

# Probiotics for treating eczema (Review)

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[Intervention review]

# Probiotics for treating eczema

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## ABSTRACT

### Background

Probiotics have been proposed as an effective treatment for eczema, and recently a number of clinical trials have been undertaken.

### Objectives

To assess the effects of probiotics for the treatment of eczema

### Search strategy

We searched the Cochrane Skin Group Specialised Register (to April 2008), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 2,2008) MEDLINE (from 2003 to April 2008), EMBASE (from 2005 to April 2008), PsycINFO, AMED and LILACS (from inception to April 2008) and ISI Web of Science (to December 2006) and reference lists of articles. We also searched registries of ongoing clinical trials, conference proceedings and searched for adverse events.

### Selection criteria

Randomised controlled trials of live orally ingested microorganisms for the treatment of eczema.

### Data collection and analysis

Two authors independently applied eligibility criteria, assessed the quality of trials and extracted data. We contacted study authors for more information where necessary. We recorded adverse events from the included studies, and from the separate adverse events search.

### Main results

Twelve randomised controlled trials involving 781 participants met the inclusion criteria. All trial participants were children. There was no significant difference in participant or parent-rated symptom scores in favour of probiotic treatment (5 trials, 313 participants). Symptom severity on a scale from 0 to 20 was 0.90 points lower after probiotic treatment than after placebo (95%CI -1.04, 2.84;  $p = 0.36$ ). There was also no significant difference in participant or parent-rated overall eczema severity in favour of probiotic treatment (3 trials, 150 participants). There was no significant difference in investigator rated eczema severity between probiotic and placebo treatments (7 trials, 588 participants). On a scale from 0 to 102 investigator rated eczema severity was 2.46 points lower after probiotic treatment than after placebo treatment (95%CI -2.53, 7.45  $p = 0.33$ ). Significant heterogeneity was noted between the results of

individual studies, which may be explained by the use of different probiotic strains. Subgroup analysis by age of participant, severity of eczema, presence of atopy or presence of food allergy did not identify a population with different treatment outcomes to the population as a whole. The adverse events search identified some case reports of infections and bowel ischaemia caused by probiotics.

### **Authors' conclusions**

The evidence suggests that probiotics are not an effective treatment for eczema, and probiotic treatment carries a small risk of adverse events.

## PLAIN LANGUAGE SUMMARY

### Probiotics for treating eczema

There is not enough evidence to recommend using probiotics for the treatment of eczema.

Eczema is a skin condition characterised by an itchy red rash, which affects between 5 and 20% of people at some time in their life. People with eczema have different bacteria in their gut to people without eczema, and sometimes they have inflammation in their gut. It may be possible to treat eczema symptoms by changing the mix of gut bacteria or by reducing inflammation in the gut. One type of treatment that might achieve this is probiotics - these are live micro-organisms taken by mouth such as the *Lactobacillus* bacteria found in unpasteurised milk and yoghurt. This review of twelve trials found that probiotics do not reduce eczema symptoms such as itching, nor do they change the overall severity of eczema judged by patients or their doctors. The results varied between different trials but overall do not suggest that probiotics are an effective treatment for eczema. Further studies of new probiotics are needed, because it is possible that different types of probiotics which haven't yet been studied in eczema treatment could be more effective. Probiotics can rarely cause infections and gut problems.

## BACKGROUND

### Description of the condition

#### Disease definition

Eczema is a non-infective chronic inflammatory skin disease characterised by an itchy red rash. The terms 'eczema' and 'dermatitis' have been used synonymously, and eczema is associated with atopy. 'Atopy' is defined as a genetic predisposition to become sensitised and produce IgE antibodies in response to ordinary exposures to allergens (Johansson 2004). Despite the association between eczema and atopy, up to 40% of children with eczema do not have atopy when defined according to allergy tests such as skin prick tests (Bohme 2001; Flohr 2004). A revised nomenclature for allergy (Johansson 2001) has been updated by the World Allergy Organisation (Johansson 2004). The new nomenclature is based on the mechanisms that initiate and mediate allergic reactions. The term 'eczema' is proposed to replace the previous term 'atopic eczema/dermatitis syndrome'. What was termed Atopic Eczema Dermatitis Syndrome in 2001 is now thought to be not one single disease but rather an aggregation of several diseases with certain characteristics in common. The term 'atopy' cannot be used until an IgE sensitisation has been confirmed by IgE antibodies in the blood or by a positive Skin Prick Test (SPT) to common environmental or dietary allergens such as pollen, house dust mite, cow's milk or egg. If this is done then the term 'eczema' can be split into 'atopic eczema' and 'non-atopic eczema'.

For the purpose of this review the term 'eczema' will be used and will include eczema where IgE sensitisation has been confirmed, eczema where IgE sensitisation is absent, and eczema where IgE sensitisation has not been assessed.

#### Epidemiology and causes

Eczema is the most common inflammatory skin disease of childhood, affecting 5 to 20% of children at any one time (Williams

1999; Hoare 2000). The cumulative prevalence of eczema varies from 20% in Northern Europe and the USA to 5% in the south-eastern Mediterranean (Thestrup 2002). Only 2% of children under the age of 5 years have severe disease, and 84% have mild disease as judged by a specialist dermatology assessment (Emerson 1998). Around 2% of adults have eczema and many of these have a more chronic and severe form (Charman 2002). Eczema is often associated with other atopic diseases (Beck 2000) such as asthma, allergic rhinitis, or food allergies and sufferers often have a family history of allergic disease. There is wide variation in the prevalence of eczema between different countries, and some studies suggest that the prevalence is increasing in developed countries (Williams 1999; Robertson 2004). The cause of eczema is not well understood and is probably a combination of genetic and environmental factors (Cookson 2002). In recent years, research has pointed to the possible role of environmental agents such as house dust mite (Van Bever 2002), pollution (Polosa 2001), and microbes (Bjorksten 2001).

#### Clinical features

Eczema may be acute (short-term and severe) with predominantly redness, vesicles and oozing, or it may be chronic (long-term) with scaling, skin thickening, altered pigmentation and exaggerated surface markings. The condition affects mainly the creases of the elbows and knees, and the face and neck, although it can affect any part of the body. The severity of eczema is variable, ranging from localised mild scaling to generalised involvement of the whole body, with redness, oozing and secondary infection. Itching is the predominant symptom which can induce a vicious cycle of scratching, leading to skin damage which in turn leads to more itching - the so called "itch scratch itch" cycle. There is a tendency to a dry sensitive skin, even in those who have 'grown out' of the disease. This is thought to be due to a defect in the lipid barrier of the epidermis (Proksch 2003). In adulthood, the skin (especially of the hands) may be prone to inflammation in the presence of

environmental irritants such as soaps (Archer 2000).

### Natural history

Eczema usually starts within the first 6 months of life, and by 1 year, 60% of those likely to develop it will have done so. Remission occurs by the age of 15 years in 60 to 70% of cases, although some relapse later. In the more severely affected child, development and puberty may be delayed (Baum 2002).

### Impact

Eczema varies in severity, often from one hour to the next. Severity can be measured in a number of ways. A systematic review of named outcome scales for eczema found that of the 13 named scales in use at that time, only one (Severity Scoring of Atopic Dermatitis, SCORAD) had been fully tested for validity, repeatability and responsiveness (Charman 2000).

The itching and scratching can adversely affect quality of life through chronic sleep disturbance and this may have an impact on family life. In children, the social and emotional impact on the family can be greater than that of type I diabetes (Su 1997). The disease can be associated with complications such as bacterial and viral infections (McHenry 1995). The unsightly appearance of the skin and the need to apply greasy ointments can limit a child's inclination to participate in social and sporting activities and thus affect their confidence. Adults with eczema often have low self-esteem and relationships can be difficult to initiate and sustain. Everyday tasks such as housework, gardening, childcare and food preparation present problems when the skin on the hands is cracked. Promotion at work may be blocked for people who do not 'look good'.

Eczema also has considerable costs to the community as a whole. For example the cost of childhood eczema to the Australian community was estimated at AU\$316.7 million (US\$239.3 million; Euro195.9 million) per year in 1999 (Kemp 1999). The health-care costs of eczema in adults are comparable to those of epilepsy, emphysema and other chronic diseases (Ellis 2002). Direct costs to the family are encountered when purchasing treatments, special clothing and bedding and incurring extra laundry expenses; indirect costs are experienced from lost working days when parents are looking after an unwell child. The wider economic implications lie in the costs of health professionals, the lost opportunities of parents of sick children who do not have the option of seeking employment and the child who, as a result of missing schooling, faces employment limitations.

### Description of the intervention

There is currently no cure for eczema, however, a wide range of treatments are employed which aim to control the symptoms (Fennessy 2000; Hoare 2000; Lamb 2002). Health professionals assist people in the management of their disease using a variety of

treatment methods; these include emollients, topical steroids, topical tars, topical tacrolimus and pimecrolimus. Other treatments such as wet wrap dressings, phototherapy, the avoidance of triggers such as food allergens and complementary therapies (Ernst 2000) are also used. Many of the treatments are of unknown effectiveness (Hoare 2000). Emollients and topical corticosteroids are universally recommended (Smethurst 2002). Treatment regimens can be time consuming and expensive for those affected and their families, and there is a need for new treatments which are effective, cheap and simple to administer.

### How the intervention might work

#### Rationale for using probiotics to treat eczema

The intestinal microflora (or intestinal microbiota) is the large collection of micro-organisms which live in the human intestine and confer intestinal, immune and nutritional benefits on the host. The composition of the intestinal microflora has been found to be different in those with eczema, and such differences may precede the development of active eczema. The most consistent finding in such studies is a reduced proportion of *Bifidobacteria* species in the faeces of infants with eczema (Bjorksten 2001; Kalliomaki 2001; Murray 2005). This has led to the hypothesis that an aberrant intestinal microbiota may cause or worsen eczema.

Gastrointestinal disorders such as eosinophilic enteropathies and food allergies are also more common in children with eczema, and in some cases can exacerbate the disease (Werfel 2004). Probiotics are a treatment that may alter the intestinal microbiota of people with eczema. Probiotics are live micro-organisms (for example *Lactobacillus* species) which when administered in adequate amounts confer a health benefit on the host (FAO/WHO 2002). They are effective treatments for some gastrointestinal disorders characterised by a disturbed intestinal microbiota such as infectious diarrhoea (Gionchetti 2000; Allen 2003). Their precise mode of action is not well established, but they have been shown to reduce markers of intestinal inflammation and intestinal permeability in disease states, and this might change the way in which antigens present in the intestine are recognised by the immune system (Pessi 2000; Rosenfeldt 2004). Some probiotics have also been shown to alter the overall composition of the intestinal microbiota (Sepp 1993; Spanhaak 1998). Probiotics are not the same as prebiotics, which are non-digestible sugars found in some foods that encourage the growth of certain types of bacteria in the intestine.

Probiotics are widely consumed worldwide in the form of fermented milk, and are potentially a cheap and accessible treatment for eczema. Probiotics may be particularly effective in young children, as the composition of the intestinal microbiota is unstable during the first two years of life and might therefore be more amenable to modulation (Yoshioka 1983). Although all probiotics have certain properties in common (low pathogenicity, resistance to gastric acid and bile salt digestion, and adherence to the intesti-

nal mucosa), the clinical and laboratory effects of probiotics can vary markedly between species (Christensen 2002; Allen 2003).

## Why it is important to do this review

Probiotics have recently been marketed in infant formula, and are recommended by some practitioners for the treatment of eczema. They are increasingly used by consumers for the treatment and prevention of a range of disorders, and have now been formally investigated in a number of clinical trials for the treatment of eczema. Their role in treating eczema is nevertheless controversial (Williams 2005). Moreover recent reports suggest that probiotics can occasionally cause serious adverse effects (Hennequin 2000; De Groote 2005; Land 2005; Besselink 2008). It is therefore important to formally assess the evidence for the efficacy of probiotics in treating eczema.

The rationale for this review is therefore:

- 1) eczema is a common disease with a negative impact on the individual, their family and their community;
- 2) new treatments are needed for eczema;
- 3) probiotics are increasingly being used for the treatment of eczema;
- 4) cases of probiotic sepsis have been reported;
- 5) no formal meta-analysis of probiotics for the treatment of eczema has yet been published.

## OBJECTIVES

To assess the effects of probiotics in treating eczema.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials of probiotics for the treatment of eczema.

#### Types of participants

Participants of any age with eczema diagnosed by a doctor. Participants with other specific forms of eczema such as contact eczema were not included in the study.

The National Health Service Technology Assessment systematic review of treatments for eczema (Hoare 2000) used specific terms to identify trial participants. A modified classification of these terms was used as listed in Table 1. The list classifies conditions as eczema and as specific forms of eczema not included in this review. One of the authors (RB) scrutinized those studies which used the terms in the 'possible atopic eczema' category (such as 'childhood eczema') and only included the study if the description of the participants indicated the absence of such specific forms as 'allergic contact eczema'.

Table 1. Terms used to categorise trial participants with eczema

| Forms of eczema included         | Forms of eczema excluded       |
|----------------------------------|--------------------------------|
| Atopic eczema                    | Seborrheic eczema              |
| Atopic dermatitis                | Contact eczema                 |
| Besnier's prurigo                | Allergic contact eczema        |
| Neurodermatitis atopica (German) | Irritant contact eczema        |
| Flexural eczema/ dermatitis      | Discoid/ nummular eczema       |
| Periorbital eczema               | Asteatotic eczema              |
| Childhood eczema                 | Varicose/ stasis eczema        |
| Infantile eczema                 | Photo-/ light-sensitive eczema |

**Table 1. Terms used to categorise trial participants with eczema**

|                          |                                 |
|--------------------------|---------------------------------|
| <i>(Continued)</i>       |                                 |
| 'Eczema' unspecified     | Chronic actinic dermatitis      |
| Constitutional eczema    | Dyshydrotic eczema              |
| Endogenous eczema        | Pompholyx eczema                |
| Chronic eczema           | Hand eczema                     |
| Neurodermatitis          | Frictional lichenoid dermatitis |
| Neurodermatitis (German) | Lichen simplex                  |
|                          | Occupational dermatitis         |
|                          | Prurigo                         |

**Types of interventions**

Ingested live micro-organisms, including bacteria, fungi or yeasts, ingested singly or in combination.

Comparators could be no treatment, placebo or other active intervention. Studies using another microorganism or microbial product as the sole comparator were excluded. Studies that included an adjunct to the active treatment (such as antibiotics, other dietary management eg allergen avoidance or prebiotic supplementation, and standard eczema treatments such as topical corticosteroids) were not excluded from the review.

**Types of outcome measures****Primary outcomes**

- (1) Short-term changes in participant-rated, parent-rated or principal carer-rated symptoms of eczema
- (2) Short-term changes in quality of life

**Secondary outcomes**

- (1) Long-term changes during the six month period after the active treatment has ceased in participant-rated, parent-rated or principal carer-rated symptoms of eczema
- (2) Long-term changes in quality of life
- (3) Short-term and long-term changes in the need for other eczema treatment
- (4) Investigator-rated eczema severity
  - (i) Short-term changes in global eczema severity as measured by a trained investigator or a medical practitioner
  - (ii) Long-term changes in global eczema severity or change in the number of eczema flares as measured by participants, parents, principal carers or a medical practitioner

- (5) Changes in the number of days lost from school or work due to eczema symptoms during active treatment
- (6) Adverse events during the treatment period

For the above outcome measures:

- short-term outcomes refer to the period during active treatment;
- long-term outcomes refer to the six month period after the active treatment has ceased;
- where available we used changes in participant-rated, parent-rated or principal carer-rated global eczema severity in preference to assessments of specific eczema symptoms;
- quality of life changes as measured by participants, their parent or their principal carer from a published scale were assessed (eg [Finlay 1996](#); [Chren 1997](#));
- in addition to assessment of global symptom/disease severity, when available we assessed changes in a composite rating scale using a published named scale (e.g. SCORAD [Kunz 1997](#)). Where this was not available we attempted to assess the trial author's modification of such a scale, or their own composite rating scale.

**Search methods for identification of studies****Electronic searches**

We searched the Cochrane Skin Group Specialised Register (to April 2008) using the following search terms:- ((atopic and (dermatitis or eczema)) or neurodermatitis or (eczema and (child\* or infant\*)) or (besnier\* and prurigo)) AND (probiotic\* or lactobacill\* or bifidobacter\* or lactococc\* or saccharomyc\* or (streptococcus and thermophilus) or (bacillus flora and subtilis) or (enterococcus and faec\*) or (intestin\* and (microflora or microbiotica)))

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (issue 2,2008) using the strategy in [Appendix 1](#).

We searched MEDLINE (OVID) (from 2003 to April 2008) using the strategy in [Appendix 2](#) and we searched EMBASE (from 2005 to April 2008) using the strategy in [Appendix 3](#). The UK Cochrane Centre has an ongoing project to systematically search MEDLINE and EMBASE for reports of trials which are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE to 2003 and in EMBASE to 2005. Further searching has been undertaken for this review by the Cochrane Skin Group to cover the years that have not been searched by the UKCC.

We searched PsycINFO (from inception to April 2008) using the EMBASE search strategy and AMED (Allied and Complementary Medicine) (from inception to April 2008) using the MEDLINE search strategy as they translated well into the respective databases. We searched LILACS (Latin American and Caribbean Health Science Information database) (from inception to April 2008) using the strategy in [Appendix 5](#).

ISI Web of Science (which contains the Science Citation Index) was searched (to 4th December 2006) using the following search terms: topic=(atopic and probiotic\* and (clinical and trial\*))

### Ongoing Trials

We searched the metaRegister of Controlled Trials on [www.controlled-trials.com](http://www.controlled-trials.com), [www.clinicaltrials.gov](http://www.clinicaltrials.gov), and the Ongoing Skin Trials Register on [www.nottingham.ac.uk/ongoingskintrials](http://www.nottingham.ac.uk/ongoingskintrials) for ongoing trials on 2<sup>nd</sup> May 2008, using the terms 'eczema', 'probiotic' and 'probiotics'.

### Searching other resources

### References lists

We checked the bibliographies of published studies and reviews for possible references to RCTs.

### Unpublished literature

We contacted named investigators for further information regarding the nature and status of identified studies.

### Language

We did not impose any language restrictions, however it was not necessary to seek translations during this review.

### Adverse Events

We searched MEDLINE for adverse effects of probiotics (from 1966 to 11th July 2006), using the strategy in [Appendix 4](#).

We searched included and excluded RCTs for reports of adverse events.

### Handsearching

We handsearched the conference proceedings of the European Academy of Allergology and Clinical Immunology and the American Academy of Asthma, Allergy and Immunology 2006 meetings for abstracts of trials relevant to the review.

## Data collection and analysis

### Selection of studies

Titles and abstracts identified from the searches were independently checked by two authors (RB and MT). We excluded those studies which did not refer to a randomised controlled trial of probiotics for treating eczema. The same two authors (RB and MT) independently assessed each study to determine whether it met the pre-defined selection criteria. There were no major differences of opinion identified between the authors.

### Data extraction and management

Two authors (RB and FB) independently extracted the data. There were no major differences of opinion, and it did not prove necessary for a third author to arbitrate over data extraction. We contacted trial authors for all included studies by email or post to obtain complete data sets. We piloted a data collection form and used this to summarise the trials. Two authors (RB and FB) checked and entered the data. Where complete datasets were available from trial authors, we used such data to calculate summary statistics such as mean and standard deviation prior to data entry. Complete datasets were supplied by the authors of five studies ([Rosenfeldt 2003](#); [Weston 2005](#); [Brouwer 2006](#); [Passeron 2006](#); [Sistek 2006](#)). Summary data were supplied by the author of one study ([Viljanen 2005](#)). No response to requests for information were received from the authors of five studies ([Majamaa 1997](#); [Isolauri 2000](#); [Taniuchi 2005](#); [Folster-Holst 2006](#); [Gruber 2007](#)). The author of one study responded that they were unable to supply their data for meta-analysis [Kirjavainen 2003](#).

### Assessment of risk of bias in included studies

The quality assessment involved an evaluation of the following components for each included study, since there is some evidence that these are associated with biased estimates of treatment effect ([Juni 2001](#)):

- (a) the method of generation of the randomisation sequence;
- (b) the method of allocation concealment - considered 'adequate' if it was clear from publications or correspondence with authors that the treatment assignment of each consecutive study participant could not be anticipated by the investigator(s). For example if

treatment allocation was done by a third party such as a pharmacy department, allocation concealment was considered adequate; (c) who was blinded / not blinded (participants, clinicians, outcome assessors);

(d) how many participants were lost to follow-up in each treatment arm, and whether participants were analysed in the groups to which they were originally randomised (available case analysis), whether any participants were excluded after randomisation and whether data were imputed for participants lost to follow-up. The quality assessment also included:

(e) whether or not the study aims, interventions (including doses of viable probiotic used, mode of administration and duration of treatment) and outcome measures were clearly defined;

(f) whether an assessment of treatment compliance was made;

(g) whether non-study probiotics were adequately excluded from participants' diets

### Measures of treatment effect

A weighted pooled treatment effect was calculated across studies using a random effects model. We expressed the results as odds ratio (OR) and 95% confidence intervals (CI) for dichotomous outcomes and difference in means (MD and 95% CI) for continuous outcomes. Where studies reported participant- or investigator-rated symptoms on categorical scales (eg [Passeron 2006](#)) we made the data dichotomous by defining a cut-off at good improvement in eczema versus mild improvement, no change or worsening of eczema.

### Unit of analysis issues

#### Cross-over trials

We initially analysed cross-over trials using appropriate paired analyses to estimate paired MD (continuous outcomes) and paired OR (dichotomous outcomes) with standard errors. We then combined outcome data from cross-over trials and parallel group trials using the generic inverse variance method. We also analysed the data from parallel trials and cross-over trials as separate subgroups, since cross-over studies may not be appropriate for probiotic studies as the duration of treatment effect is not well established.

#### Studies with multiple treatment groups

Where studies reported more than one active intervention arm, we combined the two active interventions and analysed them together. We also analysed data from these studies as separate subgroups to assess the effect of the different strains of the probiotics.

#### Trials reporting non-parametric statistics

Where trials reported using non-parametric summary statistics, we did not convert data to parametric summary statistics since the

trials did not have large sample sizes and we could not assume that the data were non skewed.

### Dealing with missing data

We assessed pooled data using available case analysis, rather than intention to treat analysis with imputation. Where the nature of missing data was not clear, we contacted study authors for clarification. Where studies failed to report summary statistics such as standard deviations, we contacted the authors for further information.

### Assessment of heterogeneity

We assessed heterogeneity in studies using  $I^2$ . Where we found substantial heterogeneity between studies ( $I^2 > 50\%$ ) we explored possible reasons for this heterogeneity, including participant factors such as disease severity, treatment factors such as probiotic strain or dose, and study factors such as the methodological quality criteria described above. Where we detected extreme levels of heterogeneity between the trials ( $I^2 > 85\%$ ), we did not perform the meta-analysis.

### Assessment of reporting biases

We did not perform formal assessment of reporting bias such as a funnel plot, due to the limited number of studies with data available for inclusion in primary analyses.

### Data synthesis

Where studies employed different tools to measure the same outcome, we calculated a pooled estimate of effect across the studies using the standardised mean difference (SMD and 95% CI). Where it was not possible to perform a meta-analysis, we described the findings narratively.

### Subgroup analysis and investigation of heterogeneity

The subgroup analyses planned for this review were:

1. analysis by age (under 2 years vs 2 to 12 years vs over 12 years);
2. concurrent treatment with antibiotics vs no concurrent treatment with antibiotics;
3. atopic vs non atopic study participants, where atopy is defined as at least one positive Skin Prick Test (SPT) or Radioallergosorbent Test (RAST) to a common allergen;
4. participants with formally diagnosed (ie double blind placebo controlled food challenge) food allergy vs those without a formally diagnosed food allergy;
5. participants with evidence of intestinal inflammation vs those without such evidence;
6. participants with mild eczema (SCORAD under 15) vs moderate eczema (SCORAD 15 to 40) vs severe eczema (SCORAD over 40) at baseline.

## Sensitivity analysis

We performed sensitivity analyses to examine the effects of excluding poor quality studies, defined as those studies where the randomisation process is unclear, where participants, clinicians or outcome assessors were not blinded or where there was no intention to treat analysis.

## Other

We consulted a consumer (JT) throughout the review, particularly regarding the readability and clarity of the completed review.

# RESULTS

## Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

## Results of the search

Our searches identified 79 citations and abstracts, and a further 717 citations from the adverse events searches. Screening by two independent authors (RB and MT) identified the studies described below. The search of ongoing trials registers returned six results - two studies were published during the preparation of the review, and we included these ([Brouwer 2006](#); [Sistek 2006](#)); one study has recently been completed but is not yet published, and three studies are still ongoing.

## Included studies

We included twelve studies with 781 participants in this review, which are described in the [Characteristics of included studies](#). All studies were randomised controlled trials, 11 parallel group trials and 1 cross-over trial. The studies involved sample sizes of 27 to 252 participants each, and took place in primary or secondary care settings in mainly European centres. All studies evaluated probiotics in children, and a majority (8 of 12) evaluated their effects in children under 18 months age. One study only assessed children who had atopic eczema ([Sistek 2006](#)), one study only assessed children with low levels of Bifidobacteria in their faeces ([Taniuchi 2005](#)). Eleven studies used a Lactobacillus species as the probiotic intervention, most commonly Lactobacillus rhamnosus strains (n = 10) either alone or in combination with other probiotic bacteria.

Co-interventions included extensively hydrolysed infant formula (n = 6) and prebiotic preparations (n = 2). Placebo groups most commonly received either the co-intervention alone, or micro-crystalline cellulose. Three studies reported parent- or participant-

rated overall change in eczema severity during the study treatment. Eleven studies reported the SCORAD index, and unpublished data were obtained from the authors of four trials for parent- or participant-rated changes in eczema symptoms during the study treatment (SCORAD part C). Two studies reported quality of life measures, and four studies reported assessments of the need for other eczema treatment during the study intervention.

## Excluded studies

We excluded 11 publications reporting RCTs from the review, and describe these in the [Characteristics of excluded studies](#). In two cases it could not be ascertained whether all study participants had eczema. In seven cases the publications did not report outcomes relevant to this study. In two cases the study intervention was not a probiotic.

## Ongoing studies

We identified one ongoing study in which some participants have eczema and would meet criteria for inclusion in this review [CAMEL](#). The trial is scheduled to finish in 2008. We identified one completed but unpublished study where the study investigators declined to provide data [Murray](#). We identified two other ongoing studies of probiotics for the treatment of eczema [Goossens](#); [Land](#).

## Studies awaiting assessment

A search in April 2008 identified two further studies which are awaiting assessment ([Matsumoto 2007](#); [Roessler 2007](#)).

## Risk of bias in included studies

### Allocation

In eight studies ([Majamaa 1997](#); [Isolauri 2000](#); [Kirjavainen 2003](#); [Rosenfeldt 2003](#); [Taniuchi 2005](#); [Brouwer 2006](#); [Folster-Holst 2006](#); [Gruber 2007](#)) the concealment of treatment allocation were not described, and in seven of these the method for generating the randomisation sequence was not described ([Majamaa 1997](#); [Isolauri 2000](#); [Kirjavainen 2003](#); [Rosenfeldt 2003](#); [Taniuchi 2005](#); [Brouwer 2006](#); [Folster-Holst 2006](#)) [Table 2](#). In the remaining four included studies ([Viljanen 2005](#); [Weston 2005](#); [Passeron 2006](#); [Sistek 2006](#)) treatment was allocated by a third party such as a pharmacy department using a computer generated randomisation sequence. In these four studies treatment allocation was adequately concealed - the third party was not involved in screening or enrolling participants, and the clinical trial staff enrolling participants did not have access to the randomisation sequence.

**Table 2. Methodological quality of included studies**

| <b>Study</b>   | <b>Treatment allocation</b> | <b>Blinding</b>                                  | <b>Loss to follow-up</b>                                                                                                                                           | <b>Clarity of methods</b>                                                                                                                    | <b>Compliance</b>                                               | <b>Dietary management</b>                                  |
|----------------|-----------------------------|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------|
| Brouwer 2006   | Method not described        | Unclear                                          | One participant lost to follow-up after randomisation. Available case analysis used, with no exclusions after randomisation and no imputation of data.             | Clear                                                                                                                                        | No compliance measures described                                | Adequate exclusion of other probiotics during study        |
| Gruber 2007    | Method not described        | Described as 'double blind' but no details given | No loss to follow-up. Four participants excluded from analysis after randomisation.                                                                                | Unclear what the placebo was; otherwise clear                                                                                                | 92.5% of doses taken by probiotic group; 94.4% by placebo group | Not stated, other than an encouragement to avoid allergens |
| Isolaauri 2000 | Method not described        | Described as 'double blind' but no details given | Loss to follow-up not stated. Not clear whether available case analysis was used.                                                                                  | Unclear - dose and duration of probiotic treatment received not clearly described. Severity of participant eczema at baseline not described. | No compliance measures reported                                 | Not stated                                                 |
| Majamaa 1997   | Method not described        | Described as 'double blind' but no details given | Loss to follow-up data not given. Not clear whether available case analysis was used. Four participants excluded from analysis after randomisation, based on later | Unclear - precise dose of probiotic received by participants not stated                                                                      | No compliance measures described                                | Not stated                                                 |

**Table 2. Methodological quality of included studies**

|                    |                                                                                                                                          |                                                                 |                                                                                                                                                                                                                                            |       |                                  |                                                         |
|--------------------|------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|----------------------------------|---------------------------------------------------------|
| <i>(Continued)</i> |                                                                                                                                          |                                                                 |                                                                                                                                                                                                                                            |       |                                  |                                                         |
|                    |                                                                                                                                          |                                                                 | negative food challenge.                                                                                                                                                                                                                   |       |                                  |                                                         |
| Passeron 2006      | Treatment allocated by hospital pharmacy according to a computer generated randomisation sequence.                                       | Participants, clinicians and outcome assessors were all blinded | Nine participants lost to follow-up. Available case analysis used, with no exclusions after randomisation. A secondary analysis was performed by the authors using imputation of missing data, but was not included in this meta-analysis. | Clear | No compliance measures described | Not stated                                              |
| Rosenfeldt 2003    | Method not described                                                                                                                     | Described as 'double blind' but no details given                | Fifteen participants excluded from analysis after randomisation, for reasons including poor compliance, exacerbation of eczema and loss to follow-up. No available case analysis performed.                                                | Clear | No compliance measures described | Adequate exclusion of other probiotics during study     |
| Sistek 2006        | Treatment allocated by a third party according to a computer generated randomisation sequence. Third party not otherwise involved in the | Participants, clinician and outcome assessor blind              | One study withdrawal. Available case analysis was used, with no exclusions after randomisation and no imputation of data.                                                                                                                  | Clear | Assessed by two telephone calls  | One participant noted to have taken non-study probiotic |

**Table 2. Methodological quality of included studies**

| <i>(Continued)</i> |                                                                                                       |                                                        |                                                                                                                                                                                    |                                                           |                                                                                  |                                                     |
|--------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------|
|                    | study.                                                                                                |                                                        |                                                                                                                                                                                    |                                                           |                                                                                  |                                                     |
| Taniuchi 2005      | Method not described                                                                                  | Unclear                                                | Loss to follow-up not reported. Not clear whether available case analysis was used.                                                                                                | Clear                                                     | No compliance measure described                                                  | Not stated                                          |
| Viljanen 2005      | Treatment allocated by a remote third party according to a computer generated randomisation sequence. | Participants, clinicians and outcome assessor blinded  | Twenty-two participants were lost to follow-up. Analysis was by 'treatment received' because four participants who did not tolerate the study formula were excluded from analysis. | Method for diagnosing eczema not described                | No compliance measures described                                                 | Not stated                                          |
| Weston 2005        | Treatment allocated by hospital pharmacy according to a computer generated randomisation sequence.    | Outcome assessor blind, and also stated 'double blind' | Three participants lost to follow-up. Available case analysis was used, with no exclusions after randomisation and no imputation of data.                                          | Clear                                                     | Sachet counts and parent-completed sachet administration chart. Good compliance. | Adequate exclusion of other probiotics during study |
| Kirjavainen 2003   | Method not described                                                                                  | Described as 'double blind' but no details given       | No loss to follow-up data given. Analysis was by 'treatment received' because five participants who did not tolerate the study formula were excluded from analysis after           | Unclear - intended duration of study treatment not stated | No compliance measures reported                                                  | Not stated                                          |

**Table 2. Methodological quality of included studies**

| (Continued)        |                      |                                                  |                                                                       |       |                                 |            |
|--------------------|----------------------|--------------------------------------------------|-----------------------------------------------------------------------|-------|---------------------------------|------------|
|                    |                      |                                                  | randomisation.                                                        |       |                                 |            |
| Folster-Holst 2006 | Method not described | Described as 'double blind' but no details given | Six participants lost to follow-up. Available case analysis was used. | Clear | No compliance measures reported | Not stated |

**Blinding**

In two studies (Taniuchi 2005; Brouwer 2006) blinding of participants, clinicians or outcome assessors was not stated. Six studies (Majamaa 1997; Isolauri 2000; Kirjavainen 2003; Rosenfeldt 2003; Folster-Holst 2006; Gruber 2007) were described as 'double blind' but did not specify who was blinded. In three studies (Viljanen 2005; Passeron 2006; Sistek 2006) participants, clinicians and outcome assessors were all blinded. In one study (Weston 2005) it was stated that the outcome assessor was blinded and that the study was double blind but blinding of participants and clinicians was not explicitly stated.

**Follow up and exclusions****Follow-up and exclusions**

In three studies (Majamaa 1997; Isolauri 2000; Taniuchi 2005) there was no information available regarding losses to follow-up or how missing data was treated in the analyses. Five studies (Weston 2005; Brouwer 2006; Folster-Holst 2006; Passeron 2006; Sistek 2006) used available case analysis. In three studies it was unclear whether the investigators used available case analysis (Majamaa 1997; Isolauri 2000; Taniuchi 2005). In the remaining four studies some participants were excluded from analysis after they had been randomised (Kirjavainen 2003; Rosenfeldt 2003; Viljanen 2005; Gruber 2007). Overall losses to follow-up were reported were low, with the exception of one study (Rosenfeldt 2003) in which 26% of participants were lost to follow-up.

**Selective reporting**

There was no evidence of selective reporting or other potential sources of internal bias in the studies, and publication bias was not formally assessed using a funnel plot due to the small numbers of studies included in analyses of primary outcome measures.

**Effects of interventions****Primary outcome measures****(1) Short-term changes in participant-rated, parent-rated or principal carer-rated symptoms of eczema**

The authors of five studies (Rosenfeldt 2003; Weston 2005; Passeron 2006; Sistek 2006; Gruber 2007) with 313 participants supplied published or unpublished data on parent- or participant-rated symptom scores at the end of the study treatments (SCORAD part C). This measurement is a visual analogue scale of itch and sleep disturbance ranging from 0 to 20. Pooled data from these studies (Analysis 1.1) showed no significant improvement in favour of probiotic treatment MD -0.90 (95% CI -2.84, 1.04;  $p = 0.36$ ). There was significant heterogeneity between the studies for this outcome measure ( $I^2 = 77\%$ ). This was largely accounted for by the Gruber 2007 study. The reason for this heterogeneity is not clear, but the use of different probiotic strains in the different studies may be important.

Four trials reported parent-rated overall evaluation of symptoms of eczema at the end of study treatment, however one trial (Folster-Holst 2006) did not provide any numerical data for this outcome. Therefore we included the remaining 3 trials (Rosenfeldt 2003; Weston 2005; Passeron 2006) in the analysis, which comprised of 150 participants. We dichotomised the scale of two studies (Rosenfeldt 2003; Weston 2005) as 'better' versus 'worse or the same'. We dichotomised the scale of the other study (Passeron 2006), measured from 1 (worse) to 6 (much better), as '4 to 6' versus '1 to 3'. Pooling of the data from these studies (Analysis 1.2) showed no significant reduction in the risk of worsened/unchanged eczema in probiotic treated individuals OR 0.40 (95% CI 0.14, 1.15;  $p = 0.09$ ). We detected moderate levels of heterogeneity between the trials ( $I^2 = 47.4\%$ ), which appeared to be related to the Rosenfeldt 2003 trial. Possible reasons for this heterogeneity include the adequate exclusion of other probiotic sources in this cross-over trial, or the higher methodological quality of the parallel group studies (defined as stating using an intention to treat analysis, and adequate methods of allocation concealment and randomisation sequence generation being clearly described).

**(2) Short-term changes in quality of life**

Quality of life data were available from two studies (Weston 2005; Folster-Holst 2006). The data from the study by Weston 2005 using the Dermatitis Family Impact Questionnaire (Lawson 1998) are shown in tabular form (Table 3), and show no significant dif-

ference in the quality of life score change during treatment between probiotic and placebo treated participants. The data from the study by [Folster-Holst 2006](#), using a different published scale ([Ruden 1999](#)), showed no significant difference between probiotic and placebo groups - mean scores at the end of treatment were 19.9 (Probiotic) vs 19.1 (placebo). It is not clear from the report whether a higher or lower score on the scale used indicates improved quality of life, and the authors did not respond to a request for further information regarding the study.

**Table 3. Quality of Life Measures (Weston 2005)**

|        | Probiotic 8 weeks | Placebo 8 weeks | Probiotic 16 weeks | Placebo 16 weeks |
|--------|-------------------|-----------------|--------------------|------------------|
| N      | 26                | 27              | 26                 | 27               |
| Median | -2                | -2              | -2.5               | -3               |
| IQR    | -5 to -0.7        | -6 to +2        | -5 to -1           | -7.2 to +2       |

## Secondary outcome measures

### (I) Long-term changes during the six month period after the active treatment has ceased in participant-rated, parent-rated or principal carer-rated symptoms of eczema

Data from 6 studies (433 participants) were available for long-term changes in eczema severity. However, data from only 2 of the studies ([Weston 2005](#); [Sistek 2006](#)) comprising of 102 participants could be pooled due to differences or insufficient reporting of data. These two trials reported SCORAD scores at four weeks and eight weeks after cessation of study treatment respectively. A pooled analysis of the data ([Analysis 1.3](#)) showed a significant improvement in the participant/parent-rated symptom score in favour of probiotic treatment (MD -2.27 95%CI -3.97, -0.58 points on SCORAD part C). One of the studies ([Weston 2005](#)) also reported a dichotomised global assessment by parents after cessation of probiotic treatment, however no significant long-term difference in the risk of worsened or unchanged eczema was seen between the probiotic and placebo interventions (OR 0.63; 95% CI 0.21, 1.88; data not presented).

The other 4 studies comprised of 331 participants, and none of the individual studies demonstrated a significant difference in outcomes between probiotic and placebo treatments. One study ([Majamaa 1997](#)) presented in [Table 4](#) reported median SCORAD scores of 16 (Interquartile range (IQR) 6 to 25) in probiotic-treated infants, and 14 (IQR 2 to 38) in placebo-treated infants 1 month after ceasing the study intervention with no statistical analysis presented. A second study ([Isolauri 2000](#)) reported median SCORAD scores of 0 in all active and placebo treated groups at 6 month follow-up, however the duration of study interventions is not clear in this study. One study ([Viljanen 2005](#)) reported mean changes in SCORAD score four weeks after the study interventions had ceased. Lactobacillus rhamnosus GG (LGG)-treated infants had a mean reduction of 22.9 points, Probiotic Mix-treated infants 20.4 points and placebo treated infants 20.3 points, with no statistically significant difference between treatment groups at this time point. Finally one study ([Folster-Holst 2006](#)) reported mean SCORAD scores 4 weeks after the study interventions had ceased - probiotic treated participants had a mean score of 32.8, versus 30.1 for placebo.

**Table 4. Non-parametric analyses of SCORAD scores**

| Majamaa<br>1month LGG | Majamaa<br>1month Place | Majamaa 2mo<br>LGG | Majamaa 2mo<br>Placebo | Isolauri 2mo<br>LGG | Isolauri 2mo<br>Bb12 | Isolauri 2mo<br>Placebo |
|-----------------------|-------------------------|--------------------|------------------------|---------------------|----------------------|-------------------------|
|-----------------------|-------------------------|--------------------|------------------------|---------------------|----------------------|-------------------------|

**Table 4. Non-parametric analyses of SCORAD scores**

| <i>(Continued)</i> |      |       |      |      |         |       |          |
|--------------------|------|-------|------|------|---------|-------|----------|
| N                  | 13   | 14    | 13   | 14   | 9       | 9     | 9        |
| Median             | 15   | 19    | 16   | 14   | 1       | 0     | 13.4     |
| IQR                | 7-28 | 13-31 | 6-25 | 2-38 | 0.1-8.7 | 0-3.8 | 4.5-18.2 |

**Notes:**  
<sup>a</sup> IQR = Interquartile range

**(2) Long-term changes in quality of life**

There were data available for this outcome from one study ([Weston 2005](#)), which reported that the median change in quality of life score 8 weeks after the end of study treatment was -2.5 points for the probiotic group and -3.0 for the placebo group. Statistical comparison was not possible using the available data due to lack of summary statistics.

**(3) Short-term and long-term changes in the need for other eczema treatment**

Four studies reported this outcome ([Table 5](#)), but the data could not be pooled due to differences in the reporting of this outcome. For three of these four studies ([Rosenfeldt 2003](#); [Folster-Holst 2006](#); [Gruber 2007](#)) the differences between treatment groups were not statistically significant, for the fourth study ([Weston 2005](#)) the authors reported no statistical analysis. The sole study reporting long-term changes in the need for other eczema treatment ([Weston 2005](#)) found no significant difference between placebo and probiotic groups in median topical corticosteroid score eight weeks after cessation of the study intervention.

**Table 5. Assessments of need for topical corticosteroid treatment during study**

|                                                               | Rosenfeldt<br>Probiotic | Rosenfeldt<br>Placebo | Gruber<br>Probiotic | Gruber<br>Placebo | Weston<br>Probiotic | Weston<br>Placebo | Folster-H<br>Probiotic | Folster-H<br>Placebo |
|---------------------------------------------------------------|-------------------------|-----------------------|---------------------|-------------------|---------------------|-------------------|------------------------|----------------------|
| N                                                             | 39                      | 39                    |                     |                   |                     |                   |                        |                      |
| Median<br>grams<br>hydro-<br>cortisone<br>butyrate<br>applied | 7.8                     | 6.0                   |                     |                   |                     |                   |                        |                      |
| Range                                                         | 0 to 67                 | 0 to 59               |                     |                   |                     |                   |                        |                      |

|                                                                 |      |      |              |              |
|-----------------------------------------------------------------|------|------|--------------|--------------|
| Mean grams<br>1% hydro-<br>cortisone<br>applied                 | 0.8  | 3.5  |              |              |
| Standard<br>deviation                                           | 45.0 | 29.8 |              |              |
| Median<br>change in<br>topical cor-<br>ticosteroid<br>use score |      |      | 0.25         | -1.0         |
| IQR for<br>change in<br>corticos-<br>teroid score               |      |      | -6.7 to +7.0 | -8.0 to +0.7 |
| Mean<br>applications<br>per week                                |      |      | 3.0          | 3.2          |
| Standard<br>deviation                                           |      |      | 0.6          | 0.9          |

---

#### (4) Investigator-rated eczema severity

##### (i) Short-term changes in eczema severity as measured by a trained investigator or a medical practitioner

All studies reported assessments relevant to this outcome. Seven studies with 588 participants (Rosenfeldt 2003; Viljanen 2005; Weston 2005; Folster-Holst 2006; Gruber 2007; Passeron 2006; Sistek 2006) reported mean total SCORAD scores at the end of treatment. Pooled analysis of the data from these studies (Analysis 1.4) showed no significant difference between probiotic and control treatment, with a mean difference of -2.46 points (95% CI -7.45, 2.53) in favour of probiotic treatment. We detected extreme levels of heterogeneity between the trials ( $I^2 = 75.8\%$ ), which seemed to be related to parallel group trials ( $I^2 = 73.1\%$ ), in particular the Weston 2005 and Sistek 2006 trials. The reasons for this heterogeneity were not clear, but possibilities include the higher methodological quality of these two studies, their Australasian setting or their small sample sizes. In one study (Sistek 2006) there were significant baseline differences in eczema severity between placebo and probiotic treated groups which might have accounted for the increased difference in end of treatment SCORAD scores. To explore this we performed a sensitivity analysis using change scores ie the difference in SCORAD score between the start and end of treatment for each individual. These data were available for 5 studies with 439 participants (Rosenfeldt 2003; Viljanen 2005; Weston 2005; Passeron 2006; Sistek 2006) and are presented in Analysis 1.5. The data show a mean difference in SCORAD change of -2.47 points (95% CI -4.72, -0.21;  $p = 0.03$ ) in favour of probiotic treatment, with no significant heterogeneity between the trials ( $I^2 = 0\%$ ).

Data from the other studies for this outcome measure could not be pooled. One study (Taniuchi 2005) showed a significant reduction in symptom scores from baseline in both probiotic and placebo groups, but the authors did not present any statistical comparison between the two groups. Two studies (Majamaa 1997; Isolauri 2000) reported their assessments as median scores with an interquartile range (shown in Table 4) - Isolauri reported a statistically significant difference between end of treatment SCORAD for probiotic versus placebo groups, whereas Majamaa did not. One study (Brouwer 2006) used a modified SCORAD score (SCORAD parts A/B only) and found no significant difference between probiotic and control treatments. Another study (Kirjavainen 2003) reported mean total SCORAD score at the end of treatment (eight in the placebo and five in the probiotic group) without statistical analysis of this difference; additionally, the duration of active treatment varied greatly between participants in this study. The Passeron 2006 trial reported an investigator's global assessment scale of eczema improvement at the end of treatment for 39 participants; however no significant difference in the risk of worse, unchanged or mildly improved eczema was seen between probiotic

and placebo treatments (OR 0.41, 95% CI 0.07, 2.38; data not presented).

##### (ii) Long-term changes in global eczema severity or change in the number of eczema flares as measured by participants, parents, principal carers or a medical practitioner

A pooled analysis of two studies (Weston 2005; Sistek 2006; Analysis 1.6) found a significant improvement in investigator-rated eczema extent and severity in favour of probiotic treatment (MD -8.11 (95%CI -13.14,-3.09 SCORAD parts A/B). We detected no heterogeneity between these 2 studies ( $I^2 = 0\%$ ).

##### (5) Changes in the number of days lost from school or work due to eczema symptoms during active treatment

No study reported relevant outcomes for this analysis.

#### Subgroup analyses

We undertook the following planned subgroup analyses:

##### (i) Analysis by age

We analysed global eczema severity scores and symptom scores (SCORAD part C) from the studies stratified by age (Analysis 1.7 and Analysis 1.8). In the analysis of SCORAD part C scores, there was heterogeneity attributable to one study (Gruber 2007) which assessed children under 2 years of age. However in no age group was there a significant difference in symptom scores between probiotic and control treatments (age under 2 years MD -0.13 95%CI -4.18, 3.91; age 2-12 years MD 0.33 95%CI -1.94 2.60 Analysis 1.7). Global disease severity scores showed no significant heterogeneity according to age stratification ( $I^2 = 0\%$ ; Analysis 1.8). We also stratified total SCORAD scores by age group and pooled data for a total of seven trials (Analysis 1.9). We detected high levels of heterogeneity in two of the three sub-categories created for the age groups (age under 2 years,  $I^2 = 69.9\%$ ; age not categorised,  $I^2 = 77.7\%$ ). The heterogeneity seemed to be related to the Weston 2005 and Folster-Holst 2006 trials in each of the two sub-categories, and therefore the heterogeneity could not be attributed to differences in age of the participants. In no age group was there a significant difference in total SCORAD between the probiotic and control treatments (age under 2 years MD 0.74 95%CI -5.06, 6.54; age 2-12 years MD -3.28 95%CI -13.78, 7.22 Analysis 1.9). No study included in the review evaluated adults with eczema.

##### (ii) Analysis by antibiotic use during study intervention

One study (Viljanen 2005) separately evaluated participants not exposed to antibiotics during the intervention period, but did not report any end-of-treatment outcomes for this group.

##### (iii) Analysis by atopy

One study (Sistek 2006) included only participants with proven atopy, and another study (Viljanen 2005) separately evaluated treatment effects in participants with atopy. SCORAD scores at the end of treatment could not be pooled for these studies due to extreme levels of heterogeneity between the trials ( $I^2 = 91.5\%$ , Analysis 1.10). There was no significant difference in SCORAD scores between the probiotic and placebo groups when studies with a mix of atopic and non-atopic participants were analysed (MD -1.73; 95% CI -7.29, 3.83;  $p = 0.54$ ), and we detected high levels of heterogeneity ( $I^2 = 68.0\%$ ).

#### (iv) Analysis by food allergy

One study (Viljanen 2005) separately evaluated SCORAD scores in participants with proven cow's milk allergy. They found (Analysis 1.11) no significant difference in end of treatment SCORAD scores between probiotic and placebo treated participants (MD 1.15; 95% CI -3.20, 5.50). We found no significant difference in SCORAD scores when we evaluated studies with a mix of food allergic and non-food allergic participants (MD -3.19; 95% CI -10.59, 4.20), however we detected extreme levels of heterogeneity between the trials ( $I^2 = 75.6\%$ ).

#### (v) Analysis by intestinal inflammation

No study provided data for this subgroup analysis.

#### (vi) Analysis by disease severity

Four studies with 253 participants (Weston 2005; Passeron 2006; Sistek 2006; Gruber 2007) provided sufficient data to stratify end of treatment SCORAD scores by disease severity (Analysis 1.12). There was no evidence for a difference in treatment efficacy according to disease severity (severe eczema, MD -7.00; 95% CI -15.34, 1.34; moderate eczema, MD -3.45; 95% CI -10.34, 3.45; mild eczema -5.53; 95% CI -15.29, 4.23).

#### (vii) Analysis by probiotic species or strain

This subgroup analysis was not *a priori* specified in the study protocol, but we undertook the analysis due to the use of the same probiotic strain in seven studies and the heterogeneity noted between study results for some outcomes in this review. For this analysis studies were categorised as using *Lactobacillus rhamnosus* GG (LGG) either alone or in combination, or using other *Lactobacillus* strains (either alone or in combination). The pooled data (Analysis 1.13) show a significant difference in treatment effectiveness between the two groups. We found a significantly higher SCORAD score for eczema severity after treatment with the LGG strain compared to placebo - SCORAD score 3.37 points (95% CI 0.55, 6.20;  $p = 0.02$ ) in favour of placebo. We found a significantly lower SCORAD score for the other *Lactobacillus* strains compared to placebo - SCORAD score -7.64 points (-11.65, -3.62;  $p < 0.01$ ) in favour of probiotic treatment. We found low

levels of heterogeneity in both comparisons ( $I^2 = 0\%$  and  $10\%$ , respectively).

#### (6) Adverse events during the treatment period

Studies reported adverse events in 99/304 participants in 5 trials (Weston 2005; Folster-Holst 2006; Passeron 2006; Sistek 2006; Gruber 2007). One of these participants with vomiting withdrew from their study. Pooling of these data (Analysis 1.14) shows no significant difference in adverse event rate between probiotic and control groups (OR 1.57; 95% CI 0.78, 3.15,  $I^2 = 0\%$ ). No other study provided sufficient data to estimate adverse event rates.

## DISCUSSION

### Summary of main results

Five studies (Rosenfeldt 2003; Weston 2005; Passeron 2006; Sistek 2006; Gruber 2007) reported visual analogue scores of eczema symptoms (pruritus and sleep loss; SCORAD part C score) assessed by parents or participants - the data from these studies suggest that probiotics are not an effective treatment for eczema symptoms, albeit with significant heterogeneity between studies. Three studies reported global assessments of disease improvement during treatment by parents or participants - pooled dichotomised data from these studies do not support the hypothesis that probiotic treatment leads to an improvement in eczema severity, again with significant heterogeneity between studies. Two studies reported quality of life data (Weston 2005; Folster-Holst 2006), and suggest that probiotic treatment does not improve the quality of life of eczema sufferers.

There was evidence from two studies (Weston 2005; Sistek 2006) that probiotic treatment leads to a small reduction in SCORAD part C eczema symptom score during the period after treatment has ceased. This finding was not supported by the data from four other studies that could not be pooled (Majamaa 1997; Isolauri 2000; Viljanen 2005; Folster-Holst 2006). Furthermore four other studies found that (Rosenfeldt 2003; Weston 2005; Folster-Holst 2006; Gruber 2007) probiotic treatment did not reduce the need for other eczema treatment such as topical corticosteroids.

All studies reported at least one investigator-assessed or composite eczema severity score. The data from five studies (Majamaa 1997; Isolauri 2000; Kirjavainen 2003; Taniuchi 2005; Brouwer 2006) could not be pooled, but individually showed no change in eczema severity with probiotic treatment. A meta-analysis of data from the seven remaining studies also showed no change in eczema severity with probiotic treatment. We found significant heterogeneity in this meta-analysis, which was accounted for by three studies (Rosenfeldt 2003; Weston 2005; Sistek 2006) reporting greater benefit in favour of probiotic treatment. One of these studies (Sistek 2006) had a significant imbalance in disease severity between treatment groups at baseline. We therefore performed

the same meta-analysis using change scores rather than end-of-treatment scores - two of the seven studies (Folster-Holst 2006; Gruber 2007) could not be included in this meta-analysis due to insufficient data. The pooled analysis showed a mean difference in SCORAD change of -2.47 points (95% CI -4.72, -0.21;  $p = 0.03$ ) in favour of probiotic treated participants. No study reported changes in school or work absenteeism due to illness.

We undertook subgroup analyses as per the study protocol, with an additional subgroup analysis according to probiotic strain used. We found no subgroup-specific effects when we analysed the data by age of study population, by the presence of atopy or food allergy in the study population or by disease severity. There were no data available for the planned subgroup analyses of antibiotic exposure or intestinal inflammation. The analysis by probiotic strain used showed a SCORAD score 3.37 points (95% CI 0.55, 6.20;  $p = 0.02$ ) higher in participants treated with the probiotic LGG compared to placebo. The end of treatment SCORAD score was 7.64 points (95% CI 3.62, 11.65;  $p < 0.01$ ) lower in participants treated with other *Lactobacillus* strains compared to placebo. Although this was a post-hoc analysis the results suggest that some probiotic strains may be more effective than others in treating eczema, and this confirms previous data showing that different probiotic strains have different effects on clinical outcomes and immune responses (Christensen 2002; Allen 2003). The implication of this is that novel probiotic strains which have not yet been studied for the treatment of eczema may have significant effects.

Four trials reported adverse events, with no significant difference between probiotic and placebo groups. We identified a number of case reports describing the development of bacterial or fungal sepsis and bowel ischaemia related to probiotic use.

The adverse events search revealed four case reports of sepsis related to probiotic use (Lestin 2003; Riquelme 2003; Cherifi 2004; De Groote 2005), including one death (Lestin 2003). The adverse events search also found five reports of human safety assessments using probiotics (Wolf 1998; Makelainen 2003; Connolly 2005; Burton 2006; Srinivasan 2006), and four review articles of probiotic safety (Salminen 1998; Ishibashi 2001; Borriello 2003; Boyle 2006). The safety assessments demonstrated no adverse effects of probiotics in humans, but the case reports and review articles documented a total of 42 cases of suspected or proven probiotic sepsis (Boyle 2006). The authors did not definitively identify the probiotic origin of the infective organism in all of these 42 cases, and it was not possible to quantify the risk of such outcomes from the data available. A recent report described an increased risk of fatal bowel ischaemia in critically ill patients treated with one particular combination of probiotics (Besselink 2008). One review proposed some relative contraindications to probiotic use in view of the risk of sepsis (Boyle 2006).

## Overall completeness and applicability of evidence

The number of studies and number of participants included in primary outcome analyses were small. While there was no evidence found that probiotic treatment changes eczema symptoms, the confidence intervals for the findings are wide and there was significant heterogeneity between studies for the primary outcome of eczema symptoms. A reduction in SCORAD part C score of 2.84 points and an OR of worsening/unchanged eczema of 0.14 both fall within the 95% CI for the primary outcomes. Further studies reporting parent or participant-rated eczema symptoms or global eczema severity would help to clarify whether probiotics have a role in eczema treatment.

The number of studies and participants was greater in secondary outcome analyses, leading to narrower confidence intervals. The pooled data for SCORAD scores at the end of treatment show no significant difference between probiotic and control treatments, and suggest that if probiotic treatment does have a beneficial effect then it is unlikely to reduce end of treatment SCORAD scores by greater than 7.45 points relative to placebo treatment.

No study evaluated the use of probiotics to treat eczema in adults, nor in adolescents over 13 years age. Only two studies reported quality of life data, and just four studies clearly stated the presence and nature of any adverse events, and the treatment groups in which they occurred.

## Quality of the evidence

The overall quality of studies was mixed, largely due to missing information regarding randomisation procedures, blinding and loss to follow-up. We assessed four studies (Viljanen 2005; Weston 2005; Passeron 2006; Sistik 2006) as being of high quality. In one of these (Sistik 2006) there was a chance imbalance in disease severity at baseline.

## Potential biases in the review process

The analyses of SCORAD change scores was a post-hoc analysis, justified by the imbalance in treatment severity at baseline in one included study. Any conclusions based on these data must therefore be guarded. The subgroup analysis by probiotic strain used was not predefined in the study protocol, and we undertook this due to the observation that seven studies used the same probiotic strain. The analysis suggests that some probiotic strains may be more effective than others for the treatment of eczema, however conclusions based on this post-hoc analysis must also be guarded.

## Agreements and disagreements with other studies or reviews

The data summarised in this review suggest that probiotics are ineffective for the treatment of eczema. Previous studies found an association between the composition of the intestinal microbiota and eczema (Bjorksten 2001; Kalliomaki 2001), and increased gastrointestinal symptoms in children with eczema (Caffarelli 1998).

These previous studies suggest that either the composition of the intestinal microbiota is important in the pathophysiology of eczema, or that intestinal mucosal abnormalities associated with eczema lead to secondary changes in the resident intestinal microbiota. There is evidence that probiotics can lower the increased intestinal permeability associated with eczema (Rosenfeldt 2004), and some studies suggest that the use of probiotics or prebiotics during early infancy may prevent the development of eczema (Kalliomaki 2003; Moro 2006; Kukkonen 2007; Osborn 2007). Probiotics may be therefore be ineffective for treating eczema because the decrease in intestinal permeability associated with their use is insufficient to lead to the resolution of established disease.

## AUTHORS' CONCLUSIONS

### Implications for practice

The data suggest that probiotics are not an effective treatment for eczema symptoms and are not effective at overall control of eczema. This conclusion is based on analysis of small numbers of participants, and a significant benefit cannot be confidently excluded. However analysis of composite severity score (SCORAD) data suggests that any reduction in eczema severity from probiotic treatment is likely to be modest (less than 7.45 points on the total SCORAD score) and therefore unlikely to be clinically significant. Probiotic treatment is generally safe, however it can lead to adverse events including sepsis and bowel ischaemia - the precise risk of

such events is difficult to quantify, but is likely to be very low for most people.

### Implications for research

Future studies should stratify the randomisation of participants by eczema severity, in order to avoid baseline imbalances between treatment groups. Future studies should also report parent- or participant-rated symptoms or global assessments of disease control, and should publish quality of life scores such as the Dermatitis Family Impact Questionnaire (Lawson 1998). Thorough reporting of adverse events is needed in future probiotic studies. Further probiotic eczema treatment studies would help to clarify whether specific probiotic strains have a greater effect on eczema severity and symptoms than the strains studied to date, and might evaluate their efficacy in adolescent/adult populations.

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## REFERENCES

### References to studies included in this review

- Brouwer 2006** {published and unpublished data}  
Brouwer ML, Wolt-Plompen SAA, Dubois AEJ, Van der Heide S, Jansen DF, Hoijer MA, et al. No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial. *Clinical and Experimental Allergy* 2006;**36**:899–906.
- Folster-Holst 2006** {published data only}  
Folster-Holst R, Muller F, Schnopp N, Abeck D, Kreiselmair I, Lenz T, et al. Prospective, randomized controlled trial on Lactobacillus rhamnosus in infants with moderate to severe atopic dermatitis. *British Journal of Dermatology* 2006;**155**:1256–61.
- Gruber 2007** {published data only (unpublished sought but not used)}  
Gruber C, Wendt M, Sulser C, Lau S, Kulig M, Wahn U, et al. Randomised placebo-controlled trial of Lactobacillus rhamnosus GG as treatment of atopic dermatitis in infancy. *Allergy* 2007;**62**:1270–1276.
- Isolauri 2000** {published data only}  
Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. *Clinical and Experimental Allergy* 2000;**30**:1604–10.
- Kirjavainen 2003** {published data only}  
Kirjavainen PV, Salminen SJ, Isolauri E. Probiotic bacteria in the management of atopic disease: underscoring the importance of viability. *Journal of pediatric gastroenterology and nutrition* 2003;**36**:223–7.
- Majamaa 1997** {published data only}  
Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. *Journal of Allergy and Clinical Immunology* 1997;**99**:179–85.
- Passeron 2006** {published and unpublished data}  
Passeron T, Lacour J-P, Fontas E, Ortonne J-P. Prebiotics and synbiotics: two promising approaches for the treatment of atopic dermatitis in children above 2 years. *Allergy* 2006;**61**:431–7.
- Rosenfeldt 2003** {published and unpublished data}  
Rosenfeldt V, Benfeldt E, Nielsen SD, Michaelsen KF, Jeppesen DL, Valerius NH, et al. Effect of probiotic Lactobacillus strains in children with atopic dermatitis. *Journal of Allergy and Clinical Immunology* 2003;**111**:389–95.
- Sistek 2006** {published and unpublished data}  
Sistek D, Kelly R, Wickens K, Stanley T, Fitzharris P, Crane J. Is the effect of probiotics on atopic dermatitis confined to food sensitized

- children?. *Clinical and Experimental Allergy* 2006;**36**:629–33.
- Taniuchi 2005** {published data only}  
Hattori K, Yamamoto A, Sasai M, Taniuchi S, Kojima, T, Kobayashi Y, et al. Effects of administration of bifidobacteria on fecal microflora and clinical symptoms in infants with atopic dermatitis. *Arerugi - Japanese Journal of Allergology* 2003;**52**(1):20–30.
- \* Taniuchi S, Hattori K, Yamamoto A, Sasai M, Hatano Y, Kojima T, et al. Administration of Bifidobacterium to infants with atopic dermatitis: changes in fecal microflora and clinical symptoms. *The Journal of Applied Research* 2005;**5**(2):387–96.
- Viljanen 2005** {published and unpublished data}  
Viljanen M, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, et al. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. *Allergy* 2005;**60**:494–500.
- Weston 2005** {published and unpublished data}  
Weston S, Dunstan J, Roper J, Breckler L, Halbert A, Richmond P, et al. Probiotics provide clinical benefit in moderate and severe atopic dermatitis: a randomised controlled trial. *The Journal of Investigative Dermatology* 2005;**125**:596.
- Weston S, Halbert A, Richmond P, Prescott SL. Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Archives of Disease in Childhood* 2005;**90**(9):892–7.
- Weston S, Richmond P, Halbert A, Prescott SL. Effects of probiotics in infants with atopic dermatitis: a randomised double blind placebo controlled trial. *Australasian Journal of Dermatology* 2004;**45**:A13.
- tran, reduces murine and human allergic reaction. *FEMS Immunology & Medical Microbiology* 2006;**46**(3):400–9.
- Pohjavuori 2004** {published data only}  
Pohjavuori E, Viljanen M, Korpela R, Kuitunen M, Tüttanen M, Vaarala O, et al. Lactobacillus GG effect in increasing IFN-gamma production in infants with cow's milk allergy. *Journal of Allergy and Clinical Immunology* 2004;**114**(1):131–6.
- Prescott 2005** {published data only}  
Prescott SL, Dunstan JA, Hale J, Breckler L, Lehmann H, Weston S, et al. Clinical effects of probiotics are associated with increased interferon-gamma responses in very young children with atopic dermatitis. *Clinical and Experimental Allergy* 2005;**35**(12):1557–64.
- Rosenfeldt 2004** {published data only}  
Rosenfeldt V, Benfeldt E, Valerius NH, Paerregaard A, Michaelsen KF. Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *Journal of Pediatrics* 2004;**145**(5):612–6.
- Viljanen 2005b** {published data only}  
Viljanen M, Pohjavuori E, Haahtela T, Korpela R, Kuitunen M, Sarneo A, et al. Induction of inflammation as a possible mechanism of probiotic effect in atopic eczema-dermatitis syndrome. *Journal of Allergy & Clinical Immunology* 2005;**115**(6):1254–9.
- Viljanen 2005c** {published data only}  
Viljanen M, Kuitunen M, Haahtela T, Juntunen-Backman K, Korpela R, Savilahti E. Probiotic effects on faecal inflammatory markers and on faecal IgA in food allergic atopic eczema/dermatitis syndrome infants. *Pediatric Allergy and Immunology* 2005;**16**(1):65–71.

## References to studies excluded from this review

- Arvola 2006** {published data only}  
Arvola T, Ruuska T, Keranen J, Hyoty H, Salminen S, Isolauri E. Rectal bleeding in infancy: clinical, allergological, and microbiological examination. *Pediatrics* 2006;**117**(4):760–8.
- Ikezawa 2004** {published data only}  
Ikezawa Z, Kondo M, Okajima M, Nishimura Y, Kono M. Clinical usefulness of oral itraconazole, an antimycotic drug, for refractory atopic dermatitis. *European Journal of Dermatology* 2004;**14**(6):400–6.
- Kalliomaki 2003** {published data only}  
Kalliomaki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo controlled trial. *Lancet* 2003;**361**(9372):1869–71.
- Laitinen 2005** {published data only}  
Laitinen K, Kalliomaki M, Poussa T, Lagstrom H, Isolauri E. Evaluation of diet and growth in children with and without atopic eczema: follow-up study from birth to 4 years. *British Journal of Nutrition* 2005;**94**(4):565–74.
- Leung 2004** {published data only}  
Leung TF, Ma KC, Cheung LTF, Lam CWK, Wong E, Wan H, et al. A randomized, single-blind and crossover study of an amino acid-based milk formula in treating young children with atopic dermatitis. *Pediatric Allergy and Immunology* 2004;**15**(6):558–61.
- Ogawa 2006** {published data only}  
Ogawa T, Hashikawa S, Asai Y, Sakamoto H, Yasuda K, Makimura Y. A new synbiotic, Lactobacillus casei subsp. casei together with dex-

## References to studies awaiting assessment

- Matsumoto 2007** {published data only}  
Matsumoto M, Aranami A, Ishige A, Watanabe K, Benno Y. LKM512 yoghurt consumption improves the intestinal environment and induces the T-helper type 1 cytokine in adult patients with intractable atopic dermatitis. *Clinical and Experimental Allergy* 2007;**37**:358–370.
- Roessler 2007** {published data only}  
Roessler A, Friedrich U, Vogelsang H, Bauer A, Kaatz M, Hipler UC, et al. The immune system in healthy adults and patients with atopic dermatitis seems to be affected differently by a probiotic intervention. *Clinical and Experimental Allergy* 2007;**38**:93–102.

## References to ongoing studies

- CAMEL** {published and unpublished data}  
Hol. Cow's milk allergy mediated by elimination and probiotics. ISRCTN 04799749. [: ISRCTN 04799749]
- Goossens** {published data only}  
Goossens. Effects of synbiotics in infants with atopic dermatitis. ISRCTN 69085979. [: ISRCTN 69085979]
- Land** {published data only}  
Land. The effects of probiotics in atopic dermatitis. NCT00378300.
- Murray** {published data only}  
Murray. Probiotics in Atopic Dermatitis in Infancy. ISRCTN 41490500. [: ISRCTN 41490500]

## Additional references

### Allen 2003

Allen SJ, Okoko B, Martinez E, Gregorio G, Dans LF. Probiotics for treating infectious diarrhoea. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD003048.pub2]

### Archer 2000

Archer CB. The pathophysiology and clinical features of atopic dermatitis. In: Williams H editor(s). *Atopic Dermatitis. The epidemiology, causes and prevention of atopic eczema*. 1st Edition. Cambridge: Cambridge University Press, 2000:25–40.

### Baum 2002

Baum WF, Schneyer U, Lantusch AM, Kloditz E. Delay of growth and development in children with bronchial asthma, atopic dermatitis and allergic rhinitis. *Experimental & Clinical Endocrinology & Diabetes* 2002;**110**(2):53–9.

### Beck 2000

Beck LA, Leung DY. Allergen sensitization through the skin induces systemic allergic responses. *Journal of Allergy & Clinical Immunology* 2000;**106**(5 Suppl):S258–63.

### Besselink 2008

Besselink MGH, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised double-blind placebo-controlled trial. *Lancet* 2008;**371**:651–9.

### Bjorksten 2001

Bjorksten B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. *Journal of Allergy and Clinical Immunology* 2001;**108**(4):516–20.

### Bohme 2001

Bohme M, Svensson A, Kull I, Nordvall SL, Wahlgren CF. Clinical features of atopic dermatitis at two years of age: a prospective, population-based case-control study. *Acta Dermato-Venerologica* 2001;**81**(3):193–7.

### Borriello 2003

Borriello SP, Hammes WP, Holzapfel W, Marteau P, Schrezenmeir J, Vaara M, et al. Safety of probiotics that contain lactobacilli or bifidobacteria. *Clinical Infectious Diseases* 2003;**36**(6):775–80.

### Boyle 2006

Boyle RJ, Robins-Browne RM, Tang ML. Probiotic use in clinical practice: what are the risks?. *American Journal of Clinical Nutrition* 2006;**83**(6):1256–64.

### Burton 2006

Burton JP, Wescombe PA, Moore CJ, Chilcott CN, Tagg JR. Safety assessment of the oral cavity probiotic *Streptococcus salivarius* K12. *Applied & Environmental Microbiology* 2006;**72**(4):3050–3.

### Caffarelli 1998

Caffarelli C, Cavagni G, Deriu FM, Zanotti P, Atherton DJ. Gastrointestinal symptoms in atopic eczema. *Archives of Disease in Childhood* 1998;**78**(3):230–4. [MEDLINE: 9613352]

### Charman 2000

Charman C, Williams HC. Outcome measures of disease severity in atopic eczema. *Archives of Dermatology* 2000;**136**:763–9.

### Charman 2002

Charman C, Williams HC. Epidemiology. In: Thomas Bieber, Donald YM Leung editor(s). *Atopic Dermatitis*. 1st Edition. New York: Marcel Dekker Inc, 2002:21–42.

### Cherifi 2004

Cherifi S, Robberecht J, Miendje Y. *Saccharomyces cerevisiae* fungemia in an elderly patient with *Clostridium difficile* colitis. *Acta Clinica Belgica* 2004;**59**(4):223–4.

### Chren 1997

Chren MM, Lasek RT, Flocke SA, Zyzanski SJ. Improved discriminative and evaluative capability of a refined version of SKINDEX, a quality-of-life instrument for patients with skin diseases. *Archives of Dermatology* 1997;**133**:1433–40.

### Christensen 2002

Christensen HR, Frokiaer H, Pestka JJ. Lactobacilli differentially modulate expression of cytokines and maturation surface markers in murine dendritic cells. *Journal of Immunology* 2002;**168**(1):171–8.

### Connolly 2005

Connolly E, Abrahamsson T, Bjorksten B. Safety of D(-)-lactic acid producing bacteria in the human infant. *Journal of Pediatric Gastroenterology & Nutrition* 2005;**41**(4):489–92.

### Cookson 2002

Cookson W. Genetics and genomics of asthma and allergic diseases. *Immunological Review* 2002;**190**:195–206.

### De Groote 2005

De Groote MA, Frank DN, Dowell E, Glode MP, Pace NR. Lactobacillus rhamnosus GG bacteremia associated with probiotic use in a child with short gut syndrome. *The Pediatric Infectious Disease Journal* 2005;**24**(3):278–80.

### Ellis 2002

Ellis CN, Drake LA, Prendergast MM, Abramovits W, Boguniewicz M, Daniel CR, et al. Cost of atopic dermatitis and eczema in the United States. *Journal of the American Academy of Dermatology* 2002;**46**(3):361–70.

### Emerson 1998

Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *British Journal of Dermatology* 1998;**139**(1):73–6.

### Ernst 2000

Ernst E, Pittler MH, Stevinson C. Complementary/alternative medicine in dermatology: evidence-assessed efficacy of two diseases and two treatments. *American Journal of Clinical Dermatology* 2000;**3**(5):341–8.

### FAOWHO 2002

Report FAOWHO. Guidelines for the evaluation of probiotics in food. [www.who.int/entity/foodsafety/fs\\_management/en/probiotic\\_guidelines.pdf](http://www.who.int/entity/foodsafety/fs_management/en/probiotic_guidelines.pdf). London, Ontario, Canada, 2002.

### Fennessy 2000

Fennessy M, Coupland S, Popay J, Naysmith K. The epidemiology and experience of atopic eczema during childhood: a discussion paper on the implications of current knowledge for health care, public health policy and research. *Journal of Epidemiology & Community Health* 2000;**54**(8):581–9.

- Finlay 1996**  
Finlay AY. Measurement of disease activity and outcome in atopic dermatitis. *The British Journal of Dermatology* 1996;**135**:509–15.
- Flohr 2004**  
Flohr C, Johansson SGO, Wahlgren C-F, Williams H. How atopic is atopic dermatitis?. *The Journal of Allergy and Clinical Immunology* 2004;**114**:150–8.
- Gionchetti 2000**  
Gionchetti P, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;**119**(2):305–9.
- Hennequin 2000**  
Hennequin C, Kauffmann-Lacroix C, Jobert A, Viard JP, Ricour C, Jacquemin JL, et al. Possible role of catheters in *Saccharomyces boulardii* fungemia. *European Journal of Clinical Microbiology and Infectious Diseases* 2000;**19**(1):16–20.
- Hoare 2000**  
Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technology Assessment (Winchester, England)* 2000;**4**(37):1–191.
- Ishibashi 2001**  
Ishibashi N, Yamazaki S. Probiotics and safety. *American Journal of Clinical Nutrition* 2001;**73**(2 Suppl):S465–70.
- Johansson 2001**  
Johansson SGO, Hourihane J, Bousquet J, Brujinzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy: an EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–24.
- Johansson 2004**  
Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *The Journal of Allergy and Clinical Immunology* 2004;**113**:832–6.
- Juni 2001**  
Juni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. *BMJ* 2001;**323**:42–6.
- Kalliomaki 2001**  
Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *Journal of Allergy and Clinical Immunology* 2001;**107**(1):129–34.
- Kemp 1999**  
Kemp AS. Atopic eczema: its social and financial costs. *Journal of Paediatrics and Child Health* 1999;**35**(3):229–31.
- Kukkonen 2007**  
Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *Journal of Allergy and Clinical Immunology* 2007;**119**(1):192–8. [MEDLINE: 17208601]
- Kunz 1997**  
Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997;**195**(1):10–9.
- Lamb 2002**  
Lamb SR, Rademaker M. Pharmacoeconomics of drug therapy for atopic dermatitis. *Expert Opinion on Pharmacotherapy* 2002;**3**(3):249–55.
- Land 2005**  
Land MH, Rouster-Stevens K, Woods CR, Cannon ML, Cnota J, Shetty AK. *Lactobacillus* sepsis associated with probiotic therapy. *Pediatrics* 2005;**115**(1):178–81.
- Lawson 1998**  
Lawson V, Lewis-Jones MS, Finlay AY, et al. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. *British Journal of Dermatology* 1998;**138**(1):107–13.
- Lestin 2003**  
Lestin F, Pertschy A, Rimek D. Fungemia after oral treatment with *Saccharomyces boulardii* in a patient with multiple comorbidities [Fungämie nach oraler Gabe]. *Deutsche Medizinische Wochenschrift* 2003;**128**(48):2531–3.
- Makelainen 2003**  
Makelainen H, Tahvonen R, Salminen S, Ouwehand AC. In vivo safety assessment of two *Bifidobacterium longum* strains. *Microbiology & Immunology* 2003;**47**(12):911–4.
- McHenry 1995**  
McHenry PM, Williams HC, Bingham EA. Management of atopic eczema. Joint Workshop of the British Association of Dermatologists and the Research Unit of the Royal College of Physicians of London. *BMJ* 1995;**310**(6983):843–7.
- Moro 2006**  
Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U, Boehm G. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. *Archives of Disease in Childhood* 2006;**91**(10):814–9. [MEDLINE: 16873437]
- Murray 2005**  
Murray CS, Tannock GW, Simon MA, Harmsen HJ, Welling GW, Custovic A, et al. Fecal microbiota in sensitized wheezy and non-sensitized non-wheezy children: a nested case-control study. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2005;**35**(6):741–5.
- Osborn 2007**  
Osborn DA, Sinn JK. Probiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD006475.pub2]
- Pessi 2000**  
Pessi T, Sutas Y, Hurme M, Isolauri E. Interleukin-10 generation in atopic children following oral *Lactobacillus rhamnosus* GG. *Clinical and Experimental Allergy* 2000;**30**(12):1804–8.
- Polosa 2001**  
Polosa R. The interaction between particulate air pollution and allergens in enhancing allergic and airway responses. *Current Allergy & Asthma Reports* 2001;**1**(2):102–7.
- Proksch 2003**  
Proksch E, Jensen JM, Elias PM. Skin lipids and epidermal differentiation in atopic dermatitis. *Clinical Dermatology* 2003;**21**(2):134–44.

**Riquelme 2003**

Riquelme AJ, Calvo MA, Guzman AM, Depix MS, Garcia P, Perez C, et al. Saccharomyces cerevisiae fungemia after Saccharomyces boulardii treatment in immunocompromised patients. *Journal of Clinical Gastroenterology* 2003;**36**(1):41–3.

**Robertson 2004**

Robertson CF, Roberts MF, Kappers JH. Asthma prevalence in Melbourne schoolchildren: have we reached the peak?. *Medical Journal of Australia* 2004;**180**(6):273–6.

**Ruden 1999**

Ruden U, Wahn U, Kehrt, R. [Entwicklung und Validierung eines krankheitsspezifischen Fragebogens zur Erfassung der Lebensqualität von Eltern neurodermitiskrankter Kinder]. *Z Gesundheitswiss* 1999;**4**:335–350.

**Salminen 1998**

Salminen S, von Wright A, Morelli L, Marteau P, Brassart D, de Vos WM, et al. Demonstration of safety of probiotics - a review. *International Journal of Food Microbiology* 1998;**44**(1-2):93–106.

**Sepp 1993**

Sepp E, Mikelsaar M, Salminen S. Effect of lactobacillus casei strain GG administration on the gastrointestinal microbiota of newborns. *Microbial Ecology in Health and Disease* 1993;**6**:309–14.

**Smethurst 2002**

Smethurst D. Atopic eczema. *Clinical Evidence*. London: BMJ, 2002: 1664–82.

**Spanhaak 1998**

Spanhaak S, Havenaar R, Schaafsma G. The effect of consumption of milk fermented by lactobacillus casei strain Shirota on the intestinal microflora and immune parameters in humans. *European Journal of Clinical Nutrition* 1998;**52**(12):899–907.

**Srinivasan 2006**

Srinivasan R, Meyer R, Padmanabhan R, Britto J. Clinical safety of Lactobacillus casei shirota as a probiotic in critically ill children. *Journal of Pediatric Gastroenterology & Nutrition* 2006;**42**(2):171–3.

**Su 1997**

Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. *Archives of Diseases in Childhood* 1997;**76**(2):159–62.

**Thestrup 2002**

Thestrup-Pedersen K. Treatment principles of atopic dermatitis. *Journal of the European Academy of Dermatology & Venereology* 2002;**16**(1):1–9.

**Van Bever 2002**

Van Bever HP. Early events in atopy. *European Journal of Pediatrics* 2002;**161**(10):542–6.

**Werfel 2004**

Werfel T, Breuer K. Role of food allergy in atopic dermatitis. *Current Opinions in Allergy and Clinical Immunology* 2004;**4**(5):379–85.

**Williams 1999**

Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *Journal of Allergy and Clinical Immunology* 1999;**103**(1 Pt 1):125–38.

**Williams 2005**

Williams HC. Clinical practice. Atopic dermatitis. *New England Journal of Medicine* 2005;**352**(22):2314–24.

**Wolf 1998**

Wolf BW, Wheeler KB, Ataya DG, Garleb KA. Safety and tolerance of Lactobacillus reuteri supplementation to a population infected with the human immunodeficiency virus. *Food & Chemical Toxicology* 1998;**36**(12):1085–94.

**Yoshioka 1983**

Yoshioka H, Iseki K, Fujita K. Development and differences of intestinal flora in the neonatal period in breast-fed and bottle-fed infants. *Pediatrics* 1983;**72**(3):317–21.

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Brouwer 2006

|              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods      | Three month parallel group randomised controlled trial.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Participants | Fifty infants under five months age with mild/moderate eczema diagnosed using Hanifin and Rajka criteria, and a clinical history suggestive of cow's milk allergy. All participants were exclusively formula fed, and received an extensively hydrolysed formula for three to five weeks prior to receiving the study intervention. Infants receiving antihistamines, oral corticosteroids or any probiotic/antibiotic/antimycotic in the preceding four weeks were excluded, as were those with a congenital gastrointestinal malformation. Setting primary care in the Netherlands. One participant lost to follow-up. |

**Brouwer 2006***(Continued)*

|               |                                                                                                                                                                                                                                                                    |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Interventions | Extensively hydrolysed whey-based formula given alone, with <i>Lactobacillus rhamnosus</i> at $5 \times 10^9$ cfu/100mls or with <i>Lactobacillus GG</i> at $5 \times 10^9$ cfu/100mls. The study formula was offered at all feeds during the intervention period. |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|          |                                                         |
|----------|---------------------------------------------------------|
| Outcomes | SCORAD assessed at baseline, one, two and three months. |
|----------|---------------------------------------------------------|

|       |  |
|-------|--|
| Notes |  |
|-------|--|

***Risk of bias***

| Item                    | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear            | B - Unclear |

**Folster-Holst 2006**

|         |                                                        |
|---------|--------------------------------------------------------|
| Methods | Eight week parallel group randomised controlled trial. |
|---------|--------------------------------------------------------|

|              |                                                                                                                                                                         |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Participants | Fifty-three children aged 1 to 55 months with eczema diagnosed using Hanifin and Rajka criteria. Setting German Dermatology Centre. Six participants lost to follow-up. |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|               |                                                                                                                                                                                                                              |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Interventions | <i>Lactobacillus GG</i> at $10^{10}$ cfu/day as a twice daily dose, or microcrystalline cellulose placebo. Interventions given as capsules, which were mixed with milk if bottle fed, or mixed with water if not bottle fed. |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|          |                                                                                                                                                                                                                                                                                     |
|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Outcomes | 1. Parent global assessment of disease severity<br>2. Quality of life score <a href="#">Ruden 1999</a><br>3. SCORAD<br>4. Use of topical corticosteroid and systemic antihistamine treatment. Assessments were made at two, four, six and eight weeks after the start of the study. |
|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|       |  |
|-------|--|
| Notes |  |
|-------|--|

***Risk of bias***

| Item                    | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear            | B - Unclear |

**Gruber 2007**

|         |                                                                                                                                                |
|---------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods | Twelve week parallel group randomised controlled trial.<br>The last observation carried forward approach was used for missing continuous data. |
|---------|------------------------------------------------------------------------------------------------------------------------------------------------|

|              |                                                                                                                                                                                                                  |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Participants | 106 children aged 3 to 12 months with mild/moderate eczema and SCORAD 15 to 40, not receiving antiinflammatory treatment. Four participants excluded from analysis after randomisation due to protocol breaches. |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**Gruber 2007***(Continued)*

|               |                                                                          |
|---------------|--------------------------------------------------------------------------|
| Interventions | Lactobacillus GG at $10^{10}$ cfu/day as a twice daily dose, or placebo. |
| Outcomes      | 1. SCORAD<br>2. Use of 1% hydrocortisone ointment                        |
| Notes         |                                                                          |

***Risk of bias***

| Item                    | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear            | B - Unclear |

**Isolaari 2000**

|               |                                                                                                                                                                                                                                                                                                       |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods       | Parallel group three arm randomised controlled trial. Duration of treatment unclear.                                                                                                                                                                                                                  |
| Participants  | Twenty-seven infants - ages not stated - with eczema diagnosed using the Hanifin and Rajka criteria. All infants were exclusively breast fed, and were tolerant of the study formula without added probiotic. Setting paediatric service in Finland. Unclear how many participants lost to follow-up. |
| Interventions | Extensively hydrolysed whey-dominant cow's milk formula with no probiotic added, with Lactobacillus GG added at $3 \times 10^8$ cfu/g or with Bifidobacterium lactis Bb-12 added at $1 \times 10^9$ cfu/g.                                                                                            |
| Outcomes      | SCORAD - interval of assessment unclear.                                                                                                                                                                                                                                                              |
| Notes         |                                                                                                                                                                                                                                                                                                       |

***Risk of bias***

| Item                    | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear            | B - Unclear |

**Kirjavainen 2003**

|               |                                                                                                                                                                                                                                                                                                         |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods       | Parallel group randomised controlled trial. Intended duration of treatment not clear.                                                                                                                                                                                                                   |
| Participants  | Twenty-seven infants (mean age 5.5 months) with eczema and suspected cow's milk allergy. Method for diagnosing eczema not described. Setting Hospital Paediatric department in Finland. Unclear how many participants lost to follow-up.                                                                |
| Interventions | Lactobacillus GG at $3 \times 10^{10}$ cfu/kg/day, mixed with extensively hydrolysed whey formula, or the same formula without probiotic. A third treatment arm (excluded from this review) used heat-inactivated LGG at $3 \times 10^{10}$ cfu/kg/day, mixed with extensively hydrolysed whey formula. |
| Outcomes      | SCORAD                                                                                                                                                                                                                                                                                                  |
| Notes         | Study terminated early due to adverse effects in a third treatment arm. The third treatment arm was not included in this systematic review since it involved the use of killed bacteria.                                                                                                                |

***Risk of bias***

| Item                    | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear            | B - Unclear |

### Majamaa 1997

|               |                                                                                                                                                                                                                                                                                                                               |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods       | One month parallel group randomised controlled trial.                                                                                                                                                                                                                                                                         |
| Participants  | Thirty-one children aged 2 to 16 months with eczema diagnosed using the Hanifin and Rajka criteria, and a history suggestive of cow's milk allergy. Children currently receiving systemic corticosteroid treatment were excluded. Setting of a paediatric clinic in Finland. Unclear how many participants lost to follow-up. |
| Interventions | Cow's milk elimination diet, topical eczema treatment and extensively hydrolysed cow's milk formula with or without addition of probiotic Lactobacillus GG. Probiotic given at $5 \times 10^8$ cfu/g formula.                                                                                                                 |
| Outcomes      | SCORAD assessed at one and two months.                                                                                                                                                                                                                                                                                        |
| Notes         |                                                                                                                                                                                                                                                                                                                               |

### *Risk of bias*

| Item                    | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear            | B - Unclear |

### Passeron 2006

|               |                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods       | Three month parallel group randomised controlled trial.                                                                                                                                                                                                                                                                                                                                             |
| Participants  | Forty-eight children aged 2 to 12 years with moderate/severe eczema diagnosed by UK Working Party Criteria and total SCORAD over 14. Exclusion criteria were current flare of eczema, exposure to systemic corticosteroids or immunosuppressants in the previous three months or other known immune deficiency. Setting hospital dermatology clinic in France. Nine participants lost to follow-up. |
| Interventions | Skim milk powder, potato starch and lactose containing prebiotic, with or without Lactobacillus rhamnosus Lcr35 at $3.6 \times 10^9$ cfu/day given as a three times daily dose mixed with cold water or other liquid.                                                                                                                                                                               |
| Outcomes      | 1. Parent or participant global assessment of eczema severity<br>2. SCORAD<br>3. Investigator global assessment of eczema severity<br>Assessments were at baseline, one, two and three months.                                                                                                                                                                                                      |
| Notes         | Three episodes of mild abdominal pain reported - Two in probiotic group, one in placebo (prebiotic alone) group.                                                                                                                                                                                                                                                                                    |

### *Risk of bias*

| Item                    | Authors' judgement | Description  |
|-------------------------|--------------------|--------------|
| Allocation concealment? | Yes                | A - Adequate |

## Rosenfeldt 2003

|               |                                                                                                                                                                                                                                                                                          |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods       | Six week randomised controlled cross-over trial.                                                                                                                                                                                                                                         |
| Participants  | Fifty-eight children aged 1 to 13 years with eczema diagnosed using the UK Working Party Criteria. Children who had received systemic corticosteroids at any time were excluded. Setting: hospital paediatric and dermatology departments in Denmark. 15 participants lost to follow-up. |
| Interventions | Skimmed milk powder with dextrose anhydrate 2 g/day or a mix of <i>Lactobacillus rhamnosus</i> 19070-2 and <i>Lactobacillus reuteri</i> DSM12246 at $2 \times 10^{10}$ cfu/day of each strain. Both placebo and probiotic preparations administered twice daily with 2.5 to 5ml water.   |
| Outcomes      | 1. Global self assessment by participant or parent<br>2. SCORAD<br>3. Need for other treatment - topical corticosteroid                                                                                                                                                                  |

Notes

### *Risk of bias*

| Item                    | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear            | B - Unclear |

## Sistek 2006

|               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods       | Twelve week parallel group randomised controlled trial.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Participants  | Sixty children aged 1 to 10 years with eczema diagnosed by UK Working Party criteria, SCORAD of at least ten at recruitment and a positive skin prick or RAST test to at least one common environmental or food allergen. Exclusion criteria were oral corticosteroid, immunosuppressant or antibiotic in the previous month, previous immune deficiency or malignancy and greater than ten point improvement in SCORAD during two weeks prior to commencing study treatment. Setting hospital clinic in New Zealand. One participant lost to follow-up. |
| Interventions | Microcrystalline cellulose placebo or <i>Lactobacillus rhamnosus</i> and <i>Bifidobacterium lactis</i> given together once daily at a combined total dose of $2 \times 10^{10}$ cfu/day. Treatment capsules administered as either a powder mixed with food or drink, or taken in capsule form.                                                                                                                                                                                                                                                          |
| Outcomes      | SCORAD assessed at two weeks before treatment, on commencing treatment, then 2, 12 and 16 weeks later.                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Notes One participant noted to be taking other non-investigational probiotic.

### *Risk of bias*

| Item                    | Authors' judgement | Description  |
|-------------------------|--------------------|--------------|
| Allocation concealment? | Yes                | A - Adequate |

## Taniuchi 2005

|               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods       | Three month parallel group randomised controlled trial.                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Participants  | Seventeen children aged 3 to 18 months with eczema diagnosed by Hanifin and Rajka criteria, and cows milk hypersensitivity diagnosed by suggestive history plus evidence of cow milk specific IgE. All participants had reduced levels of Bifidobacteria in their faeces (under 30% of total bacteria) and were receiving extensively hydrolysed cow's milk formula for at least two weeks prior to randomisation. Setting unclear. Unclear how many participants lost to follow-up. |
| Interventions | Raffinose prebiotic containing extensively hydrolysed cow's milk formula with or without Bifidobacterium breve M-16V at 5-15x10 <sup>9</sup> cfu/day.                                                                                                                                                                                                                                                                                                                                |
| Outcomes      | Investigator-rated eczema scoring system                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Notes         | No numerical outcome data available.                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

### *Risk of bias*

| Item                    | Authors' judgement | Description |
|-------------------------|--------------------|-------------|
| Allocation concealment? | Unclear            | B - Unclear |

## Viljanen 2005

|               |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods       | Four week parallel group randomised controlled trial.                                                                                                                                                                                                                                                                                                                                                                                                |
| Participants  | 252 infants aged under 12 months with a clinical diagnosis of eczema and a clinical history suggestive of cow's milk allergy. Infants who had received a probiotic preparation for over a week in the preceding six weeks were excluded. Participants were selected from primary care referrals to a hospital clinic in Finland. Twenty-two participants lost to follow-up.                                                                          |
| Interventions | Cow's milk elimination diet, extensively hydrolysed formula and capsules of either microcrystalline cellulose placebo, Lactobacillus GG (10 <sup>10</sup> cfu/day) or probiotic mix (Lactobacillus GG 10 <sup>10</sup> cfu/day, Bifidobacterium breve Bbi 99 at 4x10 <sup>8</sup> cfu/day, Lactobacillus rhamnosus LC705 at 10 <sup>10</sup> cfu/day and Propionibacterium JS 4x10 <sup>9</sup> cfu/day). Capsules were mixed with food twice daily. |
| Outcomes      | SCORAD assessed at the end of treatment and four weeks later.                                                                                                                                                                                                                                                                                                                                                                                        |
| Notes         |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

### *Risk of bias*

| Item                    | Authors' judgement | Description  |
|-------------------------|--------------------|--------------|
| Allocation concealment? | Yes                | A - Adequate |

**Weston 2005**

|               |                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods       | Eight week parallel group block randomised controlled trial.                                                                                                                                                                                                                                                                                                                                       |
| Participants  | Fifty-six children aged 6 to 18 months with moderate/severe eczema diagnosed by Hanifin and Rajka criteria and modified SCORAD score of at least 25 at enrolment. Those previously exposed to probiotics, currently receiving antibiotics or with other major medical problems were excluded. Community and hospital outpatient clinic setting in Australia. Three participants lost to follow-up. |
| Interventions | Lactobacillus fermentum VR1-003PCC 2x10 <sup>9</sup> cfu/day as a sachet reconstituted by parents with 5 to 10 ml water twice daily, or maltodextrin placebo.                                                                                                                                                                                                                                      |
| Outcomes      | 1. Global self assessment by parent<br>2. Dermatitis Family Impact Questionnaire <a href="#">Lawson 1998</a><br>3. SCORAD<br>4. Need for other eczema treatment - topical corticosteroid. Assessments made at baseline, 2, 4, 8 and 16 weeks.                                                                                                                                                      |
| Notes         | One probiotic treated participant withdrew due to gastrointestinal illness (vomiting).                                                                                                                                                                                                                                                                                                             |

***Risk of bias***

| Item                    | Authors' judgement | Description  |
|-------------------------|--------------------|--------------|
| Allocation concealment? | Yes                | A - Adequate |

<sup>a</sup> SCORAD - Scoring Atopic Dermatitis

UK - United Kingdom

cfu - Colony Forming Units

## Characteristics of excluded studies *[ordered by study ID]*

| Study           | Reason for exclusion                                        |
|-----------------|-------------------------------------------------------------|
| Arvola 2006     | Participants didn't have eczema.                            |
| Ikezawa 2004    | Intervention was not a probiotic.                           |
| Kalliomaki 2003 | Participants didn't have eczema.                            |
| Laitinen 2005   | Study did not report changes in eczema symptoms or severity |
| Leung 2004      | Intervention was not a probiotic                            |
| Ogawa 2006      | Study did not report changes in eczema symptoms or severity |
| Pohjavuori 2004 | Study did not report changes in eczema symptoms or severity |
| Prescott 2005   | Study did not report changes in eczema symptoms or severity |
| Rosenfeldt 2004 | Study did not report changes in eczema symptoms or severity |
| Viljanen 2005b  | Study did not report changes in eczema symptoms or severity |
| Viljanen 2005c  | Study did not report changes in eczema symptoms or severity |

## Characteristics of ongoing studies *[ordered by study ID]*

### CAMEL

|                     |                                                           |
|---------------------|-----------------------------------------------------------|
| Trial name or title | Cow's milk allergy mediated by elimination and probiotics |
| Methods             |                                                           |
| Participants        | 118 infants under 6 months with proven cow's milk allergy |
| Interventions       | Casein hydrolysate formula with or without probiotics     |
| Outcomes            |                                                           |
| Starting date       |                                                           |
| Contact information | Dr. Jeroen Hol, j.hol@erasmusmc.nl, Tel +31 104636946     |
| Notes               | ISRCTN 04799749; Trial due to complete 2008               |

## Goossens

|                     |                                                                                          |
|---------------------|------------------------------------------------------------------------------------------|
| Trial name or title | Effects of synbiotics in infants with atopic dermatitis                                  |
| Methods             | Multicenter randomised double blind placebo controlled parallel group intervention study |
| Participants        | Infants aged 0 to 7 months with eczema                                                   |
| Interventions       | Infant formula with or without synbiotics                                                |
| Outcomes            | SCORAD change after 12 weeks treatment                                                   |
| Starting date       | 1st September 2005                                                                       |
| Contact information | Dr DAM Goossens, Numico Research B.V., PO Box 7005, 6700 CA, Alkmaar, Netherlands        |
| Notes               | ISRCTN 69085979                                                                          |

## Land

|                     |                                                                              |
|---------------------|------------------------------------------------------------------------------|
| Trial name or title | The effects of probiotics in atopic dermatitis                               |
| Methods             | Randomised double blind placebo controlled parallel group intervention study |
| Participants        | Children aged six months to three years with moderate to severe eczema       |
| Interventions       | An oral probiotic                                                            |
| Outcomes            | SCORAD one month after commencing treatment with probiotic or placebo        |
| Starting date       | July 2007                                                                    |
| Contact information | Michael H Land, UCLA Medical Center, Los Angeles, California, 90095          |
| Notes               | <a href="#">NCT00378300</a>                                                  |

## Murray

|                     |                                                                                                     |
|---------------------|-----------------------------------------------------------------------------------------------------|
| Trial name or title | Probiotics in Atopic Dermatitis in Infancy                                                          |
| Methods             | Randomised double blind placebo controlled parallel group intervention study                        |
| Participants        | Infants aged three to six months with eczema                                                        |
| Interventions       | Lactobacillus paracasei and Bifidobacterium lactis                                                  |
| Outcomes            | SCORAD at the end of treatment                                                                      |
| Starting date       | 1st March 2002                                                                                      |
| Contact information | Dr. Clare Murray, North West Lung Research Centre, Wythenshawe Hospital, Southmoor Road, Manchester |

**Murray**

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*(Continued)*M23 9LT [cmurray@fs1.with.man.ac.uk](mailto:cmurray@fs1.with.man.ac.uk)

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NotesISRCTN 41490500 Trial completed

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## DATA AND ANALYSES

### Comparison 1. Probiotic vs Placebo

| Outcome or subgroup title                                                                         | No. of studies | No. of participants | Statistical method                   | Effect size           |
|---------------------------------------------------------------------------------------------------|----------------|---------------------|--------------------------------------|-----------------------|
| 1 Participant or parent-rated symptoms of eczema (SCORAD part C) at the end of treatment          | 5              |                     | Mean difference (Random, 95% CI)     | -0.90 [-2.84, 1.04]   |
| 1.1 Parallel group trials                                                                         | 4              |                     | Mean difference (Random, 95% CI)     | -0.68 [-3.07, 1.71]   |
| 1.2 Cross-over trials                                                                             | 1              |                     | Mean difference (Random, 95% CI)     | -1.80 [-3.59, -0.01]  |
| 2 Participant or parent-rated global change in eczema symptoms during treatment                   | 3              |                     | Odds ratio (Random, 95% CI)          | 0.40 [0.14, 1.15]     |
| 2.1 Parallel group trials                                                                         | 2              |                     | Odds ratio (Random, 95% CI)          | 0.70 [0.27, 1.77]     |
| 2.2 Cross-over trials                                                                             | 1              |                     | Odds ratio (Random, 95% CI)          | 0.18 [0.05, 0.60]     |
| 3 Parent or participant-rated eczema severity (SCORAD part C) (Long term)                         | 2              | 102                 | Mean Difference (IV, Random, 95% CI) | -2.27 [-3.97, -0.58]  |
| 4 Global eczema severity score (Total SCORAD) (Short term)                                        | 7              |                     | Mean difference (Random, 95% CI)     | -2.46 [-7.45, 2.53]   |
| 4.1 Parallel group studies                                                                        | 6              |                     | Mean difference (Random, 95% CI)     | -1.68 [-7.15, 3.80]   |
| 4.2 Cross-over studies                                                                            | 1              |                     | Mean difference (Random, 95% CI)     | -6.27 [-11.21, -1.32] |
| 5 Global eczema severity score (Total SCORAD) - Sensitivity analysis - Change score               | 5              |                     | Mean difference (Random, 95% CI)     | -2.47 [-4.72, -0.21]  |
| 5.1 Parallel group trial                                                                          | 4              |                     | Mean difference (Random, 95% CI)     | -2.15 [-4.64, 0.34]   |
| 5.2 Cross-over trial                                                                              | 1              |                     | Mean difference (Random, 95% CI)     | -3.93 [-9.25, 1.40]   |
| 6 Investigator-rated eczema severity (SCORAD parts A/B) (Long term)                               | 2              | 102                 | Mean Difference (IV, Fixed, 95% CI)  | -8.11 [-13.14, -3.09] |
| 7 Participant/parent-rated symptoms of eczema (SCORAD part C)(Short term)-Stratified by Age group |                |                     | Mean difference (Random, 95% CI)     | Subtotals only        |
| 7.1 Age under 2 years                                                                             | 2              |                     | Mean difference (Random, 95% CI)     | -0.13 [-4.18, 3.91]   |
| 7.2 Age 2-12 years                                                                                | 1              |                     | Mean difference (Random, 95% CI)     | 0.34 [-1.94, 2.60]    |
| 7.3 Age not categorised                                                                           | 2              |                     | Mean difference (Random, 95% CI)     | -2.23 [-3.71, -0.74]  |
| 8 Participant/parent-rated global change in symptoms of eczema (Short term) - Stratified by Age   |                |                     | Odds ratio (Random, 95% CI)          | Totals not selected   |
| 8.1 Age under 2 years                                                                             | 1              |                     | Odds ratio (Random, 95% CI)          | Not estimable         |
| 8.2 Age 2- 12 years                                                                               | 1              |                     | Odds ratio (Random, 95% CI)          | Not estimable         |
| 8.3 Age not categorised                                                                           | 1              |                     | Odds ratio (Random, 95% CI)          | Not estimable         |
| 9 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Age group              |                |                     | Mean difference (Random, 95% CI)     | Subtotals only        |
| 9.1 Age under 2 years                                                                             | 3              |                     | Mean difference (Random, 95% CI)     | 0.74 [-5.06, 6.54]    |

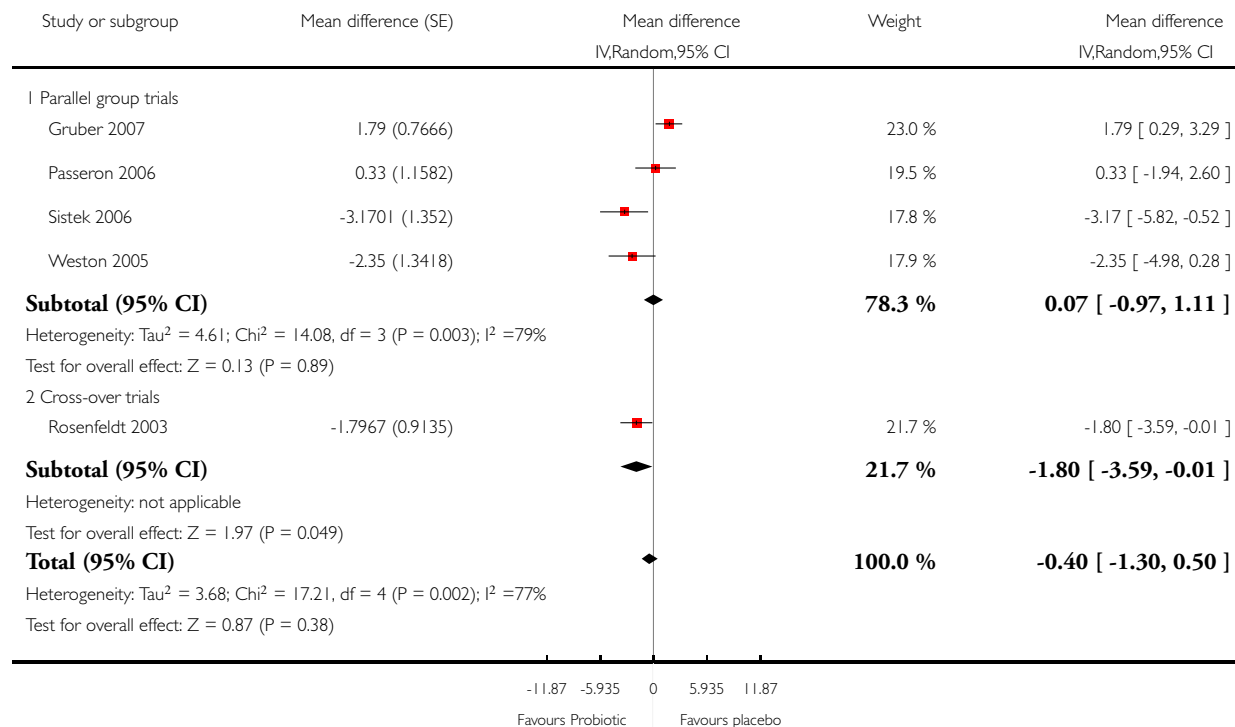
|                                                                                                           |   |     |                                      |                       |
|-----------------------------------------------------------------------------------------------------------|---|-----|--------------------------------------|-----------------------|
| 9.2 Age 2 - 12 years                                                                                      | 1 |     | Mean difference (Random, 95% CI)     | -3.29 [-13.78, 7.22]  |
| 9.3 Age not categorised                                                                                   | 3 |     | Mean difference (Random, 95% CI)     | -5.66 [-14.82, 3.50]  |
| 10 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Presence of Atopy             |   |     | Mean difference (Random, 95% CI)     | Subtotals only        |
| 10.1 Participants with atopy                                                                              | 2 |     | Mean difference (Random, 95% CI)     | -5.50 [-23.87, 12.87] |
| 10.2 Participants with unknown atopic status                                                              | 5 |     | Mean difference (Random, 95% CI)     | -1.73 [-7.29, 3.83]   |
| 11 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Challenge-Proven Food Allergy |   |     | Mean Difference (IV, Random, 95% CI) | Subtotals only        |
| 11.1 Food allergy present                                                                                 | 1 | 120 | Mean Difference (IV, Random, 95% CI) | 1.15 [-3.20, 5.50]    |
| 11.2 Unknown food allergic status                                                                         | 5 | 300 | Mean Difference (IV, Random, 95% CI) | -3.19 [-10.59, 4.20]  |
| 12 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Eczema Severity               |   |     | Mean Difference (IV, Random, 95% CI) | Subtotals only        |
| 12.1 Severe eczema (SCORAD over 40)                                                                       | 3 | 70  | Mean Difference (IV, Random, 95% CI) | -7.00 [-15.34, 1.34]  |
| 12.2 Moderate eczema (SCORAD 15-40)                                                                       | 4 | 175 | Mean Difference (IV, Random, 95% CI) | -3.45 [-10.34, 3.45]  |
| 12.3 Mild eczema (SCORAD under 15)                                                                        | 1 | 8   | Mean Difference (IV, Random, 95% CI) | -5.53 [-15.29, 4.23]  |
| 13 Global eczema severity (Total SCORAD) (Short term)-Stratified by Probiotic                             |   |     | Mean difference (Random, 95% CI)     | Subtotals only        |
| 13.1 Lactobacillus rhamnosus GG, either alone or in combination with different probiotic bacteria         | 3 |     | Mean difference (Random, 95% CI)     | 3.37 [0.55, 6.20]     |
| 13.2 Other Lactobacillus strains, either alone or in combination with different probiotic bacteria        | 4 |     | Mean difference (Random, 95% CI)     | -7.64 [-11.65, -3.62] |
| 14 Adverse events (Short term)                                                                            |   |     | Odds Ratio (M-H, Random, 95% CI)     | Subtotals only        |
| 14.1 Gastrointestinal symptoms                                                                            | 5 | 304 | Odds Ratio (M-H, Random, 95% CI)     | 1.57 [0.78, 3.15]     |

# **Analysis 1.1. Comparison 1 Probiotic vs Placebo, Outcome 1 Participant or parent-rated symptoms of eczema (SCORAD part C) at the end of treatment.**

Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

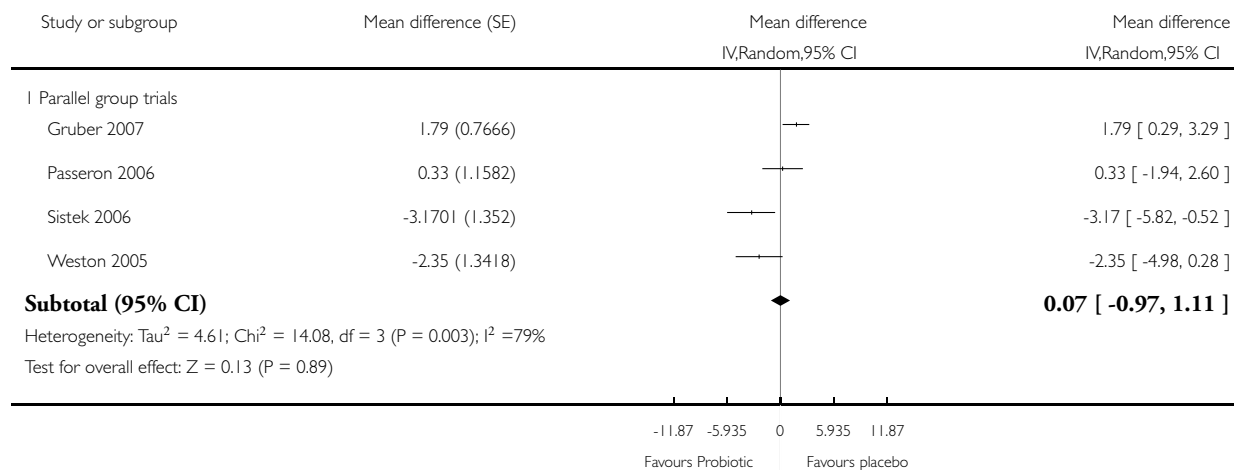
Outcome: 1 Participant or parent-rated symptoms of eczema (SCORAD part C) at the end of treatment



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

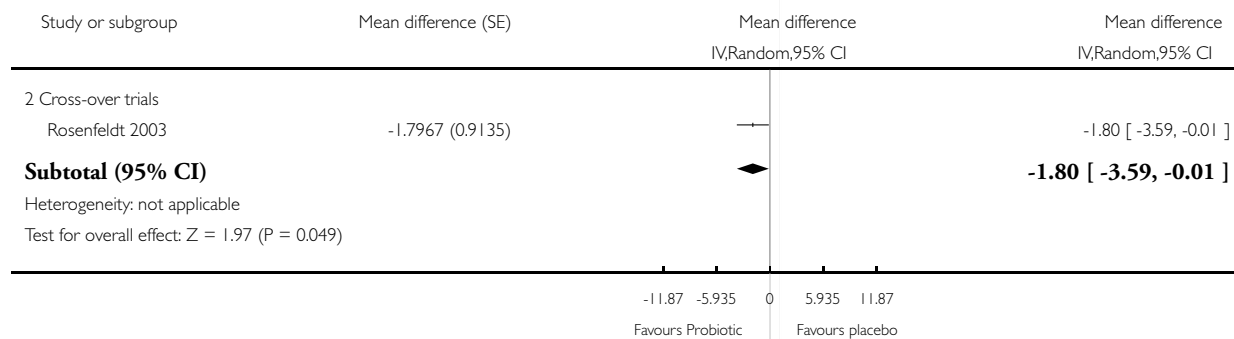
Outcome: I Participant or parent-rated symptoms of eczema (SCORAD part C) at the end of treatment



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

Outcome: I Participant or parent-rated symptoms of eczema (SCORAD part C) at the end of treatment

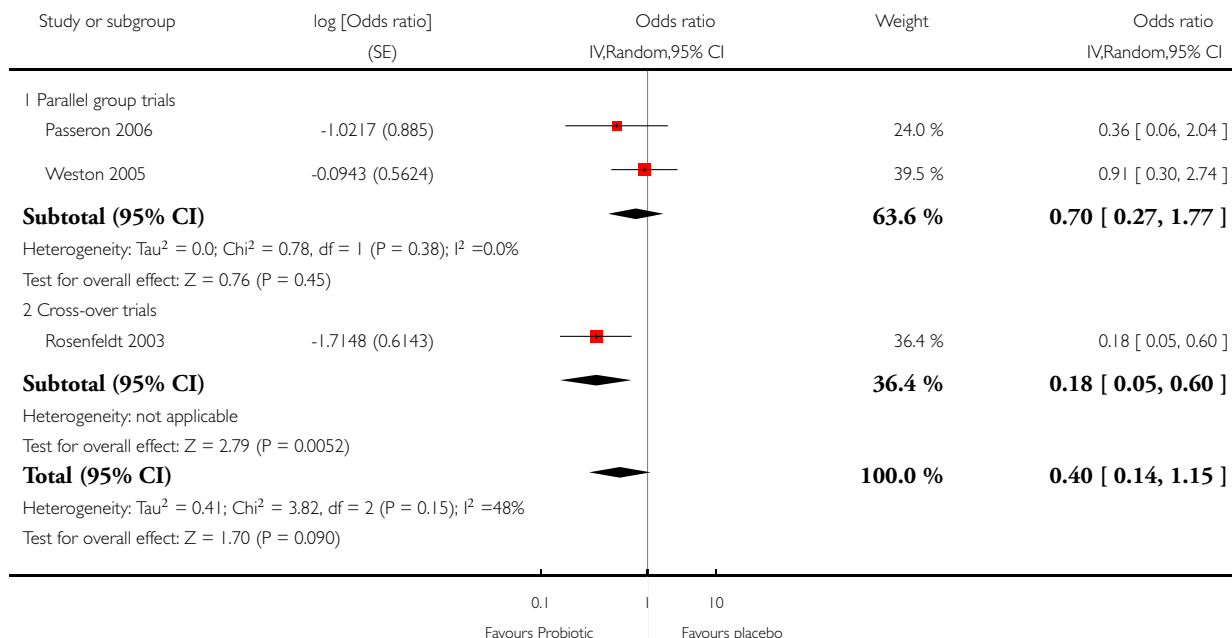


## Analysis 1.2. Comparison 1 Probiotic vs Placebo, Outcome 2 Participant or parent-rated global change in eczema symptoms during treatment.

Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

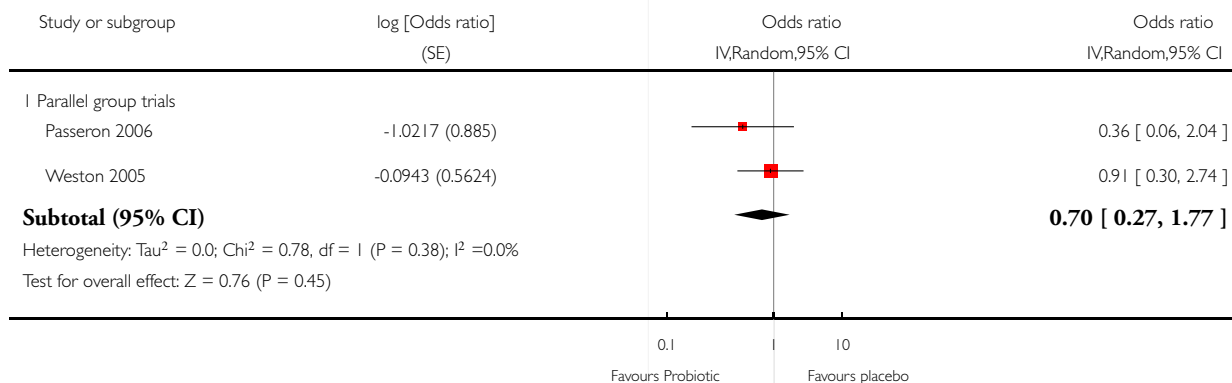
Outcome: 2 Participant or parent-rated global change in eczema symptoms during treatment



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

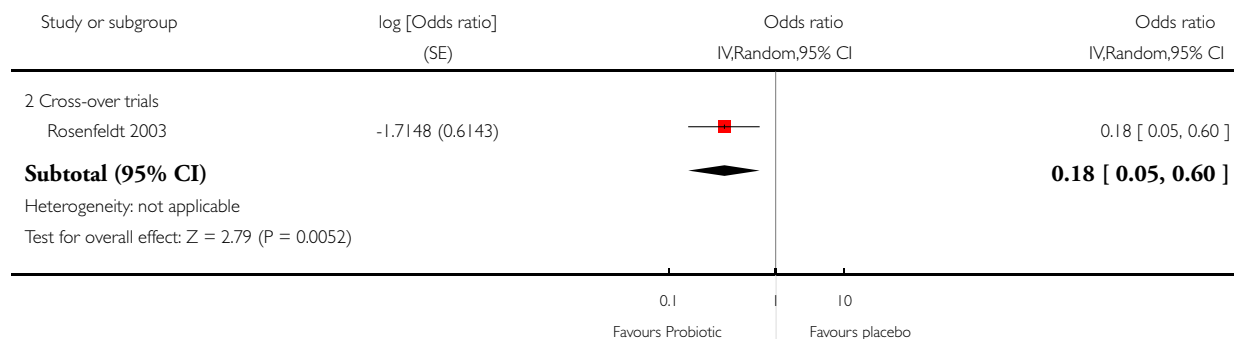
Outcome: 2 Participant or parent-rated global change in eczema symptoms during treatment



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

Outcome: 2 Participant or parent-rated global change in eczema symptoms during treatment

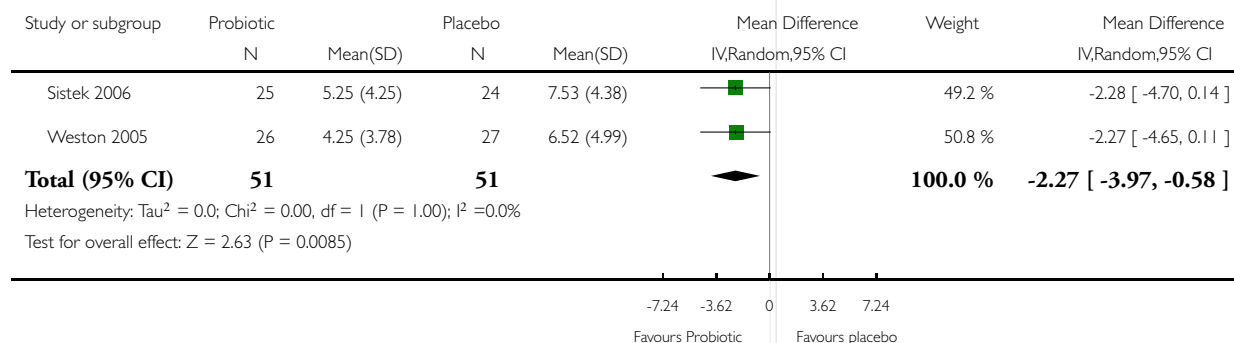


### Analysis 1.3. Comparison 1 Probiotic vs Placebo, Outcome 3 Parent or participant-rated eczema severity (SCORAD part C) (Long term).

Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

Outcome: 3 Parent or participant-rated eczema severity (SCORAD part C) (Long term)

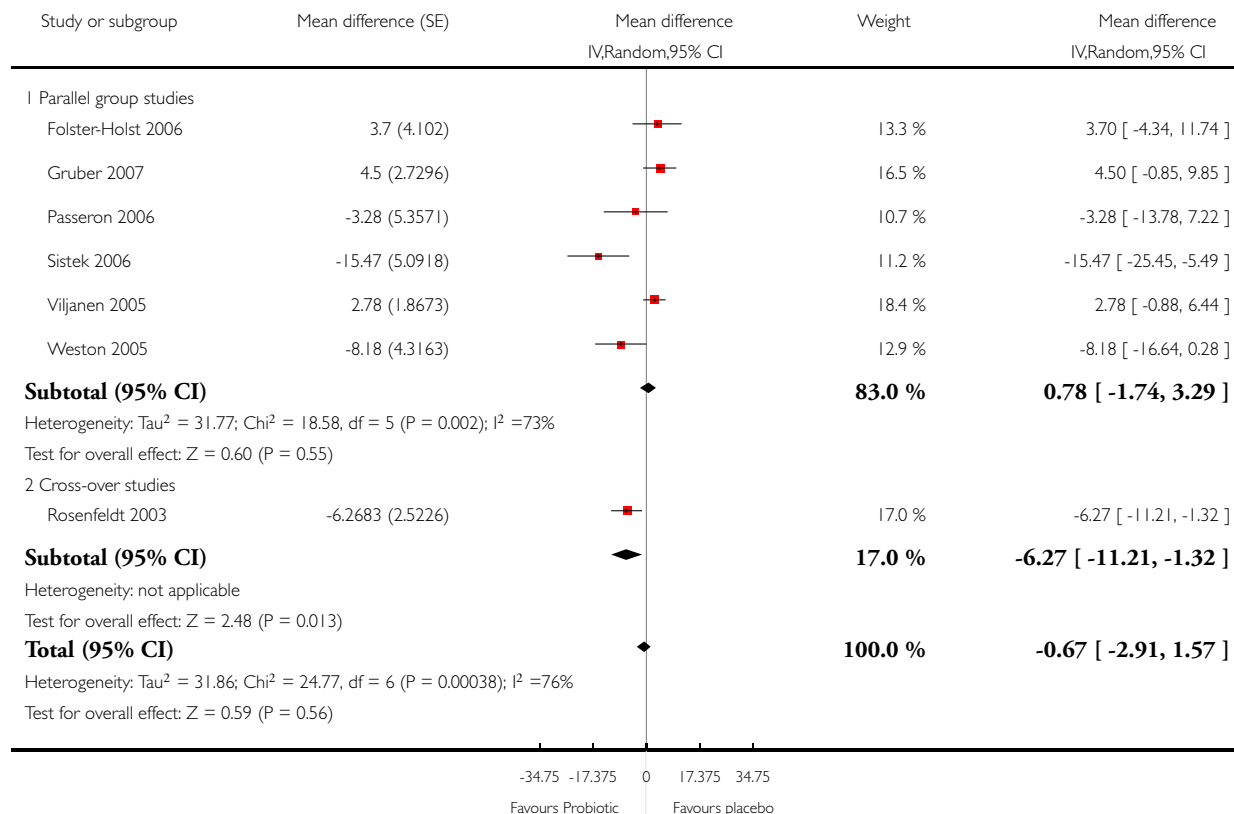


# **Analysis 1.4. Comparison 1 Probiotic vs Placebo, Outcome 4 Global eczema severity score (Total SCORAD) (Short term).**

Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

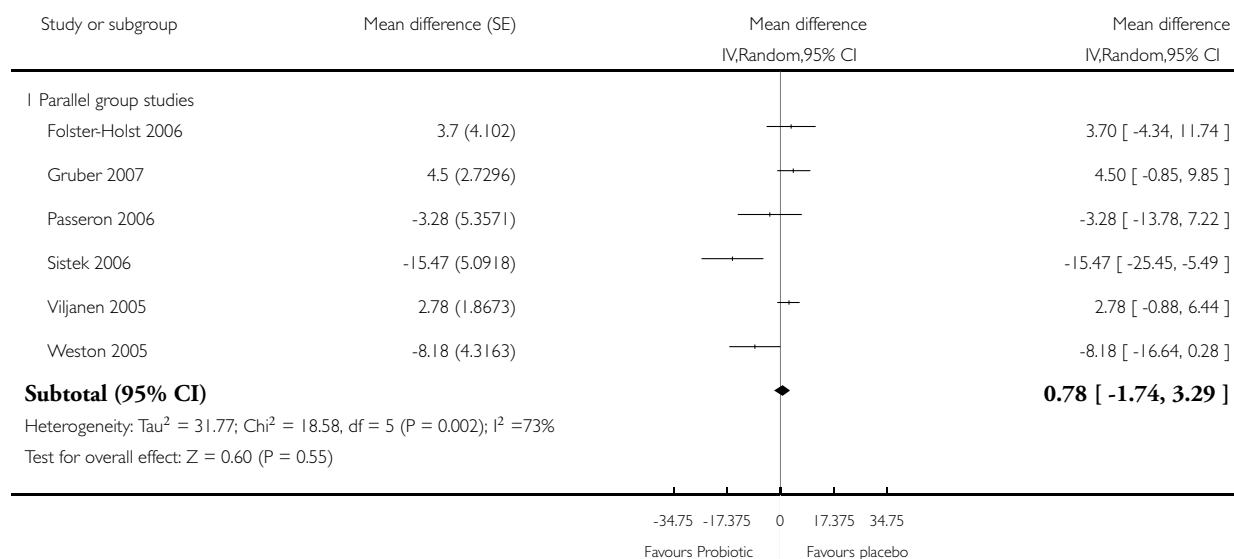
Outcome: 4 Global eczema severity score (Total SCORAD) (Short term)



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

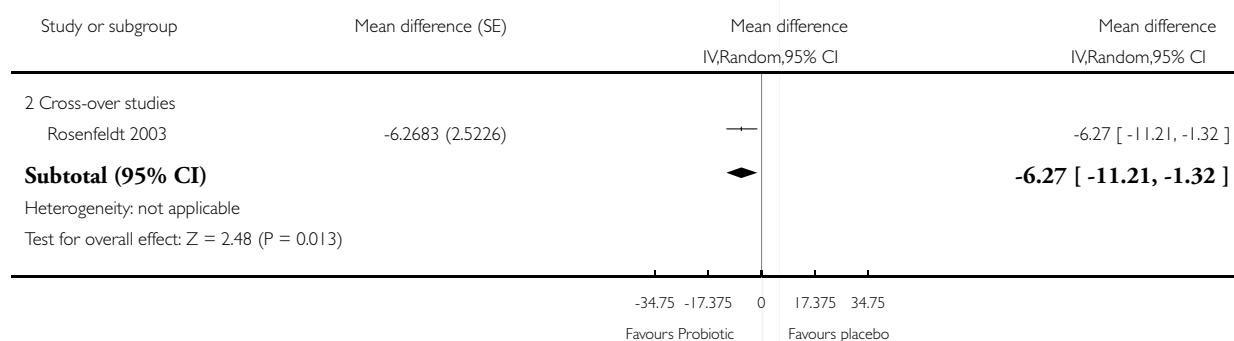
Outcome: 4 Global eczema severity score (Total SCORAD) (Short term)



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

Outcome: 4 Global eczema severity score (Total SCORAD) (Short term)

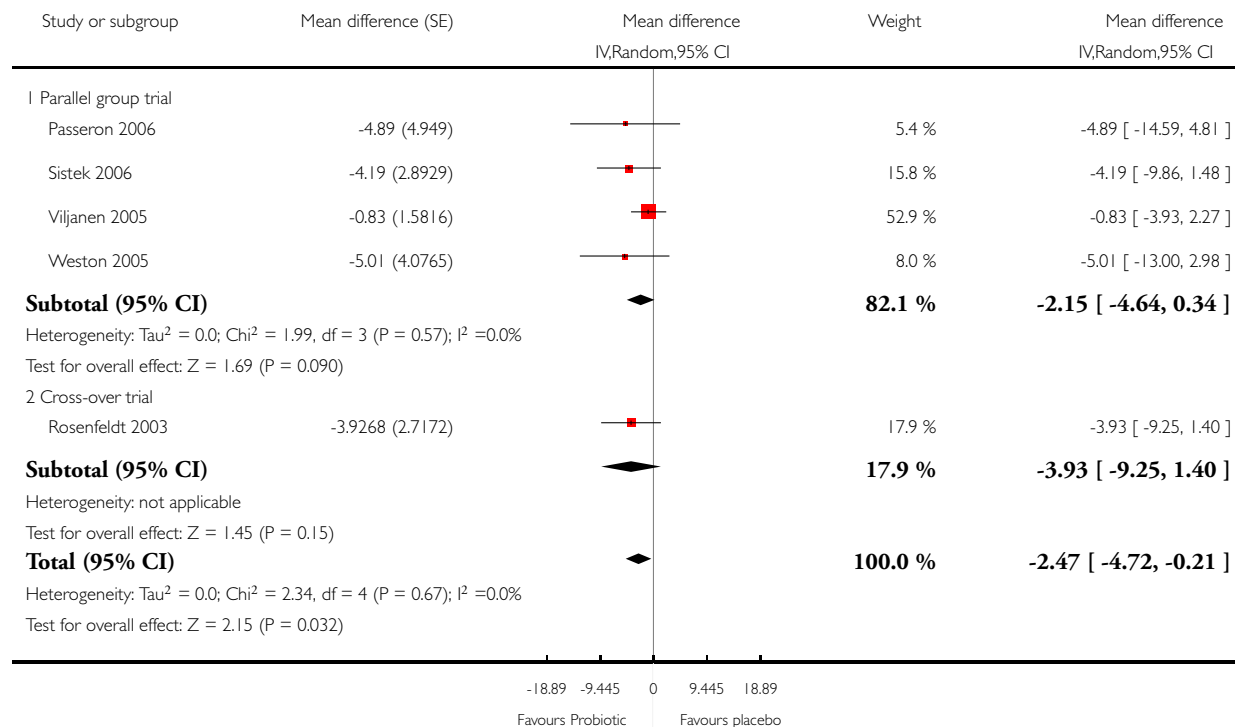


### Analysis 1.5. Comparison 1 Probiotic vs Placebo, Outcome 5 Global eczema severity score (Total SCORAD) - Sensitivity analysis - Change score.

Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

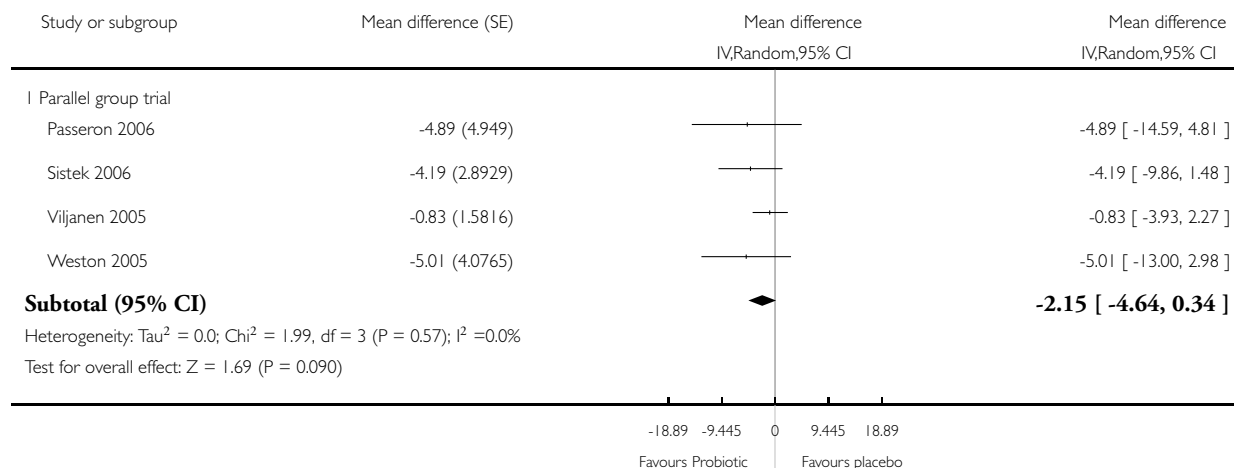
Outcome: 5 Global eczema severity score (Total SCORAD) - Sensitivity analysis - Change score



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

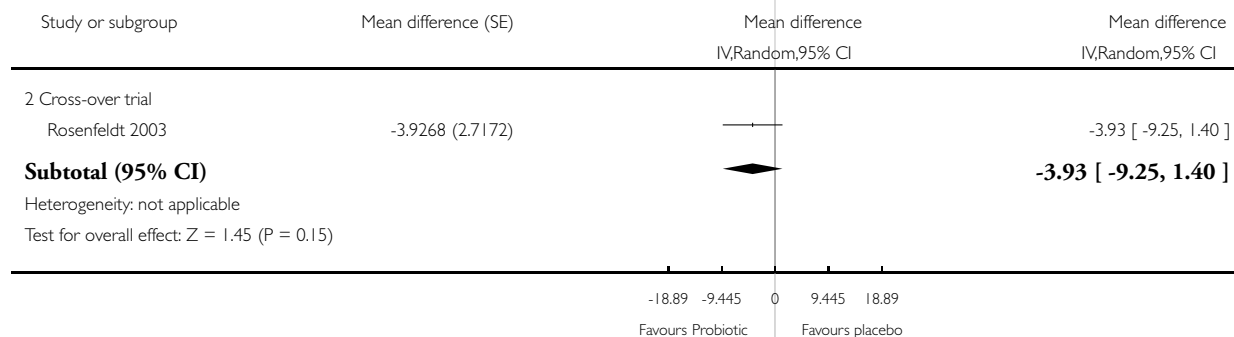
Outcome: 5 Global eczema severity score (Total SCORAD) - Sensitivity analysis - Change score



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

Outcome: 5 Global eczema severity score (Total SCORAD) - Sensitivity analysis - Change score

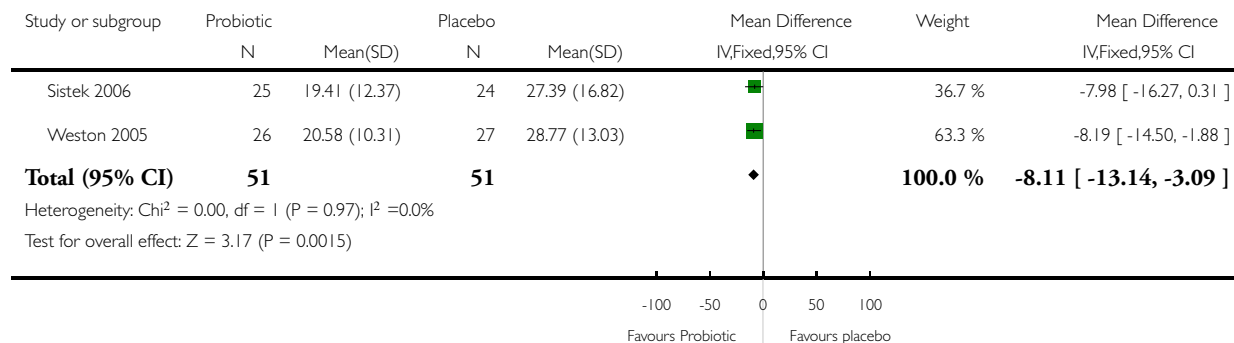


### Analysis 1.6. Comparison 1 Probiotic vs Placebo, Outcome 6 Investigator-rated eczema severity (SCORAD parts A/B) (Long term).

Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

Outcome: 6 Investigator-rated eczema severity (SCORAD parts A/B) (Long term)

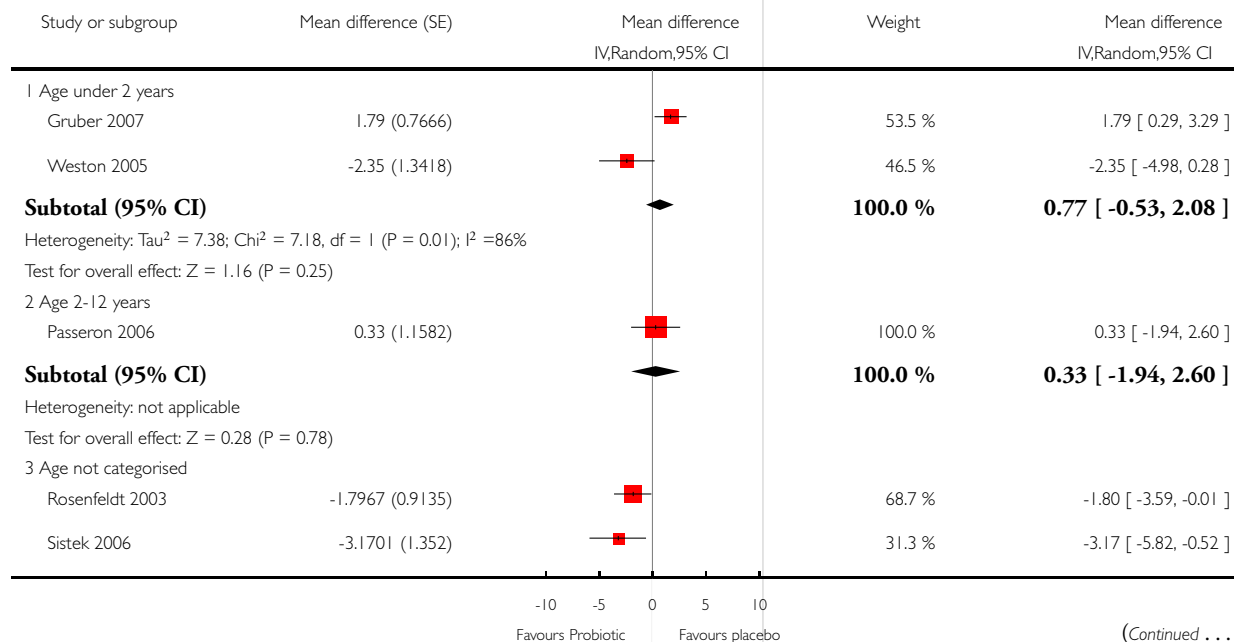


### Analysis 1.7. Comparison 1 Probiotic vs Placebo, Outcome 7 Participant/parent-rated symptoms of eczema (SCORAD part C)(Short term)-Stratified by Age group.

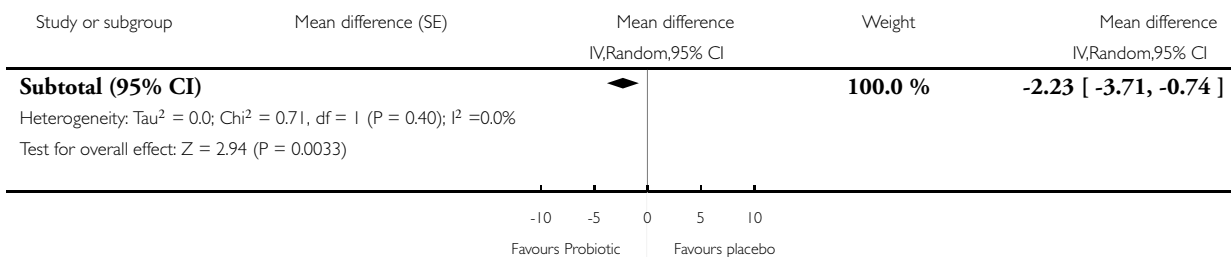
Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

Outcome: 7 Participant/parent-rated symptoms of eczema (SCORAD part C)(Short term)-Stratified by Age group



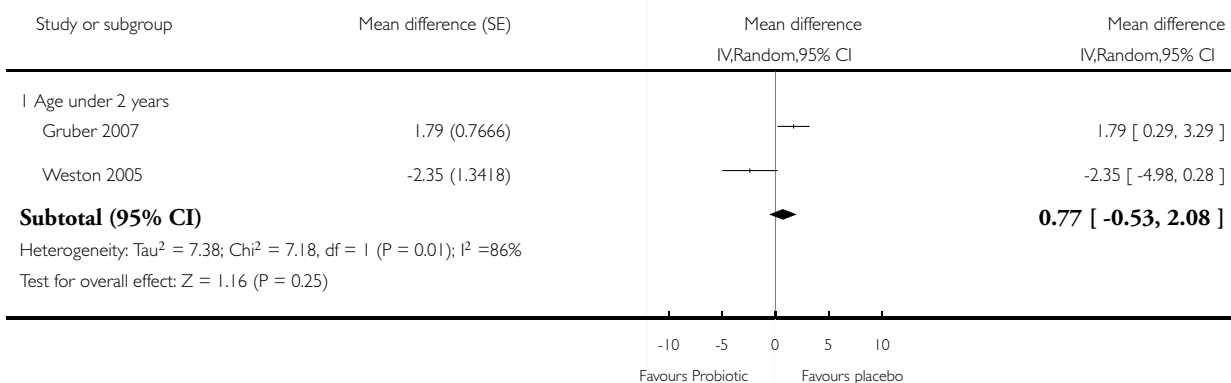
(... Continued)



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

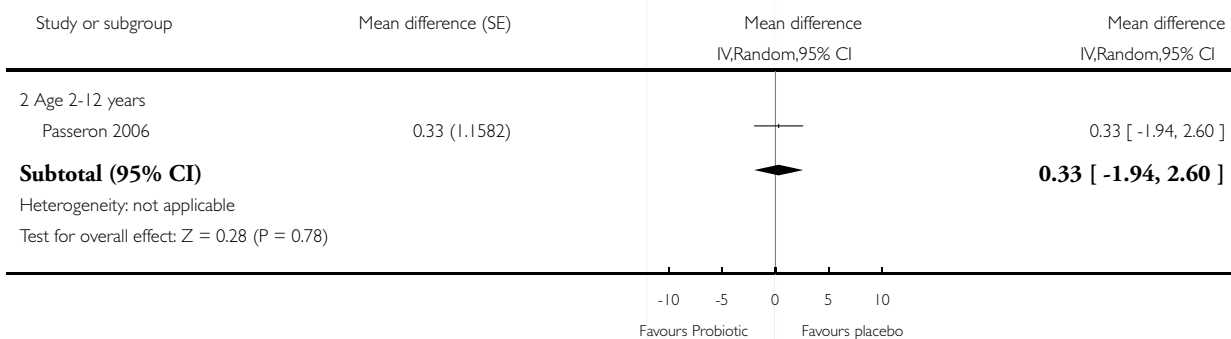
Outcome: 7 Participant/parent-rated symptoms of eczema (SCORAD part C)(Short term)-Stratified by Age group



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

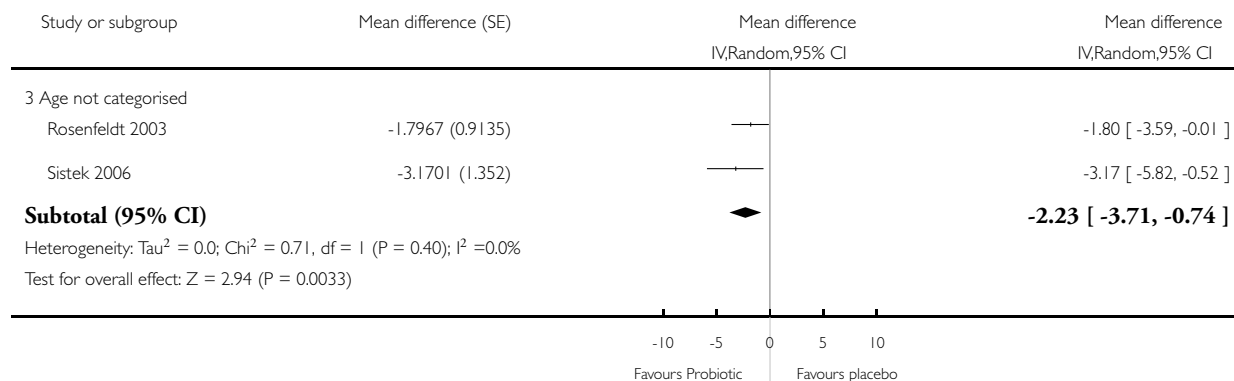
Outcome: 7 Participant/parent-rated symptoms of eczema (SCORAD part C)(Short term)-Stratified by Age group



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

Outcome: 7 Participant/parent-rated symptoms of eczema (SCORAD part C)(Short term)-Stratified by Age group

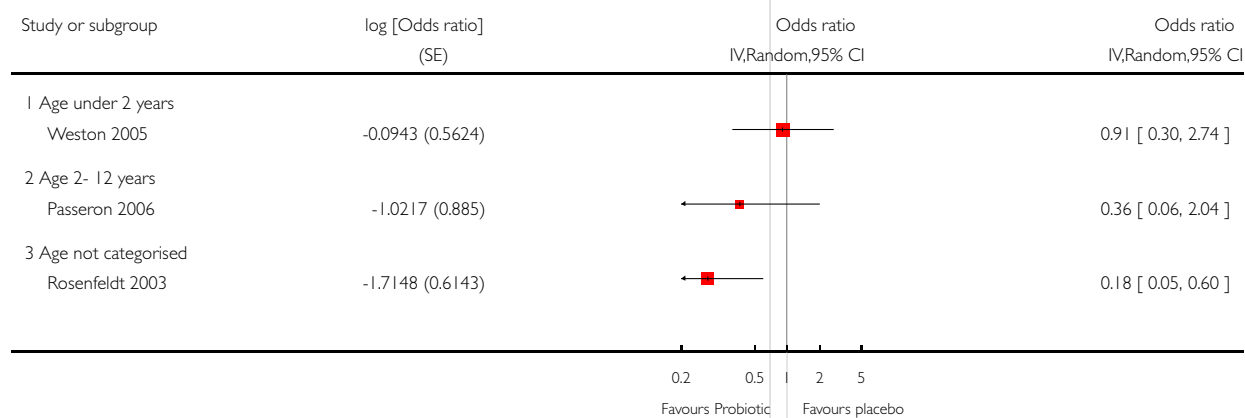


### Analysis 1.8. Comparison I Probiotic vs Placebo, Outcome 8 Participant/parent-rated global change in symptoms of eczema (Short term) - Stratified by Age.

Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

Outcome: 8 Participant/parent-rated global change in symptoms of eczema (Short term) - Stratified by Age



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

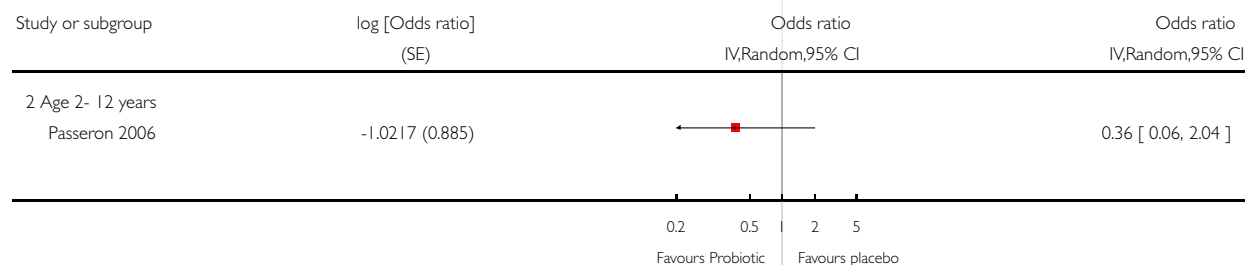
Outcome: 8 Participant/parent-rated global change in symptoms of eczema (Short term) - Stratified by Age



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

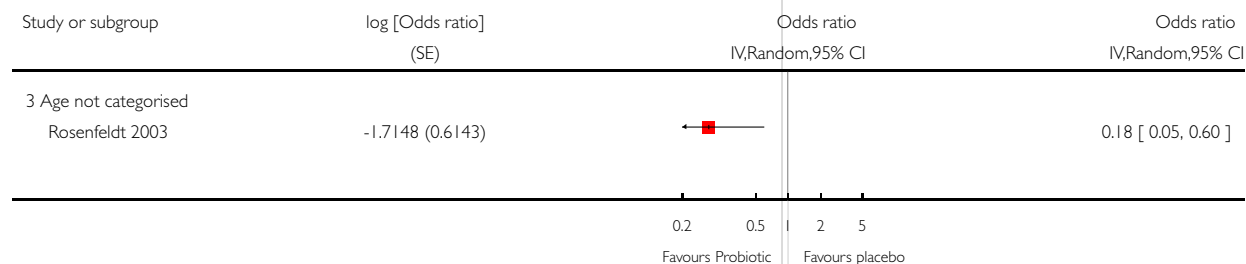
Outcome: 8 Participant/parent-rated global change in symptoms of eczema (Short term) - Stratified by Age



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

Outcome: 8 Participant/parent-rated global change in symptoms of eczema (Short term) - Stratified by Age

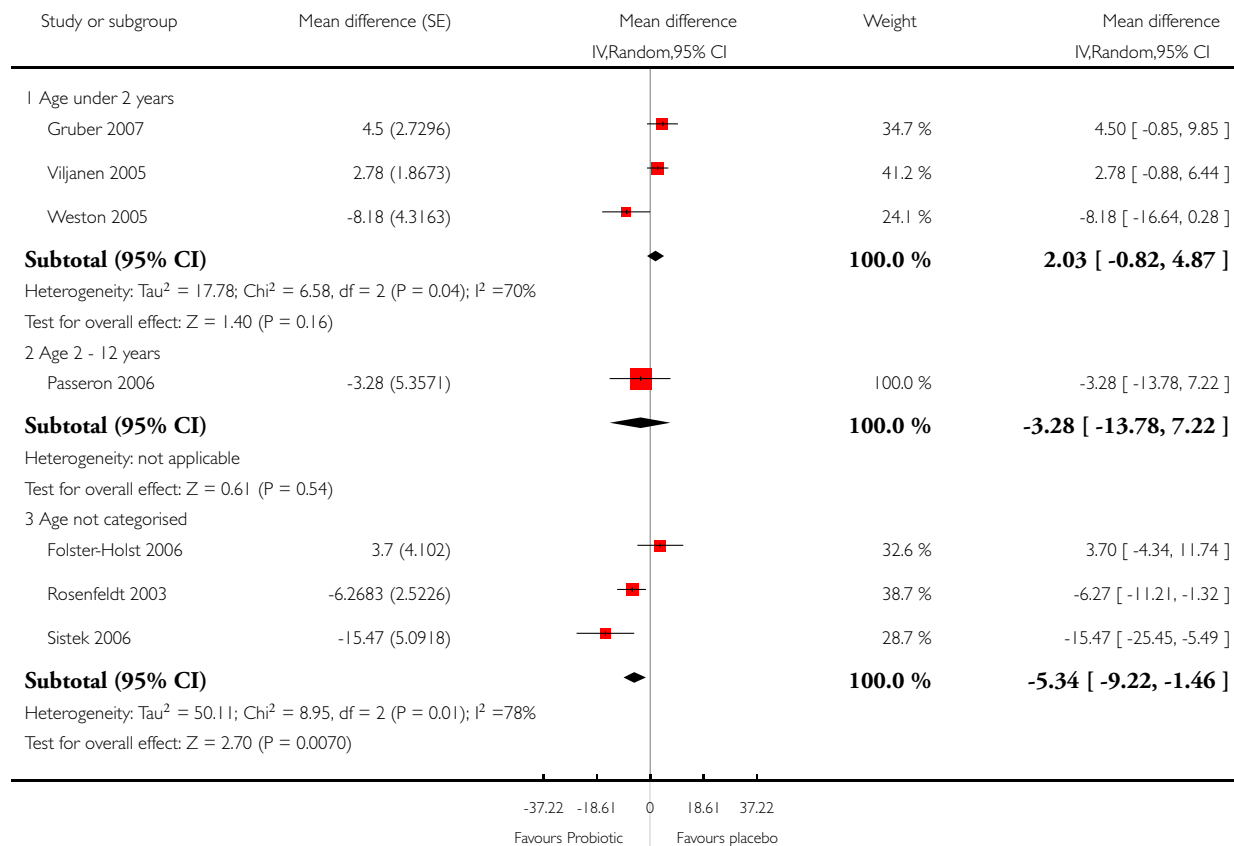


### Analysis 1.9. Comparison 1 Probiotic vs Placebo, Outcome 9 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Age group.

Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

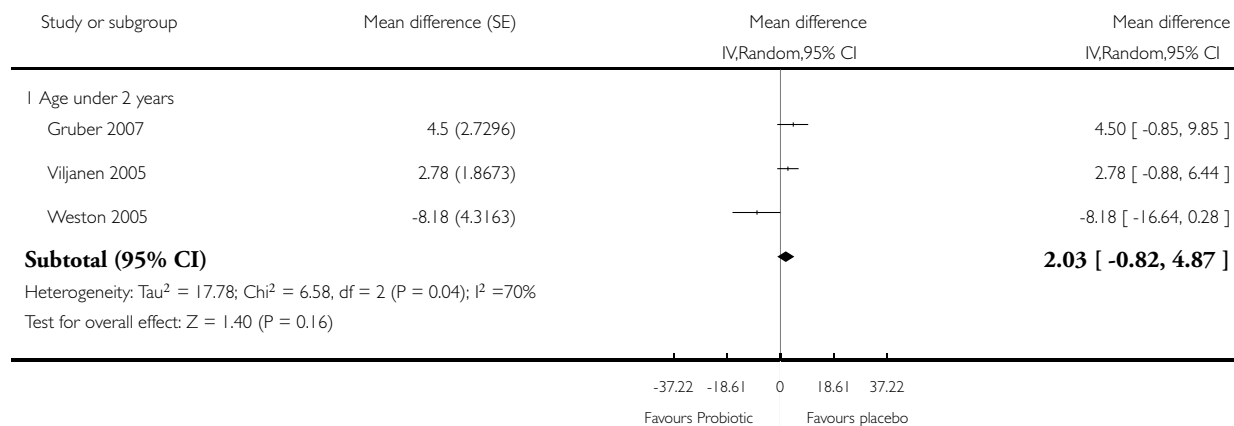
Outcome: 9 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Age group



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

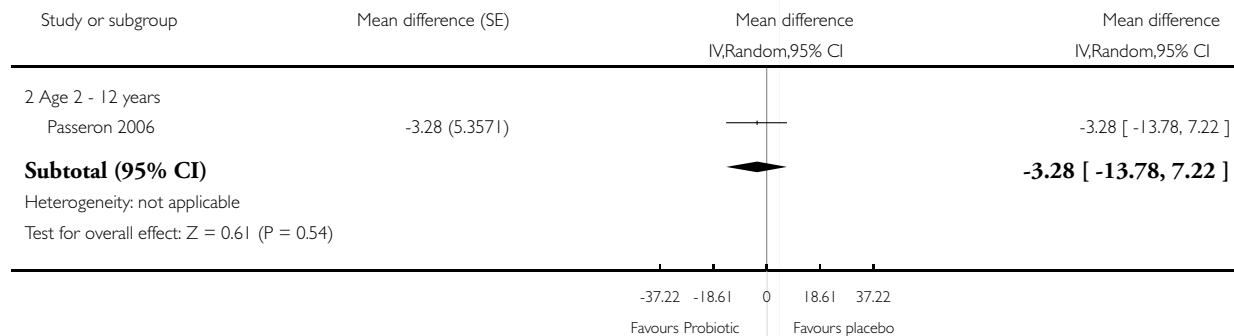
Outcome: 9 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Age group



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

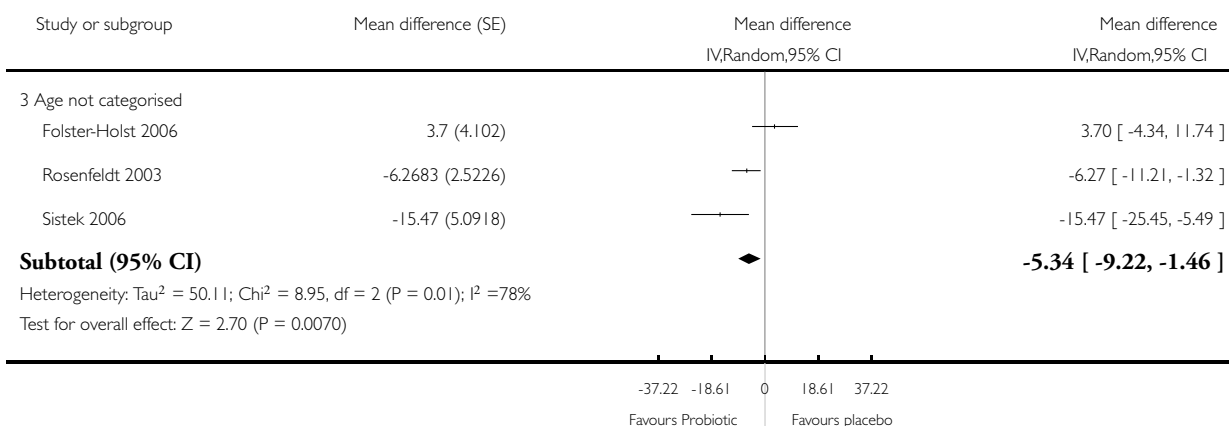
Outcome: 9 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Age group



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

Outcome: 9 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Age group

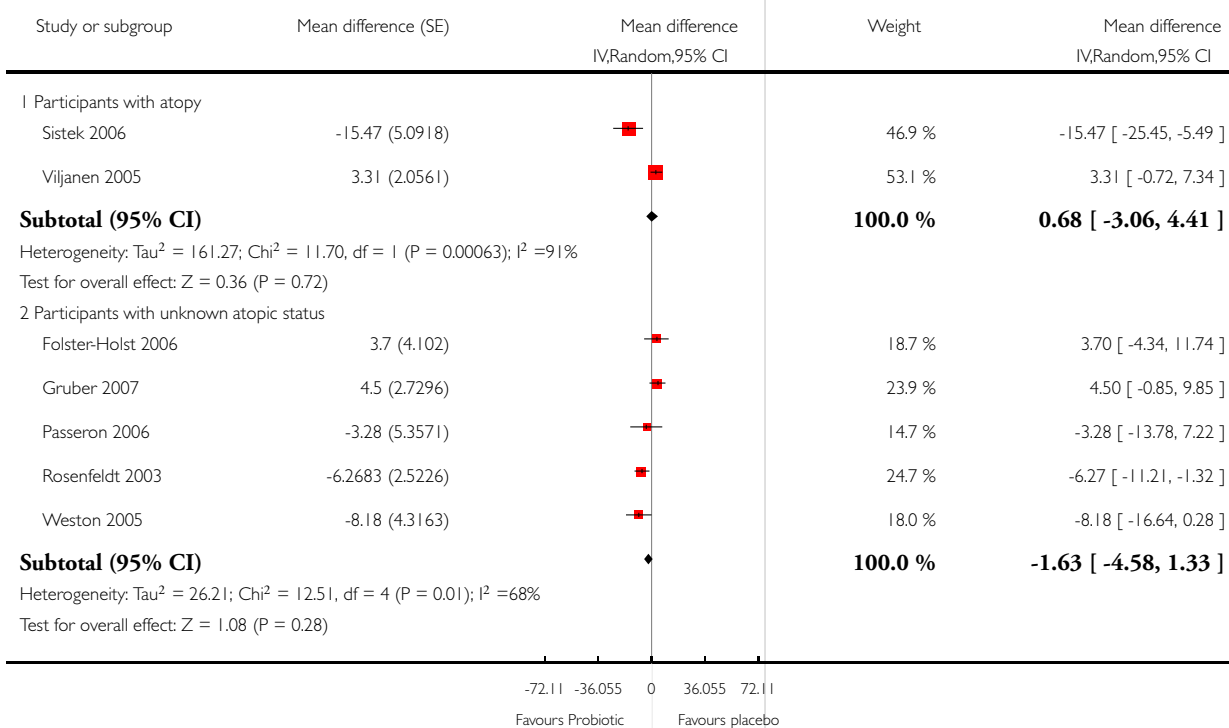


### Analysis 1.10. Comparison I Probiotic vs Placebo, Outcome 10 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Presence of Atopy.

Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

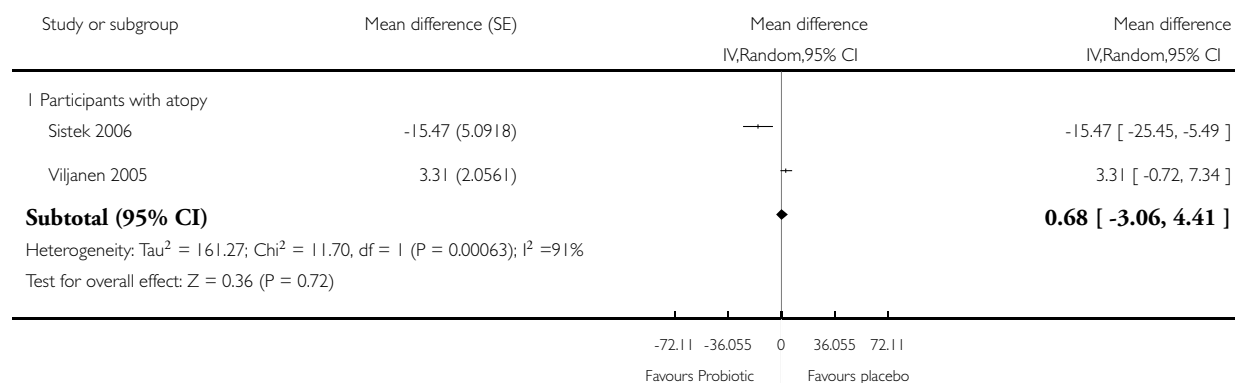
Outcome: 10 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Presence of Atopy



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

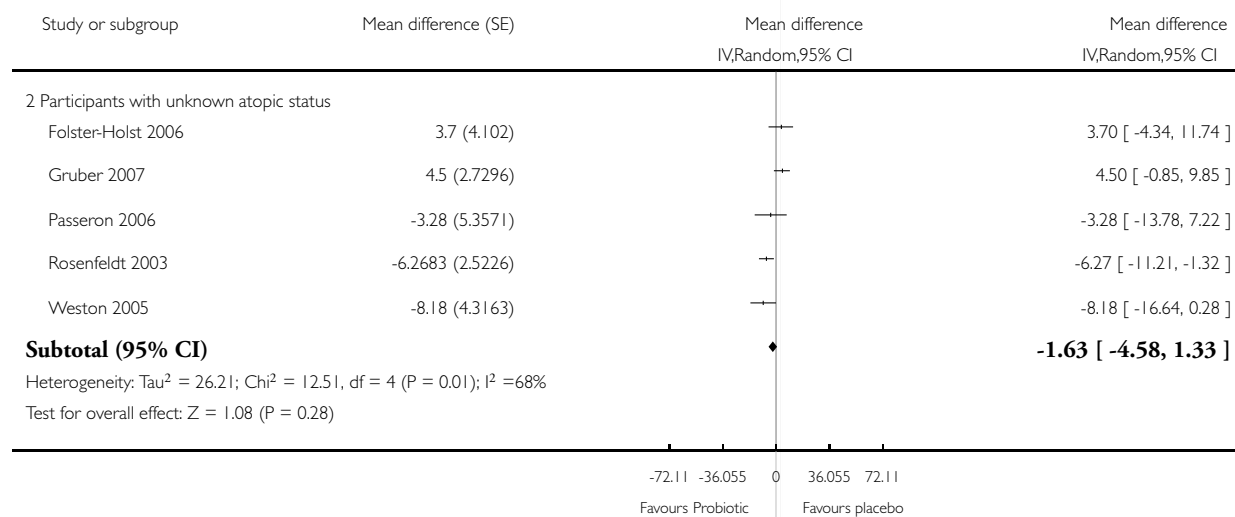
Outcome: I0 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Presence of Atopy



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

Outcome: I0 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Presence of Atopy

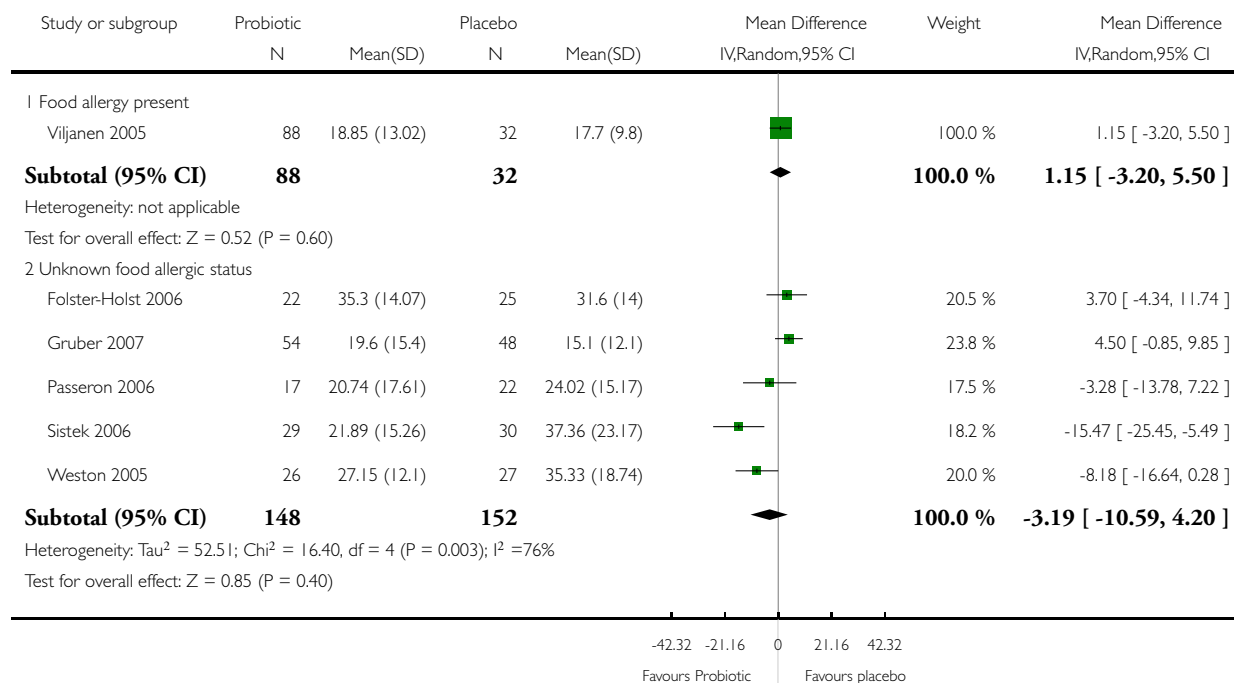


### Analysis 1.11. Comparison 1 Probiotic vs Placebo, Outcome 11 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Challenge-Proven Food Allergy.

Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

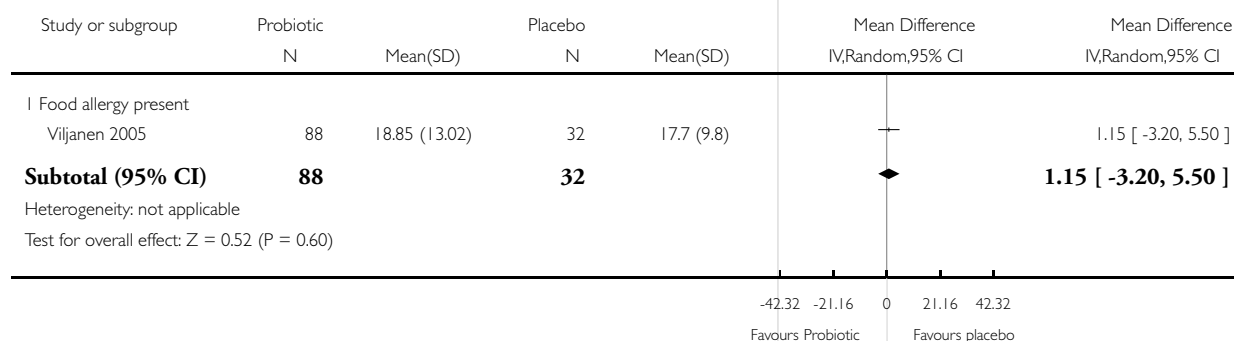
Outcome: 11 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Challenge-Proven Food Allergy



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

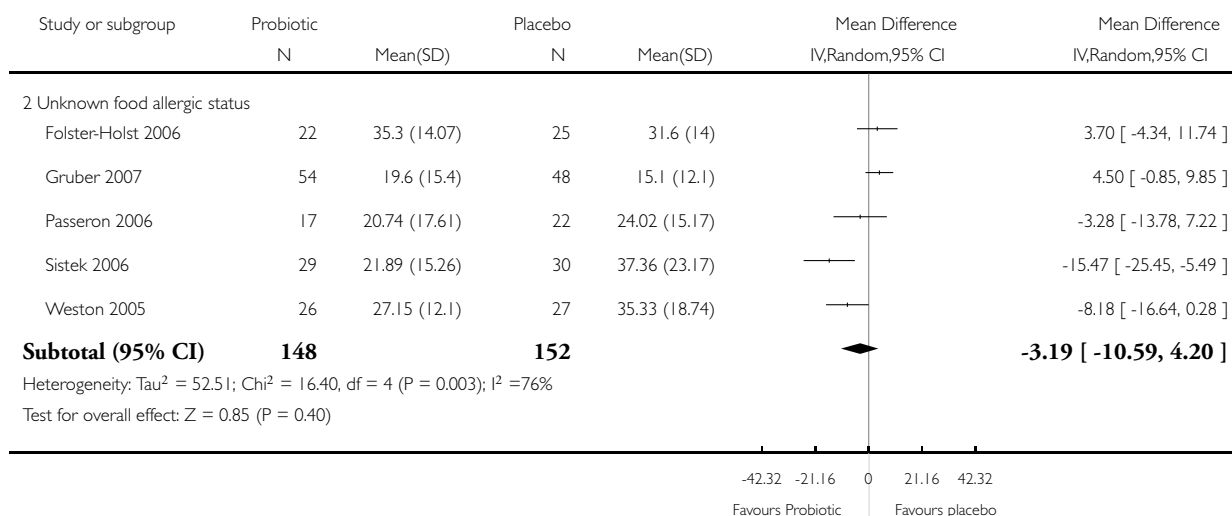
Outcome: 11 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Challenge-Proven Food Allergy



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

Outcome: I I Global eczema severity score (Total SCORAD) (Short term) - Stratified by Challenge-Proven Food Allergy

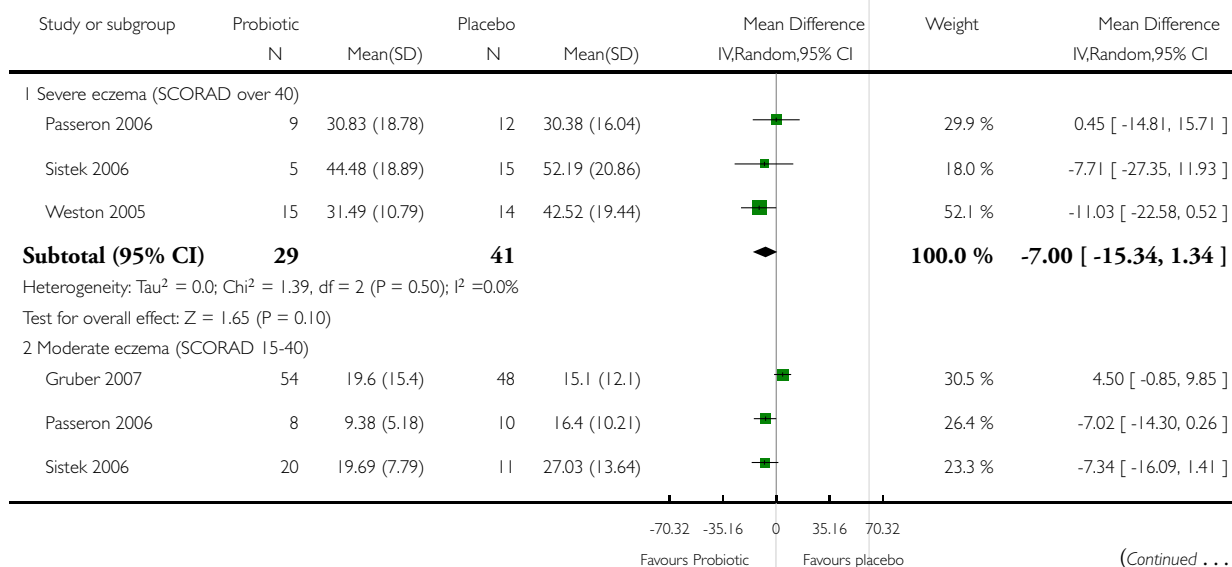


### Analysis I.12. Comparison I Probiotic vs Placebo, Outcome I2 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Eczema Severity.

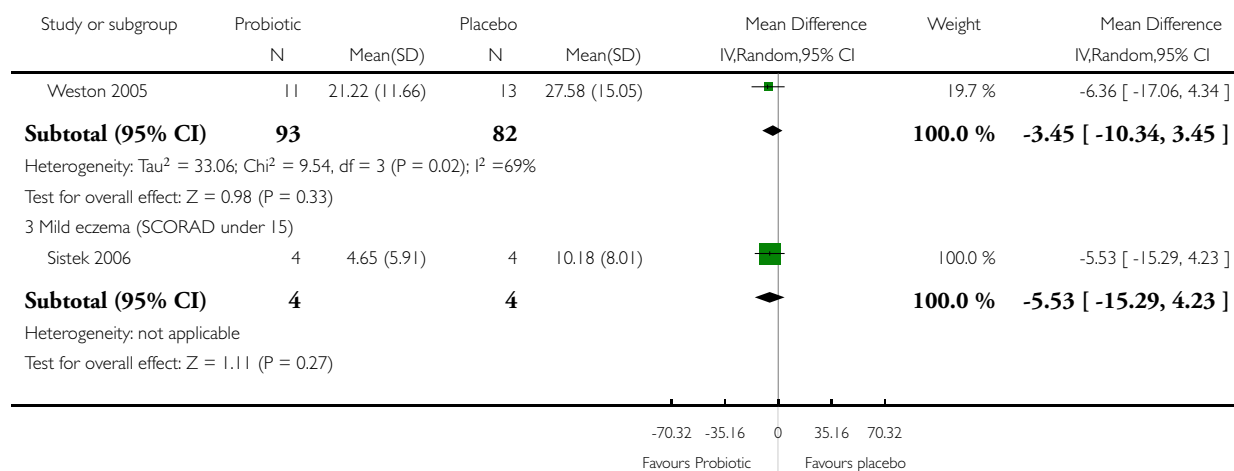
Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

Outcome: I2 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Eczema Severity



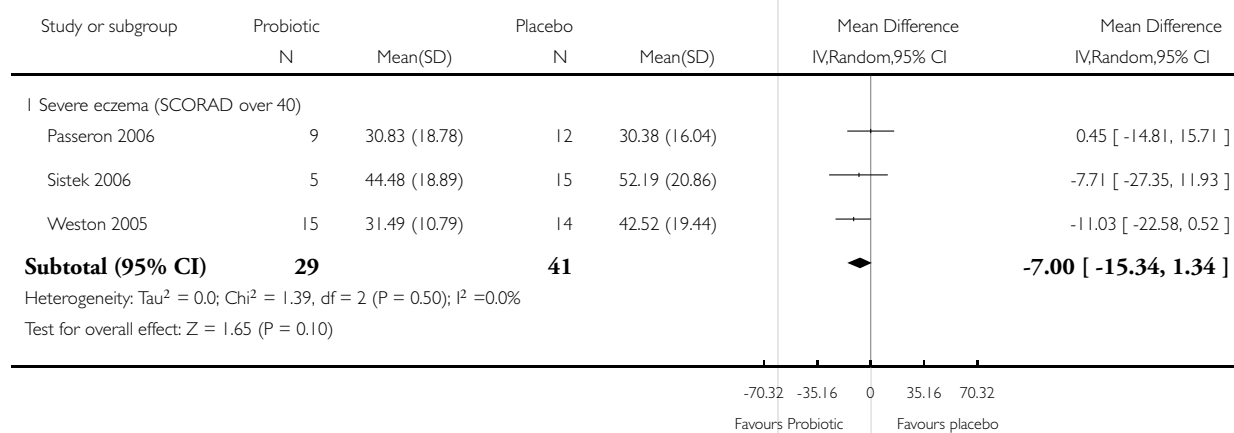
(... Continued)



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

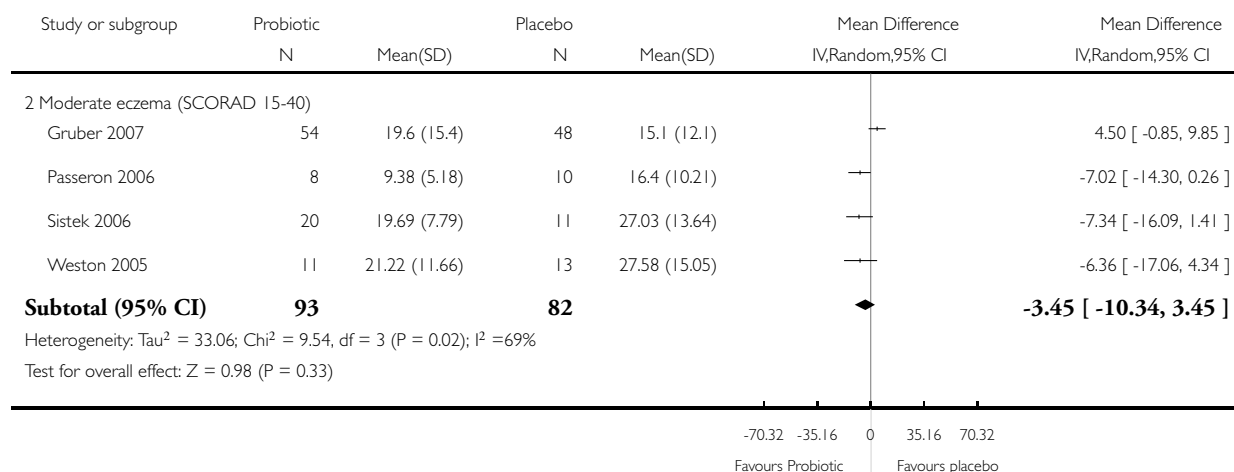
Outcome: 12 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Eczema Severity



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

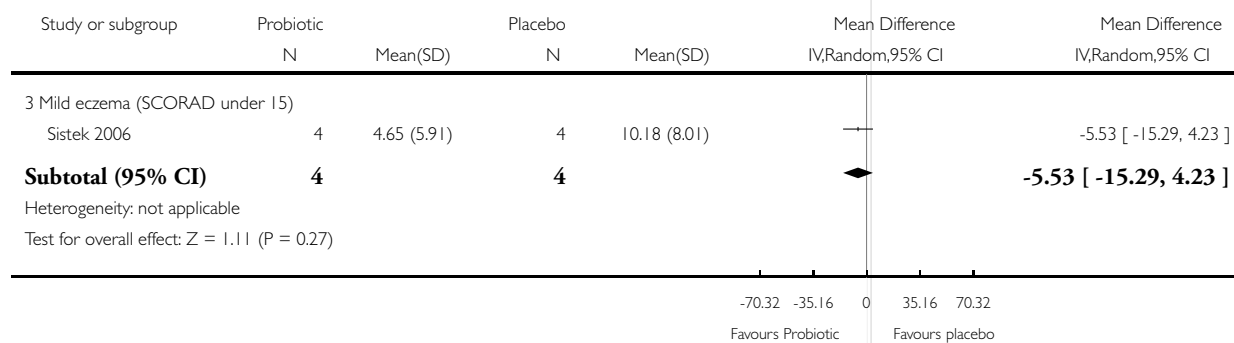
Outcome: 12 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Eczema Severity



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

Outcome: 12 Global eczema severity score (Total SCORAD) (Short term) - Stratified by Eczema Severity

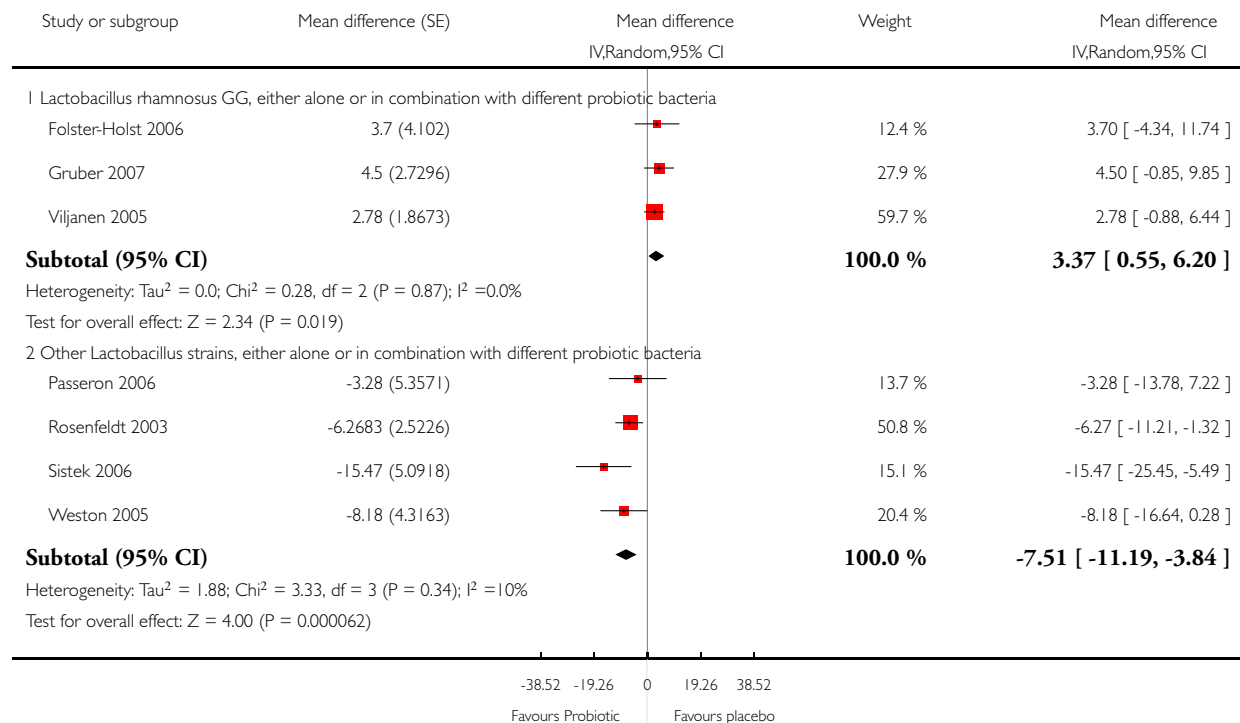


### Analysis 1.13. Comparison 1 Probiotic vs Placebo, Outcome 13 Global eczema severity (Total SCORAD) (Short term)-Stratified by Probiotic.

Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

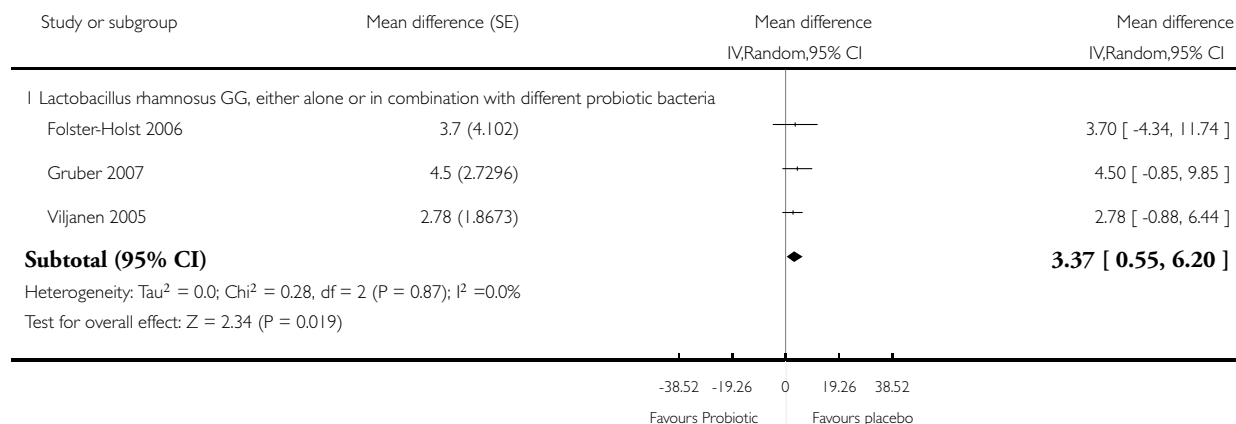
Outcome: 13 Global eczema severity (Total SCORAD) (Short term)-Stratified by Probiotic



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

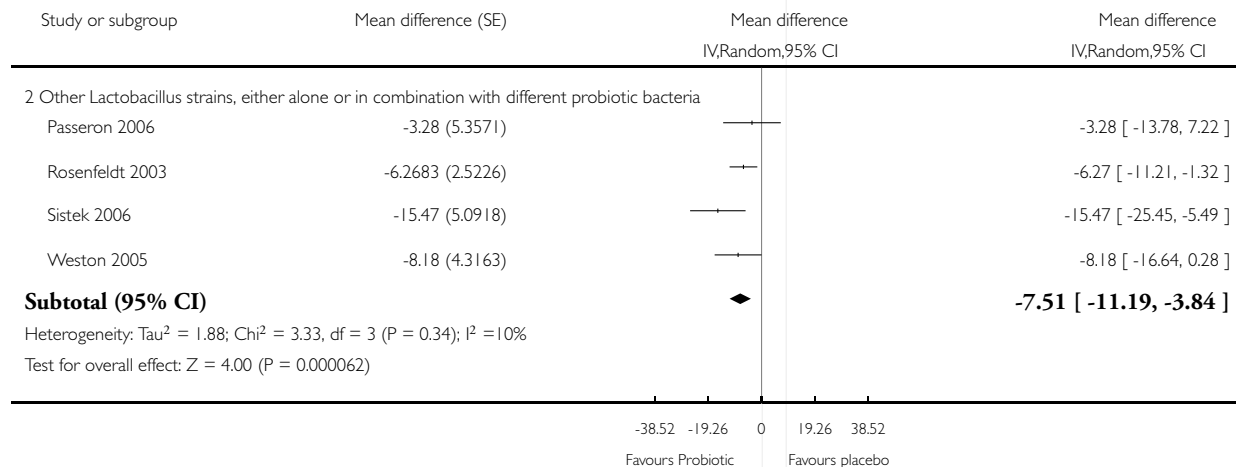
Outcome: I3 Global eczema severity (Total SCORAD) (Short term)-Stratified by Probiotic



Review: Probiotics for treating eczema

Comparison: I Probiotic vs Placebo

Outcome: I3 Global eczema severity (Total SCORAD) (Short term)-Stratified by Probiotic

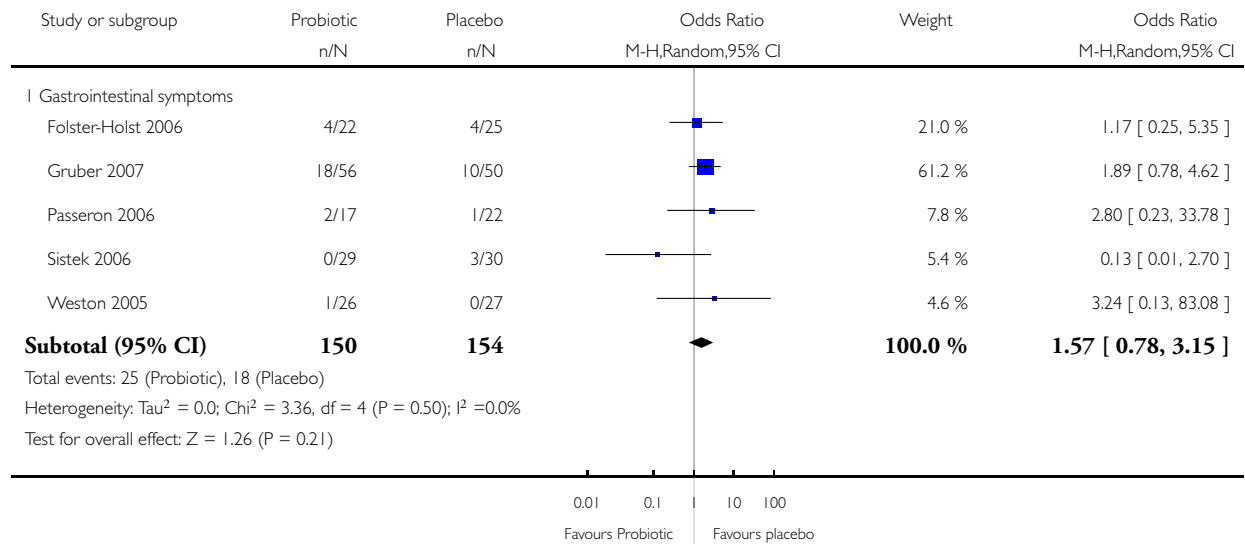


### Analysis 1.14. Comparison 1 Probiotic vs Placebo, Outcome 14 Adverse events (Short term).

Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

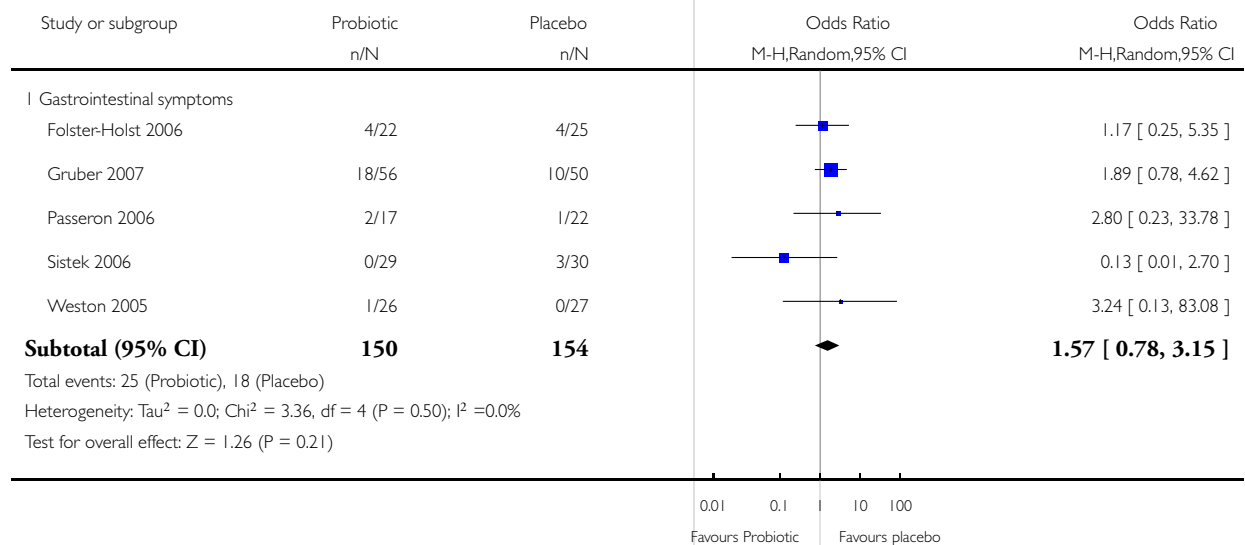
Outcome: 14 Adverse events (Short term)



Review: Probiotics for treating eczema

Comparison: 1 Probiotic vs Placebo

Outcome: 14 Adverse events (Short term)



## APPENDICES

### Appendix 1. Cochrane Library Search

- #1 atopic dermatitis in Title, Abstract or Keywords or eczema in Title, Abstract or Keywords or neurodermatitis in Title, Abstract or Keywords or child\* eczema in Title, Abstract or Keywords or infant\* eczema in Title, Abstract or Keywords in all products
- #2 besnier\* prurigo in Title, Abstract or Keywords or neurodermatitis atopica in Title, Abstract or Keywords in all products
- #3 MeSH descriptor Dermatitis, Atopic explode all trees in MeSH products
- #4 MeSH descriptor Neurodermatitis explode all trees in MeSH products
- #5 MeSH descriptor Eczema explode all trees in MeSH products
- #6 (#1 OR #2 OR #3 OR #4 OR #5)
- #7 probiotic\* in Title, Abstract or Keywords or lactobacill\* in Title, Abstract or Keywords or bifidobacter\* in Title, Abstract or Keywords or lactococc\* in Title, Abstract or Keywords or saccharomyc\* in Title, Abstract or Keywords in all products
- #8 streptococcus NEXT thermophilus in Title, Abstract or Keywords or bacillus NEXT subtilis in Title, Abstract or Keywords or enterococcus NEAR/6 faec\* in Title, Abstract or Keywords or intestin\* NEAR/6 microflora in Title, Abstract or Keywords or intestin\* NEAR/6 microbiotica in Title, Abstract or Keywords in all products
- #9 MeSH descriptor Probiotics explode all trees in MeSH products
- #10 MeSH descriptor Lactobacillus explode all trees in MeSH products
- #11 MeSH descriptor Bifidobacteriales Infections explode all trees in MeSH products
- #12 MeSH descriptor Lactococcus explode all trees in MeSH products
- #13 MeSH descriptor Saccharomyces explode all trees in MeSH products
- #14 MeSH descriptor Streptococcus thermophilus explode all trees in MeSH products
- #15 MeSH descriptor Bacillus subtilis explode all trees in MeSH products
- #16 MeSH descriptor Enterococcus faecalis explode all trees in MeSH products
- #17 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
- #18 (#6 AND #17)
- #19 SR-SKIN in All Fields in all products
- #20 (#18 AND NOT #19)

### Appendix 2. MEDLINE (OVID) Search

- 1. RANDOMIZED CONTROLLED TRIAL.pt.
- 2. CONTROLLED CLINICAL TRIAL.pt.
- 3. RANDOMIZED CONTROLLED TRIALS.mp.
- 4. RANDOM ALLOCATION.sh.
- 5. DOUBLE BLIND METHOD.sh.
- 6. SINGLE-BLIND METHOD.sh.
- 7. or/1-6
- 8. animal/ not human/
- 9. 7 not 8
- 10. CLINICAL TRIAL.pt.
- 11. CLINICAL TRIALS.mp.
- 12. (clin\$ adj25 trial\$).ti,ab.
- 13. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
- 14. PLACEBOS.sh.
- 15. placebo\$.ti,ab.
- 16. random\$.ti,ab.
- 17. RESEARCH DESIGN.sh.
- 18. or/10-17
- 19. 18 not 8
- 20. 19 not 9
- 21. COMPARATIVE STUDY.sh.
- 22. EVALUATION STUDIES.mp.
- 23. FOLLOW UP STUDIES.sh.

24. PROSPECTIVE STUDIES.sh.
25. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
26. or/21-25 27. 26 not 8 28.
- 27 not (9 or 20)
29. 9 or 20 or 28
30. atopic dermatitis.mp. or exp Dermatitis, Atopic/
31. atopic eczema.mp.
32. neurodermatitis.mp. or exp Neurodermatitis/
33. neurodermatitis atopica.mp.
34. infant\$ eczema.mp.
35. child\$ eczema.mp.
36. besniers prurigo.mp.
37. 30 or 31 or 32 or 33 or 34 or 35 or 36
38. probiotic\$.mp. or exp Probiotics/
39. lactobacillus.mp. or exp Lactobacillus/
40. bifidobacterium.mp. or exp Bifidobacterium/
41. exp Lactococcus/ or lactococcus.mp.
42. exp Saccharomyces/ or saccharomyces.mp.
43. streptococcus thermophilus.mp. or exp Streptococcus thermophilus/
44. bacillus subtilis.mp. or exp Bacillus subtilis/
45. enterococcus faecalis.mp. or exp Enterococcus faecalis/
46. intestinal microflora.mp.
47. microbiotica.mp.
48. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49. 29 and 37 and 48

### Appendix 3. EMBASE Search

- biotica.mp.
48. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
  49. 29 and 37 and 48
  50. limit 49 to yr="2003 - 2006"

### 3 EMBASE Search

1. random\$.mp.
2. factorial\$.mp.
3. crossover\$.mp.
4. placebo\$.mp. or PLACEBO/
5. (doubl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. assign\$.mp.
8. volunteer\$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. atopic dermatitis.mp. or exp Atopic Dermatitis/
15. atopic eczema.mp.
16. eczema.mp. or exp ECZEMA/
17. neurodermatitis.mp. or exp NEURODERMATITIS/

18. child\$ eczema.mp.
19. infant\$ eczema.mp.
20. besniers prurigo.mp.
21. 14 or 15 or 16 or 17 or 18 or 19 or 20
22. probiotic\$.mp. or exp Probiotic Agent/
23. exp LACTOBACILLUS/ or lactobacillus.mp.
24. exp BIFIDOBACTERIUM/ or bifidobacterium.mp.
25. lactococcus.mp. or exp LACTOCOCCUS/
26. saccharomyces.mp. or exp SACCHAROMYCES/
27. streptococcus thermophilus.mp. or exp Streptococcus Thermophilus/
28. bacillus subtilis.mp. or exp Bacillus Subtilis/
29. enterococcus faecalis.mp. or exp Enterococcus Faecalis/
30. intestinal microflora.mp. or exp Intes

#### Appendix 4. MEDLINE search for Adverse Events

1. exp product surveillance, postmarketing/ or exp adverse drug reaction reporting systems/ or exp clinical trials, phase iv/
2. adverse events.mp.
3. adverse effects.mp.
4. exp hypersensitivity/ or exp drug hypersensitivity/ or exp drug eruptions/ or exp hypersensitivity, delayed/ or exp hypersensitivity, immediate/
5. exp hypersensitivity, immediate/ or exp anaphylaxis/ or exp conjunctivitis, allergic/ or exp dermatitis, atopic/ or exp food hypersensitivity/ or exp respiratory hypersensitivity/ or exp urticaria/
6. side effect\$.mp.
7. exp Poisoning/
8. exp hepatitis, toxic/ or exp hepatitis, chronic, drug-induced/
9. exp Substance-Related Disorders/
10. exp Drug Toxicity/
11. exp Abnormalities, Drug-Induced/
12. exp Teratogens/
13. exp Mutagens/
14. exp Carcinogens/
15. metabolites.mp.
16. exp dermatitis, contact/ or exp dermatitis, allergic contact/ or exp dermatitis, irritant/ or exp dermatitis, phototoxic/
17. photoallergic reactions.mp.
18. exp dermatitis, allergic contact/ or exp dermatitis, photoallergic/
19. phototoxicity.mp.
20. sensitization.mp.
21. exp Burning Mouth Syndrome/
22. stinging.mp.
23. burning.mp.
24. fetal abnormalities.mp.
25. exp Drug Monitoring/
26. harm\$ effects.mp.
27. (toxic effects or drug effects).mp.
28. Sleep Apnea, Obstructive/
29. ARRHYTHMIA/
30. undesirable effect\$.mp.
31. (safe or safety).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32. toxicity.mp.
33. noxious.mp.
34. serious reaction\$.mp.
35. complication\$.mp.

36. treatment emergent.mp.
37. tolerability.mp.
38. (adverse adj3 (effect\$ or reaction\$ or event\$ or outcome\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39. rebound.mp.
40. Hypercalcemia/ci [Chemically Induced]
41. Urinary Calculi/ci [Chemically Induced]
42. Tachyphylaxis/ci, de [Chemically Induced, Drug Effects]
43. Substance Withdrawal Syndrome/ci, de [Chemically Induced, Drug Effects]
44. ATROPHY/ci [Chemically Induced]
45. TELANGIECTASIS/ci [Chemically Induced]
46. skin thinning.mp.
47. Liver Diseases/ci [Chemically Induced]
48. Kidney Diseases/ci [Chemically Induced]
49. Disseminated Intravascular Coagulation/ci [Chemically Induced]
50. Multiple Organ Failure/ci [Chemically Induced]
51. Stevens-Johnson Syndrome/ci [Chemically Induced]
52. Epidermal Necrolysis, Toxic/ci [Chemically Induced]
53. Heart Block/ci [Chemically Induced]
54. COMA/ci [Chemically Induced]
55. PARALYSIS/ci [Chemically Induced]
56. exp Nausea/dt [Drug Therapy]
57. exp Vomiting/dt [Drug Therapy]
58. 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 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 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59. probiotic\$.mp. or exp Probiotics/
60. 59 and 58

## Appendix 5. LILACS Search

Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control\$ or tw aleat\$ or tw random\$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic\$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Palavras] and atopic\$ or dermatitis or eczema or neurodermitis or prurigo [Palavras] and probiotic\$ or lactobacill\$ or bifidobacter\$ or lactococc\$ or saccharomyc\$ or (streptococcus and thermophilus) or (bacillus and subtilis) or (enterococcus and faec\$) [Palavras]

## WHAT'S NEW

Last assessed as up-to-date: 27 April 2008

| Date         | Event   | Description                     |
|--------------|---------|---------------------------------|
| 8 April 2008 | Amended | Converted to new review format. |

## HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 4, 2008

| Date        | Event                                              | Description           |
|-------------|----------------------------------------------------|-----------------------|
| 12 May 2006 | New citation required and conclusions have changed | Substantive amendment |

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## CONTRIBUTIONS OF AUTHORS

Link with editorial base and co-ordinate contributions from co-reviewers (RB)

Draft protocol (RB with contributions from all co-reviewers)

Run search (RB)

Identify relevant titles and abstracts from searches (RB, MT)

Obtain copies of trials (RB)

Selection of trials (RB, MT)

Extract data from trials (RB, FB)

Enter data into RevMan (RB, FB)

Carry out analysis (RB, JL)

Interpret data (RB, MT, DM, FB)

Draft final review (RB, with contributions from all co-reviewers)

Update review (RB)

## DECLARATIONS OF INTEREST

None known

## SOURCES OF SUPPORT

### Internal sources

- Murdoch Children's Research Institute, Australia.
- University of Melbourne, Australia.
- Royal Children's Hospital, Australia.
- Department of Paediatrics, Imperial College, London, UK.

## External sources

- No sources of support supplied

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title which was Probiotics for atopic eczema in the protocol to Probiotics for treating eczema on the advice of the referees.

We have made small changes to the Background on the advice of the referees.

We made small changes to the 'Criteria for considering studies for the review' to clarify issues

Data extraction was completed by RB and FB in the review, in place of RB and MT in the protocol due to time availability.

Dichotomous outcome data have been reported as OR in the review, and RR were planned in the protocol. This was due to the inclusion of a cross-over trial in the review. It is not possible to pool the data from cross-over and parallel group trials using the inverse generic variance method with RR, therefore OR have been used throughout this review to maximise the available data for meta-analyses, and for consistency of interpretation.

Finally an extra subgroup analysis was undertaken in the review which had not been specified in the protocol - outcome data were analysed according to the probiotic strain used [Analysis 1.13](#). This analysis was undertaken due the unexplained heterogeneity between studies for primary and secondary outcomes, and the use of the same probiotic strain in several studies. As discussed above, conclusions from this analysis must be guarded due to its post-hoc nature.