Probiotics Supplementation During Pregnancy or Infancy for the Prevention of Atopic Dermatitis

A Meta-analysis

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Background: The study of probiotics to prevent allergic conditions has yielded conflicting results in children. We undertook a meta-analysis of randomized controlled trials to investigate whether probiotic use during pregnancy and early life decreases the incidence of atopic dermatitis and immunoglobulin E (IgE)-associated atopic dermatitis in infants and young children.

Methods: We performed a systematic literature search in Medline, Embase, and Cochrane Library, updated to October 2011. The intervention was diet supplementation with probiotics versus placebo. Primary outcomes were incidence of atopic dermatitis and IgE-associated atopic dermatitis. We calculated summary relative risks (RRs) and corresponding 95% confidence intervals (CIs), using both fixed- and random-effects models. We computed summary estimates across several strata, including study period, type of patient, dose, and duration of intervention, and we assessed the risk of bias within and across trials.

Results: We identified 18 publications based on 14 studies. Meta-analysis demonstrated that probiotic use decreased the incidence of atopic dermatitis (RR = 0.79 [95% CI = 0.71–0.88]). Studies were fairly homogeneous (I^2 = 24.0%). The corresponding RR of IgE-associated atopic dermatitis was 0.80 (95% CI = 0.66–0.96). No appreciable difference emerged across strata, nor was there evidence of publication bias.

Conclusions: This meta-analysis provided evidence in support of a moderate role of probiotics in the prevention of atopic dermatitis and IgE-associated atopic dermatitis in infants. The favorable effect was similar regardless of the time of probiotic use (pregnancy or early life) or the subject(s) receiving probiotics (mother, child, or both).

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The hygiene hypothesis postulates a favorable effect of exposures to infectious agents on immune-mediated diseases.[1,2] This is supported by several epidemiologic studies, mostly from high-income countries, reporting an association between decreased frequency of infections (measured through direct or indirect markers) and increased incidence of allergic diseases (including asthma, rhinitis, and atopic dermatitis, and autoimmune disorders[3–5]). The issue remains, however, controversial.[6,7]

Probiotics have been defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[8] The mechanism of action by which probiotic supplementation might reduce allergic diseases has not been elucidated, but could be linked to the hygiene hypothesis, which suggests that a lack of exposure to microbes in early life can affect development of the immune system and increase susceptibility to certain disorders, such as allergies.[2] This hypothesis involves 3 classes of mechanisms that are neither mutually exclusive nor independent: antigenic competition, immune regulation, and stimulation of innate immunity (notably toll-like receptors[9]). More recently, probiotics were associated with the "revised hygiene hypothesis," as suggested by Van der Aa et al,[10] which considers changes in the intestinal colonization pattern (ie, microbiota) during infancy as an important contributor to increased allergy prevalence. Composition of the intestinal microbial flora might have a role on allergy by driving the maturation of the immune system.[11] The use of probiotics is thought to be useful in the prevention and treatment of selected allergic conditions.[12,13]

These considerations of the potential immune-regulatory role of gut microbiota on the outcome of allergic diseases are pertinent to the effect of probiotics in these infections, as indicated by a number of experimental and clinical evidence, notably for mycobacteria and various viruses or parasites.[2,4]

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Several randomized controlled trials have investigated the effect of probiotic use during pregnancy or after childbirth (or both) in the prevention of atopic dermatitis in infants and young children. A Cochrane review published in 2009[14] included 5 trials, and reported a summary relative risk (RR) for probiotic use versus nonuse of 0.82 (95% confidence interval [CI] = 0.70–0.95) for atopic dermatitis (ie, eczema) defined according to the Nomenclature Review Committee of the World Allergy Organization,[15] and an RR of 0.80 (0.62–1.02) for immunoglobulin E (IgE)-associated atopic dermatitis (ie, atopic eczema).[15] Subgroup analyses were limited by the relatively small number of studies available in 2007.

Since then, at least 9 randomized controlled trials have provided additional data on atopic dermatitis. A recent meta-analysis in Chinese, restricted to an analysis of lactic acid bacteria (alone or in combination with other probiotics), reported RRs of 0.80 (95% CI = 0.70–0.90) for atopic dermatitis and 0.78 (0.64–0.97) for IgE-associated atopic dermatitis.[16]

We conducted a formal systematic review and a meta-analysis of randomized controlled trials to investigate whether probiotic use during pregnancy and early life decreases the incidence of atopic dermatitis and IgE-associated atopic dermatitis in infants and young children. We did not consider asthma as one of the outcomes of this review, because the distinction between asthma and wheezing is difficult in young children, and asthma generally occurs at a later age than atopic dermatitis. Furthermore, there is no evidence that probiotics have an effect in the prevention of asthma.[17]

METHODS

This meta-analysis followed the PRISMA guidelines for reporting systematic reviews and meta-analyses.[18,19] We registered this review in the International Prospective Register of Systematic Reviews (PROSPERO, registration No. CRD42011001312), describing in advance the aims and methods of our investigation.[20] In March 2011, we performed a systematic literature search in the Medline database, Embase, and the Cochrane Library (reviews only) for clinical trials that investigated factors related to infection, including probiotic use, and atopic dermatitis in infants and children. The literature search was updated on 26 October 2011, during the final revision process. Full details on the search strings used are given in eAppendix 1 (http://links.lww.com/EDE/A572). We restricted our search to clinical or randomized controlled trials conducted in humans, and to the papers published in English.

Two review team members (C.P. and F.T.) retrieved and independently assessed the potentially relevant articles, and checked the reference list of all papers of interest for other pertinent publications. Abstracts and unpublished studies were not included. No studies were excluded a priori because of weakness of design or data quality, and we did not assign quality scores to the studies. A publication was included in the analysis if the following criteria were met: randomized placebo-controlled trials of use of one or more types of probiotics during pregnancy or infancy, with outcome assessment performed during infancy or childhood (ie, up to 12 years of age), reporting estimates of RR and the corresponding CI (or information sufficient to calculate them) for incidence of atopic dermatitis or IgE-associated atopic dermatitis. We excluded observational studies, interventions other than probiotic use, studies conducted in adolescents or adults, and those focused on treatment of atopic dermatitis. Discrepancies in results between review team members were discussed and resolved.

Two review team members (C.P. and C.G.) reviewed all the studies and abstracted data. With reference to the outcomes of interest, we collected separate data on 3 aspects (atopic dermatitis, IgE-associated atopic dermatitis [meaning hyper IgE-associated atopic dermatitis], and severity of atopic dermatitis) by abstracting data on number of subjects with the disease and total number of subjects in the treatment and placebo groups, and risk estimates (RRs, hazard ratios [HRs], crude or adjusted odds ratios [ORs]) and corresponding 95% CI at the end of follow-up and (when available) at other timelines. Further, we abstracted information on potential sources of bias across studies, including details on blinding, loss to follow-up in treatment and placebo group, and outcome assessors, to ascertain the internal validity of the identified trials. Discrepancies in results between review team members were further checked on the original articles, and were resolved.

We combined the RR estimates from each study. For those studies providing risk estimates other than RRs, we calculated unadjusted RRs and their 95% CI from the reported outcome distribution of subjects in the treatment and placebo groups. When more than one publication reported results from the same study (ie, with an extended follow-up period), we included in the meta-analysis the earliest publication, because of higher completion rate and an end point more similar to other studies. One trial[21] examined 2 separate probiotic groups versus placebo. Data on the 2 probiotic groups were combined into a single RR, which we included in the meta-analysis.

We calculated summary estimates of RR of atopic dermatitis and IgE-associated atopic dermatitis using both fixed-effects models (ie, as weighed averages using the inverse of the variance of the log [RR] as weight) and random-effects models (ie, as weighed averages using the inverse of the sum of the variance of the log [RR] and the moment estimator of the variance between studies as weight).[22,23] Heterogeneity between trials was assessed using the χ^2 test

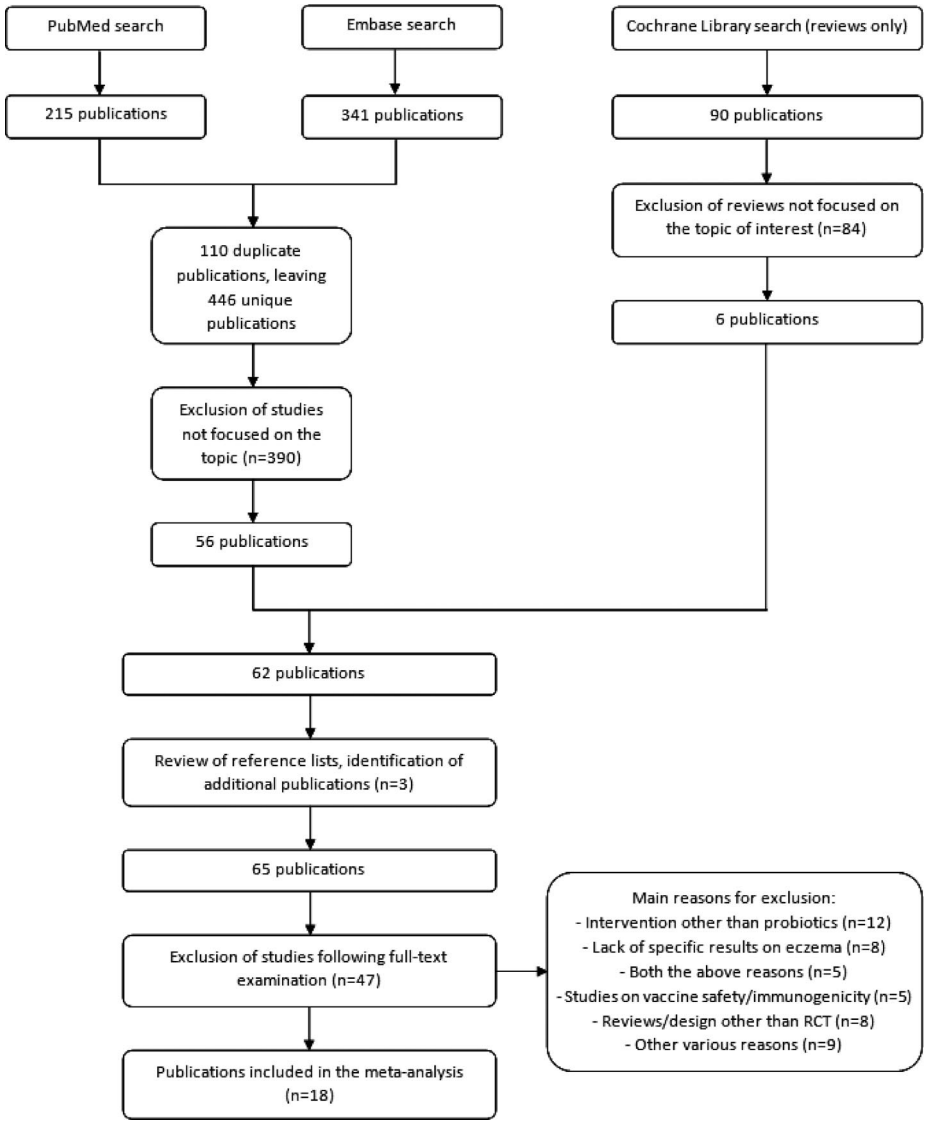

FIGURE 1. Flowchart for search and selection of publications for the meta-analysis.

and defined as a P value <0.10, and inconsistency was measured using the I^2 statistic.[24] We also computed summary estimates in several strata, including geographic area, family history of allergic diseases, characteristics of intervention (ie, period, subject, duration, dose, and number of probiotics), end point, criteria used for diagnosis of atopic dermatitis, and potential conflict of interests. In stratified analyses, we presented RRs from random-effects models, because the number of studies (and hence the power of the heterogeneity test) was low. We used meta-regression to test heterogeneity between subgroups for study-level, two-strata covariates, or a heterogeneity test otherwise.[25] Presence of publication bias was assessed by examination of funnel plots and by applying the tests proposed by Begg and Mazumdar,[26] and by Egger et al.[27] All the statistical analyses were performed using the STATA software (version 11; StataCorp, College Station, TX).

RESULTS

Figure 1 shows a flowchart for selection of articles. A total of 446 publications were identified by the combined search in PubMed and Embase, and 90 reviews were obtained from the Cochrane Library. By examining the title and abstract, 390 publications were excluded as irrelevant (mostly, studies focused on treatment rather than prevention of atopic dermatitis; investigations, commentaries, and reviews of other atopic diseases; studies of food allergies, etc.); 56 were retained for further consideration. Similarly, 84 of 90 reviews extracted from the Cochrane Database were not in the scope for this meta-analysis, leaving 6 for further consideration. The review of the reference lists of the selected publications identified 3 additional reports, providing a total of 65 papers. After

full-text examination, there were 16 publications that reported original data on probiotics use alone in the prevention of atopic dermatitis/IgE-associated atopic dermatitis,[12,21,28–41] and 2 publications (from the same study) reporting data on combined use of pre- and probiotics.[42,43] These were the basis for our meta-analysis.

Among the studies included in the meta-analysis, there were 18 papers with results on probiotics in the prevention of atopic dermatitis, based on 14 different trials. Three publications reported results with extended follow-up[32,33,42] from Kalliomaki et al[12] and Kukkonen et al,[43] and one publication provided subgroup analyses from the study of Kalliomaki et al.[37] The main characteristics of each publication are summarized in Table 1. All studies were randomized, placebo-controlled trials. Nine were conducted in Europe, and 5 in Asia or Oceania. Thirteen studies reported data on probiotics for the prevention of atopic dermatitis, 10 for the prevention of IgE-associated atopic dermatitis; 11 reported severity of atopic dermatitis but lacked sufficient detail to meta-analyze this outcome.

Table 2 reports selected quality measures of trials included in the meta-analysis. All trials were double-blinded. The proportion of subjects that completed the follow-up period did not show relevant differences between treatment and placebo groups in any of the trials. Clinical assessment of atopic dermatitis was performed by study-outcome assessors or clinicians in 12 of 14 studies. In the remaining 2 studies, atopic dermatitis was reported by parents, either as complaint in questionnaires/diaries or as diagnosed by a family doctor or other physician.

Figure 2 shows the results from each trial and overall, using a fixed-effects model, for probiotics in the prevention of atopic dermatitis. Of the 13 estimates, 10 were <1.0. The summary RR of atopic dermatitis was 0.79 (95% CI = 0.71–0.88). Results of the studies were homogeneous (I^2 = 24.0%). When we repeated the calculation of the summary RR using a random-effects model, the result was not materially changed (0.78 [0.69–0.89]). Further, excluding 2 studies in which clinical assessment of atopic dermatitis was not made by clinicians/study outcome assessors, but was rather reported by parents or diagnosed by physicians/family doctors,[35,40] the fixed-effects RR was consistent with the main analysis (0.80 [0.71–0.90]).

Figure 3 gives the results from each trial and overall, using a fixed-effects model, for probiotics in the prevention of IgE-associated atopic dermatitis. Of the 10 estimates, 7 were <1.0. The summary RR of IgE-associated atopic dermatitis was 0.80 (95% CI = 0.66–0.96; I^2 = 31.5%). When we used a random-effects model, the RR was 0.83 (95% CI = 0.65–1.06).

Table 3 reports the pooled RRs for use of probiotics in the prevention of atopic dermatitis in selected subgroups. Although limited by the small number of trials in some subgroups, probiotic supplementation was consistently associated with a reduction of atopic dermatitis incidence, with no meaningful differences among strata. The estimates within subgroups showed low-to-moderate heterogeneity. The RR of atopic dermatitis for probiotic use was somewhat lower when infants/young children had no family history of allergic diseases (RR = 0.35), but the estimate was based on only 2 studies.

Figure 4 shows the funnel plot of trials on probiotics in the prevention of atopic dermatitis. The graph did not show relevant asymmetry of the studies, as confirmed by the Egger (P = 0.41) and Begg tests (P = 0.27), providing no evidence of publication bias. However, the number of studies was too few to draw definitive conclusions about suppression of negative results.

DISCUSSION

This meta-analysis of randomized controlled trials reported a reduction of about 20% in the incidence of atopic dermatitis and IgE-associated atopic dermatitis in infants and young children, following probiotic use. The favorable effect on atopic dermatitis was similar according to the period of probiotic use (ie, after delivery only or also during pregnancy), the subject(s) receiving probiotics (ie, mother, child, or both), duration of intervention, and study end point. The effect was consistently observed in several other subgroups as well. Furthermore, assessment of bias within and across studies did not show evidence of shortcomings.

According to the hygiene hypothesis, the increasing prevalence of atopic dermatitis in high-income countries is the consequence of reduced infection and exposure to microbes during early childhood.[1,2,46–50] More recently, a study suggested a role for changes in the intestinal colonization pattern during infancy that affect the immune system.[10] The mechanisms through which gut bacteria, particularly commensals, modulate immune responses are still not well defined, but could involve aforementioned mechanisms for the hygiene hypothesis.[10,51–53]

Further supportive evidence for a role of the intestinal flora and of infectious agents in the prevention of atopic dermatitis comes from the favorable results of 2 studies on use of prebiotics[54–56] (ie, nondigestible food components that selectively stimulate the growth or activity of "healthy" bacteria in the colon[57]) and from investigations of parasites deworming, indicating higher incidence of infantile eczema when mothers were treated with albendazole versus placebo.[58,59] However, available data on these interventions are limited, and results are not entirely consistent.[60–62]

One of our aims was to summarize the data on probiotic use and severity of incident atopic dermatitis. Most studies identified did not provide detailed results on disease severity. Nevertheless, of the 11 studies that considered severity of atopic dermatitis as outcome, 9 reported no difference between treatment and placebo groups. Thus, although probi-

TABLE 1. Characteristics of Trials Included in the Meta-analysis on Probiotics and Prevention of Atopic Dermatitis

1st Author, Year	Country, Period	Trial Type	No. of Subjects	Outcome(s) Reported	No. AD in TR/PL Group	Probiotic Type(s)	Intervention Period and Subject	Dose	End of Follow-up	Main Result
Kalliomaki et al, 2001[12]	Finland, 1997–1998	RND, PC	159 mothers randomized; 132 infants completed the study (64 treated, 68 placebo)	AD; severity of AD (not detailed)	15/31	*Lactobacillus rhamnosus* GG	From 2–4 weeks before pregnancy term (mother) to 6 months of children, through breastfeeding or directly to child	2×10^{10} CFU daily	2 years of age	Frequency of AD was halved in the treatment group. Total IgE concentrations were similar in the 2 groups
Rautava et al, 2002[37a]	Finland, 1997–1998	RND, PC	62 mothers breastfeeding until 3 months of child were randomized; 57 completed the study (27 treated, 30 placebo)	AD	4/14	*L. rhamnosus* GG	From 2–4 weeks before pregnancy term to 3 months of children, through breastfeeding only	2×10^{10} CFU daily	2 years of age	Frequency of AD was 15% in the treatment group and 47% in the placebo group
Kalliomaki et al, 2003[32a]	Finland, 1997–1998	RND, PC	159 mothers randomized; 107 infants completed the study (53 treated, 54 placebo)	AD	14/25	*L. rhamnosus* GG	From 2–4 weeks before pregnancy term (mother) to 6 months of children, through breastfeeding or directly to child	2×10^{10} CFU daily	4 years of age	RR of AD at 4 years of age was 0.57 for treatment vs. placebo group
Kalliomaki et al, 2007[33a]	Finland, 1997–1998	RND, PC	159 mothers randomized; 115 infants completed the study (53 treated, 62 placebo)	AD	23/41	*L. rhamnosus* GG	From 2–4 weeks before pregnancy term (mother) to 6 months of children, through breastfeeding or directly to child	2×10^{10} CFU daily	7 years of age	The cumulative risk of AD at 7 years of age was lower in the treatment than placebo group (RR = 0.64)
Rautava et al, 2006[36]	Finland, 2000–2002	RND, PC	81 infants enrolled; 72 completed the study (32 treated, 40 placebo)	AD	4/8	*L. rhamnosus* GG and *Bifidobacterium lactis* Bb12	From starting artificial feeding of child (before 2 months, inclusion criteria) to 12 months	1×10^{10} CFU daily for each probiotic type	1 year of age	AD was manifested by 13% of those in the treatment and 20% in the placebo group

(*Continued*)

TABLE 1. (*Continued*)

1st Author, Year	Country, Period	Trial Type	No. of Subjects	Outcome(s) Reported	No. AD in TR/PL Group	Probiotic Type(s)	Intervention Period and Subject	Dose	End of Follow-up	Main Result
Abrahamsson et al, 2007[28]	Sweden, 2001–2003	RND, PC	232 mothers recruited and randomized; 188 infants completed the study (95 treated, 93 placebo)	AD; IgE-associated AD; severity of AD (not detailed)	34/32	*Lactobacillus reuteri*	From 4 weeks before pregnancy term (mother) to 12 months (child)	1×10^8 CFU daily	2 years of age	Similar cumulative incidence of AD. Lower IgE-associated AD in the treatment group
Taylor et al, 2007[39]	Australia, 2002–2005	RND, PC	231 mothers recruited, 226 randomized; 175 infants completed the study (88 treated, 87 placebo)	AD; IgE-associated AD; severity of AD	38/34	*Lactobacillus acidophilus* LAVRI-A1	From birth to 6 months (child)	3×10^9 CFU daily	1 year of age	No difference between groups for any AD. Higher proportion of IgE-associated AD in the treatment (26%) vs. placebo (14%) group
Kukkonen et al, 2007[43]	Finland, 2000–2003	RND, PC	1521 mothers eligible, 1223 randomized; 925 infants completed the study (461 treated, 464 placebo)	AD; IgE-associated AD; severity of AD (not detailed)	120/150	Probiotic and prebiotic mix; *L. rhamnosus* GG, *L. rhamnosus* LC705, *Bifidobacterium breve* Bb99, *Propionibacterium freudenreichii*	From 36 weeks of gestation (mother) to 6 months of age (child)	LGG: 5×10^9; LC705: 5×10^9; Bb99: 2×10^8; Pf: 2×10^9 CFU; all twice daily	2 years of age	Both AD and IgE-associated AD were reduced (ORs = 0.7 and 0.6, respectively) in the treatment group
Kuitunen,[b] 2009[42]	Finland, 2000–2003	RND, PC	1521 mothers eligible, 1223 randomized; 891 infants completed the study (445 treated, 446 placebo)	AD; IgE-associated AD	175/193	Probiotic and prebiotic mix; *L. rhamnosus* GG, *L. rhamnosus* LC705, *B. breve* Bb99, *P. freudenreichii*	From 36 weeks of gestation (mother) to 6 months of age (child)	LGG: 5×10^9; LC705: 5×10^9; Bb99: 2×10^8; Pf: 2×10^9 CFU; all twice daily	5 years of age	No difference between groups for AD overall nor for IgE-associated AD. In cesarean-delivered children, the OR of AD was 0.43 for treatment vs. placebo group
Huurre et al, 2008[31]	Finland, NR	RND, PC	171 mothers enrolled; 140 infants completed the study (72 treated, 68 placebo)	IgE-associated AD	NR	*L. rhamnosus* GG and *B. lactis* Bb12	From the first trimester of pregnancy to the end of breastfeeding (mother)	1×10^{10} CFU daily for each probiotic type	1 year of age	IgE-associated AD was lower (10% vs. 18%) in the treatment vs. placebo group

(*Continued*)

TABLE 1. (*Continued*)

1st Author, Year	Country, Period	Trial Type	No. of Subjects	Outcome(s) Reported	No. AD in TR/PL Group	Probiotic Type(s)	Intervention Period and Subject	Dose	End of Follow-up	Main Result
Kopp et al, 2008[34]	Germany, 2002–2004	RND, PC	147 mothers eligible, 108 recruited, 105 randomized; 94 infants completed the study (50 treated, 44 placebo)	AD; severity of AD (not detailed)	19/14	*L. rhamnosus* GG	From 4–6 weeks before pregnancy term to 3 months after delivery (mother), then from 4 to 6 months (child)	5×10^9 CFU twice daily	2 years of age	No difference between groups
Wickens et al, 2008[21]	New Zealand, 2004–2005	RND, PC	765 mothers eligible, 512 enrolled and randomized; 446 infants completed the study (144 + 152 treated, 150 placebo)	AD; IgE-associated AD; severity of AD	57/40	2 treatment groups: 1) *L. rhamnosus* HN001; 2) *Bifidobacterium animalis* subsp. lactis HN019	From 35 weeks of gestation to as long as 6 mo post-partum if breast-feeding (mother) or from birth to 2 years (child)	HN001: 6×10^9; Bb: 9×10^9 CFU daily	2 years of age	The HRs of AD were 0.5 for *L. rhamnosus* and 0.9 for *B. animalis* vs. placebo. Similar findings were observed with severity of AD
Kim et al, 2009[41]	South Korea, 2005–2006	RND, PC	159 mothers recruited, 112 randomized; 68 infants completed the study (33 treated, 35 placebo)	AD; IgE-associated AD; severity of AD (not detailed)	12/22	*Bifidobacterium bifidum* BGN4, *B. lactis* AD011 and *L. acidophilus* AD031	From 8 weeks before pregnancy term to 3 months after delivery (mother), then from 4 to 6 months (child)	1.6×10^9 CFU daily for each probiotic type	1 year of age	Cumulative incidence of AD was lower in the treatment group. IgE-associated AD was not different in the 2 groups
Niers et al, 2009[35]	The Netherlands, 2004–2005	RND, PC	247 mothers eligible, 156 enrolled and randomized; 98 infants completed the study (50 treated, 48 placebo)	AD; IgE-associated AD; severity of AD (not detailed)	27/33	*Lactobacillus lactis* W58, *B. bifidum* W23, and *Bifidobacterium lactis* W52	From the past 6 weeks of pregnancy (mother) to 12 months of age (child)	1×10^9 CFU daily for each probiotic type	2 years of age	Parental-reported AD was lower in the treatment group at 3 months of age. The difference at 2 years was no longer significant. IgE-associated AD was similar in the 2 groups
Soh et al, 2009[38]	Singapore, 2004–2006	RND, PC	865 families eligible, 253 randomized; 245 families completed the study (124 treated, 121 placebo)	AD; IgE-associated AD; severity of AD (not detailed)	27/30	*Bifidobacteria longum* BL999, *L. rhamnosus* LPR	From birth to 6 months (child)	At least 2.8×10^8 CFU of probiotic daily	1 year of age	No difference between groups for AD overall nor for IgE-associated AD

(*Continued*)

TABLE 1. (*Continued*)

1st Author, Year	Country, Period	Trial Type	No. of Subjects	Outcome(s) Reported	No. AD in TR/PL Group	Probiotic Type(s)	Intervention Period and Subject	Dose	End of Follow-up	Main Result
West et al, 2009[40]	Sweden, 2000–2003	RND, PC	179 infants randomized; 171 infants completed the study (84 treated, 87 placebo)	AD	9/19	*Lactobacillus paracasei* F19	From 4 to 13 months (child)	1×10^8 CFU daily	13 months	Cumulative incidence of AD was significantly lower in the treatment vs. placebo group
Dotterud et al, 2010[30]	Norway, 2003–2005	RND, PC	415 mothers randomized; 278 infants completed the study (138 treated, 140 placebo)	AD; IgE-associated AD; severity of AD	29/48	*L. rhamnosus* GG, *L. acidophilus* La-5 and *B. animalis* subsp lactis Bb12	From 36 weeks of gestation to 3 months of infants, through breastfeeding only	LGG: 5×10^{10}; La: 5×10^9; Bb: 5×10^{10} CFU daily	2 years of age	Risk of AD was halved in the probiotic group. The preventive effect was most evident in those without family history of atopy. Risk of IgE-associated AD was similar in the 2 groups
Boyle et al, 2011[29]	Australia, 2006–2008	RND, PC	954 mothers eligible, 250 randomized; 210 infants completed the study (108 treated, 102 placebo)	AD; IgE-associated AD; severity of AD	35/43	*L. rhamnosus* GG	From 36 weeks gestation until delivery	1.8×10^{10} CFU daily	1 year of age	Prenatal treatment was not associated with AD, nor with AD severity, nor with IgE-associated AD

[a]Separate report from the same study of Kalliomaki et al, 2001.
[b]Separate report from the same study of Kukkonen et al, 2007.
AD indicates atopic dermatitis; CFU, colony-forming units; NR, not reported; PC, placebo-controlled; RND, randomized; TR/PL, treatment/placebo.

TABLE 2. Quality Measures of Double-blinded Randomized Controlled Trials Included in the Meta-analysis on Probiotics and Prevention of Atopic Dermatitis

1st Author, Year	% Completed the Study: Treatment Group(s)	% Completed the Study: Placebo Group	Outcome Assessment
Kalliomaki et al, 2001[12]	83.1	82.9	Performed by clinicians/study outcome assessors
Rautava et al,[a] 2002[37]	90.0	93.8	Performed by clinicians/study outcome assessors
Kalliomaki et al,[a] 2003[32]	65.9	68.8	Performed by clinicians/study outcome assessors
Kalliomaki et al,[a] 2007[33]	68.8	75.6	Performed by clinicians/study outcome assessors
Rautava et al, 2006[36]	NA	NA	Performed by clinicians/study outcome assessors
Abrahamsson et al, 2007[28]	81.2	80.9	Performed by clinicians/study outcome assessors
Taylor et al, 2007[39]	77.4	80.2	Performed by clinicians/study outcome assessors
Kukkonen et al, 2007[43]	75.6	75.7	Performed by clinicians/study outcome assessors
Kuitunen et al,[b] 2009[42]	72.9	72.8	Performed by clinicians/study outcome assessors
Huurre et al, 2008[31]	NA	NA	Performed by clinicians/study outcome assessors
Kopp et al, 2008[34]	92.6	86.3	Performed by clinicians/study outcome assessors
Wickens et al, 2008[21]	Group 1: 84.7 Group 2: 88.8	87.7	Performed by clinicians/study outcome assessors
Kim et al, 2009[41]	57.9	63.6	Performed by clinicians/study outcome assessors
Niers et al, 2009[35]	64.1	61.5	Based on diaries and/or diagnosis from family doctor or consulted physician
Soh et al, 2009[38]	97.6	96.0	Performed by clinicians/study outcome assessors
West et al, 2009[40]	94.3	96.7	Based on questionnaires/diaries and/or diagnosis from doctor
Dotterud et al, 2010[30]	65.4	68.6	Performed by clinicians/study outcome assessors
Boyle et al, 2011[29]	87.2	82.4	Performed by clinicians/study outcome assessors

[a]Separate report from the same study of Kalliomaki et al, 2001.
[b]Separate report from the same study of Kukkonen et al, 2007.
NA indicates not available.

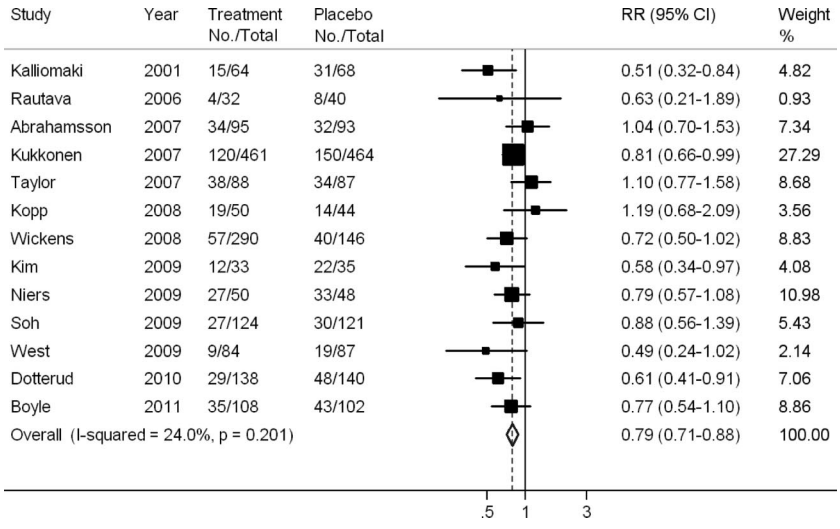

FIGURE 2. Summary RR for probiotics in the prevention of atopic dermatitis.

otics were apparently effective in reducing the incidence of atopic dermatitis, we still lack good evidence about a possible impact on disease severity. When probiotics are used for treatment of atopic dermatitis (ie, eczema), rather than prevention, there is no evidence of effect according to a Cochrane systematic review.[63] More recent data on the issue show inconsistent results.[64,65]

Several intervention regimens were used in the trials examined. For example, probiotics were given to pregnant women in some studies, and to infants at weaning in other studies. It is difficult to conceive a unifying mechanism of action of probiotics that covers all studies. According to the hygiene hypothesis, the effect of probiotics should be particularly strong in infants, whose immune system is still

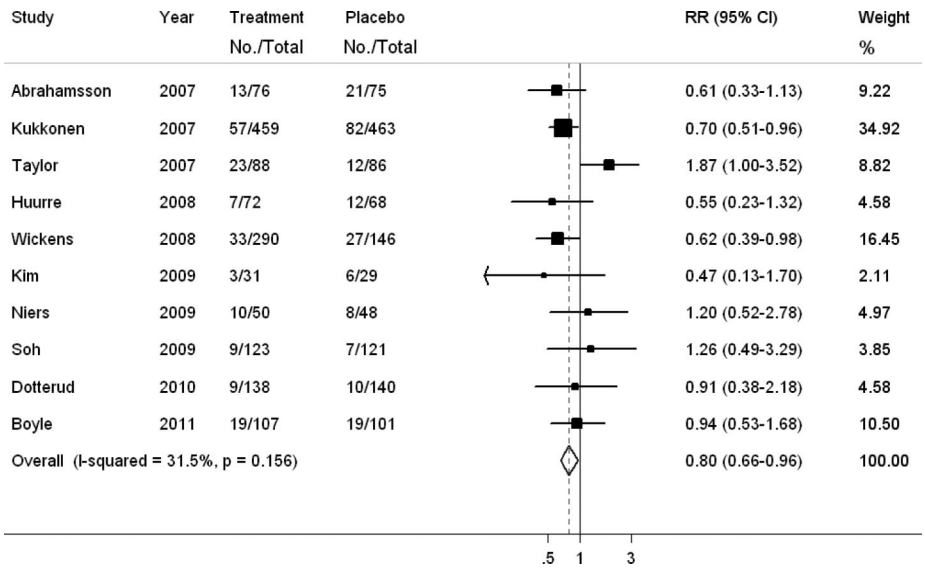

FIGURE 3. Summary RR for probiotics in the prevention of IgE-associated atopic dermatitis.

under development. The mother influences the immune development of the embryo beyond the genes transmitted or the antibodies that cross the placenta. However, the mechanisms of action of probiotics when given to mothers are still poorly understood. Efforts to disentangle the effects of probiotics in various intervention regimens by subgroup analysis did not provide useful insights; results were similar across various intervention periods and among the various intervention subjects.

In most studies, the end point for assessment of the effect of probiotics was set at 12 or 24 months of age. Results for atopic dermatitis were similar comparing 6 studies with end point $<$24 months and 7 other studies with end point at $\geq$24 months of age. Two investigations re-evaluated the data in subsequent publications after extending the follow-up period to $\geq$5 years of age.[33,42] The first reported a weaker effect of *Lactobacillus rhamnosus* GG on eczema in 7-year-old children (RR = 0.64 vs. RR = 0.51 at 2 years of age).[33] The second found no difference between probiotic and placebo groups in 5-year-old children,[42] whereas a decreased incidence was observed at 2 years of age for the probiotic group.[43] Whether probiotics have an effect on atopic dermatitis at $\geq$5 years of age is unresolved.

We examined whether the number of probiotic types or dose given had different effects on development of atopic dermatitis. Again, we did not find meaningful differences among subgroups. Although risk estimates of atopic dermatitis with use of $>$1 type of probiotic were slightly lower than those for interventions based on a single probiotic type, no statistical heterogeneity was found between subgroups. Using meta-regression models, the RR of atopic dermatitis with addition of 1 probiotic type was 0.96 (95% CI, 0.85–1.10).

We could not assess potential differences in incidence of atopic dermatitis according to various probiotic strains, as a variety of strains were tested and data on a single strain were generally very limited. The only exception was *L. rhamnosus* GG, included among probiotic strains of 6 trials, for which the summary RR was 0.74 (95% CI = 0.61–0.90; I^2 = 25%). With further reference to probiotic types, a recent Chinese meta-analysis[16] reported a similar protective role on the incidence of atopic dermatitis of a combination of lactic acid bacteria with other probiotics (RR = 0.79) and lactic acid bacteria alone (RR = 0.85).

We cannot exclude the possibility that each strain of probiotics has its own effect, and so caution is needed in interpreting our results. The modest effect might be improved by choosing additional preparations or higher doses. However, it is appropriate to combine studies that used different probiotic strains, as the hygiene hypothesis implies that the protection from allergic diseases by infectious agents is not specific to a given infectious agent. In fact, mycobacteria had a protective effect similar to that of probiotics in a comparable model.[4] Further, our findings do not relate to a given probiotic but to the therapeutic class. The existence of a specific effect of strain should at most weaken the power of the analysis.

Several earlier reviews have considered the issue of probiotic use in the prevention of atopic dermatitis, with similar findings.[14,16,66–68] However, those reviews had various limitations, including outdated pod of studies,[14,68] certain analytical pitfalls (ie, double count of the same trial,[14,16,67,68] missed papers,[67] inclusion of data on eczema in the meta-analysis of atopic eczema[14]), analysis of only selected subgroups of subjects[67] or subtypes of probiotics,[16] publication in a language other than English,[16] or lacking a formal systematic approach.[66] The current meta-analysis tried to overcome these limitations by using a strict methodology, and by adjusting formal reporting procedures using PRISMA

TABLE 3. Summary RRs for Probiotics in the Prevention of Atopic Dermatitis, According to Selected Subgroups

Subgroup	No. Studies	RR (95% CI)	I^2	Test for Heterogeneity
Intervention period				
Predelivery only	1	0.77 (0.54–1.10)	—	
Pre- and postdelivery	8	0.76 (0.65–0.89)	31%	
Postdelivery only	4	0.85 (0.61–1.19)	32%	$P = 0.54$
Intervention subject[a]				
Mother only	2	0.70 (0.53–0.91)	0%	
Child only	4	0.85 (0.61–1.19)	32%	
Mother and child	6	0.81 (0.70–0.94)	9%	$P = 0.38$
Duration of intervention				
<9 months	8	0.78 (0.65–0.94)	40%	
≥9 months	5	0.79 (0.65–0.95)	1%	$P = 0.97$
Probiotic dose				
$<1 \times 10^{10}$	6	0.78 (0.65–0.93)	7%	
$\geq 1 \times 10^{10}$	7	0.79 (0.65–0.96)	42%	$P = 0.85$
No. of probiotic types				
1	7	0.82 (0.65–1.03)	50%	
>1	6	0.76 (0.66–0.87)	0%	$P = 0.47$
End of follow-up				
Children <24 months	6	0.79 (0.62–1.00)	25%	
Children ≥24 months	7	0.78 (0.66–0.92)	33%	$P = 0.87$
Geographic area				
Europe	8	0.76 (0.64–0.91)	33%	
Asia/Oceania	5	0.81 (0.66–0.99)	21%	$P = 0.69$
Family history of allergic diseases[b]				
Yes	12	0.80 (0.70–0.91)	24%	
No	2	0.35 (0.06–2.01)	49%	$P = 0.28$
Diagnostic criteria				
Hanifin and Rajka,[44] or similar	6	0.80 (0.61–1.06)	49%	
UK Working Party,[45] or similar	5	0.78 (0.67–0.90)	0%	
Reported by parents[c]	2	0.70 (0.47–1.04)	26%	$P = 0.69$
Conflict of interest				
Apparently no	3	0.74 (0.40–1.35)	61%	
Only probiotic supplied	2	0.81 (0.61–1.07)	0%	
Yes[d]	8	0.79 (0.67–0.92)	31%	$P = 0.86$

All RRs were calculated using random-effects models.

[a]One study was excluded because it included 2 subgroups (ie, after delivery, breastfeeding mothers could decide to take probiotic/placebo themselves or to give it to the child), but did not provide their separate data.

[b]Ten studies enrolled only subjects with family history of allergic diseases, 2 studies had subjects of both subgroups and provided separate information, and 1 study had subjects of both subgroups, but did not provide separate information.

[c]Atopic dermatitis was reported by parents, either as complaint in questionnaires/diaries or as diagnosed by a family doctor or other physician.

[d]Sponsored study or at least 1 author reported conflict of interests.

guidelines.[19] Another strength of this meta-analysis is the availability of results for several subgroups, at both the patient level and study level.

The larger number of randomized controlled trials of probiotics now available allowed us to conclude, using a meta-analytic approach, that probiotics have a moderately beneficial effect on the onset of atopic dermatitis and IgE-associated atopic dermatitis in infants. This conclusion is supported by the low-to-moderate heterogeneity of results among trials, the consistency of findings in several subgroups, and apparent lack of publication bias or other major biases. Further studies could explore whether different probiotic strains have different effects on the incidence of atopic dermatitis, whether the effects of probiotics vary with breastfeeding, and aspects of their biologic mechanisms of effect.

These results provide support for the hygiene hypothesis in humans, and support a therapeutic strategy for the prevention of a common disease in young children, particularly in families at high risk for allergy. However, the average decrease of about 20% in atopic dermatitis incidence after

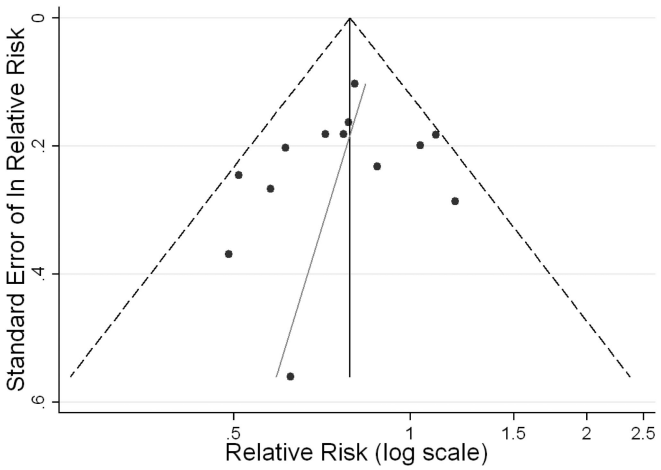

FIGURE 4. Funnel plot of trials on probiotics and prevention of atopic dermatitis with pseudo 95% confidence limits.

probiotic treatment is relatively modest. Improvements may be possible through more specific probiotic preparations in refinements, in the dose, or in the timing of administration.

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