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Title: Comparative effectiveness of probiotic strains on the prevention of pediatric atopic dermatitis: a systematic review and network meta-analysis

Short title: Probiotics to prevent atopic dermatitis

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Title: Comparative effectiveness of probiotic strains on the prevention of pediatric atopic dermatitis: a systematic review and network meta-analysis

Conflicts of Interest: Marysia Recto serves in the advisory board of A. Menarini, Abbott Nutrition and Sanofi Aventis, a speaker for A. Menarini, Abbott Nutrition, Abbott Pharma, Nutricia, RB Mead Johnson, Kalbe, Glenmark, Leo pharma, Mylan, Bayer, Natrapharm, Astra Zeneca, Galderma, and received research grants from Galderma and Novartis. Mary Anne Castor served as a speaker and facilitator for a series of research workshop sponsored by Wyeth. The relationship of Dr. Recto and Dr. Castor to the aforementioned companies do not involve the topic of probiotics. The rest of the authors have no conflicts of interest to disclose.

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Abstract

Background: Atopic dermatitis is the most common chronic skin disease affecting the pediatric population. Probiotics has been proposed to be effective in preventing the development of pediatric atopic dermatitis. Although studies show promise for the use of probiotics, the evidence is still inconclusive due to significant heterogeneity and imprecision.

Objective: To determine the comparative effectiveness of the different types of probiotic strains in preventing the development of atopic dermatitis among pediatric patients.

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Methodology: A systematic search of Cochrane Library, MEDLINE, TRIP Database and Centre for Research and Dissemination was conducted. Manual search of the reference lists and search for unpublished articles was also done. All randomized controlled trials available from inception until April 12, 2020 on the use of probiotics in the prevention of atopic dermatitis among children were included. The comparator groups considered are other probiotic strains and placebo. The primary outcome of interest was the development of atopic dermatitis. Two authors independently searched for articles, screened the articles for inclusion, appraised the articles using the Cochrane risk of bias tool version 2, and extracted the data. In case of disagreement, the two authors discussed the source of disagreement until consensus was reached. If consensus was not reached, an independent third party reviewer was consulted. Frequentist network meta-analysis was conducted using STATA 14 software. The ranking probabilities and surface under the cumulative ranking curve (SUCRA) values were obtained to determine ranking of the different probiotic strains based on efficacy and safety data.

Results: We included 21 original studies represented by 35 records and a total of 5,406 children with atopic dermatitis as diagnosed by clinicians or fulfillment of validated diagnostic criteria. All studies were randomized placebo-controlled trials. The top 3 probiotic preparations in terms of efficacy in reducing the risk of atopic dermatitis are Mix8 (*Lactobacillus paracasei* ST11, *Bifidobacterium longum* BL999), LP (*Lactobacillus paracase*i ssp *paracasei* F19) and Mix3 (*Lactobacillus rhamnosus* GG, *Bifidobacterium animalis* ssp *lactis* Bb-12). Mix8 compared to placebo probably reduces the risk of atopic dermatitis based on low quality evidence (RR=0.46, 95% CI 0.25 – 0.85). Mix3 compared to placebo also probably reduces the risk of atopic dermatitis based on low quality evidence (RR=0.50, 95% CI 0.27 – 0.94). It is uncertain whether LP compared to placebo reduces the risk of atopic dermatitis due to very low quality certainty of evidence (RR=0.49, 95% CI 0.20-1.19). In terms of adverse events, LGG may slightly lead to less adverse events compared to placebo based on low quality evidence (RR=0.70, 95% CI 0.32-1.52). Mix4 may slightly lead to more adverse events compared to placebo based on low quality evidence (RR=1.06, 95% CI 0.02-51.88). Based on subgroup analysis of studies involving infants, Mix3 compared to placebo probably reduces the risk of atopic dermatitis based on low quality evidence (RR=0.46, 95% CI 0.22 – 0.97). In the subgroup analysis of studies where probiotics were administered to pregnant women and to infants, LRH compared to placebo

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probably reduces the risk of atopic dermatitis based on moderate quality evidence (RR=0.54, 95% CI 0.26-1.11).

Conclusion: Certain probiotic preparations demonstrate efficacy in reducing the risk of developing atopic dermatitis when administered to pregnant women, infants, or both.

Keywords: probiotics, pediatrics, atopic dermatitis, network meta-analysis

Key Message

This study compares the effectiveness of different probiotic preparations in the prevention of atopic dermatitis in children. Certain probiotic preparations demonstrate benefit in reducing the risk of developing atopic dermatitis. Future research directly comparing the highest ranked probiotic preparations will help generate definite recommendations relevant to clinical practice.

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LIST OF ACRONYMS OF PROBIOTIC PREPARATIONS

BL	*Bifidobacterium animalis* ssp. *lactis* HN 019
LA	*Lactobacillus acidophilus* LAVRI-A1
LGG	*Lactobacillus rhamnosus* GG
LP	*Lactobacillus paracasei* ssp *paracasei* F19
LR	*Lactobacillus reuteri* ATCC55730
LRH	*Lactobacillus rhamnosus* HN001
Mix1	*Lactobacillus salivarius* CUL61, *Lactobacillus paracasei* CUL 08, *Bifidobacterium animalis* ssp. *lactis* CUL34, *Bifidobacterium bifidum* CUL20
Mix2	LGG, *Bifidobacterium animalis* ssp *lactis* Bb-12, *Lactobacillus acidophilus* La-5
Mix3	LGG, *Bifidobacterium animalis* ssp *lactis* Bb-12
Mix4	*Bifidobacterium bifidum* BGN4, *Bifidobacterium lactis* AD011, *Lactobacillus acidophilus* AD031
Mix5	*Escherichia coli* Symbio DSM 17252, *Enterococcus faecalis* Symbio DSM 16440
Mix6	*Bifidobacterium longum* BL999, *Lactobacillus rhamnosus* LPR
Mix7	*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactococcus lactis* W58,
Mix8	*Lactobacillus paracasei* ST11, *Bifidobacterium longum* BL9
Mix9	*Bifidobacterium longum* ssp *infantis*, *Streptococcus thermophilus*, *Bifidobacterium animalis* ssp *lactis*

Other Acronyms

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trials
PICO	Population, intervention, comparator, outcome
GRADE	Grading of Recommendations Assessment, Development and Evaluation
CoE	Certainty of Evidence

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I. INTRODUCTION

Atopic dermatitis is the most common chronic skin disease affecting children. The use of prenatal and postnatal probiotics has been proposed to be effective in the primary prevention of atopic dermatitis. Probiotics is defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host'.[1] Probiotics have immunomodulatory effects through suppression of the Th2-mediated response and increasing regulatory T cell-related cytokines, thus leading to decreased allergic response.[2]

Probiotics are named according to genus, species and strain. Probiotics exhibit strain-dependent effects. The effect observed from one probiotic strain may differ with another probiotic strain. Similarly, a probiotic strain can exhibit different effects when used as a single strain compared to as a mixed strain, due to possible immunomodulatory interaction of these strains.[3]

Prebiotics are non-digestible substances that act as food for healthy bacteria of the gut.[4] Synbiotics are a combination of prebiotics and probiotics.[3]

There are 13 systematic reviews on probiotics for preventing atopic dermatitis. The full text of three systematic reviews could not be retrieved for appraisal. All 10 systematic reviews show trend towards benefit of probiotics. There are certain limitations noted upon critical appraisal of these 10 systematic reviews. Two out of the 10 systematic reviews included quasi-randomized trials. Eight reviews had limitations in their search strategy since search for unpublished literature was not done or the search was limited to English literature. One review did not assess the validity of included studies. The detailed critical appraisal of these 10 systematic reviews is shown in Appendix 1.[5-14] Significant heterogeneity was found in 6 reviews. Subgroup analysis according to probiotic genus showed varying results. These varying results are expected given the strain-specific effects of probiotics. Due to the variation in results, definite clinical recommendations cannot be made.

We present a network meta-analysis that synthesized the available evidence and compared the effect of the different probiotic preparations in the prevention of atopic dermatitis among children. Compared to a standard meta-analysis, a network meta-analysis allows comparisons of the different probiotic preparations and enable exploration of the most promising

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preparations in terms of efficacy and safety. A brief overview of the unique elements of a network meta-analysis is shown in Appendix 2. We followed the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.[15]

II. METHODOLOGY

Inclusion criteria

This systematic review included all randomized controlled trials (RCTs) from inception until April 12, 2020 that evaluated the use of probiotics in preventing atopic dermatitis among pediatric patients. Studies published in any language were included.

Patients with general risk and high risk of developing allergic disease were included. Patients were considered high risk if they have at least one family member with allergic disease. Studies that initiated prenatal probiotic use through maternal probiotic administration were also included.

Studies on the oral administration of any probiotic strain or mixture of strains were included. The primary outcome of interest is the prevention of atopic dermatitis, measured qualitatively as development or non-development of atopic dermatitis as diagnosed by clinicians or fulfillment of validated diagnostic criteria. The secondary outcome of interest is the occurrence of adverse events associated with probiotic administration, measured qualitatively as presence or absence of adverse outcomes.

Exclusion criteria

Quasi-randomized trials and observational trials were excluded. Studies that involved participants already diagnosed with atopic dermatitis or other allergic diseases were excluded. Studies that reported only surrogate outcomes, and studies that evaluated prebiotics or synbiotics as the intervention of interest were also excluded.

Search Strategy

A systematic search of electronic medical literature databases including Cochrane Library, MEDLINE, TRIP Database, and Centre for Research and Dissemination was conducted. The horizontal search strategy pathway was used. The horizontal pathway is recommended for

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reviews where there are multiple interventions of interest involved. Individual search for each intervention of interest, or each probiotic single strain or mixed strain, was conducted. For each intervention of interest, the Highly Sensitive Search Strategy for identifying randomized trials in Medline from the Cochrane Handbook was used.[16] The search was limited to two-edge paths. Two-edge paths involve studies that evaluate different probiotic strains but have one common comparator, the most common of which is placebo. The search strategy can be found in the Supplementary Table I.

Manual search of the references of the retrieved articles was done. Search for unpublished articles was conducted by correspondence with experts and pharmaceutical industries, and perusing conference proceedings and books of abstracts. Clinical trial registries were also searched.

Study Selection

Two authors independently reviewed the studies obtained from the electronic and manual searches. Initial screening was done by evaluating the titles and abstracts. Studies that fit the inclusion criteria were included in the second screening. The full-text articles of these studies were retrieved and evaluated in the second screening.

In case of disagreement, the authors discussed the source of disagreement until a consensus was reached. If consensus was not reached, an independent third reviewer was consulted.

Data Extraction and Management

Two authors independently extracted data from each study. Outcome was analyzed using intention-to-treat analysis. Dropouts were determined in each study. Participants with missing data were assumed not to respond to treatment using worst-case scenario analysis to evaluate for the attrition bias. Only the available data was utilized in the network meta-analysis.

Network Geometry

Each probiotic strain or mixture of strains was represented by a node, regardless of the dose and duration of use of that probiotic strain. Placebo was also be represented by a node.

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Assessment of Risk of Bias in Included Studies

Two authors independently appraised the included studies using the Cochrane risk of bias tool version 2.[17] The parameters evaluated were randomization, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. In case of disagreement, the reviewers discussed the source of disagreement to reach a consensus. If consensus was not reached, an independent third reviewer was consulted.

Summary Measures

The number of events and total number of participants for the intervention and comparator group were obtained. The relative risk and the 95% CI were calculated using STATA 14 software.

It is expected that the included studies determined the outcome at different time periods. In the pooling of data, the overall estimate of effect was obtained regardless of difference in time period. If the outcome was determined multiple times, the longest follow-up period in which the outcome was evaluated would be used in the pooling of data. In case there are follow-up studies of the original study, the data to be pooled will be derived from the original study since the original study is most likely to have the lowest risk of attrition and performance bias.

The ranking probabilities and surface under the cumulative ranking curve (SUCRA) values were obtained to determine the relative probability of the different probiotic strains to be the most promising treatment option based on efficacy and safety data.[18]

Planned Methods of Analysis

Network meta-analysis was conducted using STATA 14 software. The frequentist approach using random-effects model incorporated in STATA 14 software was used. The Bayesian approach was not used due to the lack of established prior probabilities for the study hypothesis. The different probiotic strains were compared using direct and indirect evidence, depending on the availability of data. The number of events per group of participants was determined in order to obtain the relative risk for each pairwise comparison. The direct path effect is the relative risk and confidence interval obtained for each pairwise comparison. The indirect path effect was computed by combining the treatment effect of the two edges that make up the indirect loop. Multiple treatment comparison was conducted for pairwise comparisons

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with both direct and indirect evidence. This direct and indirect path effects were pooled using the generic inverse variance method.

Assessment of Coherence

Clinical and statistical coherence were evaluated. Clinical coherence was determined by qualitative analysis of the similarity of interventions in the direct and indirect links.

Statistical coherence or consistency was determined by evaluating both loop and design inconsistency. Loop consistency was assessed for pairwise comparisons with available direct evidence. Node splitting was done to determine similarity of the direct and indirect treatment effects. The cut-off for significant inconsistency is p-value<0.05. Design consistency was assessed through design by treatment interaction modeling, with inclusion of the inconsistency parameter. A p-value<0.05 indicates significant design inconsistency.

Qualitative Assessment of Network Meta-analysis Assumptions

Aside from coherence, the assumptions of directness, heterogeneity, and transitivity were assessed qualitatively to ensure that the network meta-analysis conducted is valid. The population, intervention, comparator and outcome (PICO) of all included studies were carefully inspected to determine if any of the assumptions were violated.[15] Since this review includes prenatal probiotic use, a possible source of violation of these assumptions could be the population of the studies. It is to be expected that there will be variation in the study population of the included studies, with some administering probiotics to pregnant women, some to infants, and some to both pregnant women and infants. Heterogeneity of studies supporting each pairwise comparison was also evaluated quantitatively using chi-square test for heterogeneity and the inconsistency statistic (I^2). Heterogeneity was considered significant for values of I^2>50% and p < 0.1.[19]

Additional Analyses

Sensitivity analysis was done to determine the stability of the primary outcome of the study. In the sensitivity analysis, only studies with overall low risk of bias were included.

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Potential publication bias was to be tested by visual inspection of the comparison-adjusted funnel plots. Subgroup analysis and meta-regression analysis was to be conducted if significant inconsistency existed.

GRADE Certainty of Evidence Appraisal

The certainty of evidence (CoE) was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The GRADE four-step approach was used. First, the direct and indirect treatment estimates were presented. Given the large number of strains included in the study, the GRADE CoE assessments were limited to the top 5 interventions for the efficacy outcome and the highest and lowest ranked interventions for the safety outcome. Second, the quality of evidence of the direct and indirect treatment estimates were determined. This is based on 6 domains: risk of bias or study limitations, inconsistency and heterogeneity, indirectness, imprecision, and publication bias. For the indirect evidence treatment estimates, the lower CoE of the component edges determined the CoE rating of the indirect loop. Third, the network meta-analysis estimate was presented. Lastly, the quality of evidence of the network-meta analysis effect estimate was determined. For comparisons where only direct or indirect evidence is available, the quality rating was based on the CoE assessment of the effect estimate from the available evidence. However, for comparisons where both direct and indirect evidence are available, the higher CoE assessment was used as the quality rating for the network meta-analysis estimate. This CoE assessment may be rated down if inconsistency exists.[20]

Registration

The review was not registered with PROSPERO. It was only registered in our local registry, under the Research Grants Administration Office of the University of the Philippines Manila.

III. RESULTS

Results of the Search

A total of 735 records were identified from electronic database search, and manual search yielded an additional 7 records. The search flow diagram is shown in Figure 1.

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After removal of duplicate records, the abstracts of the remaining 494 records were screened. There were four withdrawn studies due to inadequate funding, inadequate participants, safety concerns and non-viability of the objectives. There was one study that was still ongoing. A total of 434 records were excluded because the participants, intervention, outcome or method of these studies did not meet the inclusion criteria of this systematic review. Of the remaining 55 records, the full text articles of two records could not be retrieved despite maximal efforts.

In the screening of the 53 full-text articles, 18 records were excluded. Reasons for exclusion include use of synbiotics in four studies, report of surrogate markers in seven studies, outcome of atopic dermatitis but not diagnosed by a clinician or by validated diagnostic criteria in four studies, and non-randomized trials in three studies. Finally, 35 records were included in this review.[21-55]

Included Studies

Among the 35 studies included in this systematic review, 14 were follow-up studies of completed RCTs (Abrahamsson 2013, Allen 2014, Davies 2018, Simpson 2015, Prescott 2008, Jensen 2012, Kalliomaki 2003, Kalliomaki 2007, Loo 2014, Wickens 2012, Wickens 2013, Wickens 2018, Gorissen 2014, West 2013).[20,22,23,27,30,31,33,34,39,41-43,45,49]. The 21 original studies involved a total of 5,406 children with atopic dermatitis. All studies were randomized placebo-controlled trials.

A total of 15 probiotic preparations were evaluated among the 21 studies. There were 6 single probiotic strains and 9 mixed probiotic preparations. There were two multi-arm trials that evaluated two probiotic strains and placebo. The remaining 19 studies compared probiotics to placebo. The characteristics of the included studies can be found in the Supplementary Table II.

Presentation of Network Structure

The network geometry of the primary outcome of this study is shown in Figure 2. There are 16 nodes, representing 15 probiotic preparations and placebo. The largest node is placebo, with 2,312 patients assigned to placebo across all the studies. There are two multi-arm trials which provide head-to-head comparisons between probiotic preparations and to placebo. The rest of the trials compare probiotic strains to placebo. The thickest link is the pairwise comparison of LGG and placebo, with five studies contributing evidence for this comparison. This is followed

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by the pairwise comparison of Mix3 and placebo, with three studies providing data. The pairwise comparisons of LRH and placebo, and Mix6 and placebo, each have two studies providing data.

Risk of Bias in Included Studies

Table I summarizes the risk of bias per domain and the overall risk of bias of studies included in this network meta-analysis. Of the 21 included studies, 5 had overall high risk of bias, 10 had overall some concerns for bias, and 6 had overall low risk of bias.

Assessment of NMA Assumptions

Directness

All included studies were direct. All studies were RCTs involving probiotic administration to pregnant women, infants, or both. The outcomes reported were development of atopic dermatitis, adverse events, or both.

Heterogeneity

There are only four pairwise comparisons with more than one study providing evidence for these comparisons, namely LRH and placebo, Mix6 and placebo, LGG and placebo, and Mix3 and placebo. A possible source of heterogeneity is the type of population used in the studies. In the LRH and placebo pairwise comparison, one study administered probiotics to pregnant women and infants, while one study gave probiotics to pregnant women. In the Mix6 and placebo pairwise comparison, one study involved pregnant women while the other study involved infants. In the LGG and placebo pairwise comparison, three studies involved pregnant women and infants, one study involved pregnant women, and one study involved infants. In the Mix3 and placebo pairwise comparison, three studies involved infants, while one study involved pregnant women. Statistical heterogeneity was also computed using the Review Manager 5.3 software. There was no significant heterogeneity in the LRH and placebo pairwise comparison (I^2=22%), the Mix3 and placebo pairwise comparison (I^2=0%), and the LGG and placebo pairwise comparison (I^2=25%). In the Mix6 and placebo pairwise comparison, the I^2 is 76%, indicating significant heterogeneity. The forest plots are shown in the Supplementary Figures 1-4.

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Transitivity

All indirect path edges used placebo as the indirect comparator. However, the type of population used in the studies comprising the adjacent path edges could be a source of violation of the transitivity assumption.

Coherence

There are two pairwise comparisons that had more than 1 study providing direct and indirect evidence. These comparisons are LRH and BL, and Mix6 and Mix8. The interventions of the direct path edge and the terminal edges of the indirect path edges are qualitatively similar. The outcome is also qualitatively similar. A possible source of incoherence is the population of the studies. In the LRH and BL pairwise comparison, the study providing direct evidence involved pregnant women and infants. The study providing indirect evidence (LRH compared to placebo) involved infants. In the Mix6 and Mix8 pairwise comparison, the study providing direct evidence involved pregnant women, while the study providing indirect evidence (Mix6 compared to placebo) involved infants. To account for this, subgroup analysis based on the population the probiotics was administered was done.

Synthesis of Results

Effect of probiotic administration on development of atopic dermatitis

Data from 21 studies were included in the analysis of the primary outcome, the development of atopic dermatitis. These studies consisted of 20 original studies and one follow-up study, Allen 2014, since the original study reported only adverse events. The number of events and sample size for the different studies are shown in Appendix 3.

The interval plot is shown in Figure 3. Compared to placebo, Mix8 had the lowest RR, suggesting the greatest benefit compared to placebo. Mix8, Mix3 and Mix6 had confidence intervals (CI) that exclude the no-effect value. The rest of the probiotic preparations had CI that included the no-effect value. LA and Mix9 had the greatest RR at 1.10, suggesting that these preparations can potentially increase the risk for developing atopic dermatitis. However, the wide CI precludes definite conclusions to be made. The league table is shown in Appendix 4. The statistically significant estimates are in bold. Based on the pairwise comparisons, Mix3, Mix6 and Mix8 show statistically significant benefit in reducing the risk of developing atopic

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dermatitis compared to placebo. Mix8 also shows statistically significant benefit compared to LA.

The ranking probabilities and SUCRA values of the probiotic preparations are shown in Appendices 5 and 6. Based on the ranking probabilities, the three probiotic preparations with the highest relative probability to be the most effective are Mix8, LP, and Mix3. The probiotic with the lowest relative probability is LA, followed by Mix9. Results from the SUCRA values are similar, with the Mix8, Mix3 and LP having the highest relative probabilities to be the most effective. LA, followed by placebo and Mix9, had the lowest relative probabilities.

Adverse events

Data from only 10 studies were included in the analysis for adverse events since the other studies did not report adverse events as an outcome. The network geometry for the safety outcome is shown in Figure 4. The types of adverse events reported by the studies varied widely. Abrahamsson 2007 reported serious adverse events, gastroenteritis, and mild adverse events such as spitting up, colic, and constipation. Allen 2010 reported gastroenteritis, infections, gastroesophageal reflux disease, difficulty in breastfeeding, and serious adverse events defined as adverse events necessitating hospital admission. Boyle 2011 reported vomiting, colic, gastroenteritis and hospital admission. Lau 2012 reported abdominal pain and serious adverse events. Rautava 2012, Dotterud 2010, Schmidt 2019, and Kopp 2008 reported no adverse effects related to probiotics. Cabana 2017 and Kim 2010 reported no serious adverse events.

The numerical data for serious adverse events were used for the network meta-analysis, since the number of total adverse events in two studies exceeded the overall number of study participants. Using the numerical data for total adverse events would cause error in the network meta-analysis of STATA14 software. The number of events and sample size for the different studies are shown in Appendix 3.

The pairwise comparison of LGG compared to placebo had three studies contributing evidence. The rest of the pairwise comparisons only had one study providing evidence.

The interval plot shown in Figure 5 demonstrates that the point estimates and interval estimates of all comparisons include the no-effect value. Compared to placebo, LGG had the strongest protective effect with an RR of 0.70. Mix4 compared to placebo had the highest RR at 1.06. However, the wide CI precludes definite conclusions to be made.

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The ranking probabilities and SUCRA values are shown in Appendices 7 and 8. Based on the ranking probabilities, the probiotic with the highest relative probability in terms of safety is Mix2. The probiotic with the lowest relative probability is Mix4. Based on the SUCRA values, LGG has the highest relative probability to be the safest intervention. Placebo, followed by Mix4, had the lowest relative probabilities. The disparity in ranking between the ranking probabilities and SUCRA values demonstrate the lack of robustness of the data. Thus, other factors such as the efficacy of the probiotic preparations, cost, and availability must be considered in the choice of probiotics.

Exploration for Inconsistency

Evaluation of loop inconsistency through node splitting to identify similarity between direct and indirect treatment effects was not appropriate for this study. The pairwise comparisons with direct evidence came from the two multi-arm trials, and there was only one study providing indirect evidence in one of the edges. Since loop inconsistency cannot occur within a multi-arm trial and can only arise from at least three separate sets of studies, evaluation of loop inconsistency for this network meta-analysis was not appropriate.[56]

Testing of design inconsistency to evaluate similarity between two-arm and multi-arm trials resulted in a p-value of 0.028. To explore the design inconsistency, subgroup analysis on the effect of administering probiotics prenatally and postnatally was done.

Additional Analysis

Comparison-adjusted funnel plot was not appropriate to be generated for this study due to the limited number of studies supporting each pairwise comparison.

Sensitivity analysis

Sensitivity analysis was done involving data only from studies with overall low risk of bias for the efficacy outcome. The ranking of the probiotic preparations remain the same as the original analysis. The highest ranked is Mix2, followed by LRH, and LGG. The lowest ranked probiotic preparation was BL.

Subgroup analysis

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Subgroup analysis based on prenatal or postnatal use of probiotics was done. There were 8 studies that administered probiotics prenatally to pregnant women and postnatally to infants. These studies involved seven probiotic preparations, namely, BL, LGG, LR, LRH, Mix1, Mix4 and Mix7. All pairwise comparisons were not statistically significant. Compared to placebo, LRH had the strongest protective effect with an RR of 0.54 (95% CI 0.26-1.11). Mix1 had the highest RR at 1.05 (95% CI 0.57-1.94). However, the wide CI preclude definite conclusions to be made.

There were eight studies that involved infants. The probiotic preparations involved were LA, LGG, LP, Mix3, Mix5, Mix6 and Mix9. Compared to placebo, Mix3 had the strongest protective effect with an RR of 0.46 (95% CI 0.22-0.97), indicating greatest benefit in preventing the development of atopic dermatitis. LA had the highest relative risk compared to placebo at RR 1.10 (95% CI 0.77-1.58). LA compared to Mix3 showed statistically significant benefit favoring Mix3 (RR=2.38, 95% CI 1.05-5.40). Mix3 showed statistically significant benefit over Mix9 (RR=0.42, 95% CI 0.18-0.97). The rest of the pairwise comparisons were not statistically significant.

There were five studies that involved pregnant women. However, network meta-analysis could not be conducted in STATA because all pairwise comparisons were supported by one study only.

The network geometry and interval plot for the subgroups on prenatal and postnatal administration and postnatal administration are shown in Figures 6 and 7. The forest plots are shown in Figure 8. There was no source of inconsistency in the subgroups.

GRADE Certainty of Evidence Appraisal

The CoE assessments of the 5 interventions with the highest relative probabilities for efficacy, and the interventions with the highest and lowest relative probabilities for safety are summarized in Table II. Most pairwise comparisons have low to very low quality of evidence due to risk of bias, imprecision and violation of the transitivity assumption. It is uncertain whether there is any difference in the pairwise comparisons of the top 5 interventions (Mix8, LP, Mix3, Mix6 and Mix4) in preventing atopic dermatitis due to very low certainty of evidence. It is uncertain whether there is any difference in LGG and Mix2, LGG and Mix4, and Mix2 and Mix4 in the risk of developing adverse events due to very low certainty of evidence. The complete

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CoE assessments for all interventions for the efficacy outcome may be found in Supplementary Table III.

IV. DISCUSSION

Summary of Main Results

This study demonstrates the beneficial effects of certain probiotic preparations in reducing the risk of developing atopic dermatitis among the pediatric population. Mix8 compared to placebo probably reduces the risk of atopic dermatitis based on low quality evidence. Mix3 compared to placebo probably reduces the risk of atopic dermatitis based on low quality evidence. It is uncertain whether LP compared to placebo reduces the risk of atopic dermatitis due to very low quality certainty of evidence. It is uncertain whether there is any difference in the pairwise comparisons of the five highest ranked interventions, namely Mix8, LP, Mix3, Mix6 and Mix4, in preventing atopic dermatitis due to very low certainty of evidence. It is important to note that ranking of interventions based on ranking probabilities and SUCRA has limitations and can be misleading especially when the quality of evidence is mostly low to very low. The rankings generated in this network meta-analysis should be interpreted with caution and must be analyzed alongside the CoE assessments. The comparative effectiveness of these probiotic strains would be more prudently interpreted as exploratory observations rather than inferential statements.

The results of this review are consistent with the results of the previous systematic reviews and meta-analysis that show trend towards benefit of probiotics in preventing atopic dermatitis. All the studies included in the previous systematic reviews were covered in the literature search for this study. Additional studies that were recently published in 2019 were also included in this review. In the previous systematic reviews, subgroup analysis according to probiotic genus showed varying effects on the prevention of atopic dermatitis. Three systematic reviews reported significant benefit among the mixed strains subgroup,[5,6,9] while one systematic review reported no significant benefit of the mixed strains subgroup.[11] One systematic review reported significant benefit of the Lactobacilli subgroup,[11] while another systematic review reported no significant benefit of the Lactobacilli subgroup.[6] These variations in results may be explained by three factors: (1) the conduct of the systematic reviews were done in different

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years, wherein the inclusion of new studies may have modified the results of the meta-analysis, (2) critical appraisal showed differences among the reviews in terms of thoroughness in search strategy, appropriateness of inclusion criteria, assessment of validity of inclusion studies, and reproducibility of assessments (Appendix 1), and (3) the strain-specific effect of probiotics makes it difficult to analyze probiotics based on probiotic genera. This network meta-analysis explored which of the specific probiotic preparations demonstrate the most benefit in preventing atopic dermatitis in children.

It is interesting to note that the three probiotic preparations that had statistically significant benefit compared to placebo all contained mixtures of probiotic strains (Mix8, Mix3, Mix6). This result suggests the synergistic effect of the probiotic strains included in the mixture. Although the three mixtures contained different probiotic strains, they all contained a combination of *Bifidobacterium* and *Lactobacillus* strains.

Bifidobacteria and *Lactobacilli* are important elements of the normal human intestinal microbiome. In fact, breastmilk has been found to promote the growth of *Bifidobacteria* and *Lactobacilli*.[57] This would explain why most of the included studies evaluated probiotic strains belonging to these two genera. However, the immunomodulatory effects of *Bifidobacteria* and *Lactobacilli* strains differ.[55] The combination of certain *Bifidobacteria* and *Lactobacilli* strains seem to provide the most optimal synergistic effect in preventing allergies, which may be due to better simulation of the normal diversity of the human microbiome. The other probiotic genera included in this network meta-analysis are *Escherichia* (part of Mix5), *Enterococcus* (part of Mix5), and *Streptococcus* (part of Mix9). The potential benefit of the other probiotic genera that were not included in this review cannot be discounted.

Safety must also be considered alongside efficacy. Based on a systematic review on probiotics, clinically important adverse events of probiotic administration include sepsis, fungemia and gastrointestinal ischemia.[58] None of the studies reported the occurrence of these clinically important adverse events. LGG may slightly lead to less adverse events compared to placebo based on low quality evidence (RR=0.70, 95% CI 0.32-1.52). Mix4 may slightly lead to more adverse events compared to placebo based on low quality evidence (RR=1.06, 95% CI 0.02-51.88). Although ranking in terms of safety was provided, the wide confidence intervals of all the probiotic preparations compared to placebo preclude any definite conclusions to be made.

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An important limitation of this study is the limited number of studies supporting each pairwise comparison and the dearth of studies providing direct evidence between the various probiotic preparations. Multiple treatment comparison could not be done for most of the pairwise comparisons. The limited number of studies may have likely resulted in the lack of statistically significant results for most pairwise comparisons.

Another limitation is the presence of inconsistency most likely due to the variation in study population used. Based on subgroup analysis of studies involving infants, Mix3 compared to placebo probably reduces the risk of atopic dermatitis based on low quality evidence (RR=0.46, 95% CI 0.22–0.97). Mix3 compared to Mix9 probably reduces the risk of atopic dermatitis based on low quality evidence (RR=0.42, 95% CI 0.18-0.97). LA compared to Mix3 may increase the risk of atopic dermatitis based on very low quality evidence (RR=2.38, 95% CI 1.05-5.40).

In the subgroup analysis of studies involving pregnant women and infants, LRH compared to placebo probably reduces the risk of atopic dermatitis based on moderate quality evidence (RR=0.54, 95% CI 0.26-1.11). LRH compared to Mix1 may reduce the risk of atopic dermatitis based on low quality evidence (RR=0.52, 95% CI 0.20–1.32).

V. CONCLUSIONS

A. Implications for Practice

Certain probiotic preparations demonstrate benefit in reducing the risk of atopic dermatitis. Based on low certainty of evidence, Mix8 and Mix3 probably reduce the risk of developing atopic dermatitis compared to placebo.

Based on the available evidence, definite recommendations on the timing, dose and duration of administration cannot be made. Based on subgroup analysis, Mix3 probably reduces the risk of atopic dermatitis based on low quality evidence compared to placebo when given to infants. The study that evaluated Mix8 administered the intervention to pregnant women.

The doses used in the included studies ranged from 3×10^7 to 5.5×10^{10} colony forming units (CFU) daily. The onset of prenatal administration ranged from the first trimester until 2 to 4 weeks before expected date of confinement. The duration of postnatal administration to infants ranged from 3 months to 2 years.

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B. Implications for Research

Future research that directly compare the highest ranked probiotics will greatly improve the robustness of available evidence and provide greater impact among clinicians. Furthermore, research on the optimal timing, dose, and duration of probiotic administration will provide much needed information for clinicians in prescribing probiotics for preventing atopic dermatitis.

VI. IMPACT STATEMENT

This study compares the effectiveness of different probiotic preparations in the prevention of atopic dermatitis in children. Certain probiotic preparations demonstrate benefit in reducing the risk of developing atopic dermatitis. Future research directly comparing the highest ranked probiotic preparations will help generate definite recommendations relevant to clinical practice.

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Table I. Risk of bias of included studies

Study	Domain 1: Risk of bias arising from the randomization process	Domain 2: Risk of bias due to deviations from the intended interventions	Domain 3: Risk of bias due to missing outcome data	Domain 4: Risk of bias in measurement of the outcome	Domain 5: Risk of bias in selection of the reported result	Overall risk of bias
Efficacy outcome						
Abrahamsson 2007	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Allen 2014	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Boyle 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cabana 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dotterud 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Huurre 2008	Some concerns	Some concerns	Some concerns	Low risk	Low risk	Some concerns
Kalliomaki 2001	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kim 2010	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns
Kopp 2008	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns
Lau 2012	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Niers 2009	High risk	Some concerns	Some concerns	Low risk	Low risk	High risk
Ou 2012	Low risk	Low risk	High risk	Low risk	Low risk	High risk
Plummer 2019	Some concerns	Low risk	Some conerns	Low risk	Low risk	Some concerns
Rautava 2006	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Rautava 2012	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns

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Schmidt 2019	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns
Soh 2009	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Taylor 2007	Low risk	High risk	Low risk	Low risk	Low risk	High risk
West 2009	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Wickens 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wickens 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Safety outcome						
Abrahamsson 2007	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Allen 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Boyle 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cabana 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dotterud 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kim 2010	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns
Kopp 2008	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns
Lau 2012	Low risk	Low risk	High risk	Low risk	Low risk	High risk
Rautava 2012	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns
Schmidt 2019	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns

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Table II. GRADE certainty of evidence appraisal for efficacy estimates

Efficacy Outcome						
Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	Relative risk (95% CI)	Quality of evidence	Relative risk (95% CI)	Quality of evidence	Relative risk (95% CI)	Quality of evidence
Mix8 and placebo	0.46 (0.25, 0.85)	Low quality[a]	-	-	0.46 (0.25, 0.85)	Low quality[a]
LP and placebo	0.49 (0.20, 1.19)	Very low quality[b]	-	-	0.49 (0.20, 1.19)	Very low quality[b]
Mix3 and placebo	0.50 (0.27, 0.94)	Low quality[a]	-	-	0.50 (0.27, 0.94)	Low quality[a]
Mix6 and placebo	0.58 (0.37, 0.92)	Very low quality[b]	-	-	0.58 (0.37, 0.92)	Very low quality[b]
Mix4 and placebo	0.58 (0.28, 1.18)	Low quality[a]	-	-	0.58 (0.28, 1.18)	Low quality[a]
Mix8 and LP	-	-	0.94 (0.32, 2.75)	Very low quality[c]	0.94 (0.32, 2.75)	Very low quality[c]
Mix8 and Mix3	-	-	0.92 (0.38, 2.23)	Very low quality[d]	0.92 (0.38, 2.23)	Very low quality[d]
Mix8 and Mix6	0.96 (0.47, 1.98)	Low quality[a]	0.46 (0.20, 1.05)	Very low quality[c]	0.79 (0.41, 1.53)	Very low quality[e]
Mix8 and Mix4	-	-	0.80 (0.31,	Very low	0.80 (0.31,	Very low

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			2.04)	quality[d]	2.04)	quality[d]
LP and Mix3	-	-	0.98 (0.33, 2.91)	Very low quality[c]	0.98 (0.33-2.91)	Very low quality[c]
LP and Mix6	-	-	0.84 (0.31, 2,28)	Very low quality[c]	0.84 (0.31, 2,28)	Very low quality[c]
LP and Mix4	-	-	0.85 (0.27, 2.64)	Very low quality[c]	0.85 (0.27, 2.64)	Very low quality[c]
Mix3 and Mix6	-	-	0.86 (0.39, 1.87)	Very low quality[c]	0.86 (0.39, 1.87)	Very low quality[c]
Mix3 and Mix4	-	-	0.86 (0.33, 2.24)	Very low quality[d]	0.86 (0.33, 2.24)	Very low quality[d]
Mix6 and Mix4	-	-	1.01 (0.43, 2.35)	Very low quality[c]	1.01 (0.43, 2.35)	Very low quality[c]
Safety outcome						
Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	Relative risk (95% CI)	Quality of evidence	Relative risk (95% CI)	Quality of evidence	Relative risk (95% CI)	Quality of evidence
LGG and placebo			0.70 (0.32, 1.52)	Low quality[a]	0.70 (0.32, 1.52)	Low quality[a]
Mix2 and placebo	1.01 (0.02, 50.77)	Moderate quality[f]	-	-	1.01 (0.02, 50.77)	Moderate quality[f]
Mix4 and placebo	1.06 (0.02,	Low quality[a]	-	-	1.06 (0.02,	Low quality[a]

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	51.88)				51.88)	
LGG and Mix2			0.69 (0.01, 37.21)	Very low quality[d]	0.69 (0.01, 37.21)	Very low quality[d]
LGG and Mix4			0.66 (0.01, 34.92)	Very low quality[d]	0.66 (0.01, 34.92)	Very low quality[d]
Mix2 and Mix4	-	-	0.96 (0.004, 238.87)	Very low quality[d]	0.96 (0.004, 238.87)	Very low quality[d]

[a] Downgraded due to risk of bias, imprecision

[b] Downgraded due to very serious risk of bias, imprecision

[c] Downgraded due to very serious risk of bias, imprecision, violation of transitivity

[d] Downgraded due to risk of bias, imprecision, violation of transitivity

[e] Downgraded due to risk of bias, imprecision, inconsistency

[f] Downgraded due to imprecision

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Appendix 1. Critical Appraisal of Related Literature

Parameters	Kuang and Jiang 2019	Zuccotti et al., 2015	Cao et al., 2015	Cuello-Garcia et al., 2015	Mansfield et al., 2014	Panduru et al., 2014	Doege et al., 2012	Pelucchi et al., 2012	Lee et al., 2008	Osborn and Sinn, 2007
Were the criteria for inclusion of studies appropriate?	Yes	Included quasi-randomized controlled trials	Excluded studies with follow-up less than 5 years	Yes	Yes	Yes	Yes	Yes	Yes	Included quasi-randomized controlled trials
Was the search for eligible studies thorough?	Limited to English literature	Search for unpublished literature not done, limited to English literature	Search for unpublished literature not done	Yes	Search for unpublished literature not done, limited to English literature or with available English translation	Limited to English literature	Search for unpublished literature not done	Search for unpublished literature not done	Search for unpublished literature not done	Yes
Was validity of the included studies assessed?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Were the assessments of the studies reproducible?	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	Yes

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Number of studies included in review	7	17	6	29	27 articles reporting on 16 RCTs	16	7	18	6	5
Population involved	Pregnant women	Pregnant women, infants, or both	Pregnant women and infants, or infants only	Pregnant women, infants, or both	Pregnant women, infants, or both	Pregnant women, infants, or both	Pregnant and breastfeeding women	Pregnant women, infants, or both	Pregnant women, infants, or both	Pregnant women and infants, or infants only
Overall Results	Favors probiotics (RR 0.68, 95% CI 0.58-0.81), I^2=0%	Favors probiotics (RR 0.78, 95% CI 0.69-0.89), I^2=57%	Favors probiotics (RR 0.86, 95% CI 0.77-0.96), I^2=46%	Favors probiotics (RR 0.72, 95% CI 0.61-0.85), I^2=52%	Favors probiotics (RR 0.74, 95% CI 0.62-0.88), I^2=62.2%	Favors probiotics (OR 0.56, 95% CI 0.52-0.6), I^2=67.99%	-	Favors probiotics (OR 0.79, 95% CI 0.71-0.88), I^2=24%	Favors probiotics (RR 0.69, 95% CI 0.57-0.83), I^2=54.8%	Trend towards benefit (RR 0.80, 95% CI: 0.62-1.02), I^2 = 65.1%
Subgroup analysis	LGG subgroup: RR 0.65 (95% CI 0.46-0.92), I^2=19.6% Mixture of strains subgroup	Mixed probiotics subgroup RR 0.54 (95% CI 0.43-0.68) I^2=38% Lactobacilli subgroup	Pregnant women and infants subgroup RR 0.83 (95% CI 0.74-0.94) I I^2=47 Infants subgroup RR	Pregnant women or pregnant women and infants subgroup RR 0.72 (95% CI 0.61-0.85) I^2=52%	Mixtures including Lactobacillus subgroup RR 0.74 (95% CI 0.60-0.90) Mixtures including	Prenatal and postnatal subgroup OR 0.54 (95% CI 0.50-0.59) Postnatal subgroup	Mixed strains subgroup OR 0.92 (95% CI 0.83-1.02), I^2=0% Lactobacilli subgroup	Pregnant women and infant subgroup RR 0.81 (95% CI 0.70-0.94) I^2=9% Infant only		

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	RR 0.70 (95% CI 0.57-0.85) I^2=0%	RR 0.9 (95% CI 0.77-1.05) I^2=46% Bifidobacteria subgroup RR 0.89 (95% CI 0.73-1.08) I^2=0	0.98 (95% CI 0.73-1.31) I^2=56%	Infants or pregnant women and infants subgroup RR 0.81 (95% CI 0.70-0.94)	Bifidobacterium subgroup RR 0.70 (95% CI 0.56-0.88)	OR 0.89 (95% CI 0.59-1.35) Prenatal subgroup OR 0.83 (95% CI 0.56-1.22)	OR 0.82 (95% CI 0.71-0.95), I^2=0%	subgroup RR 0.85 (95% CI 0.61-1.19) I^2=32% Pregnant women only subgroup RR 0.70 (95% CI 0.53-0.91) I^2=0%		

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Appendix 2. Overview of the elements of a systematic review and network meta-analysis

Elements of a systematic review	Considerations for a network meta-analysis
Search strategy	• The search should capture all interventions of interest • The horizontal pathway search strategy is recommended for reviews where there are multiple interventions of interest. In this strategy, individual search for each probiotic preparation was done. • Two-edge paths involve studies that evaluate different probiotic strains but have one common comparator, the most common of which is placebo.
Qualitative synthesis of evidence	• The network geometry presents the interventions of interest as nodes, and the studies comparing the interventions of interest as links between the nodes. • Directness, heterogeneity, transitivity and coherence must be qualitatively evaluated
Quantitative synthesis of evidence	• Direct evidence is derived from studies that directly compare interventions of interest • Indirect evidence is derived from studies with one or more intermediate comparators • Multiple treatment comparison incorporates both direct and indirect evidence • League tables summarize the treatment effects of each pairwise comparison. The table is read from left to right. Relative risk and 95% confidence intervals less than 1 indicate superiority of the first intervention over the comparator. • Inconsistency for network meta-analysis is assessed through 2 components: loop and design inconsistency. Loop consistency identifies similarity between direct and indirect treatment effects and can be assessed using node splitting. Design consistency

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	identifies similarity between estimates from two-arm and multi-arm trials and can be assessed using a design-by-treatment interaction model. • Ranking probabilities and surface under the cumulative ranking curve reflect the ranking of the interventions of interestfor each outcome evaluated.
Interpretation of results	• The GRADE approach for rating quality of evidence for network meta-analysis is used.
Reporting findings	• The PRISMA extension statement for reporting systematic reviews incorporating network meta-analysis is followed.

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Appendix 3. Data for efficacy and safety outcome

Efficacy Outcome				
Study	**Intervention/Comparator**	**Number of events**	**Sample size**	**Timing of Outcome**
Abrahamsson 2007	LR	34	95	2 years
	Placebo	32	93	
Allen 2014	Mix1	73	214	2 years
	Placebo	72	222	
Boyle 2011	LGG	42	122	1 year
	Placebo	47	120	
Cabana 2017	LGG	28	92	2 years
	Placebo	26	92	
Kalliomaki 2001	LGG	15	64	2 years
	Placebo	31	68	
Kopp 2008	LGG	14	50	2 years
	Placebo	12	44	
Ou 2012	LGG	16	65	3 years
	Placebo	16	64	
Dotterud 2010	Mix2	29	138	2 years
	Placebo	48	140	
Huurre 2008	Mix3	7	72	1 year
	Placebo	12	68	
Rautava 2006	Mix3	4	32	1 year
	Placebo	8	40	
Schmidt 2019	Mix3	5	119	6 months
	Placebo	14	122	
Taylor 2007	LA	38	88	1 year
	Placebo	34	87	
Kim 2010	Mix4	12	33	1 year
	Placebo	22	35	

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Lau 2012	Mix5	89	303	3 years
	Placebo	97	303	
Soh 2009	Mix6	27	124	1 year
	Placebo	30	121	
Rautava 2012	Mix6	21	73	2 years
	Mix8	20	70	
	Placebo	44	62	
Wickens 2008	LRH	23	157	2 years
	BL	38	158	
	Placebo	43	159	
Wickens 2018	LRH	37	203	1 year
	Placebo	43	200	
Niers 2009	Mix7	27	50	2 years
	Placebo	33	48	
Plummer 2019	Mix9	35	118	2 years
	Placebo	37	137	
West 2009	LP	9	84	13 months
	Placebo	19	87	
Safety Outcome				
Study	**Intervention/Comparator**	**Number of events**	**Sample size**	**Timing of Outcome**
Abrahamsson 2007	LR	0	95	2 years
	Placebo	0	93	
Allen 2010	Mix1	27	220	6 months
	Placebo	36	234	
Boyle 2011	LGG	9	122	1 year
	Placebo	13	120	
Cabana 2017	LGG	0	92	2 years
	Placebo	0	92	
Kopp 2008	LGG	0	50	2 years

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	Placebo	0	44	
Dotterud 2010	Mix2	0	138	2 years
	Placebo	0	140	
Kim 2010	Mix4	0	33	1 year
	Placebo	0	35	
Lau 2012	Mix5	73	303	3 years
	Placebo	74	303	
Rautava 2012	Mix6	0	79	2 years
	Mix8	0	74	
	Placebo	0	70	
Schmidt 2019	Mix3	0	119	6 months
	Placebo	0	122	

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Appendix 4. League table for efficacy outcome

BL										
0.89 (0.38, 2.06)	LA									
1.14 (0.59, 2.20)	1.28 (0.65, 2.53)	LGG								
2.00 (0.69, 5.76)	2.25 (0.77, 6.57)	1.76 (0.69, 4.49)	LP							
0.94 (0.40, 2.22)	1.06 (0.44, 2.54)	0.83 (0.41, 1.67)	0.47 (0.16, 1.39)	LR						
1.43 (0.77, 2.64)	1.61 (0.75, 3.43)	1.26 (0.72, 2.19)	0.71 (0.26, 1.93)	1.51 (0.70, 3.29)	LRH					
0.93 (0.42, 2.09)	1.05 (0.46, 2.39)	0.82 (0.43, 1.55)	0.47 (0.16, 1.32)	0.99 (0.43, 2.29)	0.65 (0.32, 1.34)	Mix1				
1.60 (0.68, 3.78)	1.80 (0.75, 4.32)	1.40 (0.70, 2.85)	0.80 (0.27, 2.37)	1.70 (0.70, 4.12)	1.12 (0.51, 2.44)	1.72 (0.74, 3.98)	Mix2			
1.97 (0.83, 4.65)	2.21 (0.92, 5.31)	1.73 (0.86, 3.50)	0.98 (0.33, 2.91)	2.09 (0.86, 5.07)	1.38 (0.63, 3.01)	2.11 (0.91, 4.90)	1.23 (0.50, 3.00)	Mix3		
1.70 (0.67, 4.26)	1.91 (0.75, 4.87)	1.49 (0.69, 3.25)	0.85 (0.27, 2.64)	1.80 (0.70, 4.64)	1.19 (0.51, 2.77)	1.82 (0.74, 4.49)	1.06 (0.41, 2.74)	0.86 (0.33, 2.24)	Mix4	
1.07 (0.48, 2.38)	1.20 (0.53, 2.72)	0.94 (0.50, 1.76)	0.53 (0.19, 1.51)	1.13 (0.49, 2.60)	0.75 (0.37, 1.53)	1.15 (0.53, 2.50)	0.67 (0.29, 1.54)	0.54 (0.24, 1.25)	0.63 (0.26, 1.55)	Mix5

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1.68 (0.80, 3.54)	1.90 (0.89, 4.05)	1.48 (0.85, 2.58)	0.84 (0.31, 2.28)	1.79 (0.82, 3.88)	1.18 (0.62, 2.26)	1.81 (0.88, 3.72)	1.05 (0.48, 2.29)	0.86 (0.39, 1.87)	0.99 (0.43, 2.32)	1.57 (0.77, 3.21)	Mix6				
1.25 (0.55, 2.86)	1.41 (0.61, 3.26)	1.10 (0.57, 2.13)	0.62 (0.22, 1.80)	1.32 (0.56, 3.12)	0.87 (0.42, 1.84)	1.34 (0.60, 3.00)	0.78 (0.33, 1.84)	0.64 (0.27, 1.50)	0.74 (0.29, 1.85)	1.17 (0.53, 2.60)	0.74 (0.35, 1.56)	Mix7			
2.13 (0.91, 4.99)	**2.40 (1.01, 5.70)**	1.88 (0.94, 3.75)	1.07 (0.36, 3.13)	2.26 (0.94, 5.45)	1.49 (0.69, 3.23)	2.29 (0.99, 5.25)	1.33 (0.55, 3.22)	1.08 (0.45, 2.62)	1.26 (0.49, 3.23)	1.99 (0.87, 4.55)	1.27 (0.66, 2.45)	1.71 (0.73, 4.00)	Mix8		
0.89 (0.38, 2.10)	1.01 (0.42, 2.40)	0.79 (0.39, 1.58)	0.45 (0.15, 1.32)	0.95 (0.39, 2.30)	0.63 (0.29, 1.36)	0.96 (0.41, 2.22)	0.56 (0.23, 1.36)	0.45 (0.19, 1.11)	0.53 (0.20, 1.36)	0.84 (0.26, 1.92)	0.53 (0.24, 1.15)	0.72 (0.30, 1.69)	0.42 (0.17, 1.01)	Mix9	
0.98 (0.55, 1.76)	1.10 (0.60, 2.02)	0.86 (0.63, 1.18)	0.49 (0.20, 1.19)	1.04 (0.56, 1.94)	0.69 (0.43, 1.09)	1.05 (0.60, 1.84)	0.61 (0.33, 1.15)	**0.50 (0.27, 0.94)**	0.58 (0.28, 1.18)	0.92 (0.53, 1.58)	**0.58 (0.37, 0.92)**	0.79 (0.44, 1.41)	**0.46 (0.25, 0.85)**	1.10 (0.59, 2.06)	Placebo

Appendix 5. Ranking probabilities for efficacy outcome

Rank	Placebo	BL	LA	LGG	LP	LR	LRH	Mix1	Mix2	Mix3	Mix4	Mix5	Mix6	Mix7	Mix8	Mix9
Best	0	0	0	0	26.4	0.1	1.2	0	8.6	19.5	11.9	0.3	3.0	1.5	27.3	0.2
2nd	0	0.4	0.2	0	16.8	0.1	3.7	0.2	9.7	17.5	13.2	1.2	10.3	1.9	24.4	0.4
3rd	0	1.1	0.3	0.3	11.0	0.9	5.9	0.8	12.5	18.3	12.1	1.9	15.8	3.5	14.8	0.8
4th	0	1.9	1.0	1.4	9.4	1.7	8.8	1.0	12.0	13.1	9.8	2.1	18.8	5.6	12.6	0.8
5th	0	2.3	1.3	2.0	7.6	3.3	12.3	1.8	11.8	0.7	10.5	3.7	16.3	7.5	6.8	2.1
6th	0	5.3	2.6	5.4	6.5	4.4	14.5	2.7	9.6	6.1	10.2	4.2	12.3	8.6	4.8	2.8
7th	0.1	5.9	3.9	11.2	5.1	5.7	13.1	4.4	7.5	4.3	8.1	6.0	8.2	9.5	3.2	3.8
8th	1.1	6.8	4.5	13.8	5.0	5.2	10.8	4.6	7.0	2.8	6.1	9.7	5.6	9.2	2.6	5.2
9th	3.2	8.4	5.1	16.0	3.4	7.6	8.7	5.1	4.9	2.4	5.0	10.1	3.4	10.2	1.2	5.3
10th	9.9	8.6	6.3	13.9	2.2	7.4	7.2	8.6	4.3	1.2	4.1	7.7	2.6	8.5	0.6	6.9
11th	21.4	7.7	6.7	11.4	2.0	7.9	5.4	8.6	2.5	0.7	1.9	9.3	1.4	5.9	1.1	6.1

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12th	25.6	6.3	6.4	11.0	0.6	8.0	3.5	7.8	2.7	1.3	2.3	10.0	1.3	6.9	0.1	6.2
13th	21.5	7.6	9.4	5.6	1.3	9.9	2.9	10.4	2.3	1.1	1.1	9.6	0.9	7.2	0.2	9.0
14th	12.5	13.8	13.9	4.5	1.0	10.8	1.3	11.6	2.7	0.6	1.2	8.2	0	5.4	0.2	12.3
15th	4.0	12.9	15.4	2.7	0.8	12.7	0.6	16.5	1.1	0.3	1.4	9.6	0.1	5.5	0.1	16.3
Worst	0.7	11.0	23.0	0.8	0.9	14.3	0.1	15.9	0.8	0.1	1.1	6.4	0	3.1	0	21.8

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Appendix 6. SUCRA values for efficacy outcome

Treatment	SUCRA
Mix8	85.7
Mix3	80.7
LP	78.5
Mix6	73.0
Mix4	70.9
Mix2	67.8
LRH	59.6
Mix7	47.1
LGG	42.2
Mix5	36.2
BL	31.1
LR	29.4
Mix1	25.4
Mix9	23.8
Placebo	16.3
LA	15.9

Appendix 7. Ranking probabilities for safety outcome

Rank	Placebo	LGG	LR	Mix1	Mix2	Mix3	Mix4	Mix5	Mix6	Mix8
Best	0	4.3	17.0	1.3	18.0	14.7	13.0	0.2	16.0	15.5
2nd	0.5	13.0	12.9	7.4	11.7	13.1	12.2	1.3	14.3	13.6
3rd	3.7	20.5	9.9	16.0	8.3	9.4	7.7	4.5	8.6	11.4
4th	9.2	19.5	5.8	23.5	5.5	5.9	6.2	11.5	6.3	6.6
5th	18.3	16.7	4.6	20.4	3.6	4.2	4.1	20.1	4.2	3.8
6th	27.1	9.9	4.1	16.6	3.2	3.4	4.2	23.3	4.2	4.0
7th	21.8	8.0	5.9	8.8	7.8	6.7	6.1	20.2	6.5	8.2
8th	14.0	5.5	10.6	4.6	11.7	10.5	11.4	11.8	10.3	9.6

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9th	5.1	2.2	13.1	1.4	13.2	14.9	16.0	5.3	15.2	13.6
Worst	0.3	0.4	16.1	0	17.0	17.2	19.1	1.8	14.4	13.7

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Appendix 8. SUCRA values for safety outcome

Treatment	SUCRA
LGG	62.6
Mix1	58.8
Mix8	51.1
LR	50.2
Mix6	49.9
Mix2	48.6
Mix3	47.7
Mix5	44.0
Mix4	44.5
Placebo	42.6

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FIGURE LEGENDS

Figure 1. Search flow diagram

The search flow diagram shows the number of records searched, screened, retrieved, appraised, and included in the network meta-analysis.

Figure 2. Network geometry (efficacy outcome)

The network geometry represents the interventions evaluated in the study. The size of the nodes are proportional to the number of study participants assigned to the intervention, while the thickness of the lines is proportional to the number of studies providing data for each pairwise comparison.

Figure 3. Interval plot of probiotic preparations compared to placebo (efficacy outcome)

The interval plot shows the relative risk and 95% CI of each probiotic preparation compared to placebo in terms of efficacy. Relative risk values less than 1 indicate that the probiotic preparation is superior to placebo in preventing atopic dermatitis.

Figure 4. Network geometry (safety outcome)

This network geometry represents the interventions evaluated in the study in terms of safety. The size of the nodes are proportional to the number of study participants assigned to the intervention, while the thickness of the lines is proportional to the number of studies providing data for each pairwise comparison.

Figure 5. Interval plot of probiotic preparations compared to placebo (safety outcome)

The interval plot shows the relative risk and 95% CI of each probiotic preparation compared to placebo in terms of safety. Relative risk values less than 1 indicate that the probiotic preparation is safer compared to placebo in the development of adverse events.

Figure 6. Network geometry for subgroup analysis

The network geometry for the subgroup on prenatal and postnatal administration is shown on the left (A) and for the subgroup on postnatal administration is shown on the right (B). In Figure A, there are 8 nodes, 7 probiotic preparations and 1 placebo. There are 3 studies

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supporting the pairwise comparison of LGG and placebo. The rest of the pairwise comparisons have only 1 study providing evidence. In Figure B, there are 8 nodes, 7 probiotic preparations and 1 placebo. There are 2 studies supporting the pairwise comparison for Mix3 and placebo. The rest of the pairwise comparisons have only 1 study providing evidence.

Figure 7. Interval plots for subgroup analysis

The interval plots for the subgroup on prenatal and postnatal administration is shown on the left (A) and for the subgroup on postnatal administration is shown on the right (B).

Figure 8. Forest plots for subgroup analysis

The forest plots for the subgroup on prenatal and postnatal administration is shown on the left (A) and for the subgroup on postnatal administration is shown on the right (B).

Supplementary Figure 1. Forest plot comparing LRH and Placebo (efficacy outcome)

Two studies reported data on the pairwise comparison of LRH and placebo. The pooled relative risk is 0.75 (95% CI 0.54, 1.04). There is no significant heterogeneity.

Supplementary Figure 2. Forest plot comparing Mix3 and Placebo (efficacy outcome)

Three studies reported data on the pairwise comparison of Mix3 and placebo. The pooled relative risk is 0.49 (95% CI 0.28, 0.86). There is no significant heterogeneity.

Supplementary Figure 3. Forest plot comparing LGG and Placebo (efficacy outcome)

Five studies reported data on the pairwise comparison of LGG and placebo. The pooled relative risk is 0.86 (95% CI 0.70, 1.06). There is no significant heterogeneity.

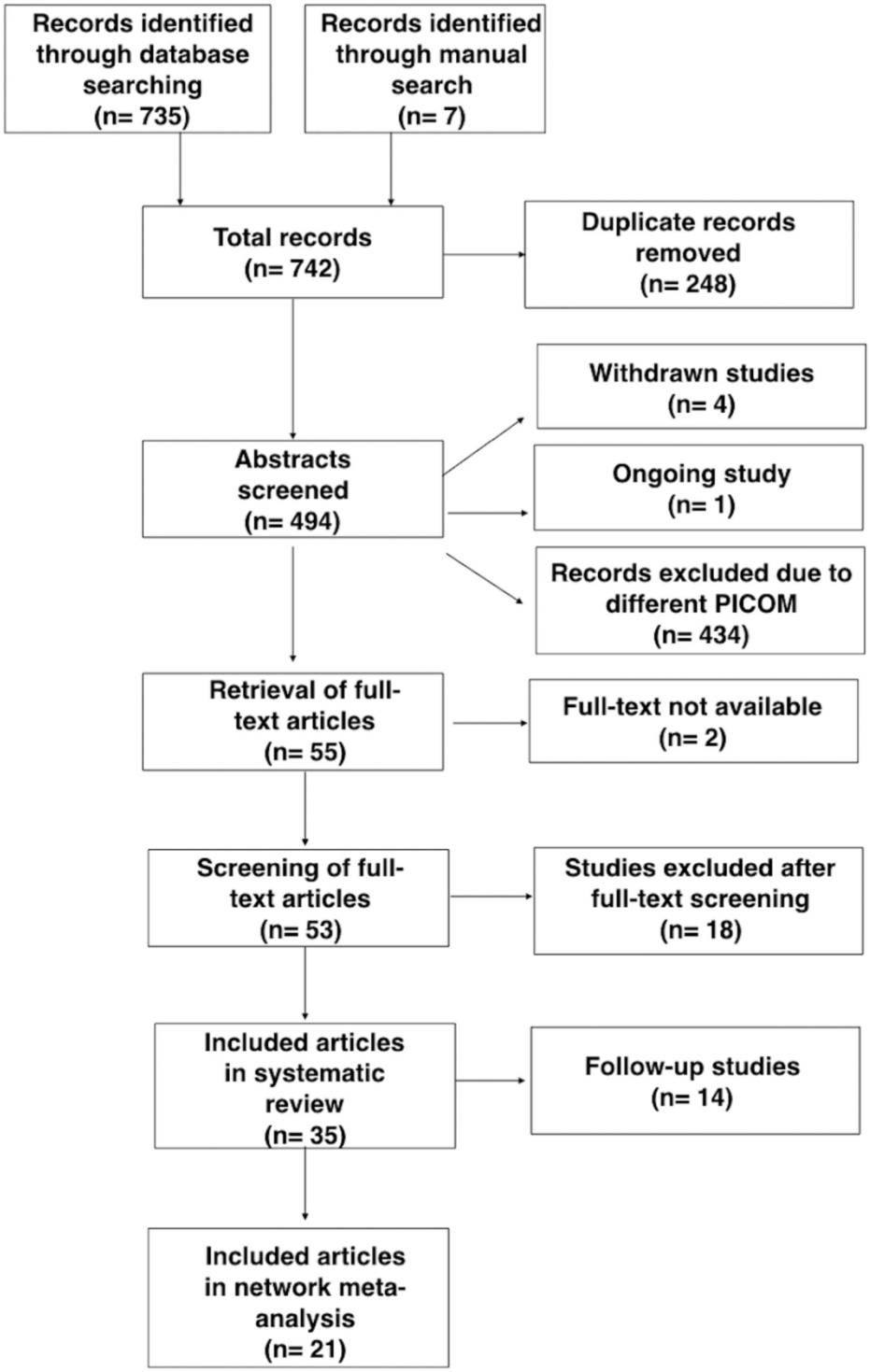
Supplementary Figure 4. Forest plot comparing Mix6 and Placebo (efficacy outcome)

Two studies reported data on the pairwise comparison of Mix6 and placebo. The pooled relative risk is 0.68 (95% CI 0.48, 0.96). There is significant heterogeneity.

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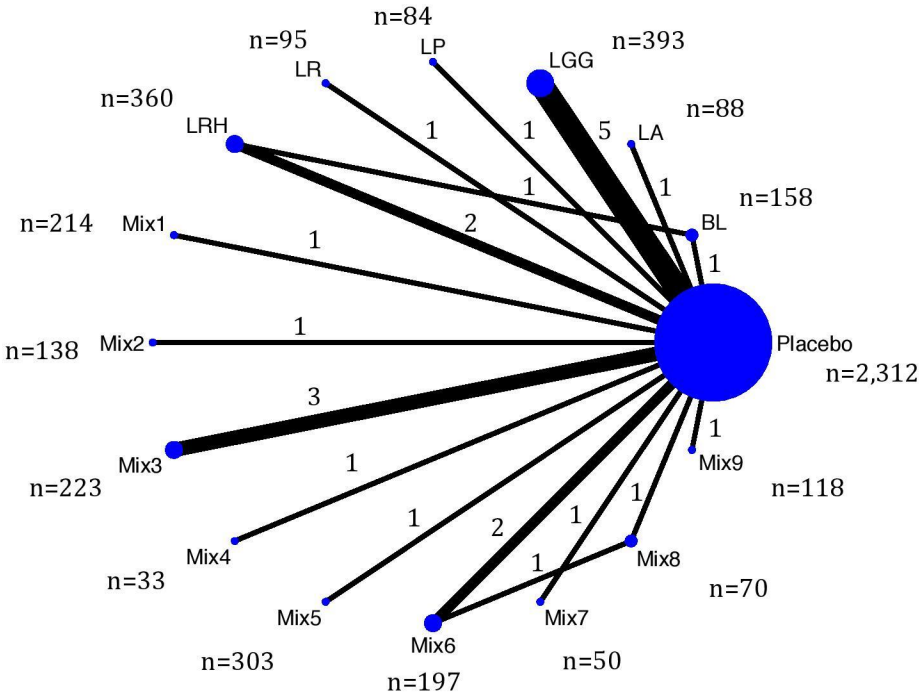
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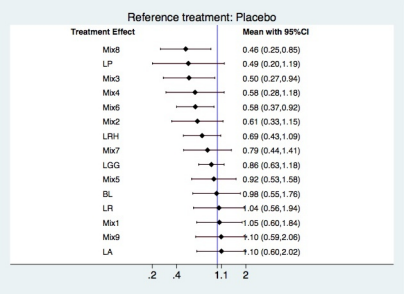
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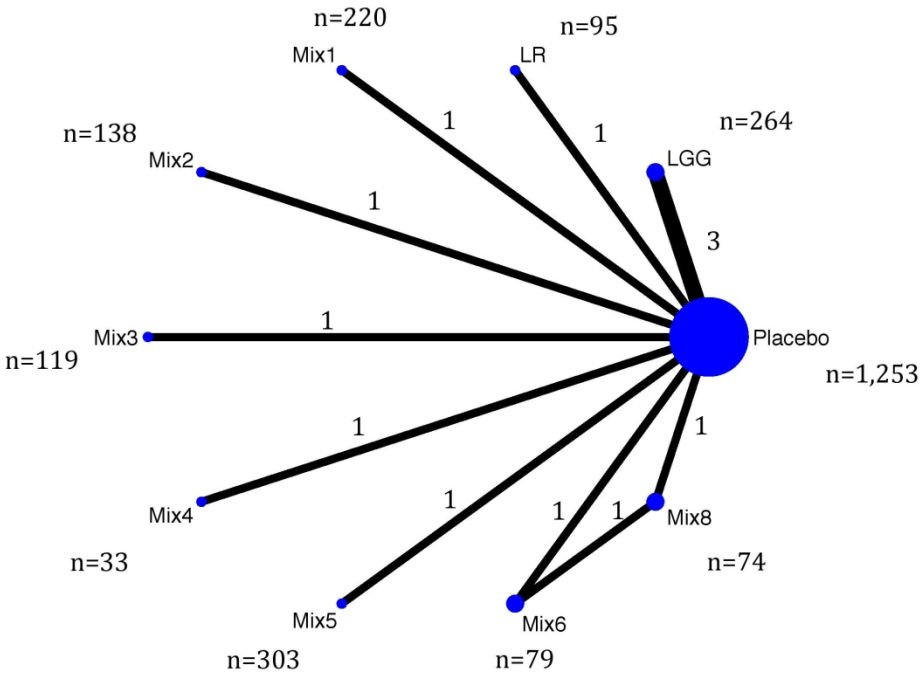


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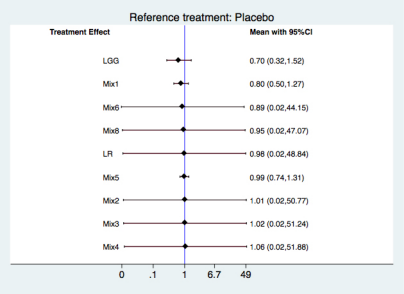
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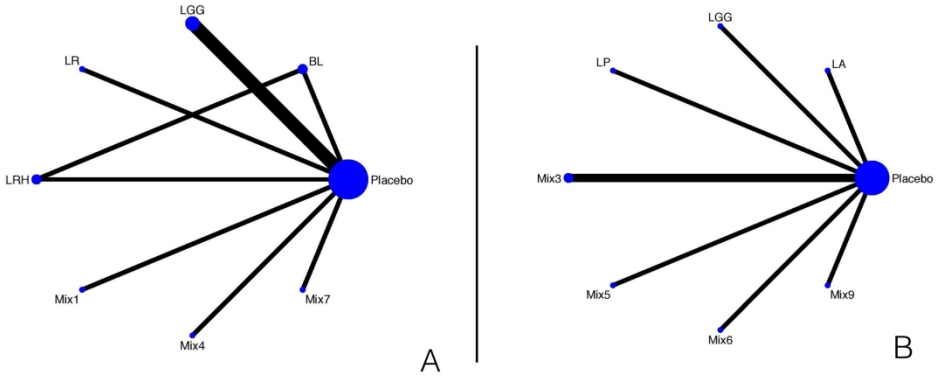


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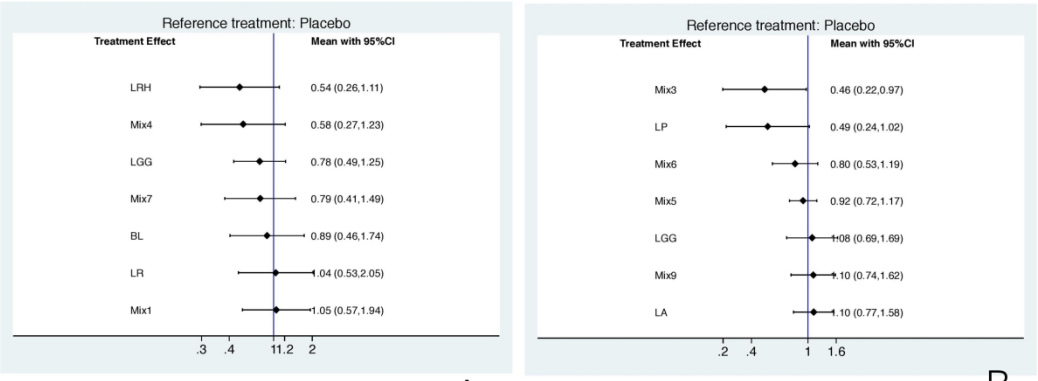
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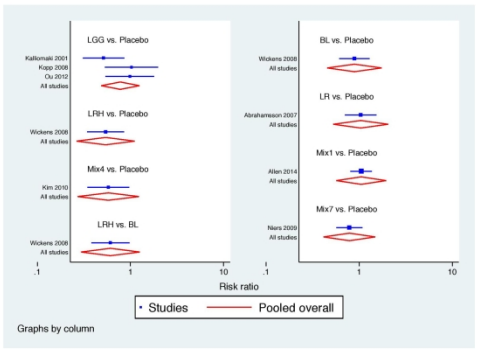
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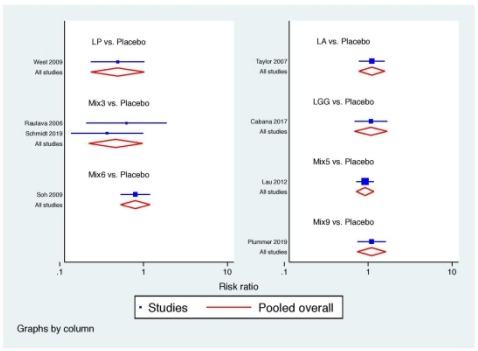
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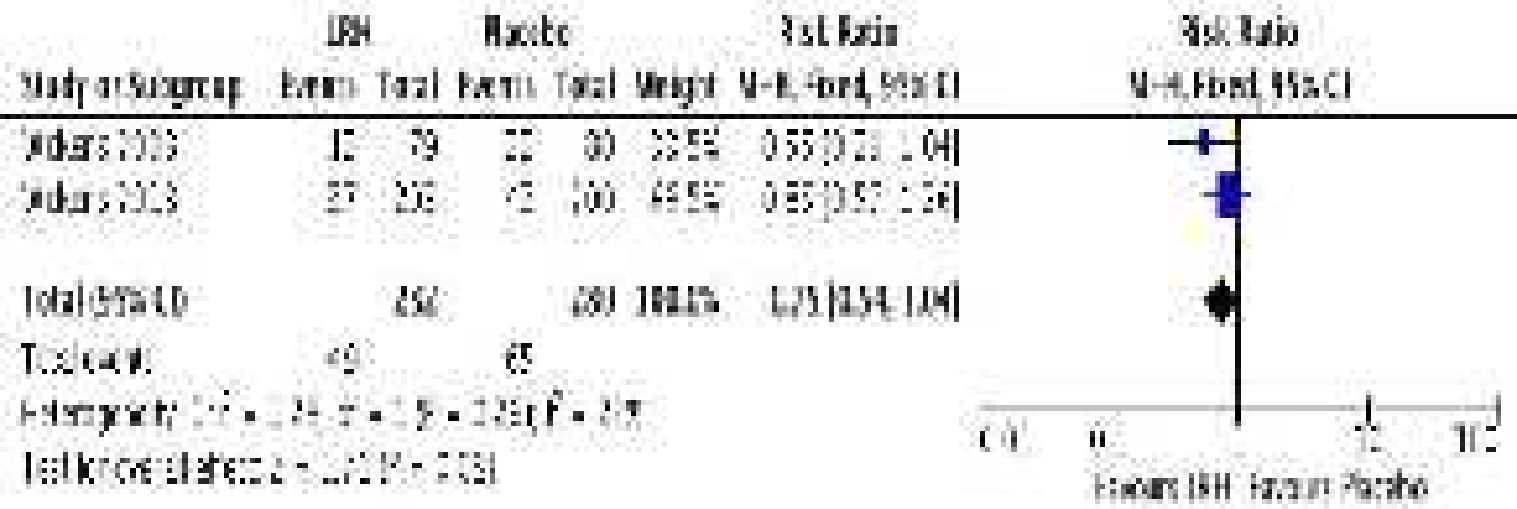
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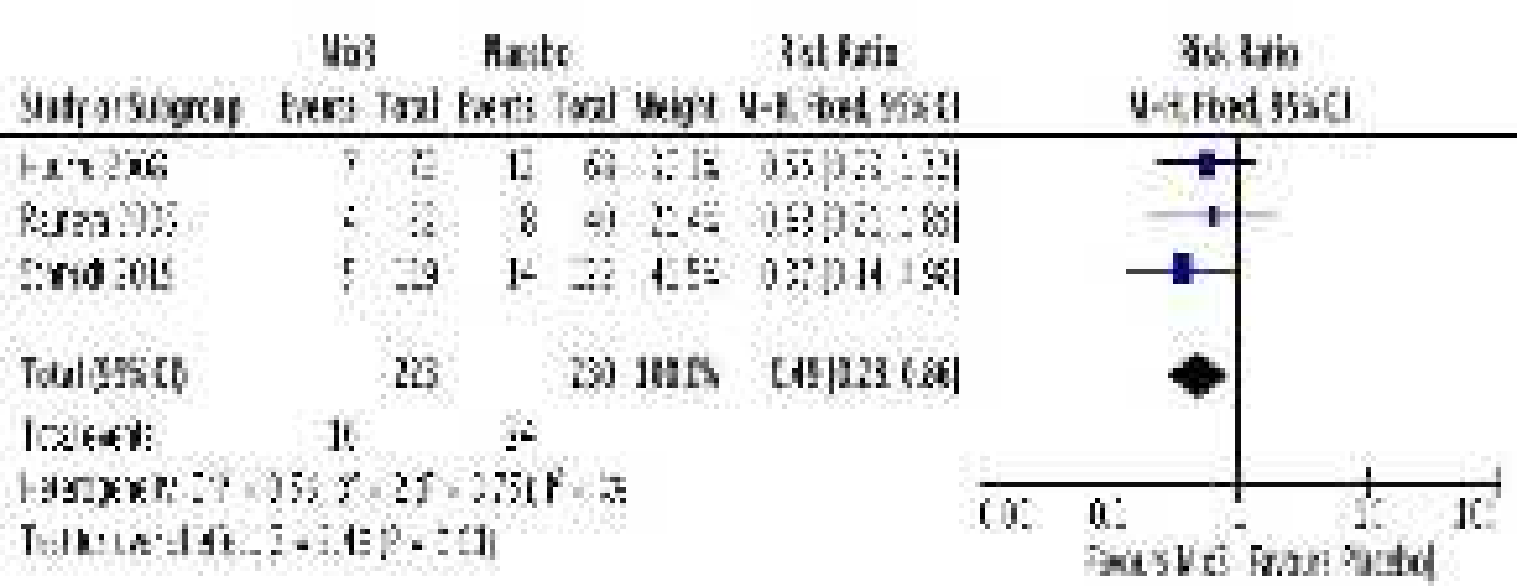


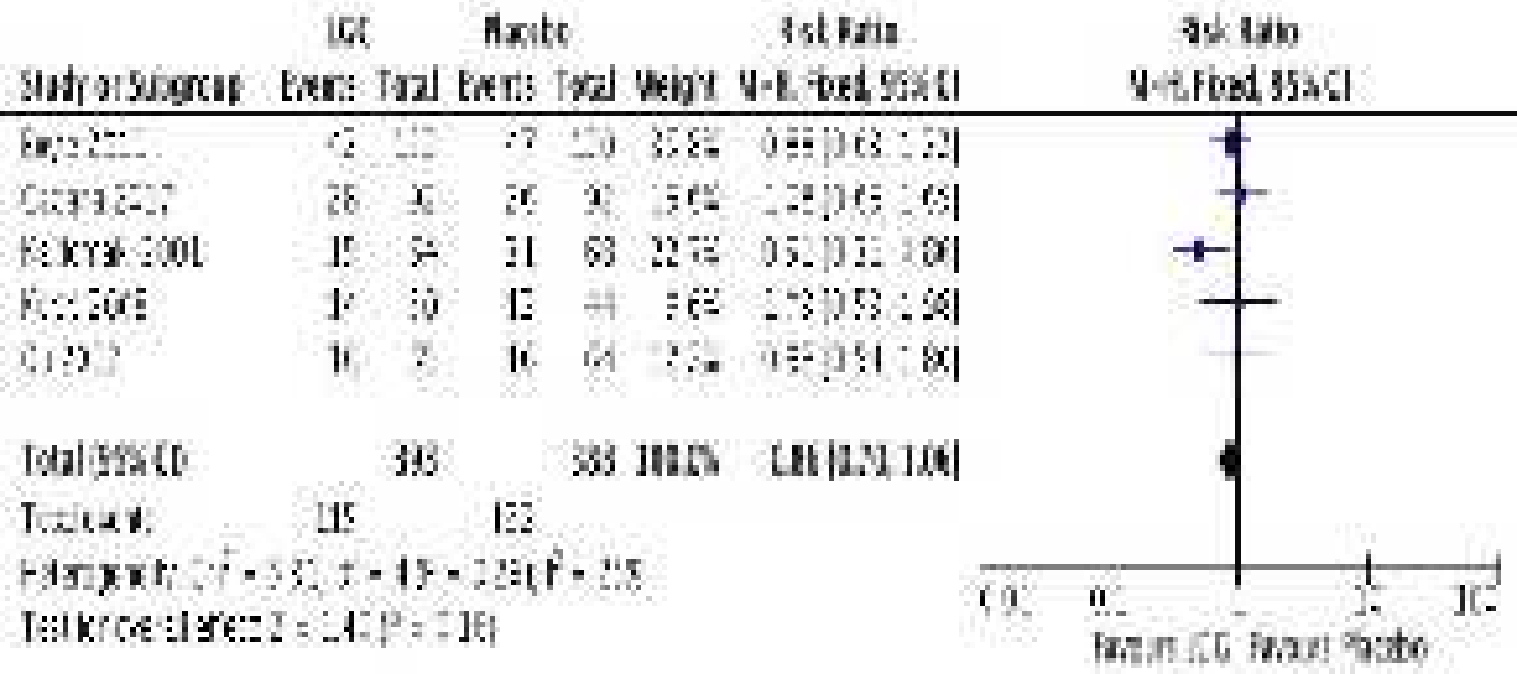
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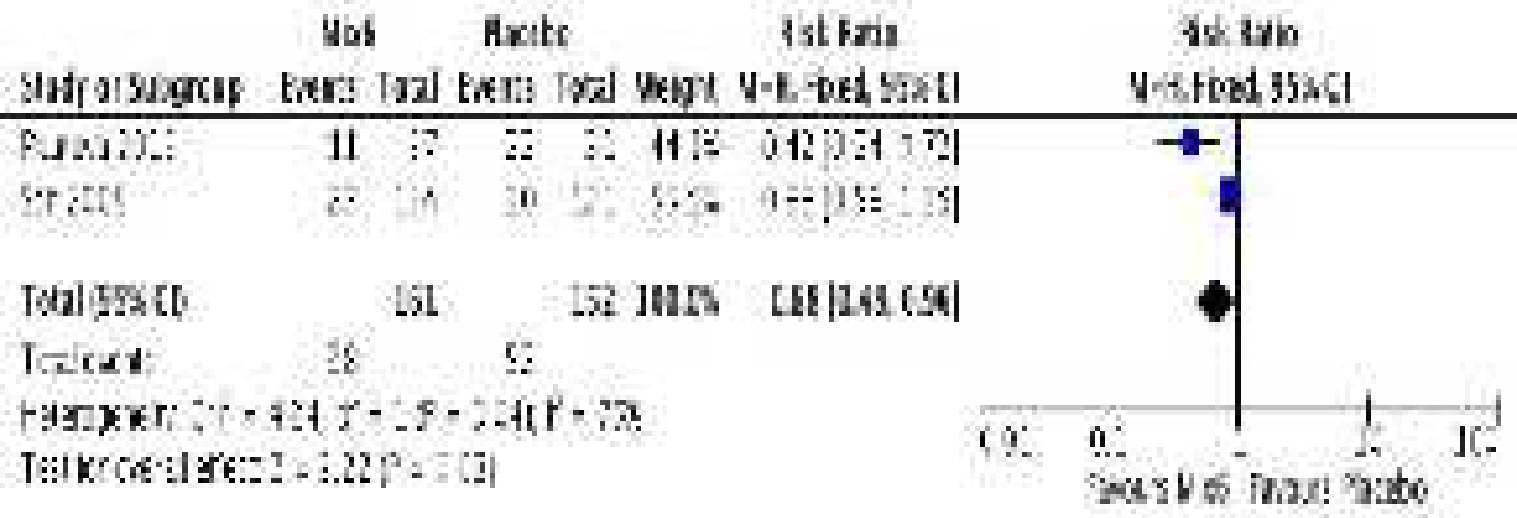
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LDH
Placebo
Risk Ratio
Risk Ratio
Events
Total
Weight
M-H, Fixed, 95% CI
Favours LDH
Favours Placebo


Mn3
Events Total
Placebo
Events Total
Weight
Risk Ratio
M-H, Fixed, 95% CI
Risk Ratio
M-H, Fixed, 95% CI
Total (95% CI)
Total events:
Heterogeneity:
Test for overall effect:
0.01
0.1
1
10
100
Favours Mn3
Favours Placebo


LGT
Placebo
Risk Ratio
Risk Ratio
Total (95% CI)
Total events:
Test for overall effect:
Favours LGT
Favours Placebo


Mab
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Total (95% CI)
Total events:
Heterogeneity:
Test for overall effect:
0.01
0.1
1
10
100
Favours Mab
Favours Placebo

Supplementary Table I. Search Strategy

MEDLINE Search		
Search	**Query**	**Items Found**
1	**Search "randomized controlled trial" [Publication Type]**	**479413**
2	**Search "controlled clinical trial" [Publication Type]**	**567560**
3	**Search randomized [Title/Abstract]**	**474101**
4	**Search placebo [Title/Abstract]**	**201960**
5	**Search clinical trial as topic [MeSH Terms]**	**323796**
6	**Search randomly [Title/Abstract]**	**308676**
7	**Search trial [Title]**	**196210**
8	**Search #1 or #2 or #3 or #4 or #5 or #6**	**1284721**
9	**Search animals {MeSH Terms]**	**22200070**
10	**Search humans [MeSH Terms]**	**17636168**
11	**Search #9 and #10**	**17636168**
12	**Search #9 not #11**	**4563902**
13	**Search #8 not #12**	**1187457**
14	**Search probiotic**	**24016**
15	**Search probiotics**	**20639**
16	**Search "Probiotics" [Mesh]**	**14880**
17	**Search lactobacillus**	**35935**
18	**Search lactobacilli**	**7426**
19	**Search "Lactobacillus" [Mesh]**	**26792**
20	**Search bifidobacterium**	**8273**
21	**Search bifidobacteria**	**3622**
22	**Search "Bifidobacterium" [Mesh]**	**5462**
23	**Search bacillus**	**99489**
24	**Search bacilli**	**118867**
25	**Search "Bacillus" [Mesh]**	**64587**
26	**Search escherichia**	**372377**
27	**Search "Escherichia" [Mesh]**	**269574**
28	**Search saccharomyces**	**131783**

29	**Search “Saccharomyces” [Mesh]**	**106351**
30	**Search Propionibacterium**	**7082**
31	**Search propionibacteria**	**475**
32	**Search “Propionibacterium” [Mesh]**	**5192**
33	**Search streptococcus**	**104244**
34	**Search streptococci**	**22342**
35	**Search “Streptococcus” [Mesh]**	**75654**
36	**Search lactococcus**	**7094**
37	**Search lactococcu**	**515**
38	**Search “Lactococcus” [Mesh]**	**4898**
39	**Search #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38**	**736420**
40	**Search atopic dermatitis**	**25859**
41	**Search atopic eczema**	**27283**
42	**Search “Dermatitis, Atopic” [Mesh]**	**18513**
43	**Search SCORAD**	**876**
44	**Search EASI**	**421**
45	**Search ADASI**	**17**
46	**Search IGADA**	**5**
47	**Search #40 or #41 or #42 or #43 or #44 or #45 or #46**	**27534**
48	**Search #47 and #39 and #13**	**227**
Cochrane Library		
1	**probiotic**	**4216**
2	**probiotics**	**4305**
3	**MeSH descriptor: [Probiotics] explode all trees**	**1756**
4	**lactobacillus**	**4101**
5	**lactobacilli**	**901**
6	**MeSH descriptor: [Lactobacillus] explode all trees**	**1467**
7	**bifidobacterium**	**2095**
8	**bifidobacteria**	**717**

9	**MeSH descriptor: [Bifidobacterium] explode all trees**	**646**
10	**bacillus**	**1893**
11	**MeSH descriptor: [Bacillus] explode all trees**	**80**
12	**Escherichia**	**2914**
13	**MeSH descriptor: [Escherichia] explode all trees**	**642**
14	**enterococcus**	**1005**
15	**MeSH descriptor: [Enterococcus] explode all trees**	**254**
16	**saccharomyces**	**489**
17	**MeSH descriptor: [Saccharomyces] explode all trees**	**157**
18	**propionibacterium**	**406**
19	**MeSH descriptor: [Propionibacterium] explode all trees**	**154**
20	**streptococcus**	**4670**
21	**MeSH descriptor: [Streptococcus] explode all trees**	**1703**
22	**lactococcus**	**104**
23	**MeSH descriptor: [Lactococcus] explode all trees**	**14**
24	**#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23**	**16331**
25	**Atopic dermatitis**	**3942**
26	**Atopic eczema**	**1771**
27	**eczema**	**3457**
28	**MeSH descriptor: [Dermatitis, Atopic] explode all trees**	**1566**
29	**scorad**	**642**
30	**easi**	**432**
31	**igada**	**6**
32	**adasi**	**8**
33	**#25 or #26 or #27 or #28 or #29 or #30 or #31 or #32**	**6003**
34	**#24 and #33**	**418**
Trip Database		
1	**Atopic dermatitis, probiotics**	**59**
Centre for research and dissemination		
1	**Atopic dermatitis, probiotics**	**9**

Supplementary Table II. Characteristics of Included Studies

Study	Country	No. of participants	General risk or high risk[a]	Study participants	Probiotic strain	Daily Dose	Duration of prenatal probiotic use	Duration of postnatal probiotic use	Control group	Outcome	Time period	Follow up study
Abrahamsson 2007	Sweden	232	High risk	Pregnant women and infants	LR	1 x 10^8 CFU	36 weeks age of gestation until delivery	12 months	Placebo	Development of atopic dermatitis, adverse events	2 years	Abrahamsson 2013
Allen 2010	UK	454	General risk	Pregnant women and infants	Mix1	1 x 10^{10} CFU	36 weeks age of gestation until delivery	6 months	Placebo	Adverse events	6 months	Allen 2014 Davies 2018
Boyle 2011	Australia	250	High risk	Pregnant women	LGG	1.8 x 10^{10} CFU	36 weeks age of gestation until delivery	None	Placebo	Development of atopic dermatitis, adverse events	1 year	None
Cabana 2017	USA	184	High risk	Infants	LGG	1 x 10^{10} CFU	None	6 months	Placebo	Development of atopic dermatitis, adverse events	6 months, 2 years	None
Dotterud 2010	Norway	415	General risk	Pregnant women	Mix2	5.5 x 10^{10} CFU	36 weeks age of gestation until delivery	3 months (given to mother)	Placebo	Development of atopic dermatitis, adverse events	2 years	Simpson 2015
Huurre 2008	Finland	171	High risk	Pregnant women	Mix3	2 x 10^{10} CFU	First trimester	4 months (given to mother)	Placebo	Development of atopic dermatitis	12 months	None
Kalliomaki 2001	Finland	159	High risk	Pregnant women and infants	LGG	1 x 10^{10} CFU	2-4 weeks before expected date of confinement	6 months	Placebo	Development of atopic dermatitis	2 years	Kalliomaki 2003 Kalliomaki 2007
Kim 2010	Korea	112	High risk	Pregnant women and infants	Mix4	4.8 x 10^9 CFU	8 weeks before expected date of confinement	3 months (mother) 4-6 months (infant)	Placebo	Development of atopic dermatitis, adverse events	3,6,12 months	None

Kopp 2008	Germany	105	High risk	Pregnant women and infants	LGG	1 x 10^{10} CFU	4-6 weeks before expected date of confinement	6 months (if breastfed, first 3 months given to mother, next 3 months infant. If not breastfed, 6 months to infant)	Placebo	Development of atopic dermatitis, adverse events	2 years	None
Lau 2012	Germany	606	High risk	Infants starting 5 weeks old	Mix5	3 – 9.5 x 10^{7} CFU	None	26 weeks	Placebo	Development of atopic dermatitis, adverse events	5, 13, 21, 31 weeks, 12, 24, 36 months	None
Niers 2009	Netherlands	156	High risk	Pregnant women and infants	Mix7	3 x 10^{9} CFU	6 weeks before expected date of confinement	12 months	Placebo	Development of atopic dermatitis	3, 12, 24 months	Gorissen 2014
Ou 2012	Taiwan	191	High risk	Pregnant women and infants	LGG	1 x 10^{10} CFU	24 weeks age of gestation until delivery	6 months (If breastfed, given to mother. If not breastfed, given to infant)	Placebo	Development of atopic dermatitis	6, 18, 36 months	None
Plummer 2019	Australia	288	General risk	Very preterm infants	Mix9	1 x 10^{9} CFU	None	Until 8-25 months corrected age	Placebo	Development of atopic dermatitis	2 years	None
Rautava 2006	Finland	81	General risk	Infants	Mix3	1 x 10^{10} CFU	None	12 months	Placebo	Development of atopic dermatitis	12 months	None
Rautava 2012	Finland	241	High risk	Pregnant women	Mix6 Mix8	1 x 10^{9} CFU	2 months before expected date of	2 months (given to mother)	Placebo	Development of atopic dermatitis, adverse events	2 years	None

							confinement					
Schmidt 2019	Denmark	290	General risk	Infants	Mix3	1 x 10^9 CFU	None	6 months	Placebo	Development of atopic dermatitis, adverse events	6 months	None
Soh 2009	Singapore	253	High risk	Infants	Mix6	2.8 x 10^8 CFU	None	6 months	Placebo	Development of atopic dermatitis	12 months	Loo 2014
Taylor 2007	Australia	218	High risk	Infants	LA	3 x 10^9 CFU	None	6 months	Placebo	Development of atopic dermatitis	12 months	Prescott 2008 Jensen 2012
West 2009	Sweden	179	General risk	Infants	LP	1 x 10^8 CFU	None	From 4 to 13 months of age	Placebo	Development of atopic dermatitis	13 months of age	West 2013
Wickens 2008	New Zealand	512	High risk	Pregnant women and infants	LRH BL	6 x 10^9 CFU 9 x 10^9 CFU	35 weeks age of gestation until delivery	2 years (If breastfed, mother is also given until 6 months)	Placebo	Development of atopic dermatitis	2 years	Wickens 2012 Wickens 2013 Wickens 2018
Wickens 2018	New Zealand	423	High risk	Pregnant women	LRH	6 x 10^9 CFU	14-16 weeks age of gestation until delivery	6 months (given to mother if breastfeeding)	Placebo	Development of atopic dermatitis	12 months	None

[a] Participants are considered high risk if they have at least 1 family member with allergic disease

BL - *Bifidobacterium animalis* ssp. *lactis* HN 019, LA - *Lactobacillus acidophilus* LAVRI-A1, LGG – *Lactobacillus rhamnosus* GG, LP – *Lactobacillus paracasei* ssp *paracasei* F19, LR - *Lactobacillus reuteri* ATCC55730, LRH - *Lactobacillus rhamnosus* HN001, Mix1- *Lactobacillus salivarius* CUL61, *Lactobacillus paracasei* CUL 08, *Bifidobacterium animalis* ssp. *lactis* CUL34, *Bifidobacterium bifidum* CUL20, Mix 2- LGG, *Bifidobacterium animalis* ssp *lactis* Bb-12, *Lactobacillus acidophilus* La-5, Mix3- LGG, *Bifidobacterium animalis* ssp *lactis* Bb-12, Mix4 - *Bifidobacterium bifidum* BGN4, *Bifidobacterium lactis* AD011, *Lactobacillus acidophilus* AD031, Mix5- *Escherichia coli* Symbio DSM 17252, *Enterococcus faecalis* Symbio DSM 16440, Mix6- *Bifidobacterium longum* BL999, *Lactobacillus rhamnosus* LPR, Mix7 - *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactococcus lactis* W58, Mix8- *Lactobacillus paracasei* ST11, *Bifidobacterium longum* BL999, Mix 9 – *Bifidobacterium longum ssp. infantis, Streptococcus thermophilus, Bifidobacterium animalis ssp. lactis.*

Supplementary Table III. GRADE certainty of evidence appraisal for all estimates (efficacy outcome)

Efficacy Outcome						
Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	Relative risk (95% CI)	Quality of evidence	Relative risk (95% CI)	Quality of evidence	Relative risk (95% CI)	Quality of evidence
BL and LA	-	-	0.89 (0.38, 2.06)	Very low quality[a]	0.89 (0.38, 2.06)	Very low quality[a]
BL and LGG	-	-	1.14 (0.59, 2.20)	Very low quality[a]	1.14 (0.59, 2.20)	Very low quality[a]
BL and LP	-	-	2.00 (0.69, 5.76)	Very low quality[a]	2.00 (0.69, 5.76)	Very low quality[a]
BL and LR	-	-	0.94 (0.40, 2.22)	Low quality[b]	0.94 (0.40, 2.22)	Low quality[b]
BL and LRH	1.58 (0.82, 3.04)	Moderate quality[c]	1.28 (0.54, 3.04)	Low quality[d]	1.43 (0.77, 2.64)	Low quality[e]
BL and Mix1	-	-	0.93 (0.42, 2.09)	Low quality[b]	0.93 (0.42, 2.09)	Low quality[b]
BL and Mix2	-	-	1.60 (0.68, 3.78)	Low quality[d]	1.60 (0.68, 3.78)	Low quality[d]
BL and Mix3	-	-	1.97 (0.83, 4.65)	Very low quality[f]	1.97 (0.83, 4.65)	Very low quality[f]
BL and Mix4	-	-	1.70 (0.67, 4.26)	Low quality[b]	1.70 (0.67, 4.26)	Low quality[b]
BL and Mix5	-	-	1.07 (0.48, 2.38)	Very low quality[f]	1.07 (0.48, 2.38)	Very low quality[f]
BL and Mix6	-	-	1.68 (0.80, 3.54)	Very low quality[a]	1.68 (0.80, 3.54)	Very low quality[a]
BL and Mix7	-	-	1.25 (0.55,	Very low	1.25 (0.55,	Very low

			2.86)	quality[g]	2.86)	quality[g]
BL and Mix8	-	-	2.13 (0.91, 4.99)	Very low quality[f]	2.13 (0.91, 4.99)	Very low quality[f]
BL and Mix9	-	-	0.89 (0.38, 2.10)	Very low quality[f]	0.89 (0.38, 2.10)	Very low quality[f]
BL and Placebo	0.98 (0.55, 1.76)	Moderate quality[c]	-	-	0.98 (0.55, 1.76)	Moderate quality[c]
LA and LGG	-	-	1.28 (0.65, 2.53)	Very low quality[a]	1.28 (0.65, 2.53)	Very low quality[a]
LA and LP	-	-	2.25 (0.77, 6.57)	Very low quality[g]	2.25 (0.77, 6.57)	Very low quality[g]
LA and LR	-	-	1.06 (0.44, 2.54)	Very low quality[a]	1.06 (0.44, 2.54)	Very low quality[a]
LA and LRH	-	-	1.61 (0.75, 3.43)	Very low quality[a]	1.61 (0.75, 3.43)	Very low quality[a]
LA and Mix1	-	-	1.05 (0.46, 2.39)	Very low quality[a]	1.05 (0.46, 2.39)	Very low quality[a]
LA and Mix2	-	-	1.80 (0.75, 4.32)	Very low quality[a]	1.80 (0.75, 4.32)	Very low quality[a]
LA and Mix3	-	-	2.21 (0.92, 5.31)	Very low quality[a]	2.21 (0.92, 5.31)	Very low quality[a]
LA and Mix4	-	-	1.91 (0.75, 4.87)	Very low quality[a]	1.91 (0.75, 4.87)	Very low quality[a]
LA and Mix5	-	-	1.20 (0.53, 2.72)	Very low quality[g]	1.20 (0.53, 2.72)	Very low quality[g]
LA and Mix6	-	-	1.90 (0.89, 4.05)	Very low quality[a]	1.90 (0.89, 4.05)	Very low quality[a]
LA and Mix7	-	-	1.41 (0.61, 3.26)	Very low quality[a]	1.41 (0.61, 3.26)	Very low quality[a]

LA and Mix8	-	-	2.40 (1.01, 5.70)	Very low quality[a]	2.40 (1.01, 5.70)	Very low quality[a]
LA and Mix9	-	-	1.01 (0.42, 2.40)	Very low quality[g]	1.01 (0.42, 2.40)	Very low quality[g]
LA and Placebo	1.10 (0.60, 2.02)	Very low quality[g]	-	-	1.10 (0.60, 2.02)	Very low quality[g]
LGG and LP	-	-	1.76 (0.69, 4.49)	Very low quality[a]	1.76 (0.69, 4.49)	Very low quality[a]
LGG and LR	-	-	0.83 (0.41, 1.67)	Very low quality[a]	0.83 (0.41, 1.67)	Very low quality[a]
LGG and LRH	-	-	1.26 (0.72, 2.19)	Very low quality[a]	1.26 (0.72, 2.19)	Very low quality[a]
LGG and Mix1	-	-	0.82 (0.43, 1.55)	Very low quality[a]	0.82 (0.43, 1.55)	Very low quality[a]
LGG and Mix2	-	-	1.40 (0.70, 2.85)	Very low quality[a]	1.40 (0.70, 2.85)	Very low quality[a]
LGG and Mix3	-	-	1.73 (0.86, 3.50)	Very low quality[a]	1.73 (0.86, 3.50)	Very low quality[a]
LGG and Mix4	-	-	1.49 (0.69, 3.25)	Very low quality[a]	1.49 (0.69, 3.25)	Very low quality[a]
LGG and Mix5	-	-	0.94 (0.50, 1.76)	Very low quality[a]	0.94 (0.50, 1.76)	Very low quality[a]
LGG and Mix6	-	-	1.48 (0.85, 2.58)	Very low quality[a]	1.48 (0.85, 2.58)	Very low quality[a]
LGG and Mix7	-	-	1.10 (0.57, 2.13)	Very low quality[a]	1.10 (0.57, 2.13)	Very low quality[a]
LGG and Mix8	-	-	1.88 (0.94, 3.75)	Very low quality[a]	1.88 (0.94, 3.75)	Very low quality[a]
LGG and Mix9	-	-	0.79 (0.39,	Very low	0.79 (0.39,	Very low

			1.58)	quality[a]	1.58)	quality[a]
LGG and Placebo	0.86 (0.63, 1.18)	Very low quality[g]	-	-	0.86 (0.63, 1.18)	Very low quality[g]
LP and LR	-	-	1.51 (0.70, 3.29)	Very low quality[a]	1.51 (0.70, 3.29)	Very low quality[a]
LP and LRH	-	-	0.99 (0.43, 2.29)	Very low quality[a]	0.99 (0.43, 2.29)	Very low quality[a]
LP and Mix1	-	-	1.70 (0.70, 4.12)	Very low quality[a]	1.70 (0.70, 4.12)	Very low quality[a]
LP and Mix2	-	-	2.09 (0.86, 5.07)	Very low quality[a]	2.09 (0.86, 5.07)	Very low quality[a]
LP and Mix3	-	-	1.80 (0.70, 4.64)	Very low quality[a]	1.80 (0.70, 4.64)	Very low quality[a]
LP and Mix4	-	-	1.13 (0.49, 2.60)	Very low quality[a]	1.13 (0.49, 2.60)	Very low quality[a]
LP and Mix5	-	-	1.79 (0.82, 3.88)	Very low quality[g]	1.79 (0.82, 3.88)	Very low quality[g]
LP and Mix6	-	-	1.32 (0.56, 3.12)	Very low quality[a]	1.32 (0.56, 3.12)	Very low quality[a]
LP and Mix7	-	-	2.26 (0.94, 5.45)	Very low quality[a]	2.26 (0.94, 5.45)	Very low quality[a]
LP and Mix8	-	-	0.95 (0.39, 2.30)	Very low quality[a]	0.95 (0.39, 2.30)	Very low quality[a]
LP and Mix9	-	-	1.04 (0.56, 1.94)	Very low quality[g]	1.04 (0.56, 1.94)	Very low quality[g]
LP and Placebo	1.51 (0.70, 3.29)	Very low quality[g]	-	-	1.51 (0.70, 3.29)	Very low quality[g]
LR and LRH	-	-	0.99 (0.43, 2.29)	Very low quality[f]	0.99 (0.43, 2.29)	Very low quality[f]

LR and Mix1	-	-	1.70 (0.70, 4.12)	Low quality[b]	1.70 (0.70, 4.12)	Low quality[b]
LR and Mix2	-	-	2.09 (0.86, 5.07)	Very low quality[f]	2.09 (0.86, 5.07)	Very low quality[f]
LR and Mix3	-	-	1.80 (0.70, 4.64)	Very low quality[f]	1.80 (0.70, 4.64)	Very low quality[f]
LR and Mix4	-	-	1.13 (0.49, 2.60)	Low quality[b]	1.13 (0.49, 2.60)	Low quality[b]
LR and Mix5	-	-	1.79 (0.82, 3.88)	Very low quality[f]	1.79 (0.82, 3.88)	Very low quality[f]
LR and Mix6	-	-	1.32 (0.56, 3.12)	Very low quality[a]	1.32 (0.56, 3.12)	Very low quality[a]
LR and Mix7	-	-	2.26 (0.94, 5.45)	Very low quality[g]	2.26 (0.94, 5.45)	Very low quality[g]
LR and Mix8	-	-	0.95 (0.39, 2.30)	Very low quality[f]	0.95 (0.39, 2.30)	Very low quality[f]
LR and Mix9	-	-	1.04 (0.56, 1.94)	Very low quality[f]	1.04 (0.56, 1.94)	Very low quality[f]
LR and Placebo	1.51 (0.70, 3.29)	Low quality[b]	-	-	1.51 (0.70, 3.29)	Low quality[b]
LRH and Mix1	-	-	0.65 (0.32, 1.34)	Very low quality[f]	0.65 (0.32, 1.34)	Very low quality[f]
LRH and Mix2	-	-	1.12 (0.51, 2.44)	Low quality[d]	1.12 (0.51, 2.44)	Low quality[d]
LRH and Mix3	-	-	1.38 (0.63, 3.01)	Very low quality[f]	1.38 (0.63, 3.01)	Very low quality[f]
LRH and Mix4	-	-	1.19 (0.51, 2.77)	Very low quality[f]	1.19 (0.51, 2.77)	Very low quality[f]
LRH and Mix5	-	-	0.75 (0.37,	Very low	0.75 (0.37,	Very low

			1.53)	quality[f]	1.53)	quality[f]
LRH and Mix6	-	-	1.18 (0.62, 2.26)	Very low quality[a]	1.18 (0.62, 2.26)	Very low quality[a]
LRH and Mix7	-	-	0.87 (0.42, 1.84)	Very low quality[a]	0.87 (0.42, 1.84)	Very low quality[a]
LRH and Mix8	-	-	1.49 (0.69, 3.23)	Very low quality[f]	1.49 (0.69, 3.23)	Very low quality[f]
LRH and Mix9	-	-	0.63 (0.29, 1.36)	Very low quality[f]	0.63 (0.29, 1.36)	Very low quality[f]
LRH and Placebo	0.69 (0.43, 1.09)	Moderate quality[c]	-	-	0.69 (0.43, 1.09)	Moderate quality[c]
Mix1 and Mix2	-	-	1.72 (0.74, 3.98)	Very low quality[f]	1.72 (0.74, 3.98)	Very low quality[f]
Mix1 and Mix3	-	-	2.11 (0.91, 4.90)	Very low quality[f]	2.11 (0.91, 4.90)	Very low quality[f]
Mix1 and Mix4	-	-	1.82 (0.74, 4.49)	Low quality[b]	1.82 (0.74, 4.49)	Low quality[b]
Mix1 and Mix5	-	-	1.15 (0.53, 2.50)	Very low quality[f]	1.15 (0.53, 2.50)	Very low quality[f]
Mix1 and Mix6	-	-	1.81 (0.88, 3.72)	Very low quality[a]	1.81 (0.88, 3.72)	Very low quality[a]
Mix1 and Mix7	-	-	1.34 (0.60, 3.00)	Very low quality[g]	1.34 (0.60, 3.00)	Very low quality[g]
Mix1 and Mix8	-	-	2.29 (0.99, 5.25)	Very low quality[f]	2.29 (0.99, 5.25)	Very low quality[f]
Mix1 and Mix9	-	-	0.96 (0.41, 2.22)	Very low quality[f]	0.96 (0.41, 2.22)	Very low quality[f]
Mix1 and Placebo	1.05 (0.60, 1.84)	Low quality[b]	-	-	1.05 (0.60, 1.84)	Low quality[b]

Mix2 and Mix3	-	-	1.23 (0.50, 3.00)	Very low quality[f]	1.23 (0.50, 3.00)	Very low quality[f]
Mix2 and Mix4	-	-	1.06 (0.41, 2.74)	Very low quality[f]	1.06 (0.41, 2.74)	Very low quality[f]
Mix2 and Mix5	-	-	0.67 (0.29, 1.54)	Very low quality[f]	0.67 (0.29, 1.54)	Very low quality[f]
Mix2 and Mix6	-	-	1.05 (0.48, 2.29)	Very low quality[a]	1.05 (0.48, 2.29)	Very low quality[a]
Mix2 and Mix7	-	-	0.78 (0.33, 1.84)	Very low quality[a]	0.78 (0.33, 1.84)	Very low quality[a]
Mix2 and Mix8	-	-	1.33 (0.55, 3.22)	Low quality[b]	1.33 (0.55, 3.22)	Low quality[b]
Mix2 and Mix9	-	-	0.56 (0.23, 1.36)	Very low quality[f]	0.56 (0.23, 1.36)	Very low quality[f]
Mix2 and Placebo	0.61 (0.33, 1.15)	Moderate quality[c]	-	-	0.61 (0.33, 1.15)	Moderate quality[c]
Mix3 and Mix4	-	-	0.86 (0.33, 2.24)	Very low quality[f]	0.86 (0.33, 2.24)	Very low quality[f]
Mix3 and Mix5	-	-	0.54 (0.24, 1.25)	Very low quality[f]	0.54 (0.24, 1.25)	Very low quality[f]
Mix3 and Mix6	-	-	0.86 (0.39, 1.87)	Very low quality[a]	0.86 (0.39, 1.87)	Very low quality[a]
Mix3 and Mix7	-	-	0.64 (0.27, 1.50)	Very low quality[a]	0.64 (0.27, 1.50)	Very low quality[a]
Mix3 and Mix8	-	-	1.08 (0.45, 2.62)	Very low quality[f]	1.08 (0.45, 2.62)	Very low quality[f]
Mix3 and Mix9	-	-	0.45 (0.19, 1.11)	Very low quality[f]	0.45 (0.19, 1.11)	Very low quality[f]
Mix3 and Placebo	0.50 (0.27,	Low quality[b]	-	-	0.50 (0.27,	Low quality[b]

	0.94)				0.94)	
Mix4 and Mix5	-	-	0.63 (0.26, 1.55)	Very low quality[f]	0.63 (0.26, 1.55)	Very low quality[f]
Mix4 and Mix6	-	-	0.99 (0.43, 2.32)	Very low quality[a]	0.99 (0.43, 2.32)	Very low quality[a]
Mix4 and Mix7	-	-	0.74 (0.29, 1.85)	Very low quality[g]	0.74 (0.29, 1.85)	Very low quality[g]
Mix4 and Mix8	-	-	1.26 (0.49, 3.23)	Very low quality[f]	1.26 (0.49, 3.23)	Very low quality[f]
Mix4 and Mix9	-	-	0.53 (0.20, 1.36)	Very low quality[f]	0.53 (0.20, 1.36)	Very low quality[f]
Mix4 and Placebo	0.58 (0.28, 1.18)	Low quality[b]	-	-	0.58 (0.28, 1.18)	Low quality[b]
Mix5 and Mix6	-	-	1.57 (0.77, 3.21)	Very low quality[a]	1.57 (0.77, 3.21)	Very low quality[a]
Mix5 and Mix7	-	-	1.17 (0.53, 2.60)	Very low quality[a]	1.17 (0.53, 2.60)	Very low quality[a]
Mix5 and Mix8	-	-	1.99 (0.87, 4.55)	Very low quality[f]	1.99 (0.87, 4.55)	Very low quality[f]
Mix5 and Mix9	-	-	0.84 (0.26, 1.92)	Low quality[b]	0.84 (0.26, 1.92)	Low quality[b]
Mix5 and Placebo	0.92 (0.53, 1.58)	Low quality[b]	-	-	0.92 (0.53, 1.58)	Low quality[b]
Mix6 and Mix7	-	-	0.74 (0.35, 1.56)	Very low quality[a]	0.74 (0.35, 1.56)	Very low quality[a]
Mix6 and Mix8	1.04 (0.51, 2.14)	Low quality[b]	2.44 (0.37, 17.63)	Very low quality[a]	1.27 (0.66, 2.45)	Very low quality[h]
Mix6 and Mix9	-	-	0.53 (0.24, 1.15)	Very low quality[a]	0.53 (0.24, 1.15)	Very low quality[a]

Mix6 and Placebo	0.58 (0.37, 0.92)	Very low quality[g]	-	-	0.58 (0.37, 0.92)	Very low quality[g]
Mix7 and Mix8	-	-	1.71 (0.73, 4.00)	Very low quality[a]	1.71 (0.73, 4.00)	Very low quality[a]
Mix7 and Mix9	-	-	0.72 (0.30, 1.69)	Very low quality[a]	0.72 (0.30, 1.69)	Very low quality[a]
Mix7 and Placebo	0.79 (0.44, 1.41)	Very low quality[g]	-	-	0.79 (0.44, 1.41)	Very low quality[g]
Mix8 and Mix9	-	-	0.42 (0.17, 1.01)	Very low quality[f]	0.42 (0.17, 1.01)	Very low quality[f]
Mix8 and Placebo	0.46 (0.25, 0.85)	Low quality[b]	-	-	0.46 (0.25, 0.85)	Low quality[b]
Mix9 and Placebo	1.10 (0.59, 2.06)	Low quality[b]	-	-	1.10 (0.59, 2.06)	Low quality[b]

[a] Downgraded due to very serious risk of bias, imprecision, violation of transitivity
[b] Downgraded due to risk of bias, imprecision
[c] Downgraded due to imprecision
[d] Downgraded due to imprecision, violation of transitivity
[e] Downgraded due to imprecision, inconsistency
[f] Downgraded due to imprecision, risk of bias, violation of transitivity
[g] Downgraded due to imprecision, very serious risk of bias
[h] Downgraded due to risk of bias, imprecision, inconsistency