**Figure 1 PRISMA Flow Diagram**

Records identified through database searching including: PubMed (79), Cochrane CENTRAL (31) and Cochrane Reviews (3) 
(n = 113 )

Additional records identified through other sources –i.e. hand searches of identified RCTs, systematic reviews/meta-analyses, spec. society clinical guidelines  
(n = 101 )

Records after duplicates removed  
(n = 182 )

Records screened – i.e. abstracts reviewed  
(n = 182 )

Records excluded due to title/abstract screen indicating lack of relevant date  
(n = 123 )

Full-text articles assessed for eligibility  
(n = 59 )

Full-text articles excluded, with reasons  
(n = 48 )

Studies included in qualitative synthesis – RCTs (11)

Studies included in quantitative synthesis (meta-analysis)  
(n = 11 )

---

*Lactobacillus rhamnosus* used in the perinatal period for the prevention of atopic dermatitis in infants: A systematic review and meta-analysis of randomized trials. *American Journal Clinical Dermatology*. Voigt JD, Meenal L. Corresponding author email: jdv4957@aol.com
### Figure 2
Risk of bias summary

| Study            | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|------------------|---------------------------------------------|----------------------------------------|----------------------------------------------------------|-----------------------------------------------|----------------------------------------|-------------------------------------|------------|
| Dotterud 2010    | +                                           | +                                      | +                                                        | -                                             | +                                      | +                                   | +          |
| Huurre 2008      | +                                           | +                                      | +                                                        | -                                             | +                                      | +                                   | +          |
| Kalliomäki 2001  | +                                           | +                                      | +                                                        | -                                             | +                                      | +                                   | +          |
| Kopp 2008        | +                                           | +                                      | +                                                        | +                                             | +                                      | +                                   | +          |
| Kukkonen 2007    | +                                           | +                                      | +                                                        | -                                             | +                                      | +                                   | +          |
| Ou 2012          | +                                           | +                                      | +                                                        | -                                             | +                                      | +                                   | +          |
| Rautava 2002     | +                                           | +                                      | +                                                        | -                                             | +                                      | +                                   | +          |
| Rautava 2012     | +                                           | +                                      | +                                                        | -                                             | +                                      | +                                   | +          |
| Simpson 2015     | +                                           | +                                      | +                                                        | -                                             | +                                      | +                                   | -          |
| Wickens 2008     | +                                           | +                                      | +                                                        | -                                             | +                                      | +                                   | +          |
| Wickens 2018     | +                                           | +                                      | +                                                        | +                                             | +                                      | +                                   | +          |
Figure 3 - Risk of bias graph
Figure 4 - Funnel plot publication bias 2 years
Figure 5 - prenatal and breast milk postnatal

| Study or Subgroup | L rhamnosus | Placebo | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|--------------------------------|
| Events Total      | Events Total | Weight |                                  |
| Dotterud 2010     | 6 138       | 20 140  | 10.1% 0.30 [0.13, 0.73]          |
| Huurre 2008       | 7 72        | 12 68   | 10.2% 0.55 [0.23, 1.32]          |
| Rautava 2002      | 4 27        | 14 30   | 8.6% 0.32 [0.12, 0.85]           |
| Rautava 2012      | 21 73       | 44 62   | 24.2% 0.41 [0.27, 0.60]          |
| Simpson 2015      | 22 81       | 36 82   | 22.6% 0.62 [0.40, 0.95]          |
| Wickens 2018      | 37 207      | 43 200  | 24.3% 0.83 [0.56, 1.23]          |
| **Total (95% CI)**| **598**     | **582** | **100.0% 0.52 [0.38, 0.72]**     |
| Total events      | 97 169      |         |                                 |

Heterogeneity: Tau² = 0.07; Chi² = 9.74, df = 5 (P = 0.08); I² = 49%
Test for overall effect: Z = 3.90 (P < 0.0001)
Figure 6 - prenatal and infant via diet postnatal
Figure 7 - prenatal, mother and infant postnatal via diet

| Study or Subgroup | L rhamnosus | Placebo | Risk Ratio M-H, Random, 95% CI | Total (95% CI) | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|-------------------------------|---------------|-------------------------------|
| Kopp 2008         | Events 14, Total 50 | Events 12, Total 44 | Weight 26.5% | 1.03 [0.53, 1.98] |                     |
| Wickens 2018      | Events 37, Total 203 | Events 43, Total 200 | Weight 73.5% | 0.85 [0.57, 1.26] |                     |
| Total events 51, Total 253 | | Total 244, Weight 100.0% | | 0.89 [0.64, 1.25] |                     |

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)
Figure 8 - single strain L rhamnosus

| Study or Subgroup    | L rhamnosus | Placebo | Weight | Risk Ratio M-H, Random, 95% CI |
|----------------------|-------------|---------|--------|-----------------------------|
| Kalliomäki 2001      | 15          | 31      | 68     | 18.3% 0.51 [0.31, 0.86]      |
| Ou 2012              | 9           | 6       | 62     | 8.9%  1.45 [0.55, 3.84]      |
| Rautava 2002         | 4           | 14      | 30     | 8.8%  0.32 [0.12, 0.85]      |
| Rautava 2012         | 21          | 44      | 62     | 22.0% 0.41 [0.27, 0.60]      |
| Wickens 2008         | 23          | 43      | 159    | 20.0% 0.54 [0.34, 0.85]      |
| Wickens 2018         | 37          | 43      | 200    | 22.0% 0.85 [0.57, 1.26]      |
| Total (95% CI)       | 588         | 581     | 100.0% | 0.58 [0.41, 0.82]            |
| Total events         | 109         | 181     |        |                |

Heterogeneity: Tau² = 0.10; Chi² = 11.96, df = 5 (P = 0.04); I² = 58%
Test for overall effect: Z = 3.13 (P = 0.002)
Figure 9 - L rhamnosus mixed strain

| Study or Subgroup       | Mixed strain Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------------|---------------------|-------|----------------|-------|--------|-------------------------------|
| Dotterud 2010           | 6                   | 138   | 20             | 140   | 14.4%  | 0.30 [0.13, 0.73]              |
| Huurre 2008             | 7                   | 72    | 12             | 68    | 14.7%  | 0.55 [0.23, 1.32]              |
| Kukkonen 2007           | 101                 | 445   | 158            | 446   | 70.8%  | 0.64 [0.52, 0.79]              |
| Total (95% CI)          | 655                 |       | 654            |       | 100.0% | 0.56 [0.39, 0.81]              |
| Total events            | 114                 |       | 190            |       |        |                               |

Heterogeneity: Tau² = 0.04; Chi² = 2.68, df = 2 (P = 0.26); I² = 25%
Test for overall effect: Z = 3.09 (P = 0.002)
| Section/topic | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|---------------|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **TITLE**     |   |                                                                                                                                                                                                            |                   |
| Title         | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                            |                   |
| **ABSTRACT**  |   |                                                                                                                                                                                                            |                   |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 1                 |
| **INTRODUCTION** | |                                                                                                                                                                                                            |                   |
| Rationale     | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                | 2                 |
| Objectives    | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                     | 2                 |
| **METHODS**   |   |                                                                                                                                                                                                            |                   |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | N/A               |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 2-3               |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 3                 |
| Search        | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                | 3                 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                   | 2-3               |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                               | 3                 |
| Data items    | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                           | 3                 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 3                 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                  | 3                 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$, for each meta-analysis.                                                               | 3                 |
| Section/topic                      | #       | Checklist item                                                                                                                                                                                                 | Reported on page # |
|-----------------------------------|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Risk of bias across studies       | 15      | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                               | 3                 |
| Additional analyses               | 16      | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                  | 3                 |
| RESULTS                           |         |                                                                                                                                                                                                               |                   |
| Study selection                   | 17      | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                               | 4                 |
| Study characteristics             | 18      | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                 | Appen B           |
| Risk of bias within studies       | 19      | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                         | Fig 2-3           |
| Results of individual studies     | 20      | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 4-5               |
| Synthesis of results              | 21      | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                | 7-8               |
| Risk of bias across studies       | 22      | Present results of each assessment of risk of bias across studies (see Item 15).                                                                                                                                | 4                 |
| Additional analysis               | 23      | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                             | 9                 |
| DISCUSSION                        |         |                                                                                                                                                                                                               |                   |
| Summary of evidence               | 24      | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                                      | 8                 |
| Limitations                       | 25      | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                                        | 9                 |
| Conclusions                       | 26      | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                           | 9-10              |
| FUNDING                           |         |                                                                                                                                                                                                               |                   |
| Funding                           | 27      | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                                  | N/A               |

*From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).*

Page 2 of 2
Characteristics of studies

Characteristics of included studies

**Dotterud 2010**

| Methods          | RCT computer generated randomization taking place. Trial took place from Sept 2003 to Sept 2005 in Oslo, Norway. |
|------------------|-------------------------------------------------------------------------------------------------------------|
| Participants     | 415 participants N=211 probiotic; 204 control. 70%+ of mothers entered into trial had a history of atopy.    |
| Interventions    | L rhamnosus plus L acidophilus plus B. animalis (probiotic milk) vs. placebo from 36 weeks gestation til 3 months postnatally during breast feeding. Biola (Tine BA, Oslo, Norway), contained Lactobacillus rhamnosus GG (LGG), Bifidobacterium animalis subsp. lactis Bb-12 (Bb-12) and L. acidophilus La-5 (La-5), equalling 5 · 1010 colony-forming units of LGG and Bb-12, and 5 · 109 of La-5 per day for its entire shelf life. |
| Outcomes         | Atopic dermatitis defined as moderate to severe and defined according to the U.K. Working Party's diagnostic criteria for AD. |

Notes

Risk of bias table

| Bias                                      | Authors' judgement | Support for judgement |
|-------------------------------------------|--------------------|-----------------------|
| Random sequence generation (selection bias) | Low risk           | Computer randomized sequence generation |
| Allocation concealment (selection bias)    | Unclear risk       | Unclear as to when mothers started the trial - defined as drinking ‡ 250 mL of study milk on ‡ 50% of the study days. |
| Blinding of participants and personnel (performance bias) | Low risk           | Double blinded - assumes both mothers and clinicians were blinded to treatment arms. |
| Blinding of outcome assessment (detection bias) | Low risk           | Assumes clinicians who assessed patient outcomes were blinded to treatments. |
| Incomplete outcome data (attrition bias)   | High risk          | The dropout rate was 34.6% and 31.4% in the probiotic and placebo groups |
| Selective reporting (reporting bias)       | Low risk           | Reported on all outcomes listed in methods section. |
| Other bias                                 | Low risk           | The funding sources had no role in the study design, data collection, data analysis, interpretation of the study results, or writing of the manuscript. |
**Huurre 2008**

**Methods**
placebo-controlled double-blind study with nutrition modulation by dietary counselling and probiotic supplementation were studied. Study took place in Turku, Finland. Unclear as to the dates of the trial

**Participants**
171 mothers initially randomized; obtained outcomes in 140. 77%+ of mothers had a history of atopy.

**Interventions**
L rhamnosus plus bifidobacterium lactic vs. placebo supplementation during pregnancy plus breast feeding - exclusive breast feeding probiotic 4.0 (2.5-4.5) months; placebo 4.0 (2.5-5.0) months; from the first trimester of pregnancy to the end of exclusive breastfeeding.

**Outcomes**
Atopic dermatitis (not defined) at 12 months.

**Notes**

**Risk of bias table**

| Bias                                      | Authors’ judgement | Support for judgement                                                                 |
|-------------------------------------------|--------------------|---------------------------------------------------------------------------------------|
| Random sequence generation (selection bias) | Low risk           | placebo-controlled double-blind study                                                 |
| Allocation concealment (selection bias)    | Unclear risk       | Unclear as to when the study started and when patients were enrolled                  |
| Blinding of participants and personnel (performance bias) | Low risk           | Assumes mothers and clinicians were blinded to trial                                 |
| Blinding of outcome assessment (detection bias) | Low risk           | The infants were clinically examined in blinded fashion by the study nurse at 1 month of age and by the physician at 6 and 12 months of age. |
| Incomplete outcome data (attrition bias)   | High risk          | Of 171 entered 140 completed the study equal to 18.2% attrition                      |
| Selective reporting (reporting bias)       | Low risk           | All outcomes identified in methods section were reported on in results section.       |
| Other bias                                | Low risk           | Appears no conflict of interest in funding or administration of study.                 |

**Kalliomäki 2001**
Methods

Placebo controlled double blind RCT, taking place in Turku, Finland between February, 1997, and January, 1998.

Participants

159 mothers who had a family history of atopic disease were randomly assigned by computer to receive two capsules of placebo (microcrystalline cellulose) or 11010 colony-forming units of Lactobacillus GG (Valio Ltd; Helsinki, Finland) daily for 2–4 weeks before expected delivery. After delivery, breastfeeding mothers could take the capsules, otherwise children received the agents. 70%+ of mothers had a history of atopy.

Interventions

L. rhamnosus vs. placebo capsules - 2-4 weeks prior to delivery then for 6 months for breast feeding and for 6 months infants who were not breastfeeding. 159 mothers were randomly assigned by computer to receive two capsules of placebo (microcrystalline cellulose) or 11010 colony-forming units of Lactobacillus GG (Valio Ltd; Helsinki, Finland) daily for 2–4 weeks before expected delivery. After delivery, breastfeeding mothers could take the capsules, otherwise children received the agents; in the latter case, capsule contents were mixed with water then given by spoon.

Outcomes

Atopic eczema defined as pruritis, facial or extensor involvement and chronic relapsing.

Notes

Kalliomäki 2001 includes follow on studies Kallomäki 2003 (4 year follow-up) and Kallomäki 2007 (7 year follow-up)

Risk of bias table

| Bias                                      | Authors' judgement | Support for judgement |
|-------------------------------------------|--------------------|-----------------------|
| Random sequence generation (selection bias) | Low risk           | Placebo controlled double blind RCT |
| Allocation concealment (selection bias)   | Unclear risk       | Unclear as to when mothers were allocated to treatment arms and when trial began. |
| Blinding of participants and personnel (performance bias) | Low risk           | Mothers blinded and the physician (MK) who did the physical examinations, diagnoses of atopic disease, and antiasthma treatments was unaware of the contents of the capsules until March, 2000, when all data had been obtained and analysed. |
| Blinding of outcome assessment (detection bias) | Low risk           | The physician (MK) who did the physical examinations, diagnoses of atopic disease, and antiasthma treatments was unaware of the contents of the capsules until March, 2000, when all data had been obtained and analysed. |
| Incomplete outcome data (attrition bias)  | High risk          | 159 entered trial and 132 completed it. 17% attrition rate |
L. rhamnosus for eczema or dermatitis

Selective reporting (reporting bias) | Low risk | All outcomes identified in methods section were reported on in the results section.

Other bias | Low risk | Grant support was from the Finnish Foundation for Paediatric Research, the National Technology Agency of Finland, and the Allergy Research Foundation in southwest Finland.

Kopp 2008

**Methods**
A double-blind, placebo-controlled prospective trial, University of Freiberg, Germany. The recruitment of pregnant women started on July 1, 2002, and ended on June 30, 2006. The last follow-up visits at the age of 2 years were performed during September 2006.

**Participants**
105 pregnant women from families with 1 member (mother, father, or child) with atopic disease were randomly assigned to receive either the probiotic Lactobacillus GG (American Type Culture Collection 53103; 5109 colony-forming units of Lactobacillus GG twice daily) or placebo. Ninety-four families (89.5%) completed the trial. The supplementation period started 4 to 6 weeks before expected delivery, followed by a postnatal period of 6 months (3 months breastfeeding and 3 months to neonates).

**Interventions**
Lactobacillus Rhamnosus (Lactobacillus GG) vs. placebo supplement - pregnancy through first 3 months breast feeding and the following 3 months to neonates.

**Outcomes**
Atopic dermatitis at 2 years - defined as pruritis, facial or extensor involvement.

**Notes**

Risk of bias table

| Bias                                      | Authors' judgement | Support for judgement                                                                                                                                 |
|-------------------------------------------|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Random sequence generation (selection bias) | Low risk           | double-blind, placebo-controlled prospective trial. Randomization was performed in blocks of 4 according to a computerized randomization list.          |
| Allocation concealment (selection bias)    | Unclear risk       | Unclear as to when mothers were randomized and when they started trial.                                                                                |
| Blinding of participants and personnel (performance bias) | Low risk           | Patients and clinicians assessing patients were blinded to the treatment arms.                                                                           |
| Blinding of outcome assessment (detection bias) | Low risk           | The physicians (Drs Kopp and Hennemuth) who conducted the physical examinations and diagnoses of atopic disease were unaware of the contents of the capsules until the end of the study in September 2006. |
| Incomplete outcome data (attrition bias)   | Low risk           | 105 pregnant women of which 94 were assessed. 10.4% attrition rate                                                                                  |
L rhamnosus for eczema or dermatitis 01-Feb-2022

Selecting reporting (reporting bias)  | Low risk  | All outcomes identified in the methods section were evaluated in the results section.
Other bias  | Low risk  | No involvement by clinicians who worked with company or; financial support provided by company who supplied treatments.

Kukkonen 2007

**Methods**
RCT taking place in Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland from November 2000 to March 2003.

**Participants**
Mothers at 36 weeks gestation and in infants up to 6 months of age. Family history of allergies.

**Interventions**
From gestational week 36, the mothers twice daily received one capsule containing a mixture of probiotics: LGG (ATCC 53103; 59109 colony-forming units [cfu]), L. rhamnosus LC705 (DSM 7061; 59109 cfu), Bifidobacterium breve Bb99 (DSM 13692; 29108 cfu) and Propionibacterium freudenreichii ssp. shermanii JS (DSM 7076; 29109 cfu), or placebo. Their infants were given the same capsules opened and mixed with 20 drops of syrup containing 0.8 g of galacto-oligosaccharides (prebiotics) once daily from birth, continuing to 6 months after birth.

**Outcomes**
Eczema and atopic eczema as diagnosed by parents (2 years); at 5 years of life (Table 2, page 338 for 5 years; Kuitenen 2009). Eczema was diagnosed according to the Williams UK Working Party's criteria, which meant an itchy skin plus 3 or more of the following: family history of atopic disease, dry skin during the previous 12 months, history of eczema, or visible eczema at typical sites. Physicians at 10 years of age (Peldan 2017).

**Notes**
Kuitenen 2009 (5 year follow-up to Kukkonen 2007); Peldan 2017 (11 year follow-up to Kukkonen 2007)

Risk of bias table

| Bias                                      | Authors' judgement | Support for judgement |
|-------------------------------------------|--------------------|-----------------------|
| Random sequence generation (selection bias) | Low risk           | RCT using computer generated block randomization |
| Allocation concealment (selection bias)    | Unclear risk       | Unclear as to when participants were randomized and when trial began. |
| Blinding of participants and personnel (performance bias) | Low risk | Participants and clinicians were blinded to treatment arms |
| Blinding of outcome assessment (detection bias) | Low risk | investigators were blinded |
Incomplete outcome data (attrition bias) | High risk | Intent to treat analysis comprised 925 out of 1,223 randomized mothers.

Selective reporting (reporting bias) | Low risk | Outcomes identified in methods section were reported on in results section.

Other bias | Low risk | No conflicts of interest were noted.

Ou 2012

Methods
Double-blinded, placebo-controlled study, taking place in Changhua, Taiwan from Kaohsiung Chang Gung Memorial Hospital between August 2002 and January 2006.

Participants
double-blind, placebo-controlled clinical trial, pregnant women with atopic diseases determined by history, total immunoglobulin (Ig)E > 100 kU/L, and/or positive specific IgE were assigned to receive either probiotics (Lactobacillus GG; ATCC 53103; 1 9 10^10 colony-forming units daily) or placebo from the second trimester of pregnancy (starting at 24 weeks). After delivery, LGG was administered exclusively to breastfeeding mothers or to non-breast feeding neonates where it was mixed with water and given by spoon for 6 months. Both of clinical evaluation performed by questionnaires concerning any allergic symptoms and plasma total IgE, and allergen-specific IgE were obtained in high risk parents and children at 0, 6, 18, and 36 months of age. 55%+ of mothers had a history of allergic disease.

Interventions
L Rhamnosus vs. placebo supplement - provided at 24 months gestation and to breastfeeding mothers or to non-breastfeeding neonates mixed with water til 6 months.

Outcomes
Eczema ever at 18 months. Eczema severity from birth to 36 months was assessed based on the total scores of the rash areas, severity of rash elements (erythema, oedema/papule, exudates/crust, and lichenification), and duration of flaring. The severity were defined as mild (score 0–3), moderate (score 4–6), and severe (score 7–9). Children were assessed clinically by well trained paediatricians during the neonatal period and on study visits to the outpatient clinics of Paediatrics at ages 6, 18, and 36 months.

Notes
Note: Incidence of eczema in the Ou 2012 study was confined for moderate to severe cases only - 14.3% in L rhamnosus (N=64); and 10.3% in placebo (N=62).

Risk of bias table

| Bias | Authors’ judgement | Support for judgement |
|------|-------------------|----------------------|
| Random sequence generation (selection bias) | Low risk | prospective, double-blind, randomized, placebo controlled, per-protocol trial |
**Allocation concealment (selection bias)**  | **Unclear risk**  | Unclear as to whether allocation occurred immediately after randomization.

**Blinding of participants and personnel (performance bias)**  | **Low risk**  | prospective, double-blind, randomized, placebo controlled, per-protocol trial. Assumes patient and clinician were blinded.

**Blinding of outcome assessment (detection bias)**  | **Unclear risk**  | Unclear if clinician assessing outcomes was blinded.

**Incomplete outcome data (attrition bias)**  | **High risk**  | 191 randomized and 126 enrolled in the results section. 34% attrition.

**Selective reporting (reporting bias)**  | **Low risk**  | Outcomes identified in methods section were reported on in results section.

**Other bias**  | **Low risk**  | No mention of manufacturer involvement.

---

**Rautava 2002**

**Methods**

Double blind placebo controlled trial taking place in Turku, Finland.

**Participants**

In all, 159 pregnant women from atopic families were randomized to receive either Lactobacillus rhamnosus strain GG (ATCC 53103; daily dose, $2 \times 10^{10}$ colony forming units; Valio Ltd, Helsinki, Finland), or placebo (microcrystalline cellulose; Valio Ltd) during the 4 weeks before giving birth (mean, 28 days; 95% CI, 24-31) and during breast-feeding. Criteria for inclusion in this part of the study, which 62 mothers and infants fulfilled, were breast-feeding and the maternal use of probiotics or placebo until the child was 3 months of age. 60%+ of mothers had a history of atopic disease.

**Interventions**

L Rhamnosus plus B longum vs. placebo dietary food supplement - 4 weeks prior to delivery and during breast feeding til 3 months of infant age.

**Outcomes**

Atopic eczema defined as pruritis, typical morphology and distribution and a chronic relapsing course. The chronicity criterion for atopic eczema was fulfilled if the infant had 3 or more episodes of eczema (each with a duration of at least 1 month) during the first two years of life. Eczema was considered transient if there were 1 or 2 such episodes.

**Notes**

---

**Risk of bias table**

| Bias                                | Authors’ judgement | Support for judgement                  |
|-------------------------------------|--------------------|----------------------------------------|
| Random sequence generation (selection bias) | Low risk           | double-blinded, placebo controlled trial taking place in Turku Finland. Unclear as to dates study took place. |
| Bias                                      | Authors’ judgement | Support for judgement |
|-------------------------------------------|--------------------|-----------------------|
| Allocation concealment (selection bias)   | Unclear risk       | Unclear as to when patients were enrolled and when study began. |
| Blinding of participants and personnel (performance bias) | Low risk | Double blinding - assumes patient and clinician |
| Blinding of outcome assessment (detection bias) | Low risk | Assumes clinician was blinded |
| Incomplete outcome data (attrition bias)   | High risk          | 157 mothers entered into the trial. 57 completed the assessment - 64% attrition. |
| Selective reporting (reporting bias)       | Low risk           | Outcomes identified in methods section were reported on in the results section. |
| Other bias                                | Low risk           | No mention of manufacturer or clinician biases |

**Rautava 2012**

**Methods**  
Randomized double blind clinical trial taking place in Turku Finland from place between August 2005 and April 2009.

**Participants**  
241 infant mother pairs enrolled. Mothers with allergic disease and atopic sensitization were randomly assigned to receive (1) Lactobacillus rhamnosus LPR and Bifidobacterium longum BL999 (LPR1BL999), (2) L paracasei ST11 and B longum BL999 (ST111BL999), or (3) placebo, beginning 2 months before delivery and during the first 2 months of breast-feeding. The infants were followed until the age of 24 months. Inclusion criteria included women with a history of or active allergic disease.

**Interventions**  
L Rhamnosus plus B longum vs. placebo dietary food supplement - provided 2 months prior to delivery and for 2 months during breast feeding.

**Outcomes**  
Eczema at 24 months defined as pruritis, typical morphology and distribution and a chronic relapsing course.

**Risk of bias table**

| Bias                                      | Authors’ judgement | Support for judgement                                      |
|-------------------------------------------|--------------------|-----------------------------------------------------------|
| Random sequence generation (selection bias) | Low risk           | double-blind placebo-controlled trial                      |
| Allocation concealment (selection bias)   | Unclear risk       | Unclear as to when allocation occurred and when trial started. |
| Blinding of participants and personnel (performance bias) | Low risk | Double blind trial - assumes patient and clinician |
Simpson 2015

Methods
Double blind placebo controlled trial taking place in Trondheim, Norway, between September 2003 and September 2005, and the initial 6 year follow up occurred from December 2009 to December 2011.

Participants
415 women living in Trondheim, Norway, were randomised to receive daily probiotic supplementation or placebo from 36 weeks gestation until 3 months postpartum. At least 73% of family members (mother, father) had a history of atopy.

Interventions
Probiotic milk (L rhamnosus plus L acidophilus plus B animalis) vs. placebo - 36 weeks gestation until 3 months postpartum during breast feeding; children did not receive any probiotic supplementation.

Outcomes
Atopic dermatitis diagnosed as per the UKWP diagnostic criteria.

Notes

Risk of bias table

| Bias                                      | Authors' judgement | Support for judgement                                                                 |
|-------------------------------------------|--------------------|---------------------------------------------------------------------------------------|
| Random sequence generation (selection bias) | Low risk           | Double blind placebo controlled trial. Computer randomized random sequence generation. |
| Allocation concealment (selection bias)   | Unclear risk       | Unclear as to when allocation occurred and when trial started.                         |
| Blinding of participants and personnel (performance bias) | Low risk           | Double blind - assumes patient and clinician blinded.                                  |
L rhamnosus for eczema or dermatitis

| Bias                                      | Authors' judgement | Support for judgement |
|-------------------------------------------|--------------------|-----------------------|
| Blinding of outcome assessment            | Low risk           | Assumes clinician blinded. |
| (detection bias)                          |                    |                       |
| Incomplete outcome data (attrition bias)  | High risk          | 415 mothers enrolled; 163 assessed; 61% attrition. |
| Selective reporting (reporting bias)      | Low risk           | Outcomes identified in methods section were reported on in results section. |
| Other bias                                | High risk          | Authors T.Ø., O.S., C.K.D and M.R.S. participated in seminars sponsored by Tine BA. All other authors declare that they have no conflict of interest. |

**Wickens 2008**

| Methods                                      | Randomized placebo controlled double blind trial taking place in Wellington and Auckland, New Zealand, Participants were recruited from January 2004 to May 2005. |
|----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Participants                                 | 512 women; Pregnant women in Auckland and Wellington, New Zealand, were recruited to the study through maternity care providers, antenatal classes, and advertisements. They were invited to take part in the study if they or the infant’s father had a history of treated asthma, eczema, or hay fever. |
| Interventions                                | L Rhamnosus vs. placebo food supplement - 35 weeks gestation until 6 months breastfeeding; infants til 2 years of age |
| Outcomes                                     | Eczema severity assessed using the SCORAD system defined dichotomously as a score of $\geq 10$. |
| Notes                                        | Wickens 2008 had follow on studies: Wickens 2012 (4 year follow-up); Wickens 2013 (6 year follow-up) and Wickens 2018 (11 year follow-up) |

**Risk of bias table**

| Bias                                      | Authors' judgement | Support for judgement |
|-------------------------------------------|--------------------|-----------------------|
| Random sequence generation (selection bias) | Low risk           | Randomization was stratified by study center and performed in bin blocks of 15 according to a computer-generated randomization list |
| Allocation concealment (selection bias)   | Unclear risk       | Unclear as to when randomization occurred and when patients entered the trial. |
| Blinding of participants and personnel (performance bias) | Low risk           | Double blind - assumes patient and clinician blinded. |
| Blinding of outcome assessment (detection bias) | Low risk           | Assumes clinician assessing patient was blinded. |
Incomplete outcome data (attrition bias) | High risk | 512 enrolled; 446 completed study. 13% attrition rate.
Selective reporting (reporting bias) | Low risk | Outcomes identified in methods section were evaluated in results section.
Other bias | Low risk | No support from companies or from investigators obtaining monies from companies

**Wickens 2018**

**Methods**
RCT; 2 center trial between November 2012 and December 2014 in Auckland and Wellington, New Zealand

**Participants**
Pregnant females who were 14-16 weeks gestation and then breastfeeding. They were invited to take part in the study if they or the infant’s father had a history of treated asthma, eczema, or hay fever.

**Interventions**
Maternal-only Lactobacillus rhamnosus HN001 supplementation on infant allergic disease prevalence commencing in the first trimester of pregnancy through to 6 months post-partum while breastfeeding vs. placebo.

**Outcomes**
Eczema severity assessed using the SCORAD system defined dichotomously as a score of ≥ 10.

**Risk of bias table**

| Bias                                      | Authors’ judgement | Support for judgement |
|-------------------------------------------|--------------------|-----------------------|
| Random sequence generation (selection bias) | Low risk           | Randomization was stratified by study centre and performed in blocks of random length according to a computer-generated randomized list. At enrolment, research staff provided eligible women with the next available sequentially numbered capsule bottle. |
| Allocation concealment (selection bias)   | Low risk           | At enrolment, research staff provided eligible women with the next available sequentially numbered capsule bottle. |
| Blinding of participants and personnel (performance bias) | Low risk           | Both participants and research staff were blind to treatment group. |
| Blinding of outcome assessment (detection bias) | Low risk           | Assumes clinician/researchers assessing patient were blinded to treatment. |
| Incomplete outcome data (attrition bias)   | Low risk           | Of the 413 that were entered into the trial, 403 completed, 97.5% |
| Selective reporting (reporting bias)       | Low risk           | All methods identified in methods section were reported on in the results section. |
Other bias | Low risk | The authors declare they have no conflict of interest

Footnotes