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Probiotic Administration in Early Life, Atopy, and Asthma: A Meta-analysis of Clinical Trials



WHAT'S KNOWN ON THIS SUBJECT: The intestinal microbiome may play a role in immune system maturation, and it has been postulated that early-life probiotic administration may reduce the risk of allergies and asthma in childhood. To date, however, results from clinical trials have been inconsistent.



WHAT THIS STUDY ADDS: In this meta-analysis, administration of probiotics in early life may reduce total immunoglobulin E level and protect against atopic sensitization but do not seem to protect against asthma/wheezing. Future trials should carefully select probiotic strains and include longer follow-up.

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KEY WORDS

atopic sensitization, childhood asthma, childhood atopy, meta-analysis, intestinal microbiome, probiotics, total IgE

ABBREVIATIONS

CI—confidence interval

Ig—immunoglobulin

IL—interleukin

OVA—ovalbumin

RR—relative risk

SPT—skin prick test

Th1—lymphocyte T-helper 1

Th2—lymphocyte T-helper 2

WMD—weighted mean difference

Dr Elazab performed article searches and data extraction, and drafted the initial manuscript; Dr Mendy performed article searches, data extraction, and statistical analyses, and drafted the initial manuscript; Drs Gasana and Quizon participated in the interpretation of analyzed data and critically reviewed the manuscript; Dr Vieira participated in the interpretation of analyzed data and reviewed and revised the manuscript; Dr Forno conceptualized and designed the study, supervised and refereed data extraction, performed and reviewed data analysis, coordinated and supervised the draft of the initial manuscript, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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abstract



BACKGROUND AND OBJECTIVE: Probiotics may reduce the risk of atopy and asthma in children. However, results from clinical trials have been conflicting, and several of them may have been underpowered. We performed a meta-analysis of randomized, placebo-controlled trials to assess the effects of probiotic supplementation on atopic sensitization and asthma/wheeze prevention in children.

METHODS: Random-effects models were used to calculate pooled risk estimates. Meta-regression was conducted to examine the effect of potential factors on probiotics efficacy.

RESULTS: Probiotics were effective in reducing total immunoglobulin E (IgE) (mean reduction: -7.59 U/mL [95% confidence interval (CI): -14.96 to -0.22]; $P = .044$). Meta-regression showed that the reduction in IgE was more pronounced with longer follow-up. Probiotics significantly reduced the risk of atopic sensitization when administered prenatally (relative risk: 0.88 [95% CI: 0.78 to 0.99]; $P = .035$ for positive result on the skin prick test and/or elevated specific IgE to common allergens) and postnatally (relative risk: 0.86 [95% CI: 0.75 to 0.98]; $P = .027$ for positive result on skin prick test). Administration of *Lactobacillus acidophilus*, compared with other strains, was associated with an increased risk of atopic sensitization ($P = .002$). Probiotics did not significantly reduce asthma/wheeze (relative risk: 0.96 [95% CI: 0.85 to 1.07]).

CONCLUSIONS: Prenatal and/or early-life probiotic administration reduces the risk of atopic sensitization and decreases the total IgE level in children but may not reduce the risk of asthma/wheeze. Follow-up duration and strain significantly modified these effects. Future trials for asthma prevention should carefully select probiotic strain and consider longer follow-up. *Pediatrics* 2013;132:e666–e676

Worldwide prevalence of allergic diseases such as asthma, atopic dermatitis, and allergic rhinoconjunctivitis are significant and has increased over the past few decades.¹ Currently, an estimated 20% of the population worldwide suffers from some form of allergic disorder.² The hygiene hypothesis, formulated as a probable explanation for the rise in the prevalence of allergic diseases, suggests that increased cleanliness, reduced family size, and decreased childhood infections have lowered our exposure to microbes, which play a crucial role in the maturation of the host immune system during the first years of life.³

The intestinal microbial flora, or microbiome, may contribute to the pathogenesis of allergic diseases due to its substantial effect on mucosal immunity. Exposure to a normal microbial flora early in life allows for a change in the lymphocyte T-helper 1 (Th1)/ lymphocyte T-helper 2 (Th2) balance, favoring a Th1 cell response.⁴ Atopic diseases, on the contrary, involve Th2 responses to allergens⁵; abnormal allergic responses are thought to arise in the absence of a normal gut microbiome while the immune system is still developing,^{6,7} producing a shift of the Th1/Th2 cytokine balance toward a Th2 response, and a consequent activation of Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13, as well as increased production of immunoglobulin (Ig) E.⁸

Probiotics, defined as “live microorganisms, which, when administered in adequate amounts, confer a health benefit to the host” by the World Health Organization,⁹ can potentially modulate the immune response, resulting in stimulation of Th1 cytokines that can suppress Th2 responses.⁸ Several studies were therefore designed to examine the efficacy of probiotics in many allergic disorders. However, the results on atopy and asthma have been conflicting, and several of these

reports may have been underpowered. In the current study, we performed a meta-analysis of randomized controlled trials to assess whether probiotic administration during pregnancy and/or after birth decreases the incidence of atopy and asthma in young children compared with placebo.

METHODS

A protocol for this meta-analysis is registered in PROSPERO (registration number: 42013004176) (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013004176).

Data Sources

We searched Medline, Highwire, Cumulative Index to Nursing and Allied Health Literature, Web of Knowledge, and The Cochrane Central Register of Controlled Trials (Central) for randomized trials evaluating the effect of probiotic supplementation on allergic diseases in children up to March 2013. In all the databases, we used the following key words: “probiotics” in association with “asthma,” “wheeze,” “rhinitis,” “atopy,” “allergy,” “immunoglobulin,” “IgE,” “sensitization,” or “eczema.” In Medline, we searched for the following Medical Subject Headings: Probiotic AND (Asthma OR Wheeze OR Rhinitis OR Hay Fever OR Atopy OR Allergy OR Immunoglobulin OR IgE OR Sensitization OR Eczema). The search was restricted to children using the limits “Humans” and “Child: birth–18 years.” In addition, we manually screened references in the selected articles for additional relevant studies.

Study Selection

All of the studies retrieved from the different databases by using the aforementioned search strategies were imported to a Web-based reference management program (Refworks [ProQuest, Ann Arbor, MI]), and duplicates were removed. Studies on probiotics

that met the following predefined criteria were included in the meta-analysis.

Study Design

Double-blinded, randomized, placebo-controlled trials published in English (or in languages other than English, when able to translate into English by using online translation services) were included. Randomization was considered adequate when a study was described as randomized, even if the precise randomization method was not reported. Trials were included if the intervention (probiotic supplementation) was directed at the child and/or the pregnant mother. Crossover studies were considered only if analysis was performed separately for the first half of the study, and results were available.

Population

Children in whom outcomes were measured between birth and age 18 years, without atopic diseases at the time of probiotic supplementation, were included. Children with atopic diseases were considered only for the outcome “total IgE.”

Intervention

Bacterial probiotics (single strain or mixture) administered prenatally and/or postnatally within the first year of life for the prevention of atopic diseases were assessed. The use of probiotics after the first year was only considered for the outcome “total IgE” when evaluating the effect of probiotics on total IgE in both atopic and nonatopic children.

Control

Control subjects were children who received a placebo.

Outcomes

The outcomes included total IgE level, atopic sensitization, and asthma/wheeze. Total IgE levels were measured

by using immunoassay. Atopic sensitization was defined as a positive result on a skin prick test (SPT) and/or elevated specific IgE (>0.35 kU/L) to any food or inhalant allergen. When data were separately reported on positive SPT and elevated IgE, data on positive SPT were selected. Asthma/wheeze was defined as parental report of physician diagnosis or direct diagnosis by a physician participating in the trial.

Two authors (Drs Elazab and Mendy) independently screened all references according to the selection criteria. Initial selection after removal of duplicates was based on title and abstract screening, and the final selection was performed by using full texts. Exclusion criteria were: (1) ineligible study design (ie, nonrandomized, placebo-controlled trials, observational studies, crossover studies without separate analysis of the first half); (2) ineligible population (eg, animal studies, studies including adults aged >18 years); (3) ineligible intervention (eg, administration of products other than probiotics or association of probiotics with any other products such as prebiotics); (4) ineligible outcome, which included outcomes other than allergic diseases.

In the final selection, based on full-text screening, the criterion for exclusion was ineligible intervention or outcomes (study on allergic diseases that did not include data on asthma, wheeze, total IgE, or atopic sensitization after follow-up). When possible, authors who measured the outcomes of interest after follow-up but did not report the results were contacted for additional information. Differences of opinion for inclusion were resolved by agreement.

Data Extraction

Using a uniform data extraction form, two of the authors (Drs Elazab and Mendy) independently retrieved from full-text articles data on references (first author, year of publication), timing

of probiotic supplementation (prenatal and/or postnatal), strain of probiotic administered, dose and duration of supplementation, age of participants at baseline and after follow-up, outcome definitions, total number of participants, number of participants and cases in the intervention and control groups, mean total IgE levels, and corresponding SD or confidence interval (CI) (Table 1). When studies used the same population, we retained the 1 with the longest follow-up time for the appropriate analysis. Disagreements on data extraction between the 2 authors were resolved through mutual discussion and, if needed, by consulting a third author (Dr Forno). Agreement between the reviewers on study selection was determined by using the Cohen κ statistic (κ).

Quality Assessment

The methodologic quality of the individual randomized clinical trials was evaluated by using the Jadad scale.¹⁰ It is calculated by using 3 items assessing randomization, blinding, and withdrawals, resulting in a total score between 0 (lowest quality) and 5 (highest quality). Scores of 3 to 5 were considered as high quality.

Analysis

Collected data were pooled to generate summary estimates, and each study was weighted by its inverse effect size variance.¹¹ To evaluate the effect of probiotics, we calculated relative risks (RRs) for the development of asthma and atopic sensitization and weighted mean differences (WMDs) for total IgE between intervention and control groups, using DerSimonian and Laird random-effects methods. Random-effects analysis not only weights each study by its inverse variance but also includes the within- and between-studies variances; it is more conservative than fixed-effects models, providing wider CIs when there is between-study

heterogeneity.¹² We tested for heterogeneity in results across studies by using a Cochran Q statistic. Given the low test power, the significance level was defined as $P < .10$. The I^2 was used to quantify the extent of true heterogeneity.¹³ An assessment of publication bias was performed with the Egger test, based on the funnel plot and the regression of the standardized effect estimate on a measure of precision.^{14,15} Subgroup analyses by timing of probiotics administration, age group, outcome definition (SPT or elevated specific IgE for atopic sensitization; asthma or wheeze for asthma/wheeze), and meta-regression analyses were conducted to explore potential sources of heterogeneity and test the effects of different factors such as probiotic strain(s), baseline age of participants, dose administered, duration of supplementation, and duration of follow-up on the efficacy of probiotics, as well as maternal supplementation of probiotics during lactation versus direct infant supplementation. All analyses were performed in Stata version 11 (Stata Corp, College Station, TX), and a P value of .05 was considered to be statistically significant.

RESULTS

A total of 1081 articles were identified (Fig 1): 355 articles from PubMed, 44 from Cumulative Index to Nursing and Allied Health Literature, 518 from Web of Knowledge, 73 from Highwire, and 91 from the Cochrane Central Register of Controlled Trials. Of these, 25 studies were included in the meta-analysis for 20 cohorts with a total of 4031 participants.^{16–40} There was complete agreement on 697 of the 778 articles (after exclusion of duplicates) after title and abstract screening (interreader agreement: $\kappa = 79.2\%$) and on 62 of 68 articles after full text screening (interreader agreement: $\kappa = 81.8\%$). Excluded studies are listed in Supplemental Table 2.

TABLE 1 Characteristics of Randomized Clinical Trials Included in the Meta-analysis

References	Strain(s)	No. of Participants	Pre and/or Postnatal Intervention	Baseline Age (mo) ^a	Daily Dose (×10 ⁸ CFU)	Duration (mo)	Follow-up (mo)	Outcome(s)	Quality Score
Abrahamsson 2007 ¹⁶	<i>L reuteri</i>	232	Prenatal and postnatal	—	1	13	12	Asthma/wheeze, atopic sensitization	5
Allen 2012 ¹⁷	Probiotics mixture	454	Prenatal and postnatal	—	1	7	18	Atopic sensitization	4
Boyle 2011 ¹⁸	<i>Lactobacillus</i> GG	250	Prenatal and postnatal	—	180	1	12	Asthma/wheeze, atopic sensitization	5
Chen 2010 ³⁴	<i>Lactobacillus gasseri</i> A5	105	Postnatal	—	40	2	0.5	Total IgE	3
Dotterud 2010 ¹⁹	Probiotics mixture	278	Prenatal and postnatal	—	550	4	21	Asthma/wheeze, atopic sensitization	5
Giovannini 2007 ³³	<i>Lactobacillus casei</i>	187	Postnatal	47	210	12	0	Total IgE	4
Gore 2011 ³⁶	<i>B lactis</i> , <i>Lactobacillus</i> GG	111	Postnatal	5	100	3 (<i>B lactis</i>) 4 (<i>Lactobacillus</i> GG)	27 to 30	Asthma/wheeze	3
Huurre 2008 ⁴⁰	<i>Lactobacillus</i> GG, <i>B lactis</i>	171	Prenatal and postnatal	—	100	12	6	Atopic sensitization	3
Jensen 2012 ^{b26}	<i>Lactobacillus acidophilus</i>	123	Postnatal	0	30	6	54	Asthma/wheeze, atopic sensitization	4
Kalliomäki 2001 ^{c38}	<i>Lactobacillus</i> GG	159	Prenatal and postnatal	—	100	6.87	18	Atopic sensitization, total IgE	4
Kalliomäki 2003 ^{c28}	<i>Lactobacillus</i> GG	132	Prenatal and postnatal	—	100	6.87	42	Asthma/wheeze, atopic sensitization, total IgE	4
Kalliomäki 2007 ^{c20}	<i>Lactobacillus</i> GG	116	Prenatal and postnatal	—	100	6.87	78	Asthma/wheeze, atopic sensitization	4
Kim 2010 ²¹	Probiotics mixture	112	Prenatal and postnatal	—	16	5	7	Atopic sensitization	5
Kopp 2008 ²²	<i>Lactobacillus</i> GG	105	Prenatal and postnatal	—	100	7.25	18	Asthma/wheeze, atopic sensitization, total IgE	4
Niers 2009 ²³	Probiotics mixture	102	Prenatal and postnatal	—	30	13.5	12	Atopic sensitization, Total IgE	5
Ou 2012 ²⁴	<i>Lactobacillus</i> GG	191	Prenatal and postnatal	—	100	4	36	Asthma/wheeze, atopic sensitization	2
Prescott 2008 ^{b29}	<i>Lactobacillus acid</i>	153	Postnatal	0	30	6	24	Asthma/wheeze, atopic sensitization	4
Rautava 2012 ³⁹	Probiotics mixture	241	Prenatal and postnatal	—	10	4	22	Atopic sensitization	4
Rose 2011 ³⁵	<i>L rhamnosus</i> GG	131	Postnatal	16	100	6	26	Total IgE	3
Soh 2009 ²⁵	Probiotics mixture	253	Postnatal	0	0.3	6	6	Asthma/wheeze, atopic sensitization, total IgE	4
Taylor 2007 ^{b30}	<i>L acidophilus</i>	178	Postnatal	0	30	6	6	Asthma/wheeze, atopic sensitization	4
West 2009 ³⁷	<i>Lactobacillus paracasei</i>	171	Postnatal	4	1	9		Asthma/wheeze	2
Wickens 2008 ^{d31}	<i>B lactis</i> , <i>Lactobacillus</i> HN001	474	Prenatal and postnatal	—	<i>B lactis</i> : 90 L. HN001: 60	7.25	18	Atopic sensitization	5
Wickens 2012 ^{d27}	<i>B lactis</i> , <i>Lactobacillus</i> HN001	425	Prenatal and postnatal	—	<i>B lactis</i> : 90 L. HN001: 60	7.25	42	Asthma/wheeze, atopic sensitization	5
Yesilova 2012 ³²	Probiotics mixture	40	Postnatal	98	20	2	0	Total IgE	2

CFU, colony-forming unit; —, if administration began prenatally to mothers.

^a Baseline age.^b Represents cohort from Taylor 2007, Prescott 2008, and Jensen 2012.^c Represents cohort from Kalliomäki 2001, 2003, and 2007.^d Represents cohort from Wickens 2008 and 2012.

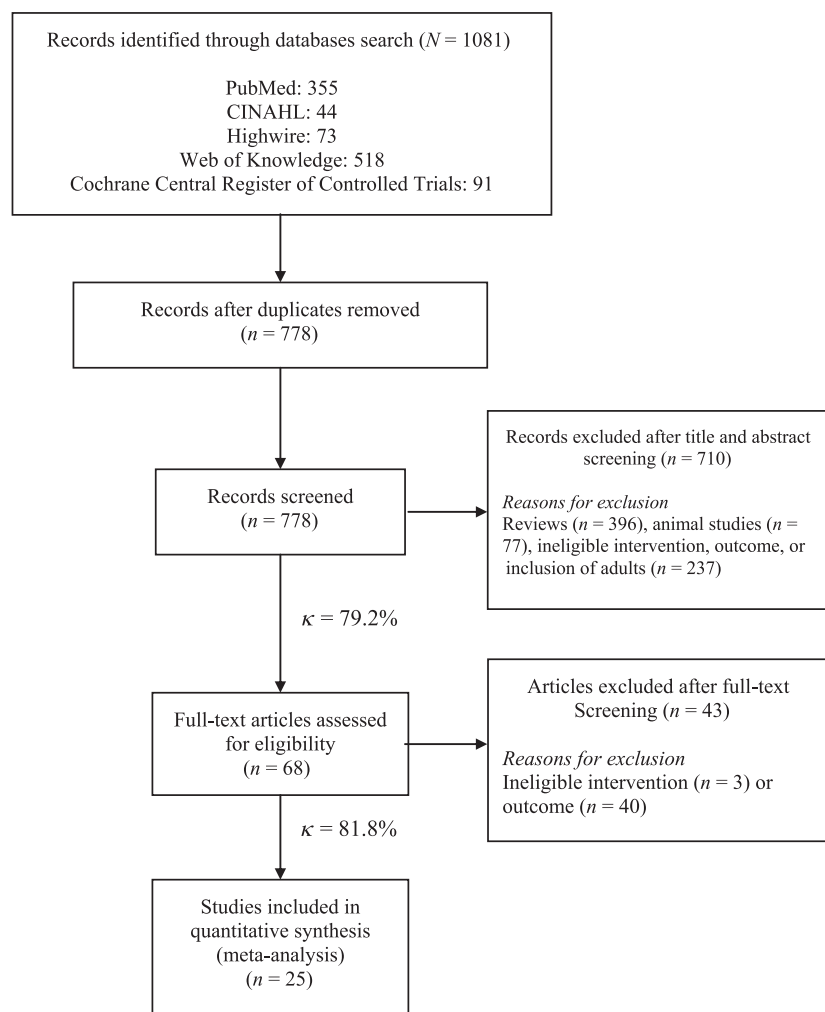


FIGURE 1

Flowchart of study selection. CINAHL, Cumulative Index to Nursing and Allied Health Literature. (Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and MetaAnalyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed.1000097

Characteristics of Included Studies

Studies that were included were published between 2001 and 2012. Trials were performed mainly in Europe^{16,17,19,20,22,23,32,33,35–37,39,40} but also in Asia,^{21,24,25,34} Australia,^{18,26} and New Zealand.³¹ Probiotics were administered prenatally (to pregnant mothers) in 2 trials,^{18,24} prenatally to pregnant mothers and postnatally directly to children in 10 trials,^{16,17,19–23,26,39,40} and only postnatally to children in 9 studies.^{25,30–33,35–37,41} Ten trials used *Lactobacillus*,^{16,18,20,22,24,26,33,35,37,41} and 8 used probiotic mixtures.^{17,19,21,23,25,32,39,40} Wickens et al,³¹ Rautava et al,³⁹ and Gore

et al³⁶ used separate *Lactobacillus* and *Bifidobacterium* arms compared with 1 placebo group. All but 2 studies^{32,37} had a Jadad score between 3 and 5 and were considered of good methodologic quality. Atopic sensitization was defined as positive SPT result and/or IgE level >0.35 kU/L to any food or inhalant allergen (eg, cat, dog, dust mite, egg white, cow milk, peanut, birch pollen, grass) in the majority of studies that assessed atopic sensitization.^{16–20,23–27,39,40} One tested only for food allergens²¹ and another only for inhalant allergens.²² Asthma/whoeeze was only reported by parents using a questionnaire,^{18,20,25,27,36,37}

and in 5 studies, verified by a physician, nurse, or asthma medication record.^{16,19,22,24,26}

A few studies used the same populations, Kalliomäki et al included a cohort of 159 mothers recruited in Finland in 3 studies^{20,28,38}; 3 studies^{26,29,30} studied a cohort of 231 atopic pregnant women delivering in Australia; and Wickens et al focused on 223 Kiwi pregnant women where they or the infant's father were atopic in 2 studies.^{27,31} However, these cohorts were included only once in the different analyses (the most recent report in each case).

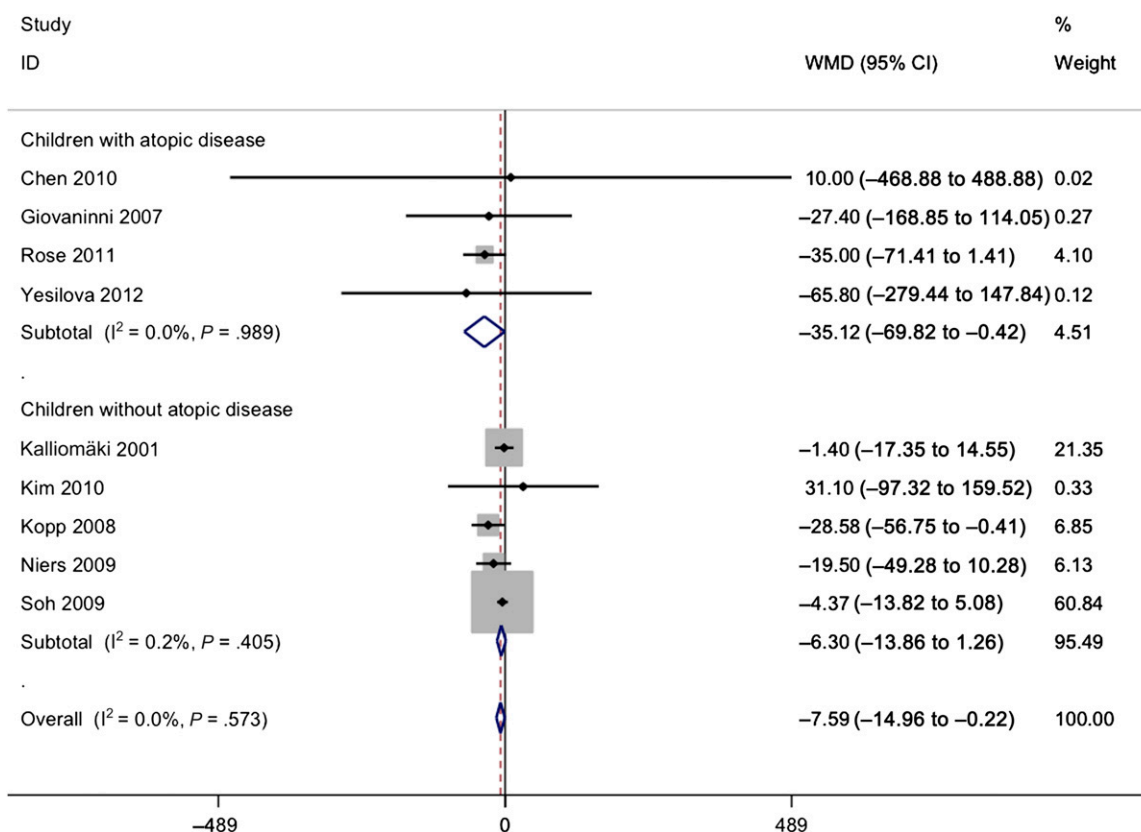
Total Serum IgE

Nine studies^{20–23,25,32–35} representing cohorts from 9 trials were included (1103 children). Overall, probiotics were effective in reducing total IgE (WMD: −7.59 U/mL [95% CI: −14.96 to −0.22]; $P = .044$), with no significant heterogeneity across studies (I^2 null, Cochran's Q test, $P = .573$) (Fig 2). In subgroup analyses, the effect of probiotics on total IgE was significant among children with atopy (WMD: −35.12 U/mL [95% CI: −69.82 to −0.42]; $P = .047$) but not in nonatopic children with family history. By age, the effect of probiotics was found significant in children aged ≥ 2 years (WMD: −12.74 U/mL [95% CI: −24.55 to −0.93]; $P = .035$).

Multivariate meta-regression analyses, including baseline age, age at follow-up, gender, treatment length, daily and total dose, and duration of follow-up, showed that length of follow-up modified the effect of probiotics on total IgE: the reduction in IgE was more pronounced with longer follow-up (correlation coefficient [β]: −1.95 [95% CI: −3.69 to −0.21]; $P = .028$) (Fig 3). Funnel plot and Egger test showed no evidence of publication bias ($P = .23$) (Fig 4).

Atopic Sensitization

Twenty-one studies^{16–31,38–40} characterizing 14 trials were included ($N = 2797$).

**FIGURE 2**

Probiotic administration and total serum IgE level. Forest plot of the mean difference in total Ig E level between the probiotics and placebo groups. Overall, probiotics were associated with decrease in mean total IgE (WMD: -7.59 U/mL [95% CI: -14.96 to -0.22]; $P = .044$). In subgroup analysis, the effect of probiotics was significant among children with atopy (-35.12 U/mL [95% CI: -69.82 to -0.42]; $P = .047$). ID, identification.

Overall, probiotics had a partially significant effect in reducing the risk of atopic sensitization, defined as positive SPT result and/or elevated specific IgE (RR: 0.90 [95% CI: 0.80 to 1.00]; $P = .060$). The reduction was significant when

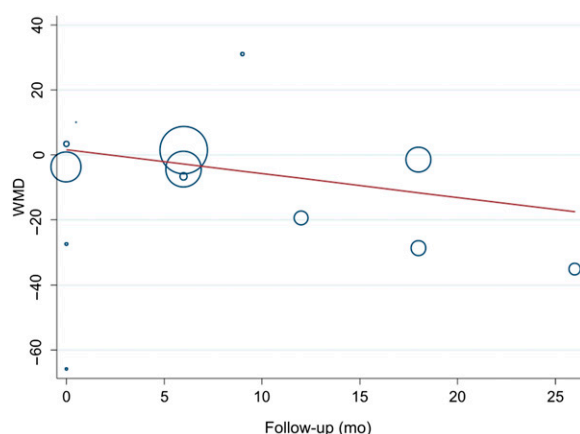
probiotics were administered prenatally and postnatally (RR: 0.88 [95% CI: 0.78 to 0.99]; $P = .035$) but not when given only postnatally ($P = .825$) (Fig 5). Subgroup analysis by definition of atopic sensitization showed a significant

protective effect of probiotics against positive result on SPT to common allergens when administered prenatally and postnatally (RR: 0.86 [95% CI: 0.75 to 0.98]; $P = .027$) (Supplemental Figure 7). The overall protective effect against atopic sensitization was close to significance (RR: 0.88 [95% CI: 0.78 to 1.00]; $P = .059$) when defined as positive result on SPT but not significant when defined as elevated specific IgE level.

Multivariate meta-regression showed that the administration of *Lactobacillus acidophilus* was associated with an increased risk of atopic sensitization (β : 0.45 [95% CI: 0.16 to 0.74]; $P = .002$). Funnel plot and Egger test showed no evidence of publication bias ($P = .57$).

Asthma/Wheeze

Fourteen studies^{16,18–20,22,24–30,36,37} from 10 trials were included ($n = 3143$).

**FIGURE 3**

Meta-regression of the effect of follow-up duration on weighted mean difference in total IgE between the probiotic and placebo groups.

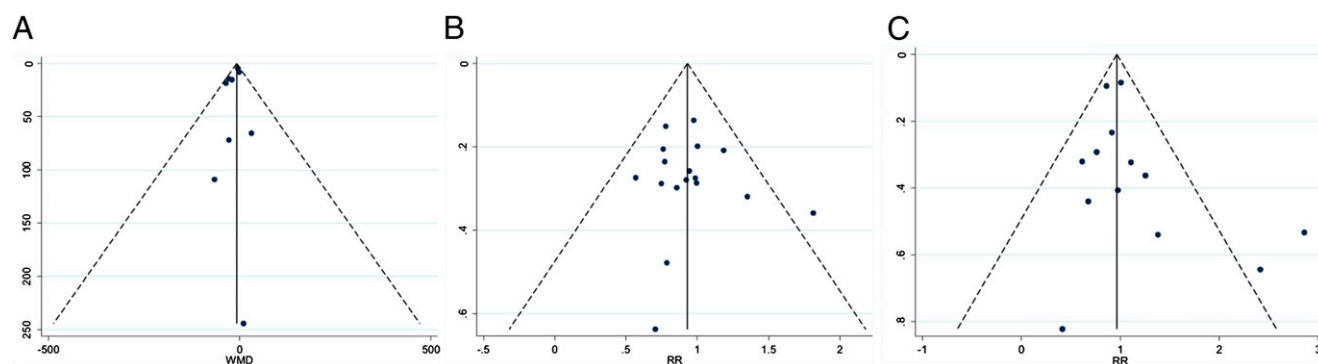


FIGURE 4

Funnel plots of the meta-analysis of probiotics with the following: A, total IgE; B, atopic sensitization; or C, asthma/wheeze.

Probiotics did not significantly reduce asthma/wheeze (RR: 0.96 [95% CI: 0.85 to 1.07]) (Fig 6). No significant association was found in subgroup analyses according to age group, treatment length, follow-up duration, probiotic strain, dose administered, or outcome definition (wheeze ever, recurrent

asthma/wheeze, atopic asthma/wheeze). Funnel plot and Egger test showed no evidence of publication bias ($P = .25$).

DISCUSSION

The results of our meta-analysis indicate that the administration of probiotics early in life is effective in

reducing IgE levels and the risk of atopic sensitization in young children but not the risk asthma or wheeze. There was no difference based on timing of administration (prenatally to mothers plus postnatally versus only postnatally) with regard to IgE, but the decrease in the risk of atopy was

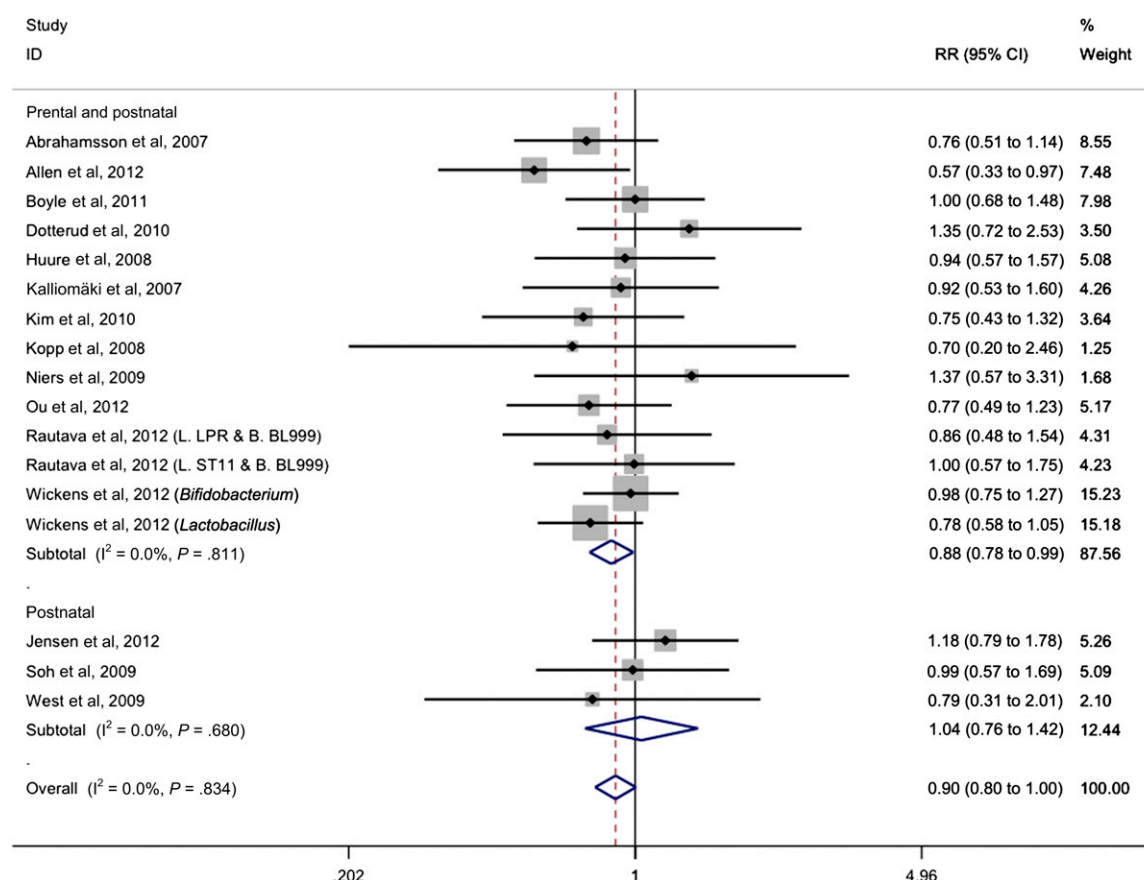


FIGURE 5

Probiotics and risk of atopic sensitization. Forest plot for the association of probiotic administration and atopic sensitization according to period of probiotic administration. Probiotics were protective against atopic sensitization when administered prenatally and postnatally (RR: 0.88 [95% CI: 0.78–0.99]; $P = .035$). ID, identification.

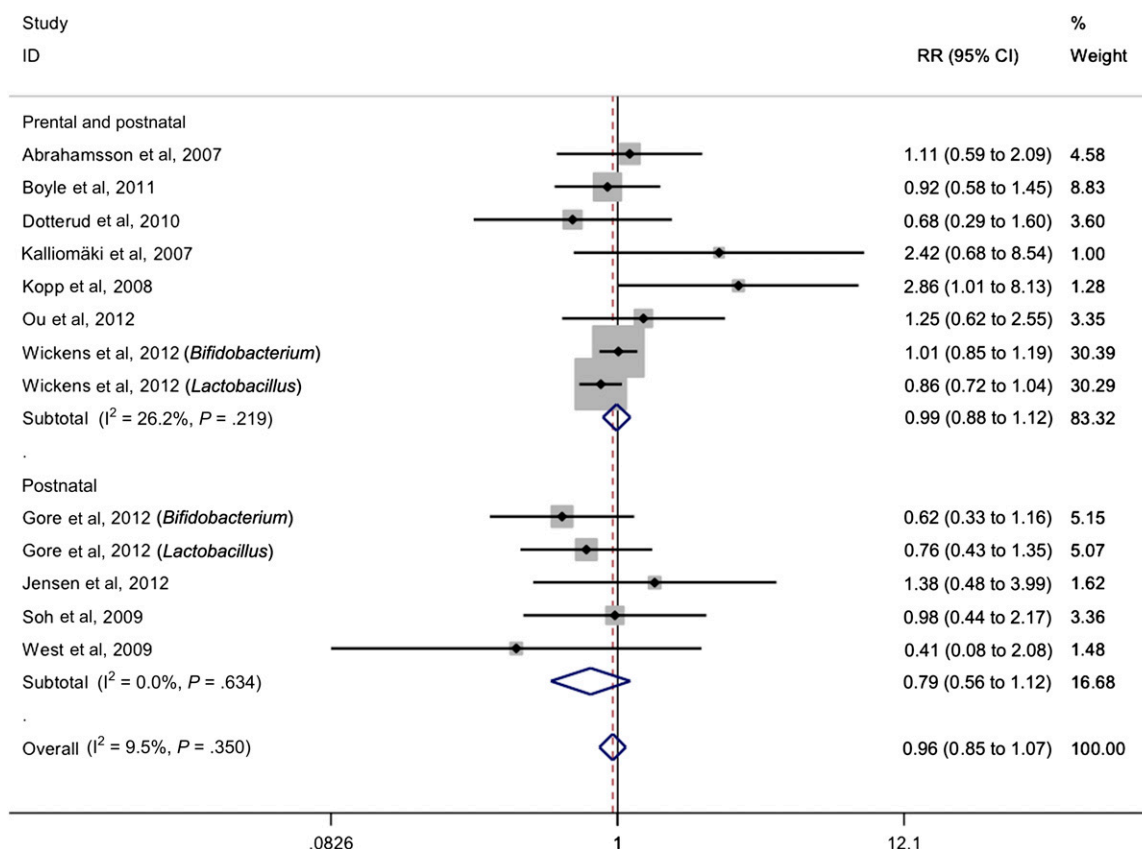


FIGURE 6

Probiotics and risk of asthma/wheeze. Forest plot for the association of probiotic administration and asthma/wheeze according to period of administration. ID, identification.

significant only when probiotics were started during pregnancy and continued after birth. Meta-regression analysis results showed that the effect of probiotics in decreasing total IgE level was more pronounced with longer follow-up periods, and that their effect in decreasing risk of atopic sensitization may depend on the specific strains administered.

These results are consistent with the hygiene hypothesis, which proposes that a relative lack of microbial exposure during infancy and early childhood may result in an imbalance between Th1- and Th2-type immune responses and may induce the development of IgE-mediated allergic responses. It has been postulated that early exposure to commensal bacteria plays a crucial role in Th1/Th2 polarization and maturation of proper immune regulatory mechanisms. The gut is the most

important source of postnatal microbial stimulation of the immune system,⁴¹ and atopic children may have different gut microbiome compared with their nonatopic peers; such differences have been found between cases of eczema and healthy controls,⁴² as well as between countries with high and low incidence of atopic diseases.⁴³ Probiotic administration early in life may promote a healthier gut microbiome, which in turn modulates the maturation of the immune response. Allergic disorders are associated with a shift of the Th1/Th2 cytokine balance toward a Th2 response. This action leads to activation of Th2 cytokines such as IL-4, IL-5, and IL-13, as well as increased IgE production. Probiotics may modulate toll-like receptors and the proteoglycan recognition proteins of enterocytes, leading to activation of dendritic cells and a Th1 response; the

resulting stimulation of Th1 cytokines can suppress Th2 responses.⁸ Pediatric studies suggest that the use of probiotics in children with atopic disorders, such as food allergies or atopic dermatitis, results in enhancement of interferon- γ production (a Th1 cytokine), decreased IgE, and decreased secretion of antigen-induced tumor necrosis factor- α , IL-5, and IL-10.^{44,45} In animal models of ovalbumin (OVA)-induced allergy, probiotics (*L acidophilus* AD031 and *Bifidobacterium lactis* AD011) significantly decrease serum levels of OVA-specific IgE, IgA, and IgG1; up-regulate interferon- γ and IL-10; and down-regulate IL-4.⁴⁶

Probiotics may also prevent atopy via low-grade systemic or local inflammation: increased plasma C-reactive protein concentrations have been found in children with eczema and cow's milk allergy who were treated with

probiotics.⁴⁶ Higher C-reactive protein levels in infants at risk for allergy at 6 months of age were associated with lower risks for eczema and allergic disease at 2 years of age after treatment with probiotics in combination with prebiotics.⁴⁷ Probiotics can induce fecal inflammatory markers, such as α_1 -antitrypsin, tumor necrosis factor- α , and calprotectin, which have been associated with higher fecal IgA levels and lower risk of IgE-associated allergic disease, suggesting minimal intestinal inflammation may play a role in their mechanism of action.⁴⁸

Although our pooled analyses found a significant effect of probiotics on total IgE and risk of atopic sensitization, we did not find a similar significant risk reduction for asthma and wheeze, which is consistent with previous studies in adults.^{49,50} Animal studies with probiotics have shown decreased inflammatory response to single but not repeated allergen challenge: in murine models of asthma sensitized with OVA, administration of *Lactobacillus reuteri* ATCC 23272, *Lactobacillus rhamnosus* GG, or *B. lactis* Bb-12 significantly decreased airway hyperreactivity and reduced inflammatory cells in bronchoalveolar lavage fluid after intranasal OVA challenge.^{51,52} *L. rhamnosus* GG and *B. lactis* also increase natural regulatory T cells in the lungs of asthmatic mice.⁵² However, MacSharry et al⁵³ reported that the inhibition of certain components of allergen-induced airway inflammation

by *Bifidobacterium longum* administration was overcome after repeated allergen exposure.

Based on the results of our meta-regression analysis for IgE and atopic sensitization, we speculate that the lack of effect of probiotics in reducing the risk of asthma/wheeze may have been due to the specific combinations of strains used in these trials or due to insufficient length of follow-up; these theories will need to be tested prospectively. Animal studies suggest that the effects of probiotics on allergen-induced airway responses may be sensitive to the organism used: *L. reuteri*, but not *Lactobacillus salivarius*, has been shown to inhibit allergic airway responses in sensitized mice,⁵¹ and a recent study by Hougee et al⁵⁴ demonstrated *Bacillus brevis* has strain-dependent immunomodulatory effects. The duration and timing of feeding are also determinants of anti-inflammatory efficacy; Forsythe et al⁵¹ found that a period of feeding of at least 9 days was required for significant inhibition of airway eosinophilia and airway hyperreactivity in mice. To be most effective, the bacterial species used as probiotics must be resistant to acid and bile to survive and make the transit through the upper gastrointestinal tract, and even the most resilient strains can be cultured in stool for only 1 to 2 weeks after ingestion; thus, regular intake is vital.⁵⁵

There are several potential limitations to our study. We included only articles published in English or with abstracts in English with sufficient information, which may not be representative of all studies conducted on the topic. Another important limitation in any meta-analysis is the variability among studies; although we used random-effects models to try to account for this variability and we performed meta-regression analysis to detect significant effect modifiers, we can only analyze covariates that are available to us from the original manuscripts. Finally, we cannot completely exclude the risk of publication bias, although funnel plots and Egger test analyses showed no evidence of such bias for any of our outcomes.

CONCLUSIONS

We found that the administration of probiotics in early life may reduce total IgE and protect against atopic sensitization but does not appear to protect against asthma and wheeze. Therefore, carefully selected probiotics administered during pregnancy and early infancy may have a role in the primary prevention of atopic diseases, particularly in high-risk infants. Future trials should consider specific strains of probiotics, longer follow-up times, and perhaps association with oligosaccharides, particularly when assessing the effects of probiotics on the reduction of risk of asthma and wheeze later in life.

REFERENCES

1. Asher MI, Montefort S, Björkstén B, et al; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368(9537):733–743
2. Warner JO, Kaliner MA, Crisci CD, et al; World Allergy Organization Specialty and Training Council. Allergy practice worldwide: a report by the world allergy organization specialty and training council. *Int Arch Allergy Immunol*. 2006;139(2):166–174
3. Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? *Br J Dermatol*. 2005;152(2):202–216
4. Kirjavainen PV, Arvola T, Salminen SJ, Isolauri E. Aberrant composition of gut microbiota of allergic infants: a target of bifidobacterial therapy at weaning? *Gut*. 2002;51(1):51–55
5. Romagnani S. Th1 and Th2 in human diseases. *Clin Immunol Immunopathol*. 1996; 80(3 pt 1):225–235
6. Ouwehand AC. Antiallergic effects of probiotics. *J Nutr*. 2007;137(3 suppl 2):794S–797S
7. Ogden NS, Bielory L. Probiotics: a complementary approach in the treatment and

- prevention of pediatric atopic disease. *Curr Opin Allergy Clin Immunol*. 2005;5(2):179–184
8. Winkler P, Ghadimi D, Schrezenmeir J, Kraehenbuhl JP. Molecular and cellular basis of microflora-host interactions. *J Nutr*. 2007;137(3 suppl 2):756S–772S
 9. Joint FAO-WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food. Guidelines for the evaluation of probiotics in food: report of a Joint FAO/WHO working group on drafting guidelines for the evaluation of probiotics in food, London, Ontario, Canada, April 30 and May 1, 2002. Available at: <ftp://ftp.fao.org/es/esn/food/wgreport2.pdf>. Accessed December 23, 2012
 10. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1–12
 11. Berman NG, Parker RA. Meta-analysis: neither quick nor easy. *BMC Med Res Methodol*. 2002;2(1):10
 12. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med*. 1997;127(9):820–826
 13. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? *Psychol Methods*. 2006;11(2):193–206
 14. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA*. 2006;295(6):676–680
 15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634
 16. Abrahamsson TR, Jakobsson T, Böttcher MF, et al. Probiotics in prevention of IgE-associated eczema: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2007;119(5):1174–1180
 17. Allen SJ, Jordan S, Storey M, et al. Probiotics and atopic eczema: a double-blind randomised controlled trial. *Arch Dis Child*. 2012;97:A2-b
 18. Boyle RJ, Ismail IH, Kivivuori S, et al. Lactobacillus GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial. *Allergy*. 2011;66(4):509–516
 19. Dotterud CK, Storror O, Johnsen R, Øien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. *Br J Dermatol*. 2010;163(3):616–623
 20. Kalliomäki M, Salminen S, Poussa T, Isolauri E. Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2007;119(4):1019–1021
 21. Kim JY, Kwon JH, Ahn SH, et al. Effect of probiotic mix (Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus) in the primary prevention of eczema: a double-blind, randomized, placebo-controlled trial. *Pediatr Allergy Immunol*. 2010;21(2 pt 2):e386–e393
 22. Kopp MV, Henneimuth I, Heinzmann A, Urbanek R. Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of Lactobacillus GG supplementation. *Pediatrics*. 2008;121(4). Available at: www.pediatrics.org/cgi/content/full/121/4/e850
 23. Niers L, Martin R, Rijkers G, et al. The effects of selected probiotic strains on the development of eczema (the PandA study). *Allergy*. 2009;64(9):1349–1358
 24. Ou CY, Kuo HC, Wang L, et al. Prenatal and postnatal probiotics reduces maternal but not childhood allergic diseases: a randomized, double-blind, placebo-controlled trial. *Clin Exp Allergy*. 2012;42(9):1386–1396
 25. Soh Shu E. A double-blind randomized placebo controlled clinical trial on the supplementation of probiotics in the first six months of life in Asian infants at risk of allergic diseases—effects on development of allergic disease and safety aspects with a two year follow-up. PhD Thesis 2009. Available at: <http://scholarbank.nus.edu.sg/handle/10635/18217>. Accessed September 16, 2012
 26. Jensen MP, Meldrum S, Taylor AL, Dunstan JA, Prescott SL. Early probiotic supplementation for allergy prevention: long-term outcomes. *J Allergy Clin Immunol*. 2012;130(5):1209–1211.e5
 27. Wickens K, Black P, Stanley TV, et al. A protective effect of Lactobacillus rhamnosus HN001 against eczema in the first 2 years of life persists to age 4 years. *Clin Exp Allergy*. 2012;42(7):1071–1079
 28. Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomized placebo-controlled trial. *Lancet*. 2003;361(9372):1869–1871
 29. Prescott SL, Wiltschut J, Taylor A, et al. Early markers of allergic disease in a primary prevention study using probiotics: 2.5-year follow-up phase. *Allergy*. 2008;63(11):1481–1490
 30. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol*. 2007;119(1):184–191
 31. Wickens K, Black PN, Stanley TV, et al; Probiotic Study Group. A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2008;122(4):788–794
 32. Yeşilova Y, Çalka Ö, Akdeniz N, Berktaş M. Effect of probiotics on the treatment of children with atopic dermatitis. *Ann Dermatol*. 2012;24(2):189–193
 33. Giovannini M, Agostoni C, Riva E, et al; Felicità Study Group. A randomized prospective double blind controlled trial on effects of long-term consumption of fermented milk containing Lactobacillus casei in pre-school children with allergic asthma and/or rhinitis. *Pediatr Res*. 2007;62(2):215–220
 34. Chen YS, Jan RL, Lin YL, Chen HH, Wang JY. Randomized placebo-controlled trial of lactobacillus on asthmatic children with allergic rhinitis. *Pediatr Pulmonol*. 2010;45(11):1111–1120
 35. Rose MA, Schubert R, Schulze J, Zielen S. Follow-up of probiotic Lactobacillus GG effects on allergic sensitization and asthma in infants at risk. *Clin Exp Allergy*. 2011;41(12):1819–1821
 36. Gore C, Custovic A, Tannock GW, et al. Treatment and secondary prevention effects of the probiotics Lactobacillus paracasei or Bifidobacterium lactis on early infant eczema: randomized controlled trial with follow-up until age 3 years. *Clin Exp Allergy*. 2012;42(1):112–122
 37. West CE, Hammarström ML, Hernell O. Probiotics during weaning reduce the incidence of eczema. *Pediatr Allergy Immunol*. 2009;20(5):430–437
 38. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet*. 2001;357(9262):1076–1079
 39. Rautava S, Kainonen E, Salminen S, Isolauri E. Maternal probiotic supplementation during pregnancy and breast-feeding reduces the risk of eczema in the infant. *J Allergy Clin Immunol*. 2012;130(6):1355–1360
 40. Huurre A, Laitinen K, Rautava S, Korkeamäki M, Isolauri E. Impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization: a double-blind placebo-controlled study. *Clin Exp Allergy*. 2008;38(8):1342–1348
 41. Guarner F, Malagelada JR. Gut flora in health and disease. *Lancet*. 2003;361(9356):512–519
 42. Forno E, Onderdonk AB, McCracken J, et al. Diversity of the gut microbiota and eczema in early life. *Clin Mol Allergy*. 2008;6(11):11
 43. Penders J, Stobberingh EE, van den Brandt PA, Thijs C. The role of the

- intestinal microbiota in the development of atopic disorders. *Allergy*. 2007;62(11):1223–1236
44. Flinterman AE, Knol EF, van Ieperen-van Dijk AG, et al. Probiotics have a different immunomodulatory potential in vitro versus ex vivo upon oral administration in children with food allergy. *Int Arch Allergy Immunol*. 2007;143(3):237–244
 45. Kim JY, Choi YO, Ji GE. Effect of oral probiotics (*Bifidobacterium lactis* AD011 and *Lactobacillus acidophilus* AD031) administration on ovalbumin-induced food allergy mouse model. *J Microbiol Biotechnol*. 2008;18(8):1393–1400
 46. Nonaka Y, Izumi T, Izumi F, et al. Antiallergic effects of *Lactobacillus pentosus* strain S-PT84 mediated by modulation of Th1/Th2 immunobalance and induction of IL-10 production. *Int Arch Allergy Immunol*. 2008;145(3):249–257
 47. Marschan E, Kuitunen M, Kukkonen K, et al. Probiotics in infancy induce protective immune profiles that are characteristic for chronic low-grade inflammation. *Clin Exp Allergy*. 2008;38(4):611–618
 48. Kukkonen K, Kuitunen M, Haahtela T, Korpela R, Poussa T, Savilahti E. High intestinal IgA associates with reduced risk of IgE-associated allergic diseases. *Pediatr Allergy Immunol*. 2010;21(1 pt 1):67–73
 49. Helin T, Haahtela S, Haahtela T. No effect of oral treatment with an intestinal bacterial strain, *Lactobacillus rhamnosus* (ATCC 53103), on birch-pollen allergy: a placebo-controlled double-blind study. *Allergy*. 2002;57(3):243–246
 50. Wheeler JG, Shema SJ, Bogle ML, et al. Immune and clinical impact of *Lactobacillus acidophilus* on asthma. *Ann Allergy Asthma Immunol*. 1997;79(3):229–233
 51. Forsythe P, Inman MD, Bienenstock J. Oral treatment with live *Lactobacillus reuteri* inhibits the allergic airway response in mice. *Am J Respir Crit Care Med*. 2007;175(6):561–569
 52. Feleszko W, Jaworska J, Rha RD, et al. Probiotic-induced suppression of allergic sensitization and airway inflammation is associated with an increase of T regulatory-dependent mechanisms in a murine model of asthma. *Clin Exp Allergy*. 2007;37(4):498–505
 53. MacSharry J, O'Mahony C, Shalaby KH, et al. Immunomodulatory effects of feeding with *Bifidobacterium longum* on allergen-induced lung inflammation in the mouse. *Pulm Pharmacol Ther*. 2012;25(4):325–334
 54. Hougee S, Vriesema AJ, Wijering SC, et al. Oral treatment with probiotics reduces allergic symptoms in ovalbumin-sensitized mice: a bacterial strain comparative study. *Int Arch Allergy Immunol*. 2010;151(2):107–117
 55. Doron S, Snyderman DR, Gorbach SL. *Lactobacillus GG*: bacteriology and clinical applications. *Gastroenterol Clin North Am*. 2005;34(3):483–498, ix

Probiotic Administration in Early Life, Atopy, and Asthma: A Meta-analysis of Clinical Trials

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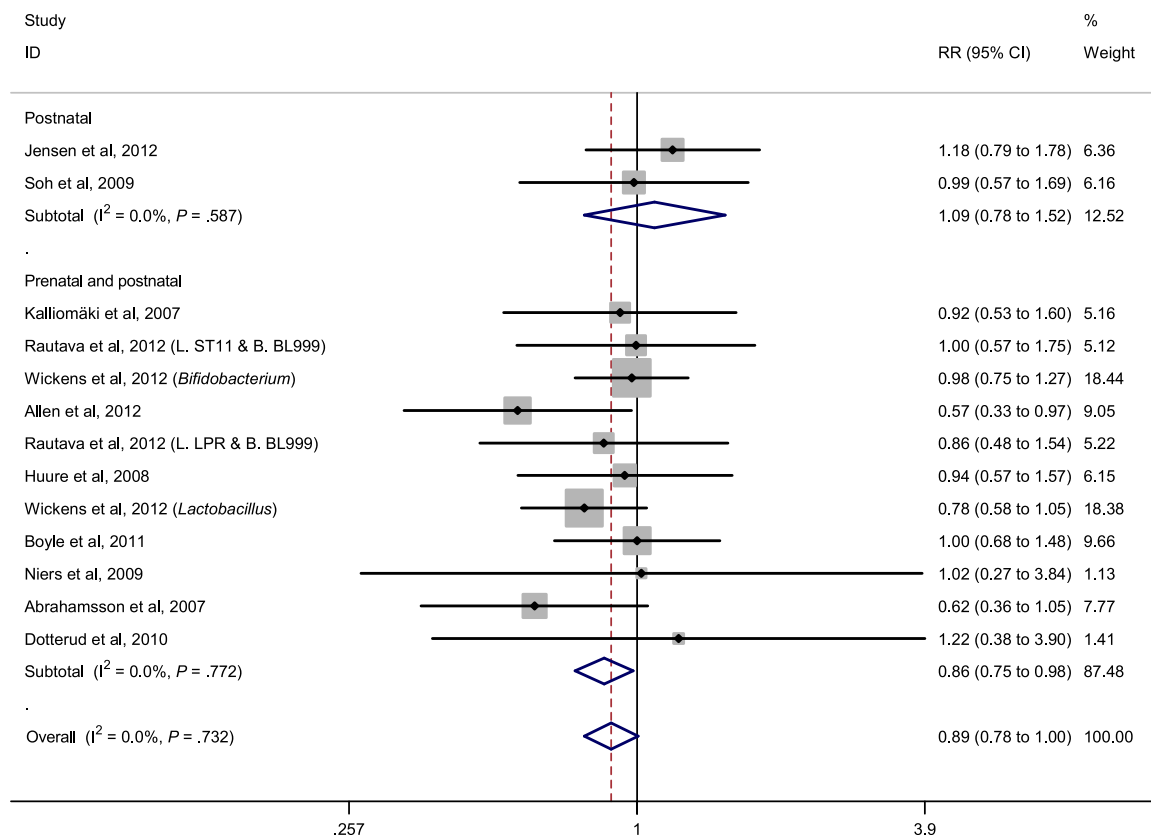
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Supplemental Information



SUPPLEMENTAL FIGURE 7

Probiotics and positive result on SPT. ID, identification.

SUPPLEMENTAL TABLE 2 Excluded Randomized Controlled Trials After Full-Text Screening

Study Identification	Study Title	Reason for Exclusion
Han et al, 2012	A randomized trial of <i>Lactobacillus plantarum</i> CJLP133 for the treatment of atopic dermatitis	No outcome of interest reported
Kuitunen et al, 2012	Impact of maternal allergy and use of probiotics during pregnancy on breast milk cytokines and food antibodies and development of allergy in children until 5 y	Prebiotics administered to the child after birth
Holscher et al, 2012	<i>B. lactis</i> Bb12 enhances intestinal antibody response in formula-fed infants: a randomized, double-blind, controlled trial	No data on outcomes of interest
Ismail et al, 2012	Prenatal administration of <i>L. rhamnosus</i> has no effect on the diversity of the early infant gut microbiota	No data on outcomes of interest
Berni Canani et al, 2012	Effect of <i>Lactobacillus</i> GG on tolerance acquisition in infants with cow's milk allergy: a randomized trial	No outcome of interest
Kukkonen et al, 2011	Airway inflammation in probiotic-treated children at 5 y	Prebiotics administered to the child after birth
Nermes et al, 2011	Interaction of orally administered <i>L. rhamnosus</i> GG with skin and gut microbiota and humoral immunity in infants with atopic dermatitis	No outcome of interest reported
Torii et al, 2011	Effects of oral administration of <i>L. acidophilus</i> L-92 on the symptoms and serum markers of atopic dermatitis in children	No outcome of interest reported
Gerasimov et al, 2010	Probiotic supplement reduces atopic dermatitis in preschool-aged children: a randomized, double-blind, placebo-controlled, clinical trial	No outcome of interest reported
Miniello et al, 2010	<i>L. reuteri</i> modulates cytokines production in exhaled breath condensate of children with atopic dermatitis	No outcome of interest reported
Lodinová-Zádníková et al, 2010	Prevention of allergy in infants of allergic mothers by probiotic <i>Escherichia coli</i>	No outcome of interest reported
Woo et al, 2010	Effect of <i>Lactobacillus sakei</i> supplementation in children with atopic eczema-dermatitis syndrome	No outcome of interest reported
Allen et al, 2010	Dietary supplementation with lactobacilli and bifidobacteria is well tolerated and not associated with adverse events during late pregnancy and early infancy	No outcome of interest reported
Pérez et al, 2010	Effect of probiotic supplementation on immunoglobulins, isoagglutinins, and antibody response in children of low socioeconomic status	No outcome of interest reported
Cukrowska et al, 2010	Probiotic <i>L. casei</i> and <i>L. paracasei</i> strains in treatment of food allergy in children	No outcome of interest reported
Gobel et al, 2010	Probiotics to young children with atopic dermatitis: a randomized, placebo-controlled trial.	No outcome of interest reported
Gutkowski et al, 2010	Effect of orally administered probiotic strains <i>Lactobacillus</i> and <i>Bifidobacterium</i> in children with atopic asthma.	No outcome of interest reported
Hoang et al, 2010	<i>L. rhamnosus</i> cell lysate in the management of resistant childhood atopic eczema	No outcome of interest reported
Ouwehand et al, 2009	Specific probiotics alleviate allergic rhinitis during the birch pollen season	No outcome of interest reported
Bruni et al, 2009	Children with cow's milk allergy can present sensitization to probiotics	No outcome of interest reported
Martínez-Cañavate et al, 2009	A probiotic dairy product containing <i>L. gasseri</i> CECT5714 and <i>Lactobacillus coryniformis</i> CECT5711 induces immunologic changes in children suffering from allergy	No outcome of interest reported
Scalabrin et al, 2009	Growth and tolerance of healthy term infants receiving hydrolyzed infant formulas supplemented with <i>L. rhamnosus</i> GG: randomized, double-blind, controlled trial	No appropriate intervention or outcome of interest reported
Kuitunen et al, 2009	Probiotics prevent IgE-associated allergy until age 5 y in children born via cesarean delivery but not in the total cohort	Prebiotics administered to children after birth
Gueniche et al, 2009	Effects of nonpathogenic gram-negative bacterium <i>Vitreoscilla filiformis</i> lysate on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study	No outcome of interest reported
Hol et al, 2008	The acquisition of tolerance toward cow's milk through probiotic supplementation: a randomized, controlled trial	No outcome of interest reported
Böttcher et al, 2008	Low breast milk TGF- β_2 is induced by <i>L. reuteri</i> supplementation and is associated with reduced risk of sensitization during infancy	Used a subset of the study by Abrahamsson et al 2007 already included in the meta-analysis
Mah et al, 2007	Effect of a milk formula containing probiotics on the fecal microbiota of Asian infants at risk for atopic diseases	No outcome of interest reported
Grüber et al, 2007	Randomized, placebo-controlled trial of <i>L. rhamnosus</i> GG as treatment of atopic dermatitis in infancy	No outcome of interest reported

SUPPLEMENTAL TABLE 2 Continued

Study Identification	Study Title	Reason for Exclusion
Lara-Villoslada et al, 2007	Beneficial effects of consumption of a dairy product containing two probiotic strains, <i>L. coryniformis</i> CECT5711 and <i>L. gasseri</i> CECT5714 in healthy children [in Spanish]	No outcome of interest reported
Flinterman et al, 2007	Probiotics have a different immunomodulatory potential in vitro versus ex vivo upon oral administration in children with food allergy	No outcome of interest reported
Fölster-Holst et al, 2006	Prospective, randomized controlled trial on <i>L. rhamnosus</i> in infants with moderate to severe atopic dermatitis	No outcome of interest reported
Brouwer et al, 2006	No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial	No outcome of interest reported
Sistek et al, 2006	Is the effect of probiotics on atopic dermatitis confined to food-sensitized children	No outcome of interest reported
Rinne et al, 2005	Effect of probiotics and breastfeeding on the <i>Bifidobacterium</i> and <i>Lactobacillus/Enterococcus</i> microbiota and humoral immune responses	No outcome of interest reported
Viljanen et al, 2005	Induction of inflammation as a possible mechanism of probiotic effect in atopic eczema-dermatitis syndrome.	No outcome of interest reported
Weston et al, 2005	Effects of probiotics on atopic dermatitis: a randomized controlled trial	No outcome of interest reported
Ciprandi et al, 2005	<i>Bacillus clausii</i> effects in children with allergic rhinitis	No outcome of interest reported
Viljanen et al, 2005	Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial	No outcome of interest reported
Pohjavuori et al, 2004	<i>Lactobacillus</i> GG effect in increasing interferon- γ production in infants with cow's milk allergy	No outcome of interest reported
Rosenfeldt et al, 2003	Effect of probiotic <i>Lactobacillus</i> strains in children with atopic dermatitis	No outcome of interest reported
Rautava et al, 2002	Probiotics during pregnancy and breastfeeding might confer immunomodulatory protection against atopic disease in the infant	No outcome of interest reported
Borchers et al, 2002	The influence of yogurt/ <i>Lactobacillus</i> on the innate and acquired immune response	No outcome of interest reported
Isolaure et al, 2000	Probiotics in the management of atopic eczema	No outcome of interest reported

TGF, transforming growth factor.