-0.7	(-1.5, 0.0)	0.05	-	
Moderate, severe	2	84	-9.8	(-23.0, 3.4)	0.15	96.50%	
Duration							0.17
≥ 3 months	4	138	-0.9	(-1.4, -0.4)	< 0.01	0.0%	
< 3 months	2	70	-5.8	(-12.8, 1.1)	0.10	96.5%	

AD: Atopic dermatitis, CI: Confidence Interval, SMD: Standardized Mean Difference

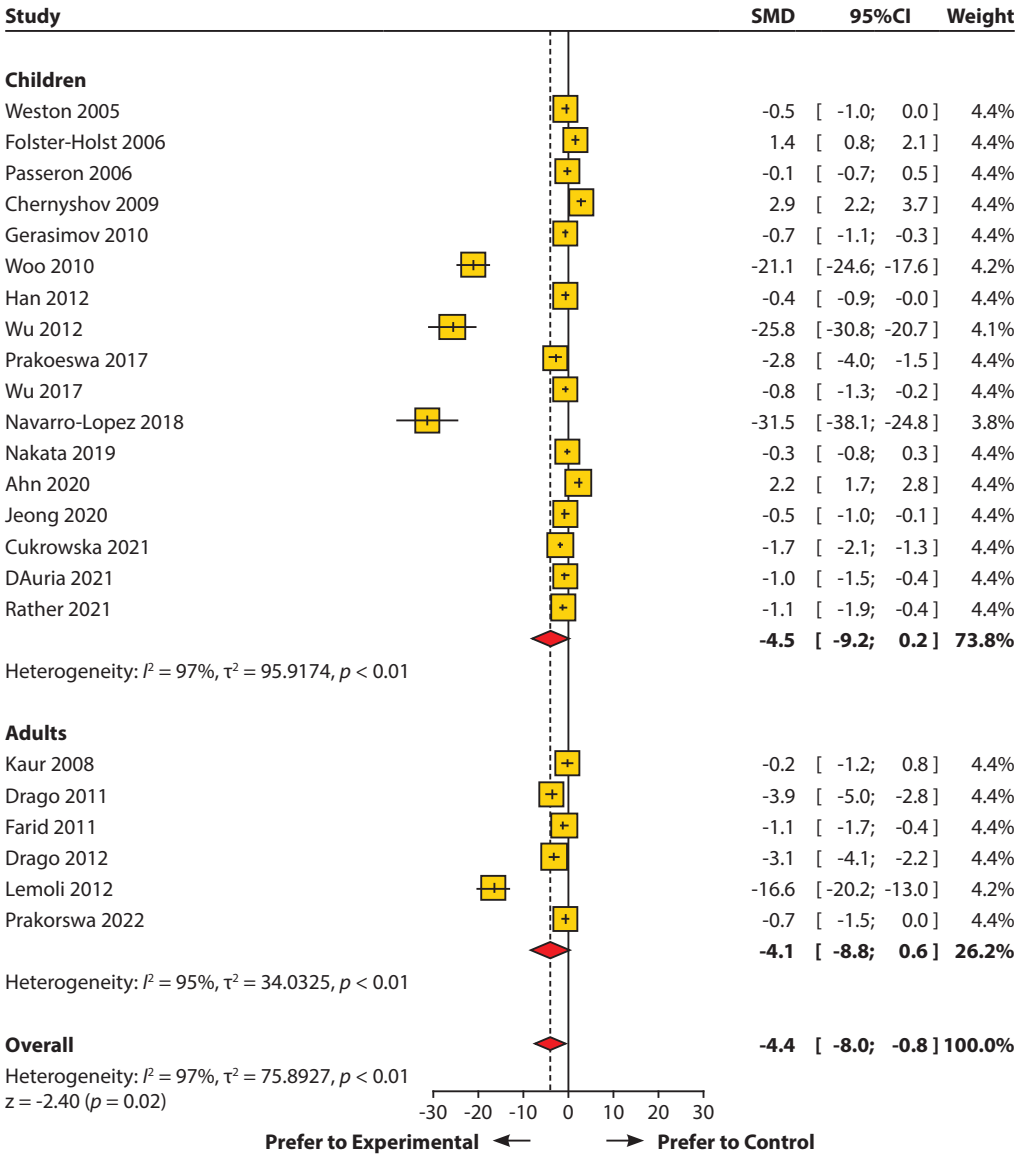

Figure 3. Subgroup analysis based on probiotic strains. (A) Therapeutic effect of probiotics including *Lactobacillus* spp. strains with or without other strains. (B) Therapeutic effect of probiotics containing only *Lactobacillus* spp. strains.

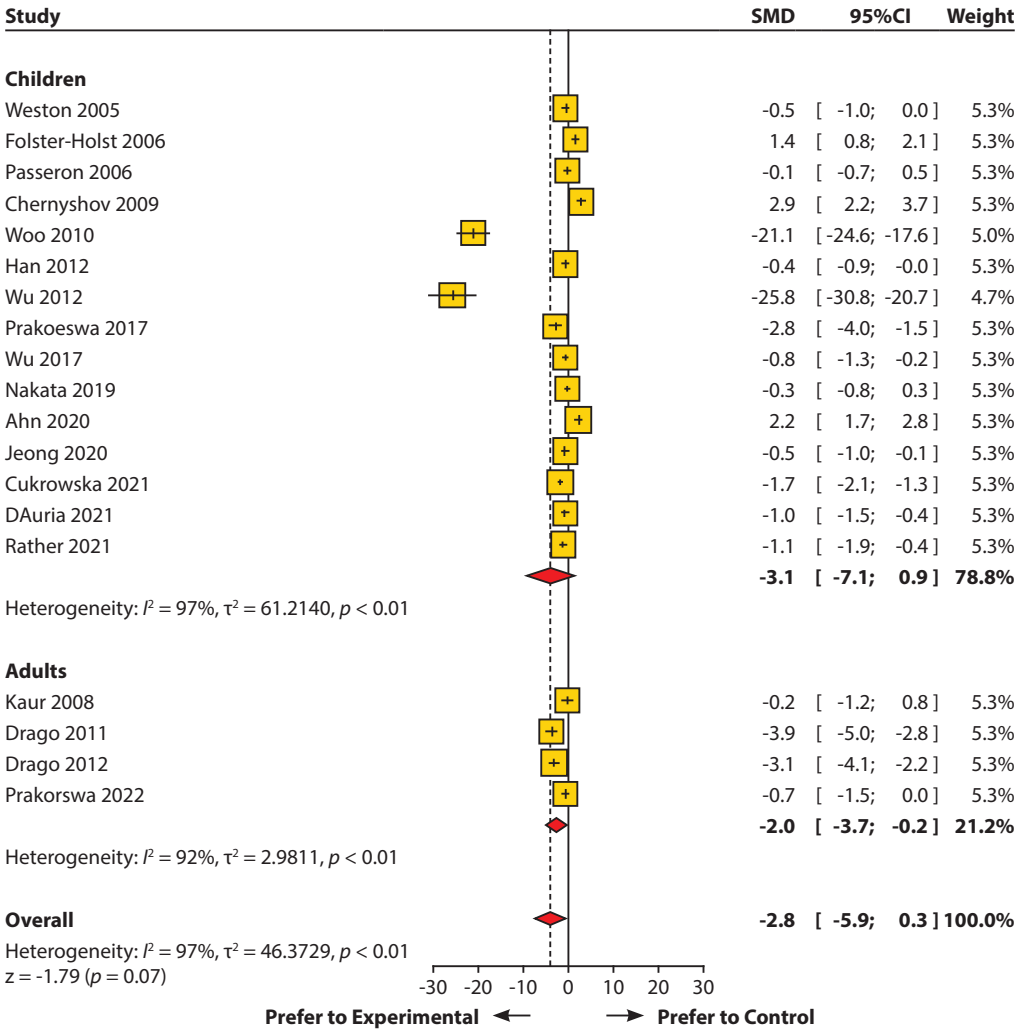

Figure 3. (Continued)

Publication bias

Egger's test was used to assess the potential publication bias in the present meta-analysis and showed that there was a significant publication bias (P < 0.01, data not shown).

Discussion

Our systematic review and meta-analysis showed that probiotic supplementation significantly decreased the severity of AD as measured by the SCORAD index. In addition, the results of the meta-analysis based on a diverse subgroup analysis of geographic region, severity of AD, duration of probiotic supplementation, and probiotic strain suggested evidence for customized treatment for patients with AD with probiotic supplementation as an adjuvant therapy. The results of the present study also suggest the need for tailored application of probiotics for the treatment of AD.

Differences in the strains, dose, and duration of probiotic supplementations and characteristics of the study population with AD, including severity and phenotypes and endotypes of AD, may be associated with inconclusive determinations of the therapeutic effects of probiotic supplementation in AD; therefore, identifying target patient groups for whom probiotic supplementation can be beneficial in the treatment of AD is important. There have been several meta-analyses conducted to evaluate the therapeutic effects of probiotic supplementation in AD.[12,17-20] Zhao et al.[21] observed similar results to ours, but their findings were based on 609 children with AD aged 36 months or less from seven studies. A recent network meta-analysis investigating the comparative effectiveness of probiotic strains for the treatment of pediatric AD observed that certain probiotics affect symptoms of AD in children, but this study did not categorize subgroups according to baseline severity.[12] However, meta-analyses investigating the therapeutic effects of probiotic supplementation for AD considering the geographic region, duration of probiotic supplementation, and probiotic strain in the total population are lacking because of the considerable heterogeneity among studies. The present study investigated the efficacy of probiotics in the treatment of AD with a subgroup analysis according to countries and geographic regions, severity of AD, duration of probiotic supplementation, and probiotic strains administered, thus providing new evidence.

The present meta-analysis showed that probiotic supplementation significantly decreased the severity of AD overall, which is consistent with the findings of previous meta-analyses performed in specific age groups including infants, children, adults, or the total population.[18-20,22] In addition to the age group, the severity of AD and duration of probiotic supplementation might affect the therapeutic effects of probiotics in patients with AD. Therefore, we investigated the therapeutic effects of probiotics in patients with AD based on the severity of AD and supplementation duration in children and adults. In children, probiotic supplementation showed significant therapeutic effects in patients with mild and moderate AD, whereas probiotic supplementation was effective in the treatment of moderate AD in adults. In both age groups, probiotic supplementation did not have a significant therapeutic effects for severe AD. The difference in the therapeutic effect according to the severity of AD might be related to the characteristic pathophysiological mechanisms underlying each severity of AD.[23] These results suggest that consideration of the severity of AD is necessary when determining whether patients with AD need to receive probiotic supplementation to improve the effectiveness of this treatment for AD; however, further studies are required to confirm the results of the present study.

The evidence regarding the appropriate duration of probiotic supplementation for the treatment of AD is unclear; this might be partially related to the inconclusive results on the therapeutic effects of probiotic supplementation. In the present meta-analysis, we found that supplementation with probiotics for more than three months showed significant therapeutic effects for AD in the total population and in adults with AD, whereas supplementation with probiotics for less than three months had no therapeutic effects for AD in the total population. The maturation status of the gut microbiome at the time of enrollment in each study and immune modulation affected by the balance between the already established gut microbiome in the host and changes in the gut microbiota caused by probiotic supplementation might be associated with differences in the therapeutic effects according to the duration of probiotic administration.[24,25]

Lactobacillus spp. with or without other strains were most commonly contained in the probiotics used for the treatment of AD, followed by *Bifidobacterium* spp. strains.[26] Therefore, we investigated the therapeutic effect of probiotics for AD based on whether *Lactobacillus* spp. or *Bifidobacterium* spp. were used alone or in combination with other strains. In the present meta-analysis, probiotics containing *Lactobacillus* spp. with or without other strains showed significant therapeutic effects for AD, whereas probiotics containing only *Lactobacillus* spp. strains had no significant therapeutic effect for AD. One meta-analysis reported that a mixture of *Bifidobacterium animalis* ssp. *lactis*, *Bifidobacterium longum*, and *Lactobacillus casei* showed the greatest therapeutic effect for AD in children among the diverse mixed or non-mixed strains of probiotics.[12] When combined with these results, a mixture of probiotics including *Lactobacillus* spp. strains might be beneficial in the treatment of AD.

In the present meta-analysis, we found that the therapeutic effects of probiotic supplementation in AD may differ based on the country and geographic region. In our meta-analysis, significant therapeutic effects for AD was observed in the EMR. The therapeutic effect of probiotics for AD was the greatest in Spain, followed by Poland, China, and Iran. The differences in the therapeutic effects of probiotics for AD according to the region might be related to differences in dietary patterns and the gut microbiota based on ethnicity as well as individual characteristics.[27] The selection of probiotics considering individual diet patterns and the gut microbiota in each ethnicity might enhance the therapeutic effect of probiotics for AD. Future studies on these issues may improve the therapeutic effect of probiotics for AD.

There are several limitations to this study. There were high levels of heterogeneity and potential publication bias among the included studies; thus, caution is necessary in interpreting the results due to the small true effect size. In addition, this might be associated with conflicting findings within the included studies. However, the considerable heterogeneities of RCTs reflect real clinical situations, including variations in the severity of AD even within an individual over time, different strains of probiotics acting in the gut even at the same dose, and various factors affecting AD exacerbations. Relatively few studies were included in the present meta-analysis because studies published in languages other than English and abstracts were excluded. Well-controlled RCTs with large number of patients can provide more robust results. Nevertheless, the present study has significant meaning in suggesting target groups that can enhance the therapeutic effects of probiotics for AD.

In conclusion, probiotic supplementation can be beneficial in the treatment of AD. The therapeutic effect can be tailored depending on age, severity of AD, probiotic strain, duration of probiotic supplementation, geographic region, ethnicity, or lifestyle to improve the therapeutic effect of probiotics for AD.

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Supplementary materials

Supplementary Table 1. Analysis of randomized clinical trials of probiotics for the treatment of atopic dermatitis depending on countries and WHO geographic regions.

Variables	Number of studies	Number of observations	SMD	95%CI	*p*-value	I^2
WHO regions						
WPR	10	599	-4.8	(-10.7, 1.1)	0.1	97.3%
EUR	12	691	-4.2	(-9.3, 1.0)	0.1	97.4%
EMR	1	40	-1.1	(-1.7, -0.4)	0.0	-
AMR	2	52	-1.7	(-3.7, 0.3)	0.1	86.9%
Country						
Australia	1	56	-0.5	(-1.0, 0.0)	0.1	-
China	1	40	-1.6	(-2.3, -0.9)	< 0.01	-
Estonia	1	16	-0.2	(-1.2, 0.8)	0.7	-
France	1	39	-0.1	(-0.7, 0.5)	0.7	-
Germany	1	47	1.4	(0.8, 2.1)	< 0.01	-
Indonesia	2	52	-1.7	(-3.7, 0.3)	0.1	86.9%

Supplementary Table 1. (Continued)

Variables	Number of studies	Number of observations	SMD	95%CI	*p*-value	I^2
Country (Continued)						
Iran	1	40	-1.1	(-1.7, -0.4)	0.0	-
Italy	4	175	-6.0	(-12.7, 0.8)	0.1	96.8%
Japan	1	45	-0.3	(-0.8, 0.3)	0.4	-
Korea	5	342	-4.1	(-12.3, 4.1)	0.3	98.2%
Netherlands	1	85	0.9	(0.5, 1.4)	< 0.01	-
Poland	1	134	-1.7	(-2.1, -1.3)	< 0.01	-
Spain	1	47	-31.5	(-38.1, -24.8)	< 0.01	-
Taiwan	2	116	-13.1	(-37.6, 11.4)	0.3	98.9%
Ukraine	2	148	1.1	(-2.5, 4.7)	0.6	98.5%

AMR: Region of the Americas, CI: Confidence Interval, EMR: Eastern Mediterranean Region, EUR: European Region, SMD: Standardized Mean Difference, WHO: World Health Organization, WPR: Western Pacific Region

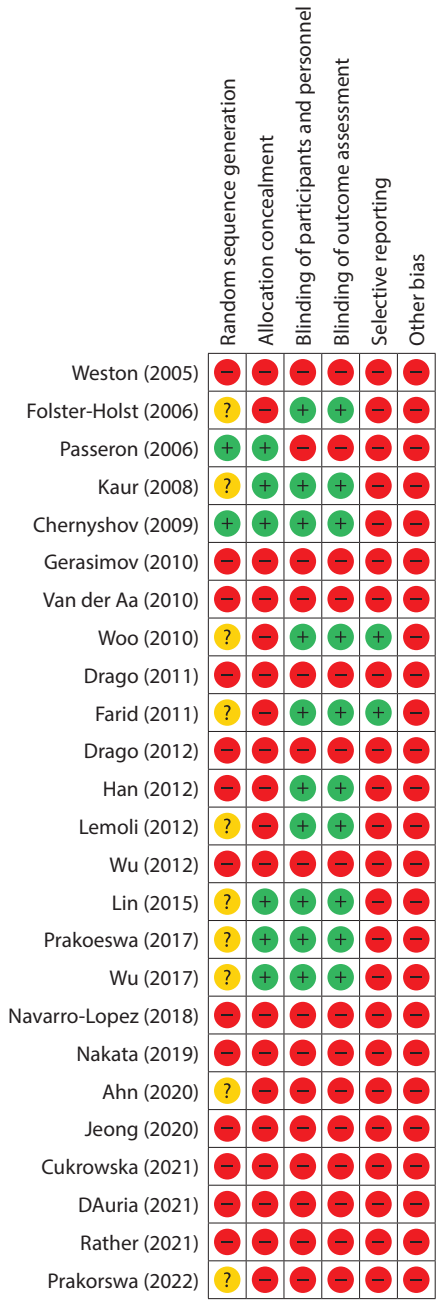
Supplementary Table 2. Therapeutic effect of *Bifidobacterium* strains in atopic dermatitis depending on the combination of other strains.

Variables	Number of studies	Number of observations	SMD	95%CI	*p*-value	I^2
Including Bifidobacterium	6	348	-8.1	(-18.2, 0.1)	0.1	97.6%
Only Bifidobacterium	2	125	-0.3	(-2.8, 2.1)	0.8	97.0%

CI: Confidence Interval, SMD: Standardized Mean Difference

Supplementary Table 3. Comparison of the therapeutic effects of probiotics in atopic dermatitis between those containing only *Lactobacillus* strain and those containing only *Bifidobacterium* strain.

Variables	Number of studies	Number of observations	SMD	95%CI	*p*-value	I^2
Only Lactobacillus	19	1034	-2.8	(-5.9, 0.3)	0.1	96.8%
Only Bifidobacterium	2	125	-0.3	(-2.8, 2.1)	0.8	97.0%



Supplementary Figure 1. Risk of bias assessment of the RCTs included in this meta-analysis.