

Probiotics in infants for prevention of allergic disease and food hypersensitivity (Review)

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ABSTRACT

Background

The composition of the intestinal microflora may be different in individuals with atopic eczema from those without this condition, and such differences may precede the development of eczema. Probiotics are live bacteria that colonize the gastrointestinal tract and provide a health benefit to the host. Probiotics added to infant feeds have the potential to prevent sensitisation of infants to dietary allergens.

Objectives

To determine the effect of probiotics given to infants for the prevention of allergic disease or food hypersensitivity.

Search strategy

This included searches of the Cochrane Central Register of Controlled Trials (Issue 1, 2007), MEDLINE (1966 - February 2007), EMBASE, PREMEDLINE, abstracts of conference proceedings and citations of published articles, and expert informants.

Selection criteria

Randomised and quasi-randomised controlled trials that compare the use of a probiotic to no probiotic; or the use a specific probiotic compared to a different probiotic; or a probiotic with added prebiotic to control.

Data collection and analysis

Assessment of trial quality, data extraction and synthesis of data were performed using standard methods of the Cochrane Neonatal Review Group.

Main results

Twelve studies were eligible for inclusion. Allergic disease and / or food hypersensitivity outcomes were assessed by 6 studies enrolling 2080 infants, but outcomes for only 1549 infants were reported. Studies generally had adequate randomisation, allocation concealment and blinding of treatment. However, the findings of this review should be treated with caution due to excess losses in patient follow-up (17% to 61%). Meta-analysis of five studies reporting the outcomes of 1477 infants found a significant reduction in infant eczema (typical RR 0.82, 95% CI 0.70, 0.95). However, there was significant and substantial heterogeneity between studies. One study reported that the difference in eczema between groups persisted to 4 years age. When the analysis was restricted to studies reporting atopic eczema (confirmed by skin prick test or specific IgE), the findings were no longer significant (typical RR 0.80, 95% CI 0.62, 1.02). All studies reporting significant benefits used probiotic supplements containing *L. rhamnosus* and enrolled infants at high risk of allergy. No other benefits were reported for any other allergic disease or food hypersensitivity outcome.

Authors' conclusions

There is insufficient evidence to recommend the addition of probiotics to infant feeds for prevention of allergic disease or food hypersensitivity. Although there was a reduction in clinical eczema in infants, this effect was not consistent between studies and caution is advised in view of methodological concerns regarding included studies. Further studies are required to determine whether the findings are reproducible.

PLAIN LANGUAGE SUMMARY

There is insufficient evidence to recommend the addition of probiotics to infant feeds for prevention of allergic disease or food reactions.

Reactions to foods and allergies (including asthma, eczema and hay fever) are common and may be increasing in developed countries. Many infants become sensitised to foods, including infant formula, through their gastrointestinal tract, a process that may be affected by the composition of the intestinal bacteria. Attempts to promote the growth of normal gastrointestinal bacteria and prevent sensitisation to foods have included the use of probiotics. Probiotics are live bacteria that colonize the gastrointestinal tract and provide a health benefit to the host. This review found that probiotics added to infant feeds may help prevent infant eczema, with one study suggesting the benefit may persist to four years of age. However, concerns regarding the quality of studies, inconsistency of findings between studies, and the fact that the benefits did not persist if restricted to infants with evidence of sensitisation to allergens, suggests that further studies are needed to confirm these results.

BACKGROUND

Food hypersensitivity and allergic disease are prevalent and represent a substantial health problem that may be increasing in developed countries (Burr 1989; Halken 2004; Prescott 2005; Schultz Larsen 1996). Genetic susceptibility plays a large role in the development of food allergy. Although less than half of those who develop childhood allergic disease have a first degree relative with a history of allergy, the risk of development of allergic diseases increases substantially with a positive family history of allergy. Approximately 10% of children without an allergic first degree relative develop allergic disease compared to 20 - 30% with an allergic first degree relative (parent or sibling) and 40 - 50% with two affected relatives (Arshad 2005; Bergmann 1997; Hansen 1993; Kjellman 1977). The manifestations of allergic disease are age dependent. Infants commonly present with symptoms and signs of atopic eczema, gastrointestinal symptoms and recurrent wheezing. Asthma and rhinoconjunctivitis become prevalent in later childhood. Sensitization to allergens tends to follow a characteristic pattern (Halken 2004), with sensitization to food allergens in the first two to three years of life, followed by indoor allergens (e.g. house dust mite and pets) and subsequently outdoor allergens (e.g. rye and timothy grass). The cumulative prevalence of allergic disease in childhood is high, with up to 7 - 8% developing a food allergy, 15 - 20% atopic eczema, and 31 - 34% developing asthma or recurrent wheezing (Halken 2004). Of these, 7 - 10% will continue to have asthma symptoms beyond five years of age (Halken 2004). Food hypersensitivities affect approximately 6% of infants less than three years of age, with the prevalence decreasing over the first decade (Sampson 2004; Osterballe 2005).

A major focus of current research is the mechanisms for the development of immune tolerance and allergen sensitization in the fetus and newborn and primary prevention strategies. This review focuses on the evidence for use of probiotics in infants for the prevention of food hypersensitivity and allergic disease. A separate review examines the effects of prebiotics compared to no prebiotics in infants for prevention of allergic disease and food hypersensitivity. Probiotics are live bacteria that colonize the gastroin-

testinal tract and provide a health benefit to the host. They have been defined as "living micro-organisms, which upon ingestion in certain numbers, exert health benefits beyond inherent general nutrition" (Guarner 1998). Probiotics have been demonstrated to have anti-inflammatory properties associated with changes in cytokine expression that could potentially facilitate T1-helper cell immune response (Heller 2003; Sudo 1997), which could inhibit the development of allergic T2-helper cell response and allergic (IgE) antibody production. Benefits from the use of probiotic bacteria have been found in systematic review of randomised trials (Allen 2004) for the treatment of infectious diarrhoea. Several randomised studies have now demonstrated efficacy from the use of probiotics in infants with active eczema (Majamaa 1997; Isolauri 2000; Rosenfeldt 2003), although not all studies have shown conclusive benefits (Viljanen 2005). Although rare, anecdotal case reports have described infants with sepsis from lactobacillus attributable to probiotic supplementation (Hammerman 2006).

An altered microbial exposure in the gastrointestinal tract may be partly responsible for the increase of allergic diseases in populations with a western lifestyle (Holt 1997). Differences in intestinal microflora are found in infants delivered by caesarean section compared to those delivered vaginally, and in breast fed versus formula fed infants (Agostoni 2004). Breast feeding promotes the colonization of bifidobacteria and lactobacilli that inhibit growth of pathogenic microorganisms and compete with potentially pathogenic bacteria for nutrients and epithelial adhesion sites. The gastrointestinal flora may modulate mucosal physiology, barrier function and systemic immunologic and inflammatory responses (Agostoni 2004; Sudo 1997). Food allergy is a manifestation of an abnormal mucosal immune response to ingested dietary antigens (Sampson 2004). The gastrointestinal barrier is a complex physiochemical and cellular barrier. However, some ingested food antigens are absorbed. The efficiency of this gastrointestinal barrier is reduced in the newborn period (Sampson 2004). Perinatal risk factors reported for asthma and / or allergic disease have included prematurity (Bernsen 2005; Jaakkola 2004; Raby 2004) and fetal growth restriction (Bernsen 2005), both of which are associated with an immature and potentially injured gastrointestinal

mucosal barrier. The composition of the intestinal microflora may be different in those with atopic eczema, and such differences may precede the development of eczema. The most consistent finding in such studies is a reduced proportion of bifidobacteria species in the faeces of infants with eczema (Bjorksten 2001; Murray 2005) and atopic sensitization (Kalliomaki 2001a), but not in the faeces of children with symptoms of asthma (Murray 2005). The recognition of the importance of intestinal flora has led to the development of strategies aimed at manipulating bacterial colonization in formula fed infants, including the use of prebiotics and probiotics.

Prevention of allergic disease is divided into primary prevention, the prevention of immunological sensitization (development of IgE antibodies); and secondary prevention, the prevention of allergic disease following sensitization (Asher 2004). A substantial proportion of infants who develop sensitization will not go on to develop clinical manifestations of allergic disease or food hypersensitivity (Halken 2004). This review focuses on the prevention of clinical allergic disease (including asthma, eczema and allergic rhinitis) and food hypersensitivity, not just sensitization (IgE responses). Since the risk of allergy and food hypersensitivity is affected by heredity, subgroup analysis will examine the effect of probiotics in populations of infants at high risk of allergy or food hypersensitivity separately to infants at low risk or not selected on the basis of heredity. Since breast feeding promotes the colonization of bifidobacteria and lactobacilli (Agostoni 2004), subgroup analysis will examine the effect of probiotics in human milk fed infants separately to probiotics in formula fed infants. Prebiotics are nondigestible food components that beneficially affect the host by selectively stimulating the growth or activity of bacteria in the colon. They can be added to infant formula. In infants, studies have demonstrated significant increases in faecal bifidobacteria in response to formula supplementation with oligosaccharides (Boehm 2002; Moro 2002; Moro 2006; Schmelzle 2003; Decsi 2005), with one study also demonstrating an increase in lactobacilli (Moro 2002). Subgroup analyses was performed to determine if the effect of probiotics is modified by the addition of a prebiotic to infant feeds.

OBJECTIVES

To determine the effect of probiotics given to infants for the prevention of allergic disease or food hypersensitivity.

Secondary objectives are:

- to determine the effect of specific strains of probiotics;
- to determine the effect of probiotics in 1) breast fed infants, 2) human milk fed infants, and 3) formula fed infants;
- to determine the effect of probiotics used for 1) early / short term infant feeding, and 2) prolonged infant feeding;

- to determine the effect of probiotics in 1) infants not selected for risk of allergy or food hypersensitivity, or at low risk, and 2) in infants at high risk of allergy or food hypersensitivity;
- to determine the effect of probiotics given to 1) low birth weight or preterm infants, and 2) appropriate for gestation age term infants;
- to determine the effect of probiotics with added prebiotics ('symbiotics') for the prevention of allergic disease and food hypersensitivity.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised and quasi-randomised controlled trials that compared the use of a probiotic to a control (placebo or no treatment), or used a specific probiotic compared to a different probiotic, or used a specific probiotic compared to the same probiotic combined with a prebiotic ('symbiotic').

Types of participants

Enterally fed infants in the first six months of life without clinical evidence of allergic disease or food hypersensitivity both with and without risk factors for allergy and food hypersensitivity.

Types of intervention

Probiotics added to human milk or infant formula, added in the manufacturing process or given separately, compared to control (placebo or no treatment); or the use a specific probiotic compared to a different probiotic; or the use a specific probiotic with added prebiotic ('symbiotic') compared to control (placebo or no treatment).

Types of outcome measures

Definitions of allergic disease and food hypersensitivity had to be consistent with the 'Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003' (Johansson 2003). Specific allergies were identified as atopic when confirmed by demonstration of an IgE response, either through skin testing or serological testing for specific IgE (e.g. RAST or EAST or CAP system).

Primary outcomes:

- All allergic disease including asthma, eczema, rhinitis or food allergy (analysis restricted to studies reporting composite manifestations of all allergic disease);
- Food hypersensitivity.

Secondary outcomes (specific allergies and food hypersensitivities):

- Asthma

- Dermatitis / eczema
- Allergic rhinitis
- Cow's milk or soy protein hypersensitivity
- Cow's milk or soy protein allergy
- Food allergy
- Urticaria
- Anaphylaxis

Potential harms:

- Growth parameters including head circumference and weight gain when receiving probiotic supplements;
- Costs: costs will include an analysis of the incremental cost per infant with allergic disease or food hypersensitivity prevented (reported in the currency of the country of assessment). Costs should include all health, family and societal related costs. Cost analyses of trials from different countries and using different methodology will not be combined in meta-analysis but reported separately if available;
- Infant feed refusal;
- Infection with probiotic bacteria.

A specific allergic disease or food hypersensitivity may be diagnosed on the basis of:

- History of recurrent and persistent symptoms typical of the allergic disease or food hypersensitivity;
- A clinician diagnosis of allergic disease or food intolerance based on clinical findings supported by the above history;
- Clinical allergic disease and food intolerance confirmed by testing including detection of allergen sensitisation by either skin testing or serological testing for specific IgE (e.g. RAST or EAST or CAP system), asthma confirmed by respiratory function testing for presence of bronchial hyper-responsiveness, and food hypersensitivity confirmed by elimination/challenge.

The following definitions of age of allergic disease were used:

- Infant allergic disease incidence: allergic disease occurring up to two years of age;
- Childhood allergic disease incidence: allergic disease occurring up to 10 years of age (or up to age of latest report between two and 10 years);
- Childhood allergic disease prevalence: allergic disease reported that was present between two and 10 years of age;
- Adolescent allergic disease: allergic disease present from 10 to 18 years age;
- Adult allergic disease: allergic disease present after 18 years age.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

See: Neonatal Review Group search strategy. The standard search strategy of the Cochrane Neonatal Review Group was used. This included electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2007), MEDLINE (1966 - February 2007), EMBASE (1980 - February 2007) and CINAHL (1982 - February 2007) and previous reviews including cross references (all articles referenced), previous reviews including cross references, abstracts, conferences (Pediatric Academic Societies 1998 - 2007; Perinatal Society of Australia and New Zealand 1998 - 2007). The MEDLINE search strategy included the following keywords, using the search fields of abstract, MeSH subject headings, exploded subject heading, publication type, subject heading word, text word, and title: A search on all fields for [infant* OR newborn* OR neonat* OR pediatric* OR paediatric*] AND [probiotic* OR Lactobacillus OR Bifidobacterium] was conducted. The search was limited to: [random* OR trial* OR comparative study OR controlled study]. EMBASE was searched using the following terms: 'probiotic\$.mp OR Probiotic Agent/exp OR Lactobacillus/exp OR lactobacillus.mp OR Bifidobacterium/exp OR bifidobacterium.mp'. CINAHL was searched using the following terms: '[(probiotic\$.mp OR lactobacillus/exp OR lactobacillus.mp OR bifidobacterium/exp OR bifidobacterium.mp) AND (infants OR newborn) AND (clinical trial OR random)]'. No language restrictions were applied.

METHODS OF THE REVIEW

Eligibility of studies for inclusion was assessed independently by each review author. The criteria and standard methods of the Cochrane Neonatal Review Group were used to assess the methodological quality of the included trials. Quality of the included trials were evaluated in terms of adequacy of randomisation and allocation concealment, blinding of parents or carers and assessors to intervention, and completeness of assessment in all randomised individuals. Each review author extracted the data separately. Data were compared and differences resolved by consensus. The standard methods of the Neonatal Review Group were used to synthesise the data. Effects are expressed as relative risk (RR), risk difference (RD) and 95% confidence intervals (CI) for categorical data, and weighted mean difference (WMD) and 95% CI for continuous data. Data was examined for heterogeneity using the chi-square test for heterogeneity. Heterogeneity was quantified using the I^2 statistic. The fixed effect model was used for meta-analysis where enrolled infants and interventions are similar and no significant

heterogeneity was found. Sources of heterogeneity were explored in subgroup analysis.

The following comparisons are prespecified:

1. Probiotics versus no probiotics (all studies);
2. Specific probiotic versus no probiotic;
3. Specific probiotic versus other specific probiotic.

The following subgroup analyses are prespecified within the above comparisons:

1. According to infant heredity for allergy or food hypersensitivity:

- Infants at high risk of allergy or food hypersensitivity (at least one first degree relative with allergic disease or food hypersensitivity);
- Infants at low risk of allergy or food hypersensitivity, or not selected on basis of heredity.

2. According to method of infant feeding:

- Infants fed human milk;
- Infants fed standard cow's milk formula;
- Infants fed with a hypoallergenic formula (consisting of hydrolysed or elemental protein).

3. According to co-intervention with prebiotic:

- Infants supplemented with prebiotic (either in infant formula or given separately);
- Infants with no prebiotic supplement.

4. According to duration of supplementation:

- Infants given early (first few days), short term (days) supplementation;
- Infants given prolonged supplementation (weeks or months).

5. According to infant maturity or birth weight:

- Infants born at or near term (healthy or appropriate for gestational age);
- Infants born preterm (< 37 weeks gestation) or low birth weight (< 2500 g).

Studies that included other allergy prevention interventions (e.g. maternal dietary avoidance measures, environmental allergy reduction measures) in the treatment and not the control group were excluded. Studies that had other allergy prevention interventions in both treatment and control groups were eligible.

A sensitivity analysis was performed to determine if the findings were affected by including only studies of adequate methodology, defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and < 10% losses to follow up.

DESCRIPTION OF STUDIES

Excluded studies and reasons for exclusion from the review are found in 'table of excluded studies'. Twelve studies were eligible for inclusion in this review - see 'table of included studies'. Allergic disease and / or food hypersensitivity outcomes were assessed by 6 studies enrolling 2080 infants but reporting outcomes for only 1549 infants.

Participants:

- Risk of allergy: Five studies (Abrahamsson 2007; Kalliomaki 2001a; Kukkonen 2006; Rautava 2002; Taylor 2006) enrolled term or near term infants at high risk of allergy or food hypersensitivity (infants with at least one first degree relative with a history of allergy or food hypersensitivity). Five studies (Brunser 2006b; Puccio 2007; Rautava 2006; Saavedra 2004; Vendt 2006) enrolled healthy term or near term infants and were not selected on the basis of a family history of allergy. Two studies (Bin-Nun 2005; Lin 2005) enrolled preterm or low birth weight infants and were not selected on the basis of a family history of allergy.
- Infant feeding: All studies used prolonged supplementation of infant feeds with probiotic supplements. Five studies (Brunser 2006b; Puccio 2007; Rautava 2006; Saavedra 2004; Vendt 2006) enrolled infants receiving prolonged formula feeding. Five studies (Abrahamsson 2007; Bin-Nun 2005; Kalliomaki 2001a; Kukkonen 2006; Taylor 2006) enrolled infants receiving either prolonged breast milk or formula feeding. Six studies (Bin-Nun 2005; Kukkonen 2006; Brunser 2006b; Rautava 2006; Saavedra 2004; Vendt 2006) enrolled infants receiving prolonged cow's milk formula feeding (with or without breast feeding). One study (Abrahamsson 2007) enrolled infants using a hydrolysed infant formula (with or without breast feeding). Two studies (Lin 2005; Rautava 2002) enrolled infants receiving prolonged exclusive breast feeding. Kalliomaki 2001a reported encouraging women to breast feed, with 60% of infants predominately breast fed at 6 months, 35% receiving predominate cow's milk based formula and 5% a hydrolysed or amino acid based formula. Taylor 2006 reported the majority of women ever breast fed (98%) and were still breast feeding at six months (72%).

Interventions:

- *L. acidophilus*: Taylor 2006 allocated infants to treatment with *Lactobacillus acidophilus* versus placebo.
- *L. johnsonii*: Brunser 2006b allocated infants to treatment with *Lactobacillus johnsonii* versus prebiotic (fructo-oligosaccharide) supplemented formula versus control formula.
- *L. reuteri*: Abrahamsson 2007 allocated infants to treatment with *Lactobacillus reuteri* versus placebo given to the mother four weeks before delivery, then mother and baby daily for 12 months.

- *L. rhamnosus*: Three studies (Kalliomaki 2001a; Rautava 2002; Vendt 2006) allocated infants to treatment with *Lactobacillus rhamnosus* GG versus placebo.
- Probiotic mixtures: Bin-Nun 2005 allocated infants to treatment with a mixture of *Bifidobacteria infantis*, *Streptococcus thermophilus*, and *Bifidobacteria bifidus* versus placebo mixed in infant feeds. Lin 2005 allocated infants to treatment with a mixture of *Lactobacillus acidophilus* and *Bifidobacterium infantis* versus control. Rautava 2006 allocated infants to treatment with a mixture of *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* versus placebo.
- Mixtures of pro and prebiotics: Kukkonen 2006 allocated infants to treatment with a probiotic and prebiotic mixture of *Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus*, *Bifidobacterium breve* and *Propionibacterium freudenreichii*, and galacto-oligosaccharide 0.8g versus placebo (no probiotic or prebiotic). Puccio 2007 allocated infants to *Bifidobacterium longum* BL999 and a prebiotic mixture containing fructo-oligosaccharides and galacto-oligosaccharides (1:9). Saavedra 2004 allocated infants to treatment with *Bifidobacterium lactis* versus placebo.
- Other outcomes: Six studies (Bin-Nun 2005; Brunser 2006b; Lin 2005; Puccio 2007; Saavedra 2004; Vendt 2006) did not report allergic disease or food hypersensitivity outcomes. Infant growth when on probiotics was reported by seven studies (Abrahamsson 2007; Bin-Nun 2005; Brunser 2006b; Kalliomaki 2001a; Puccio 2007; Saavedra 2004; Taylor 2006; Vendt 2006). Lin 2005 reported incidence of blood culture positive sepsis.

Reported bacteria counts, doses, formulations and controls are documented in 'table of included studies'.

Outcomes:

- Allergic disease and / or food hypersensitivity: assessed by six studies enrolling 2080 infants but reporting outcomes for only 1549 infants (Abrahamsson 2007; Kalliomaki 2001a; Kukkonen 2006; Rautava 2002; Rautava 2006; Taylor 2006). Abrahamsson 2007 performed blinded assessments for eczema and sensitisation (skin prick tests and specific IgE) up to two years of age. Kalliomaki 2001a performed blinded physician assessment for eczema, allergic rhinitis and asthma at two and four years of age. Sensitisation assessed by skin prick tests at 6, 12 and 24 months of age and specific IgE at 3, 12 and 24 months of age. Kukkonen 2006 performed blinded physician assessment for food hypersensitivity, eczema, asthma and allergic rhinitis at two years of age. Sensitisation assessed by skin prick tests and specific IgE at two years of age. Rautava 2002 performed physician assessment for eczema up to two years of age. Cow's milk protein hypersensitivity was confirmed by double blind placebo controlled food challenge (DBPCFC) or skin prick test for cow's milk protein sensitisation. Rautava 2006 performed physician assessment for eczema up to 12 months of age. Cow's milk protein hypersensitivity was confirmed by double blind placebo controlled food challenge (DBPCFC) or skin prick test for cow's milk protein sensitisation. Taylor 2006 performed blinded physician assessment for eczema and food allergy confirmed by a positive skin prick test to specific food at 12 months of age.

METHODOLOGICAL QUALITY

Randomisation and allocation concealment: All studies reported random method of allocation to treatment. Four studies (Bin-Nun 2005; Puccio 2007; Rautava 2002; Rautava 2006) did not report method of randomisation so allocation concealment is unclear. The other studies had an adequate allocation sequence.

Blinding of treatment: Ten studies used a placebo to blind treatment (Abrahamsson 2007; Brunser 2006b; Kalliomaki 2001a; Kukkonen 2006; Puccio 2007; Rautava 2006; Saavedra 2004; Taylor 2006; Vendt 2006). The other two studies (Bin-Nun 2005; Lin 2005) reported measures to conceal treatment allocation from treating staff.

Blinding of outcome measurement: Eight studies (Abrahamsson 2007; Bin-Nun 2005; Brunser 2006b; Kalliomaki 2001a; Kukkonen 2006; Lin 2005; Taylor 2006; Vendt 2006) reported blinding of measurement. The other four studies (Puccio 2007; Rautava 2002; Rautava 2006; Saavedra 2004) did not specifically report blinding of measurement but used a placebo so blinding is likely.

Losses to follow up: Post-randomisation losses to follow up were: Abrahamsson 2007 19% in both groups; Bin-Nun 2005 2% of enrolled infants; Brunser 2006b 34% of enrolled infants; Kalliomaki 2001a 17% of enrolled infants; Kukkonen 2006 24% of enrolled infants; Lin 2005 none reported; Puccio 2007 reported 30% infants discontinued treatment, but reported all infants in an intention to treat analysis. Rautava 2002; 61% excluded as not breast feeding or not compliant; Rautava 2006 11% of enrolled infants; Saavedra 2004 10% of enrolled infants; Taylor 2006 18% of enrolled infants; and Vendt 2006 12.5% of enrolled infants. The range of post-randomisation losses in studies using the probiotic agent *L. rhamnosus* was 17% to 61%.

Intention to treat analysis: All studies reported analyses according to group of assignment.

RESULTS

PROBIOTIC VERSUS NO PROBIOTIC - ALL INFANTS (COMPARISON 01):

Allergic disease and / or food hypersensitivity:

- Allergy (outcome 01): One study (Kukkonen 2006) reported no significant difference in all allergic disease in infants (RR 0.90, 95% CI 0.75, 1.08).
- Food hypersensitivity (outcomes 02-3): No study reported food hypersensitivity (all manifestations). Meta-analysis of 2 studies (Abrahamsson 2007; Rautava 2002) found no significant difference in food hypersensitivity manifest as gastrointestinal symptoms in infancy (typical RR 1.04, 95% CI 0.27, 4.03).
- Asthma (outcome 04): Meta-analysis of two studies (Abrahamsson 2007; Taylor 2006) found no significant difference in asthma incidence in infancy and Kalliomaki 2001a reported no significant difference in asthma prevalence in childhood.
- Eczema (outcomes 05-6): Two studies (Kalliomaki 2001a; Rautava 2002) independently reported a significant reduction in infant eczema, with meta-analysis of five studies (Abrahamsson 2007; Kalliomaki 2001a; Kukkonen 2006; Rautava 2002; Taylor 2006) finding a significant reduction in infant eczema (typical RR 0.82, 95% CI 0.70, 0.95). However, significant ($p = 0.03$) and substantial ($I^2 = 63.6\%$) heterogeneity was found. Kalliomaki 2001a reported a significant reduction in childhood eczema prevalence (RR 0.57, 95% CI 0.33, 0.97). Kukkonen 2006 reported a significant reduction in atopic eczema in infants, with meta-analysis of four studies (Abrahamsson 2007; Kukkonen 2006; Rautava 2006; Taylor 2006) finding no significant difference in atopic eczema in infants (typical RR 0.80, 95% CI 0.62, 1.02). Again, significant ($p = 0.04$) and substantial ($I^2 = 65.1\%$) heterogeneity was found.
- Allergic rhinitis (outcome 07): Abrahamsson 2007 reported no significant difference in allergic rhinitis in infants and Kalliomaki 2001a reported no significant difference in childhood prevalence of allergic rhinitis incidence.
- Food hypersensitivity and allergy (outcomes 08-10): Taylor 2006 reported no significant difference in food allergy in infants. Meta-analysis of three studies (Kalliomaki 2001a; Rautava 2002; Rautava 2006) found no significant difference in cow's milk protein hypersensitivity in infants and Kalliomaki 2001a reported no significant difference in childhood prevalence. Rautava 2006 reported no significant difference in cow's milk protein allergy in infants.
- Urticaria (outcome 11): Abrahamsson 2007 reported no significant difference in urticaria in infants.

Growth: Abrahamsson 2007 reported infants were heavier in the *L. reuteri* than the placebo group at three months of age (6.4 kg vs. 6.1 kg, $p = 0.03$, *t*-test), but not at any other time points. Bin-Nun 2005 reported the mean ($\pm$ sd) cumulative weight gain at six weeks of age was 691 ± 208 g in the probiotic group versus 594 ± 239 g in the placebo group, with the differences reported as not significant. However, RevMan analysis found that weight gain was significantly greater in the probiotic group (MD 97.00 g/6 weeks,

95% CI 24.10, 169.90). Brunser 2006b reported no differences between the study groups with respect to weight, height, weight for height, weight for age and height for age z-scores (National Center for Health Statistics) on the day of enrolment as well as during the study (data not documented in publication). Kalliomaki 2001a reported infants receiving probiotics and control had no significant difference in weight or length at two weeks, three months and six months of age when receiving treatment [at six months, mean weight (range) - probiotic: 8.4 kg (6.8 - 11.5); control 8.2 kg (6.4 - 11.0); mean length (range) - probiotic 69.1 cm (63.2 - 74.5); control: 68.2 cm (61.5 - 72.6)]. There was also no significant difference at 12 and 24 months of age. Saavedra 2004 reported z-scores for weight/age, height/age, and weight/length at the time of enrolment and at the end of participation as well as the change in z-scores over the time of participation for all subjects in each group. No significant differences between the groups were reported. Taylor 2006 reported no significant difference in weight or height at six months of age at the end of the period of treatment [Height - probiotic: 67.8 cm (se 0.3), control: 67.3 cm (se 0.3). Weight - probiotic: 7.8 kg (se 0.1), control: 7.9 kg (se 0.1)]. No significant difference was also reported at 12 months of age. Vendt 2006 reported weight, length and head circumference measured monthly and transformed into standard deviation scores (SDS). Changes in length and weight SDS at the end of the study were significantly higher in those receiving probiotic supplemented formula than those receiving regular formula (0.44 ± 0.37 versus 0.07 ± 0.06 , $P < 0.01$ and 0.44 ± 0.19 versus 0.07 ± 0.06 , $P < 0.005$, respectively). However, length and weight SDS scores were significantly lower in the probiotic group at study entry, and no adjustment was made for these differences.

Potential harms: Abrahamsson 2007 reported no significant difference in the cumulative incidence of mild adverse events (spitting-up, colic and constipation) during the first 12 months of age. At one and two months of age, more infants in the *L. reuteri* group were reported having spitting-ups than in the placebo group (26% versus 14%, $p = 0.04$, at one month of age, and 33% versus 19%, $p = 0.04$, at two months of age). There were no significant differences when the parents were asked whether their infants had any gastrointestinal problems (13% versus 9%, $p = 0.37$, at one month, and 6% versus 11%, $p = 0.28$, at two months). The cumulative incidence of infants reported to have gastrointestinal problems during the first 12 months was 21% in the *L. reuteri* group and 23% in the placebo group. No severe adverse events were reported. Bin-Nun 2005 reported a significant reduction in NEC and/or death (6/73 versus 17/72; $p = 0.025$) in preterm infants receiving probiotics compared to control. Brunser 2006b reported none of the withdrawals from the study were associated with adverse reactions to the formulas. Kalliomaki 2001a reported no significant difference in infant vomiting, total duration of crying, duration of fussing and consistency of stools in infants receiving probiotics compared to control. Kukkonen 2006 reported no significant difference in adverse events ('abdominal discomfort',

vomiting, excess crying) between probiotic and placebo groups and discontinuation because of major difficulties in swallowing product. Lin 2005 reported none of the positive blood cultures grew *Lactobacillus* or *Bifidobacterium* species. The incidence of sepsis was lower in the probiotic group (22/180 (12.2%) versus 36/187 (19.3%); $p = 0.03$). Rautava 2002 reported that “no adverse reactions or clinical side effects were observed during probiotic supplementation or clinical follow-up”. Saavedra 2004 reported significant reductions in colic or irritability frequency in infants receiving probiotics compared to control. No significant difference was reported in infant stool frequency or consistency, vomiting or fever with diarrhoea, discomfort with bowel movement, health care attention for illness or daycare absenteeism due to illness. No study reported data for costs.

SUBGROUP ANALYSES:

PROBIOTIC VERSUS NO PROBIOTIC IN INFANTS AT HIGH RISK OF ALLERGY OR FOOD HYPERSENSITIVITY (COMPARISON 02):

Allergic disease and / or food hypersensitivity:

- All allergic disease (outcome 01): One study (Kukkonen 2006) reported no significant difference in all allergic disease in infants (RR 0.90, 95% CI 0.75, 1.08).
- Food hypersensitivity (outcome 02): Meta-analysis of two studies (Abrahamsson 2007; Rautava 2002) found no significant difference in food hypersensitivity manifest as gastrointestinal symptoms in infancy (typical RR 1.04, 95% CI 0.27, 4.03).
- Asthma (outcome 03): Meta-analysis of two studies (Abrahamsson 2007; Taylor 2006) found no significant difference in asthma incidence in infancy and Kalliomaki 2001a reported no significant difference in asthma prevalence in childhood.
- Eczema (outcomes 04-5): Two studies (Kalliomaki 2001a; Rautava 2002) independently reported a significant reduction in infant eczema, with meta-analysis of five studies (Abrahamsson 2007; Kalliomaki 2001a; Kukkonen 2006; Rautava 2002; Taylor 2006) finding a significant reduction in infant eczema (typical RR 0.82, 95% CI 0.70, 0.95). However, significant ($p = 0.03$) and substantial ($I^2 = 63.6\%$) heterogeneity was found. Kalliomaki 2001a reported a significant reduction in childhood eczema prevalence (RR 0.57, 95% CI 0.33, 0.97). Kukkonen 2006 reported a significant reduction in atopic eczema in infants, with meta-analysis of three studies (Abrahamsson 2007; Kukkonen 2006; Taylor 2006) finding no significant difference in atopic eczema in infants (typical RR 0.81, 95% CI 0.63, 1.04). Again, significant ($p = 0.01$) and substantial ($I^2 = 76.2\%$) heterogeneity was found.
- Allergic rhinitis (outcome 06): Abrahamsson 2007 reported no significant difference in allergic rhinitis in infants and Kalliomaki 2001a reported no significant difference in childhood prevalence of allergic rhinitis incidence.

- Food hypersensitivity and allergy (outcomes 07-8): Taylor 2006 reported no significant difference in food allergy in infants. Meta-analysis of two studies (Kalliomaki 2001a; Rautava 2002) found no significant difference in cow's milk protein hypersensitivity in infants and Kalliomaki 2001a reported no significant difference in childhood prevalence.
- Urticaria (outcomes 09): Abrahamsson 2007 reported no significant difference in urticaria in infants.

PROBIOTIC VERSUS NO PROBIOTIC IN INFANTS NOT SELECTED ON BASIS OF RISK OF ALLERGY OR FOOD HYPERSENSITIVITY (COMPARISON 03):

Outcomes 01-3: In infants, Rautava 2006 reported no significant difference in atopic eczema (RR 0.63, 95% CI 0.21, 1.89), cow's milk protein hypersensitivity (RR 0.18, 95% CI 0.01, 3.32) and cow's milk protein allergy (RR 0.41, 95% CI 0.02, 9.84).

PROBIOTIC VERSUS NO PROBIOTIC IN INFANTS FED EXCLUSIVE HUMAN MILK (COMPARISON 04):

Outcomes 01-3: In infants, Rautava 2002 reported no significant difference in food hypersensitivity manifest as gastrointestinal symptoms (RR 1.11, 95% CI 0.17, 7.34), a significant reduction in eczema (RR 0.32, 95% CI 0.12, 0.85), and no significant difference in cow's milk protein hypersensitivity (RR 2.14, 95% CI 0.59, 7.77).

PROBIOTIC VERSUS NO PROBIOTIC IN INFANTS FED COW'S MILK FORMULA (COMPARISON 05):

Outcomes 01-3: In infants, Rautava 2006 reported no significant difference in atopic eczema (typical RR 0.63, 95% CI 0.21, 1.89), cow's milk protein hypersensitivity (RR 0.18, 95% CI 0.01, 3.32) or cow's milk protein allergy (RR 0.41, 95% CI 0.02, 9.84).

PROBIOTIC VERSUS NO PROBIOTIC IN INFANTS FED HYPOALLERGENIC INFANT FORMULA (COMPARISON 06):

Outcomes 01-6: In infants, Abrahamsson 2007 reported no significant difference in food hypersensitivity manifest as gastrointestinal symptoms (RR 0.98, 95% CI 0.14, 6.81), asthma (RR 0.69, 95% CI 0.27, 1.72), eczema (RR 1.04, 95% CI 0.70, 1.53), atopic eczema (RR 0.61, 95% CI 0.32, 1.14), allergic rhinitis (RR 0.24, 95% CI 0.03, 2.15) and urticaria (RR 2.94, 95% CI 0.31, 27.73).

PROBIOTIC WITH ADDED PREBIOTIC VERSUS NO PROBIOTIC (COMPARISON 07):

Outcomes 01-3: In infants, Kukkonen 2006 reported no significant difference for all allergic disease (RR 0.90, 95% CI 0.75, 1.08), a significant reduction in eczema (RR 0.81, 95% CI 0.66, 0.99) and a significant reduction in atopic eczema (RR 0.70, 95% CI 0.51, 0.96). Puccio 2007 reported weight gain was not significantly different (MD 0.50 g/day, 90% CI -1.48 to 2.48) - authors analysis. Puccio 2007 also reported length gain in mm/month (boys 35.1 [sd 4.2] versus 35.1 [4.4]; girls 32.2 [4.3] versus 32.2 [4.6]) and head circumference growth in mm/month (boys 17.9

[2.7] versus 17.4 [2.7]; girls 16.0 [2.8] versus 15.5 [3.0]) was also not significantly different, although it is unclear as to whether this analysis includes all infants or is restricted to the 97 of 138 infants who did not discontinue formula.

SPECIFIC PROBIOTIC VERSUS NO PROBIOTIC (COMPARISON 08):

L. rhamnosus, B. Breve and P. freudenreichii (with GOS): In infants, Kukkonen 2006 reported no significant difference for all allergic disease (RR 0.90, 95% CI 0.75, 1.08), a significant reduction in eczema (RR 0.81, 95% CI 0.66, 0.99) and a significant reduction in atopic eczema (RR 0.70, 95% CI 0.51, 0.96).

L. reuteri: In infants, Abrahamsson 2007 reported no significant difference in food hypersensitivity manifest as gastrointestinal symptoms (RR 0.98, 95% CI 0.14, 6.81), asthma (RR 0.69, 95% CI 0.27, 1.72), eczema (RR 1.04, 95% CI 0.70, 1.53), atopic eczema (RR 0.61, 95% CI 0.32, 1.14), allergic rhinitis (RR 0.24, 95% CI 0.03, 2.15) and urticaria (RR 2.94, 95% CI 0.31, 27.73).

L. rhamnosus strain GG: Rautava 2002 reported no significant difference in food hypersensitivity in infants manifested as gastrointestinal symptoms (RR 1.11, 95% CI 0.17, 7.34). Kalliomaki 2001a reported no significant difference in asthma prevalence in childhood (RR 3.06, 95% CI 0.33, 28.46). Meta-analysis of 2 studies (Kalliomaki 2001a; Rautava 2002) found a significant reduction in infant eczema (RR 0.45, 95% CI 0.29, 0.72) and Kalliomaki 2001a reported no significant difference in childhood prevalence of eczema (RR 0.57, 95% CI 0.33, 0.97). Rautava 2006 reported no significant difference in atopic eczema (RR 0.63, 95% CI 0.21, 1.89). Kalliomaki 2001a reported no significant difference in childhood prevalence of allergic rhinitis incidence (RR 2.04, 95% CI 0.75, 5.56). Meta-analysis of 3 studies (Kalliomaki 2001a; Rautava 2002; Rautava 2006) found no significant difference in cow's milk protein hypersensitivity in infants (typical RR 1.49, 95% CI 0.75, 2.96) and Kalliomaki 2001a reported no significant difference in childhood prevalence (RR 1.02, 95% CI 0.15, 6.97). Rautava 2006 reported no significant difference in cow's milk protein allergy in infants (RR 0.41, 95% CI 0.02, 9.84).

L. acidophilus: In infants, Taylor 2006 reported no significant difference in asthma (RR 1.32, 95% CI 0.30, 5.72) and eczema (RR 1.10, 95% CI 0.77, 1.58), an increase in atopic eczema of borderline significance (RR 1.87, 95% CI 1.00, 3.52), and no significant difference in food allergy, (RR 1.54, 95% CI 0.70, 3.37).

OTHER PRESPECIFIED COMPARISONS

All studies included in this review were eligible for inclusion in the analysis 'Infants given prolonged supplementation (weeks or months).' The 2 studies (Bin-Nun 2005; Lin 2005) that enrolled preterm or low birth weight infants did not report allergic disease or food hypersensitivity outcomes so separate subgroup analysis were not performed. No study compared different probiotics.

PROBIOTIC VERSUS NO PROBIOTIC - STUDIES WITH ADEQUATE METHODOLOGY (COMPARISON 09): no study met criteria for studies of adequate methodology.

DISCUSSION

The primary outcomes of this review were all manifestations of allergic disease and food hypersensitivity with one study reporting no significant difference in all allergic disease. No studies reported all manifestations of food hypersensitivity. For specific allergies in infants, no significant difference was found overall for gastrointestinal manifestations of food allergy, asthma, allergic rhinitis, food allergy (confirmed by skin prick test or specific IgE), cow's milk protein hypersensitivity, cow's milk protein allergy, and urticaria. Meta-analysis of five studies reporting the outcomes of 1477 infants found a significant reduction in infant eczema. However, there was significant and substantial heterogeneity between studies. When the analysis was restricted to studies reporting atopic eczema (confirmed by skin prick test or specific IgE) the findings were no longer significant. One study assessed outcomes up to four years of age and reported that difference in eczema persisted, but there was no significant difference in asthma, allergic rhinitis or cow's milk protein hypersensitivity. Although most studies had adequate randomisation, allocation concealment, and blinded intervention, nearly all studies had substantial losses to follow up. No study was eligible for inclusion in the prespecified analysis of studies of adequate methodology.

In subgroup analyses, all studies reporting infant and childhood eczema enrolled infants at high risk of allergy and/or food hypersensitivity. No other outcome became significant when analysis was restricted to high risk infants. Only one study reported allergic disease or food hypersensitivity outcomes in infants not selected on the basis of risk for allergy and food hypersensitivity, with no benefits reported for atopic eczema, cow's protein hypersensitivity and cow's protein allergy. One study reported a significant reduction in eczema in exclusively breast fed high risk infants. In infants fed cow's milk formula, significant reductions were reported by one study for eczema and meta-analysis of two studies found a significant reduction in atopic eczema. One study reported no significant difference in any specific allergic disease or food hypersensitivity for infants fed breast milk or an extensively hydrolysed formula. One study reported a significant reduction in eczema and atopic eczema for infants fed a combination of probiotic with prebiotic. Two studies independently reported a significant reductions in eczema in infants for probiotics including *L. rhamnosus*. One of these studies also reported a significant reduction of eczema in children. One study also reported a significant reduction in infant eczema from a mixture of *L. rhamnosus*, *B. breve*, *P. propionibacterium* and prebiotic galacto-oligosaccharide. The incidence of atopic eczema (sensitisation confirmed), but not all clinical eczema, was increased in one study using the probiotic *L.*

acidophilus. No other benefits or harms were reported for specific probiotics. However, the interpretation of results is made more difficult by the different dosing strategies used by different studies. Control group event rates for all allergic disease and eczema were 35%, a rate that is consistent with use of high risk selection criteria based on having a first degree relative with a history of allergy. The review is powered to detect differences in event rates between treatment groups of approximately 5%. Contrary to expectations, the only study enrolling infants that were exclusively breast fed had the highest control group event rate (47%) and reported the highest absolute reduction in eczema (32%). As this study excluded a substantial proportion of infants post-randomisation who were not exclusively breast fed, the results of this analysis should be viewed with caution. Since most other studies included infants both breast and formula fed, no firm conclusions regarding the effect of probiotics in solely formula fed infants can be made.

No consistent adverse effects on infant growth when on probiotics were reported. No other adverse effects attributable to probiotics were reported. One study in preterm infants reported no episodes of sepsis with probiotic bacteria. To date, treatment with probiotic bacteria appears to be safe, although the studies included in this review have insufficient power to detect uncommon outcomes including sepsis with probiotic bacteria.

There is insufficient evidence to recommend the addition of probiotics to infant feeds for prevention of allergic disease or food hypersensitivity. Although there was a reduction in clinical eczema in infants, not all studies showed a benefit and caution is advised in view of methodological concerns regarding the studies. To date, studies using *L. rhamnosus* have been the most homogenous in reporting beneficial outcomes. Further studies are required to determine whether the finding of reduced eczema persists over a longer period of time, applies to other manifestations of allergic disease and / or food hypersensitivity, is associated with reductions in allergen sensitisation, and is reproducible. Future studies should enrol infants at high risk of allergy or food hypersensitivity, consider using preparations of probiotics that have been reported to produce a reduction in infant eczema and compare groups with

and without an added prebiotic.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to recommend the addition of probiotics to infant feeds for prevention of allergic disease or food hypersensitivity. Although there was a reduction in clinical eczema in infants, this effect was not consistent between studies and caution is advised in view of methodological concerns regarding included studies.

Implications for research

Further studies are required to determine whether the finding of reduced eczema persists over a longer period of time, applies to other manifestations of allergic disease and / or food hypersensitivity, is associated with reductions in allergen sensitisation, and is reproducible. Future studies should enrol infants at high risk of allergy or food hypersensitivity, consider using preparations of probiotics that have been reported to produce a reduction in infant eczema and compare groups with and without an added prebiotic.

POTENTIAL CONFLICT OF INTEREST

JKS has been an invited speaker to industry funded meetings.

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- No sources of support supplied

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* Indicates the major publication for the study

TABLES

Characteristics of included studies

Study	Abrahamsson 2007
Methods	Randomisation: yes, stratified for study centre, used allocation list, probiotic or placebo randomly allocated to bottle. Blinding of intervention: yes, placebo used. Blinding of outcome measurement: yes. Losses to follow up: non-compliers with treatment excluded. Completed study: probiotic group 95/117 (81%); placebo group 93/115 (81%). Intention to treat analysis: yes.
Participants	Inclusion criteria: 232 families with allergic disease (one or more family members with eczema, asthma, gastrointestinal allergy, allergic urticaria, or allergic rhinoconjunctivitis) recruited at antenatal clinics. Exclusion criteria: mother reporting peanut allergy. Infants admitted to neonatal unit in first week.
Interventions	Treatment (n = 117): Lactobacillus reuteri (freeze dried, suspended in coconut and peanut oil) given to mother for 4 weeks before delivery, mother and baby daily for 12 months after delivery. Control (n = 115): placebo (same oil). Co-interventions: infants breast fed. When weaned, given whey hydrolysate formula to 6 months (both groups).
Outcomes	Primary outcomes: eczema and sensitization in first 2 years. Other outcomes: assessed by research nurses and structured telephone interview up to 2 years.

Characteristics of included studies (Continued)

	Eczema: physician confirmed. SCORAD score used. Defined as pruritic, chronic or chronically relapsing non-infectious dermatitis with typical features and distribution. Sensitization: skin prick tests at 6, 12 and 24 months. Specific IgE measured using CAP system.
Notes	Sponsored: grants from BioGaia AB, Stockholm, Sweden, the Ekhaga Foundation, the Heart and Lung foundation, the Research Council for the South-East Sweden (grant No. F2000-106), the Swedish Asthma and Allergy Association, the Swedish Research Council and the University Hospital of Linköping, Sweden.
Allocation concealment	A – Adequate

Study	Bin-Nun 2005
Methods	Randomisation: yes, method not reported. Blinding of intervention: yes. Blinding of outcome measurement: yes. Losses to follow up: yes, reported 3 (2%) infants excluded from final analysis. Intention to treat analysis: yes.
Participants	Inclusion criteria: Preterm neonates <1500 g birth weight who began feeding on a weekday. Exclusion criteria: none reported.
Interventions	Treatment (n = 72): regular feeds plus daily probiotic feeding supplement of ABC Dophilus (Solgar, division of Wyeth Consumer Healthcare, Bergen County, NJ) diluted in 3mL of expressed mother's milk when available or in 3 mL of Similac Special Care formula (Abbott Laboratories, Abbott Park, IL) when mother's milk unavailable. Control (n = 73): regular feeds plus daily supplement of 3 mL mother's milk (with nothing added) when available or premature infant formula (with nothing added) when mother's milk unavailable. Co-interventions: preterm infants given TPN, feeds increased slowly, breast milk preferred. Preterm formula used if needed.
Outcomes	Primary outcomes: clinical and radiological diagnosis of NEC according to Bell's staging criteria. Other outcomes: Infants evaluated at weekly intervals for feeding intolerance (diarrhea, abdominal distension, or vomiting) and growth data recorded. Sepsis. Did not report allergy or food hypersensitivity.
Notes	Sponsored: Supported by Mr. and Mrs. Stephen Hammerman and the Mirsky Research Fund.
Allocation concealment	B – Unclear

Study	Brunser 2006b
Methods	Randomisation: yes, computer-generated randomization table. Blinding of intervention: yes, formula products were letter-coded identical formula. Blinding of outcome measurement: yes. Losses to follow up: 40/116 (34%) Intention to treat analysis: yes.
Participants	Inclusion criteria: Healthy infants born at term, 3.5 months old, birth weight 3000-4200 g Exclusion criteria: infant antibiotic treatment in the month prior to enrolment, multiple births, presence of any degree of malnutrition, or gastrointestinal, renal or other chronic diseases.
Interventions	Treatment (n = 32): Prebiotic group received the control formula with added FOS concentration of 2 g/L (Rafilose P95, Orafiti, Tienen, Belgium), or Treatment 2 (n = 25): probiotic group received control formula enriched with 10*8 Lactobacillus johnsonii per gram of powder.; or Control (n = 33): Standard infant formula (Nan 2, Nestlé Chile, Santiago, Chile). Co-interventions: infants should not receive yogurt or any other fermented foodstuffs.
Outcomes	Primary outcomes: colonic microbiota.

Characteristics of included studies (Continued)

	Other outcomes: weight and height recorded every 15 days by study nurse. Allergy and food hypersensitivity not reported.
Notes	Sponsored: not reported. Study authors affiliated with Nestec Ltd., Vevey, Switzerland, and Nestlé Research Center, Vers-chez-les-Blanc, Switzerland.
Allocation concealment	A – Adequate

Study	Kalliomaki 2001
Methods	Randomisation: yes, computer generated. Blinding of intervention: yes, Lactobacillus GG and placebo capsules and contents looked, smelled, and tasted identical. Blinding of outcome measurement: yes. Losses to follow up: 27/159 (17%) lost. Intention to treat analysis: yes.
Participants	Inclusion criteria: family history of atopic disease: ≥ 1 family member (mother, father, or older sibling) with atopic eczema, allergic rhinitis, or asthma. Families were recruited in antenatal clinics. Exclusion criteria: none reported.
Interventions	Treatment (n = 77): Lactobacillus rhamnosus GG prenatally to mothers and postnatally whilst breastfeeding up to 6 months; if not breast fed given to infants mixed with water on spoon. Control (n = 82): placebo (microcrystalline cellulose). Co-interventions: none reported.
Outcomes	Primary outcomes: atopic disease at 2 and 4 years. Other outcomes: Blinded physician assessment for atopy. Definitions: Eczema: pruritis, facial or extensor involvement, or both, and chronic relapsing course (for 1 month or longer at the 24-month visit and on at least one previous visit. The SCORAD index used to assess eczema severity. Allergic rhinitis: most days two or more of: nasal discharge, blockage, sneezing, and itching. Asthma: based on an algorithm created by an international paediatric asthma consensus group. Diagnosed if infant had chronic or recurrent cough, wheeze or shortness of breath, or both, suggestive of asthma, and if other diagnoses were excluded and trial antiasthma treatment was effective. Sensitisation measured by: skin-prick tests at 6, 12, and 24 months; and total and specific IgE assays on cord blood and at 3, 12, and 24 months.
Notes	Sponsored: Finnish Foundation for Paediatric Research, the National Technology Agency of Finland, and the Allergy Research Foundation in Finland.
Allocation concealment	A – Adequate

Study	Kukkonen 2006
Methods	Randomisation: computer-generated block randomisation. Blinding of intervention: yes, placebo used. Blinding of outcome measurement: yes. Losses to follow up: 298/1223 (24%). Intention to treat analysis: yes.
Participants	Inclusion criteria: pregnant women with at least one parent of the unborn child had a physician-diagnosed allergic disease. Exclusion criteria: infants born < 37 weeks gestation, infants with major malformations, and B-twins.
Interventions	Treatment (n = 610): mothers took 1 capsule for 2-4 weeks before delivery containing Lactobacillus rhamnosus GG (ATCC 53103), 5×10^9 colony-forming units (cfu); L rhamnosus LC705 (DSM 7061), 5×10^9 cfu;

Characteristics of included studies (Continued)

	Bifidobacterium breve Bb99 (DSM 13692), 2×10^8 cfu; and Propionibacterium freudenreichii ssp. shermanii JS (DSM 7076), 2×10^9 cfu. Their newborn infants received 1 opened capsule containing the same probiotics mixed with 20 drops of sugar syrup containing 0.8 g of galacto-oligosaccharides once daily for 6 months after birth. Control (n = 613): placebo group mothers and infants took capsules containing microcrystalline cellulose, and infants received sugar syrup without galacto-oligosaccharides. Co-interventions: Normal adapted cow's milk-based formula replaced breast milk when breast-feeding was insufficient. The use of hypoallergenic formula was restricted to infants allergic to cow's milk.
Outcomes	Primary outcomes: any allergic disease (food allergy, eczema, asthma, and allergic rhinitis) and IgE-associated (atopic) disease at 2 years. Other outcomes: eczema and IgE sensitization. Physician assessment at 3, 6 and 24 months. Food allergy diagnosed with an open food challenge. Eczema: according to the UK Working Party's criteria (an itchy skin condition plus ≥ 3 of atopic disease in the family, dry skin during the last year, history of eczema, or visible eczema involving typical sites). Atopic eczema: if IgE associated. Severity of eczema evaluated using SCORAD score. Asthma: 2 or more physician-diagnosed wheezing episodes accompanied by persistent cough or exercise-induced symptoms. Sensitisation: skin prick tests and allergen-specific IgE levels (ImmunoCAP System) at 2 years.
Notes	Sponsored: grants from Valio Ltd; two authors employed by Valio Ltd.
Allocation concealment	A – Adequate

Study	Lin 2005
Methods	Randomisation: yes, random-number table sequence with allocations contained in opaque, sequentially numbered, sealed envelopes. Blinding of intervention: no, personnel who knew of the infants' group assignments included investigators and those on the breast milk team not involved in the care of the study infants. Blinding of outcome measurement: yes. Losses to follow up: none reported. Intention to treat analysis: yes.
Participants	Inclusion criteria: VLBW infants (birth weight <1500 g) who started to feed enterally and survived beyond the seventh day after birth. Exclusion criteria: none reported.
Interventions	Treatment (n = 180): Infloran (L. acidophilus [minimum of 1.004×10^4 356] and B infantis [minimum of 1.015×10^5 697] 125 mg/kg per dose twice daily with breast milk until discharged. Control (n = 187): breast milk without the addition of probiotics. Co-interventions: all infants only fed if feeding tolerated, grading maximum 20 ml/day.
Outcomes	Primary outcomes: incidence and severity of NEC in VLBW infants. Other outcomes: reported infection with probiotic bacteria. Allergy and food hypersensitivity not reported
Notes	No conflict of interest declared.
Allocation concealment	A – Adequate

Study	Puccio 2007
Methods	Randomisation: yes, method not reported.

Characteristics of included studies (Continued)

	Blinding of intervention: yes, coded tins used. Blinding of outcome measurement: yes. Losses to follow up: 41/138 (30%) withdrew from study but all infants reported in intention to treat analysis. Intention to treat analysis: yes.
Participants	Inclusion criteria: healthy, full-term (>37 weeks) newborn infants whose mothers had decided not to breast feed beyond 14th day. Infants were <14 d old, weighed 2500–4500 g, and were singletons. Exclusion criteria: already participating in another clinical trial, diagnosed with a congenital illness or malformation that could affect normal growth, had significant pre- or postnatal disease; had been rehospitalized for >2 d for reasons other than jaundice, or had received antibiotic treatment at the time of enrollment.
Interventions	Experimental and control formulas were powdered starter cow's milk formulas (Nan, Nestlé, Vevey, Switzerland) Treatment (n = 69): 2 x 10⁷ colony-forming units of <i>Bifidobacterium longum</i> BL999 (BAA-999, designation BB536, ATCC, Morinaga, Japan) and 4 g/L of a mixture of a GOS and a FOS (9:1). Control (n = 69): no added prebiotic or probiotic. Co-interventions: none reported.
Outcomes	Primary outcomes: weight gain during the first 4 months. Other outcomes: safety and tolerability of formula including discontinuation. Allergy and food hypersensitivity not reported
Notes	Sponsored: Nestlé Nutrition, Nestec Ltd., Vevey, Switzerland.
Allocation concealment	A – Adequate

Study	Rautava 2002
Methods	Randomisation: yes, method not reported. Blinding of intervention: yes, used placebo. Blinding of outcome measurement: reported “double-blinded”. Losses to follow up: yes, 97/159 (61%) excluded as not breast feeding or not compliant. Intention to treat analysis: yes.
Participants	Inclusion criteria: 159 pregnant women from atopic families. The assessment of maternal atopic disease was based on reported clinical history of atopic eczema, allergic rhinoconjunctivitis, or asthma. Only included if breast-feeding and maternal use of probiotics or placebo until the child was 3 months of age. Exclusion criteria: none reported.
Interventions	Randomized to receive either: Treatment (n = 30): <i>Lactobacillus rhamnosus</i> strain GG (ATCC 53103; daily dose, 2x10¹⁰ colony forming units; Valio Ltd, Helsinki, Finland), during the 4 weeks before giving birth (mean, 28 days; 95% CI, 24–31) and during breast-feeding, or Control (n = 32): placebo (microcrystalline cellulose; Valio Ltd) Co-interventions: none reported.
Outcomes	Primary outcomes: immunoprotective potential of breast milk, as assessed by the amount of anti-inflammatory transforming growth factor beta2 in the milk. Other outcomes: Infants' clinical history and status assessed at 3, 6, 12, 18, and 24 months. Atopic eczema: confirmed if the following features detected: pruritus, typical morphology and distribution, and a chronic relapsing course. Cow's milk allergy: confirmed by double-blinded, placebo controlled cow's milk challenge, when symptoms, clinical signs, or skin prick test results were suggestive of cow's milk allergy.
Notes	Sponsored: not reported.
Allocation concealment	B – Unclear

Characteristics of included studies (Continued)

Study	Rautava 2006
Methods	Randomisation: yes, method not reported. Blinding of intervention: yes, placebo used. Blinding of outcome measurement: not reported. Losses to follow up: 9/81 (11%). Intention to treat analysis: yes.
Participants	Inclusion criteria: need for artificial feeding before the age of 2 months. Intervention commenced when the need for artificial feeding arose and the supplemented formula was to be used as the sole infant formula. Exclusion criteria: Infants with chronic disease.
Interventions	81 infants randomised to receive infant formula (Enfamil, Mead Johnson Nutritional, Evansville, IN) supplemented with either: Treatment (n = 38): 1×10^{10} colony-forming units of <i>Lactobacillus rhamnosus</i> (Lactobacillus GG, American type culture collection 53103, Valio Ltd., Helsinki, Finland) and <i>Bifidobacterium lactis</i> Bb-12 (Chr. Hansen, Hoersholm, Denmark) daily until the age of 12 months, or Control (n = 43): placebo (microcrystalline cellulose). Co-interventions: none reported.
Outcomes	Primary outcomes: effects of probiotic supplementation in reducing the risk of infectious disease in infants devoid of the recommended 6 months of exclusive breast-feeding. Other outcomes: Clinical examination at 3, 7, and 12 months. Atopic eczema: criteria introduced by Hanifin. Cow's milk allergy: confirmed by double-blind, placebo-controlled cow's milk challenge. Skin prick tests at the ages of 7 and 12 months.
Notes	Funded by the Microbes and Man Research Program, Academy of Finland, and the Sigrid Juselius Foundation.
Allocation concealment	B – Unclear

Study	Saavedra 2004
Methods	Randomisation: yes, variable-size block scheme. Blinding of intervention: placebo used. Blinding of outcome measurement: not reported. Losses to follow up: yes, 13/131 (10%). Intention to treat analysis: yes.
Participants	Inclusion criteria: 131 healthy infants recruited from 27 daycare centers. Exclusion criteria: breastfeeding ≥ 3 times/d, a history of allergy to standard formula, or a history of chronic diarrhea or malabsorptive syndrome.
Interventions	Randomly assigned to: Treatment 1 (n = 44): standard formula supplemented with <i>B. lactis</i> (strain Bb 12) and <i>S. thermophilus</i> at a concentration of $\sim 1 \times 10^7$ CFU/g [high-supplement formula]; Treatment 2 (n = 43): same formula supplemented at a concentration of 1×10^6 CFU/g [low-supplement formula]; or Control (n = 44): placebo - the same formula without any supplementation Co-interventions: none reported.
Outcomes	Primary outcomes: identify any adverse effects, and to examine effects on growth, general clinical status, and intestinal health. Other outcomes: Data collected weekly through phone calls to the parents and visits to the daycare centers. Information gathered on: 1) general health status of the infant, 2) gastrointestinal signs and related symptoms, and colic or irritability; 3) dietary information, and 4) data used to monitor compliance.

Characteristics of included studies (Continued)

	Researchers measured monthly weight and length measurements. Allergy and food hypersensitivity not reported.
Notes	Sponsored: research grant from Nestlé USA. All study formulas were provided by Nestlé USA, Glendale, CA.
Allocation concealment	A – Adequate

Study Taylor 2006

Methods	Randomisation: yes, computerised randomisation schedule with allocation and dispensing by pharmacy. Groups were stratified and block-randomized according to (1) maternal allergy (asthma vs other allergy), (2) parity (first child vs 2 or more children), and (3) paternal allergy (allergy vs no allergy). Blinding of outcome intervention: yes, placebo used. Blinding of measurement: yes. Losses to follow up: 40/226 (18%). Additional control infant not reported for atopic eczema. Intention to treat analysis: yes.
Participants	Inclusion criteria: 231 pregnant, atopic women. Maternal atopy defined as doctor-diagnosed clinical history of asthma, allergic rhinitis, or eczema plus a positive skin prick test (SPT) to 1 or more common allergens. Exclusion criteria: women excluded if smoked, had other medical problems or pregnancy complications, delivered before 37 weeks gestation, or already taking probiotic supplements.
Interventions	Treatment (n = 115): 3x10⁹ / L acidophilus LAVRI-A1 in maltodextrin (Probiomix, Sydney, Australia). Supplements supplied as stable freeze-dried powder, dissolved in 1 to 2 mL sterile water and administered orally on a daily from birth to 6 months. Control (n = 111): maltodextrin alone. Co-interventions: none reported.
Outcomes	Primary outcomes: primary allergy prevention in a population of Australian children at high risk of allergic disease. Other outcomes: incidence of atopic dermatitis, food allergy, and/or sensitization. at 12 months. Detailed history and examination by the same pediatric allergist. Atopic dermatitis: typical skin lesions responsive to topical steroids. The severity determined using the severity score of atopic dermatitis (SCORAD). IgE-mediated food allergy: history of immediate symptoms after contact with and/or ingestion of food and positive SPT to the implicated food.
Notes	Sponsored: National Health and Medical Research Council of Australia and Probiomix as an industry partner. The study and all of the analyses were conducted independently of the commercial entity.
Allocation concealment	A – Adequate

Study Vendt 2006

Methods	Randomisation: yes. Randomly allocated identical packages to consecutive numbers. Blinding of intervention: yes, placebo used. Blinding of outcome measurement: yes. Losses to follow up: 15/120 (12.5%) Intention to treat analysis: yes.
Participants	Inclusion criteria: 120 healthy term infants aged from 0-2 months were recruited through four child healthcare centres. The infants had to be on formula for at least half of their daily feedings. Exclusion criteria: none reported.
Interventions	Treatment (n = 60): probiotic formula was the same, but enriched with L. rhamnosus GG (LGG, ATCC 53103). Dry bacteria were mixed to the final dry product in Valio Ltd (concentration of bacteria in the dry powder was 10⁷ CFU /g).

	Control (n = 60): placebo formula was Tutteli, Infant Formula (Valio Ltd, Helsinki, Finland), dairy milk-based spray-dried powder, from birth onwards. Co-interventions: none reported.
Outcomes	Primary outcomes: growth and faecal flora. Other outcomes: allergy and food hypersensitivity not reported.
Notes	Sponsored: by Valio Ltd, Helsinki, Finland.
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	Reason for exclusion
Bakker-Zierikzee	Randomised formula fed infants to prebiotic (galacto-oligosaccharide and fructo-oligosaccharide) versus probiotic (bifidobacterium animalis) versus standard formula. Did not report allergy or food hypersensitivity.
Brouwer 2006	Enrolled infants with atopic dermatitis.
Brunser 2006	Randomised infants at 4 months to control formula, formula plus prebiotic oligosaccharide, or formula plus probiotic (lactobacillus johnsonii). Did not report allergy or food hypersensitivity.
Chouraqui 2004	Randomised infants with acute infectious diarrhoea to bifidobacterium lactis supplemented formula or control. Did not report allergy or food hypersensitivity.
Dani 2002	Randomised preterm or low birth weight infants to Lactobacillus rhamnosus GG or control. Did not report allergy or food hypersensitivity.
Huet 2006	Allocated healthy term infants to a low protein (1.5g/100ml) formula supplemented with bifidobacterium lactis. Not randomised. Did not report allergy or food hypersensitivity.
Isolauri 2000	Enrolled infants with eczema. Randomised to probiotic formula or control.
Kirjavainen 2002	Randomised infants with early onset eczema.
Kirjavainen 2003	Randomised infants with early onset eczema and allergy to cow's milk.
Majamaa 1997	Enrolled infants with eczema and cow's milk allergy.
Manzoni 2006	Enrolled preterm infants. Reported fungal colonisation. Did not report allergy or food hypersensitivity.
Marzotto 2006	Enrolled healthy infants 12-24 months of age. Did not report allergy or food hypersensitivity.
Mohan 2006	Enrolled preterm infants. Did not report allergy or food hypersensitivity.
Pohjavuori 2004	Enrolled infants with suspected cow's milk allergy.
Rio 2004	Enrolled infants (undernourished and controls) 6-12 months. Reported episodes of diarrhoea. Did not report allergy or food hypersensitivity.
Rosenfeldt 2003	Enrolled children with atopic dermatitis.
Rosenfeldt 2004	Enrolled children with moderate and severe atopic dermatitis.
Savino 2007	Enrolled breast-fed infants with diagnosis of infantile colic. Did not report allergy or food hypersensitivity.
Shamir 2005	Enrolled infants with diarrhoea. Did not report allergy or food hypersensitivity.
Sistek 2006	Enrolled infants with current dermatitis.
Thibault 2004	Enrolled healthy infants (age 4-6 months) with regular contact with other children in day care centers or were living at home with two or more young siblings. Reported diarrhoea episodes. Did not report allergy or food hypersensitivity.
Viljanen 2005	Enrolled infants with atopic eczema.
Weizman 2006	Enrolled healthy term infants 4-10 months old from child care centers. Did not report allergy or food hypersensitivity.

Characteristics of excluded studies (Continued)

Weston 2005 Enrolled children aged 6-18 months with moderate or severe atopic dermatitis.

ANALYSES**Comparison 01. Probiotic versus no probiotic - all infants**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 All allergic disease			Relative Risk (Fixed) 95% CI	Subtotals only
02 Food hypersensitivity			Relative Risk (Fixed) 95% CI	Subtotals only
03 Food hypersensitivity (gastrointestinal symptoms)			Relative Risk (Fixed) 95% CI	Subtotals only
04 Asthma			Relative Risk (Fixed) 95% CI	Subtotals only
05 Eczema			Relative Risk (Fixed) 95% CI	Subtotals only
06 Atopic eczema			Relative Risk (Fixed) 95% CI	Subtotals only
07 Allergic rhinitis			Relative Risk (Fixed) 95% CI	Subtotals only
08 Food allergy			Relative Risk (Fixed) 95% CI	Subtotals only
09 Cow's milk protein hypersensitivity			Relative Risk (Fixed) 95% CI	Subtotals only
10 Cow's milk protein allergy			Relative Risk (Fixed) 95% CI	Subtotals only
11 Urticaria			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 02. Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 All allergic disease			Relative Risk (Fixed) 95% CI	Subtotals only
02 Food hypersensitivity (gastrointestinal symptoms)			Relative Risk (Fixed) 95% CI	Subtotals only
03 Asthma			Relative Risk (Fixed) 95% CI	Subtotals only
04 Eczema			Relative Risk (Fixed) 95% CI	Subtotals only
05 Atopic eczema			Relative Risk (Fixed) 95% CI	Subtotals only
06 Allergic rhinitis			Relative Risk (Fixed) 95% CI	Subtotals only
07 Food allergy			Relative Risk (Fixed) 95% CI	Subtotals only
08 Cow's milk protein hypersensitivity			Relative Risk (Fixed) 95% CI	Subtotals only
09 Urticaria			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 03. Probiotic versus no probiotic in infants not selected for risk of allergy or food hypersensitivity

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Atopic eczema			Relative Risk (Fixed) 95% CI	Subtotals only
02 Cow's milk protein hypersensitivity			Relative Risk (Fixed) 95% CI	Subtotals only
03 Cow's milk protein allergy			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 04. Probiotic versus no probiotic in infants fed exclusive human milk

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Food hypersensitivity (gastrointestinal symptoms)			Relative Risk (Fixed) 95% CI	Subtotals only
02 Eczema			Relative Risk (Fixed) 95% CI	Subtotals only
03 Cow's milk protein hypersensitivity			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 05. Probiotic versus no probiotic in infants fed cow's milk formula

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Atopic eczema			Relative Risk (Fixed) 95% CI	Subtotals only
02 Cow's milk protein hypersensitivity			Relative Risk (Fixed) 95% CI	Subtotals only
03 Cow's milk protein allergy			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 06. Probiotic versus no probiotic in infants fed a hydrolysed formula

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Food hypersensitivity (gastrointestinal symptoms)			Relative Risk (Fixed) 95% CI	Subtotals only
02 Asthma			Relative Risk (Fixed) 95% CI	Subtotals only
03 Eczema			Relative Risk (Fixed) 95% CI	Subtotals only
04 Atopic eczema			Relative Risk (Fixed) 95% CI	Subtotals only
05 Allergic rhinitis			Relative Risk (Fixed) 95% CI	Subtotals only
06 Urticaria			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 07. Probiotic with added prebiotic versus no probiotic

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 All allergic disease			Relative Risk (Fixed) 95% CI	Subtotals only
02 Eczema			Relative Risk (Fixed) 95% CI	Subtotals only
03 Atopic eczema			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 08. Specific probiotic versus no probiotic

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 All allergic disease			Relative Risk (Fixed) 95% CI	Subtotals only
02 Food hypersensitivity (gastrointestinal symptoms)			Relative Risk (Fixed) 95% CI	Subtotals only
03 Asthma			Relative Risk (Fixed) 95% CI	Subtotals only
04 Eczema			Relative Risk (Fixed) 95% CI	Subtotals only
05 Atopic eczema			Relative Risk (Fixed) 95% CI	Subtotals only
06 Allergic rhinitis			Relative Risk (Fixed) 95% CI	Subtotals only
07 Food allergy			Relative Risk (Fixed) 95% CI	Subtotals only
08 Cow's milk protein hypersensitivity			Relative Risk (Fixed) 95% CI	Subtotals only

09 Cow's milk protein allergy
10 Urticaria

Relative Risk (Fixed) 95% CI
Relative Risk (Fixed) 95% CI

Subtotals only
Subtotals only

COVER SHEET

Title	Probiotics in infants for prevention of allergic disease and food hypersensitivity
Authors	Osborn DA, Sinn JK
Contribution of author(s)	DAO and JKS wrote the protocol. DAO wrote the review. Both reviewers performed the literature search, independently assessed studies for eligibility, performed critical appraisal of eligible studies and data extraction, and formed a consensus on the conclusions.
Issue protocol first published	2007/2
Review first published	2007/4
Date of most recent amendment	21 August 2007
Date of most recent SUBSTANTIVE amendment	16 June 2007
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr John Sinn Staff Specialist Neonatal Unit Royal North Shore Hospital Level 5, Douglas Building Pacific Hwy St. Leonards New South Wales 2065 AUSTRALIA E-mail: jsinn@med.usyd.edu.au
DOI	10.1002/14651858.CD006475.pub2
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Editorial group	Cochrane Neonatal Group
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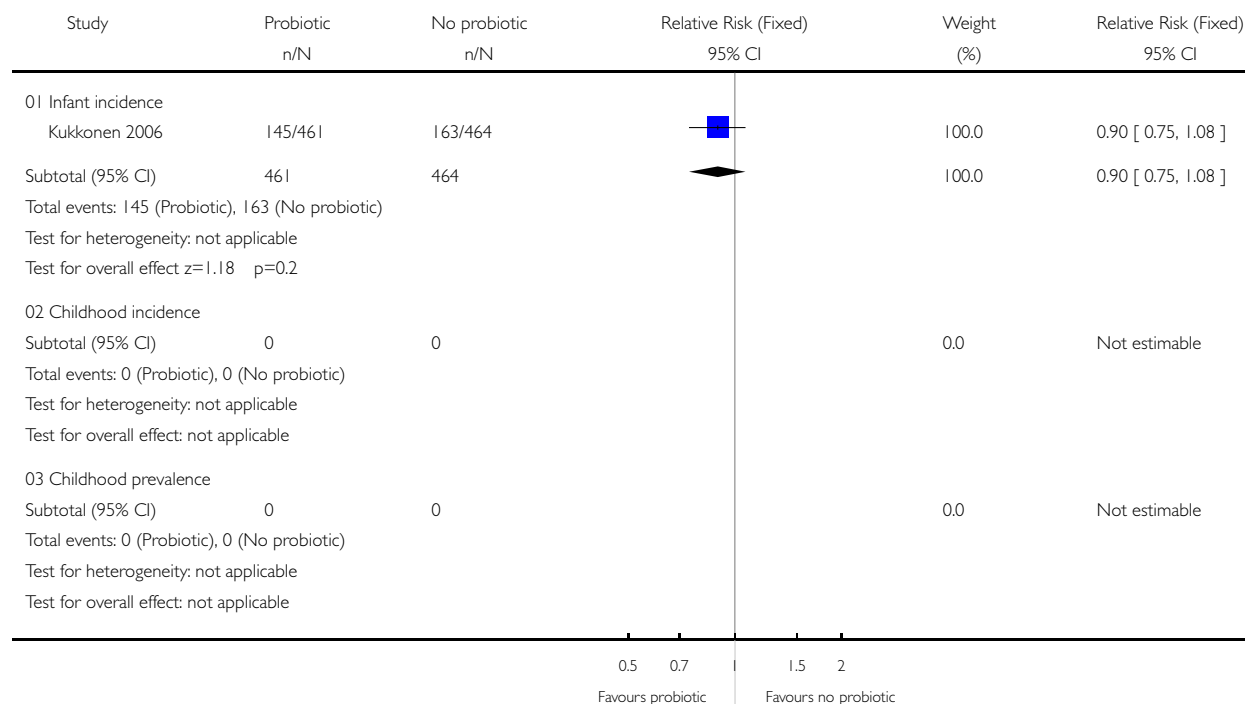
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Probiotic versus no probiotic - all infants, Outcome 01 All allergic disease

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 01 Probiotic versus no probiotic - all infants

Outcome: 01 All allergic disease

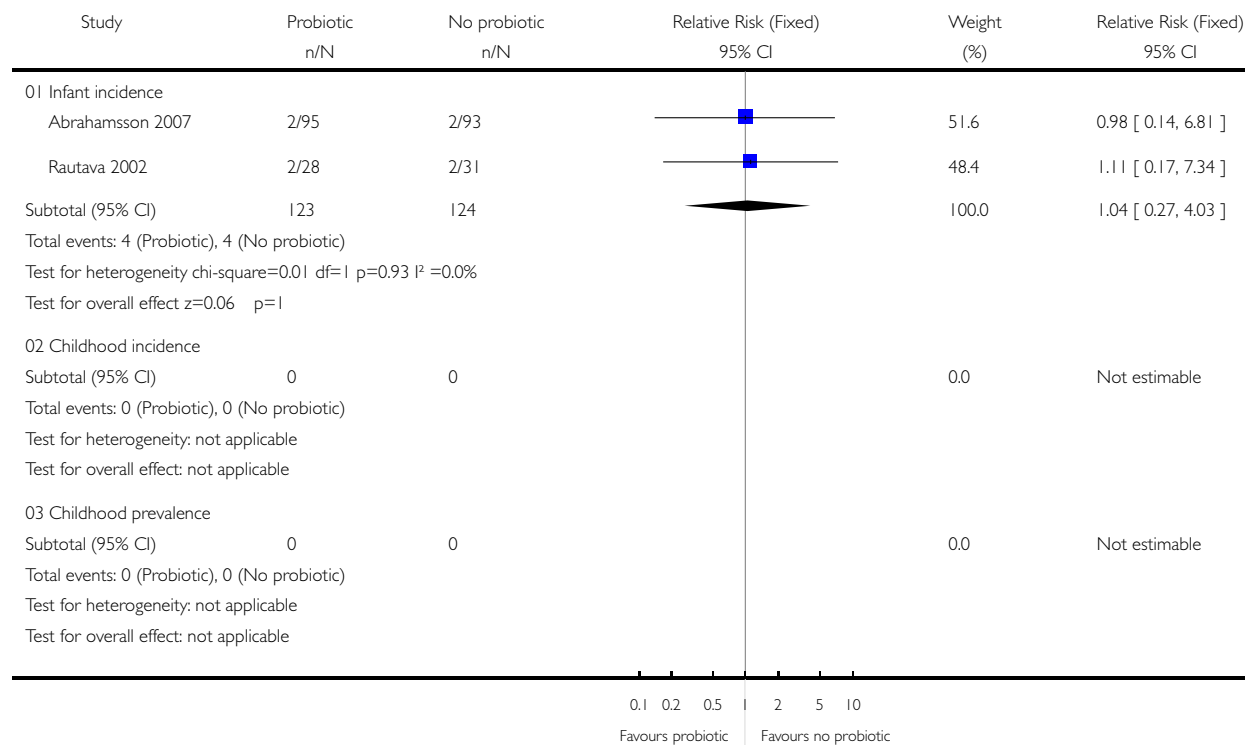


Analysis 01.03. Comparison 01 Probiotic versus no probiotic - all infants, Outcome 03 Food hypersensitivity (gastrointestinal symptoms)

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 01 Probiotic versus no probiotic - all infants

Outcome: 03 Food hypersensitivity (gastrointestinal symptoms)

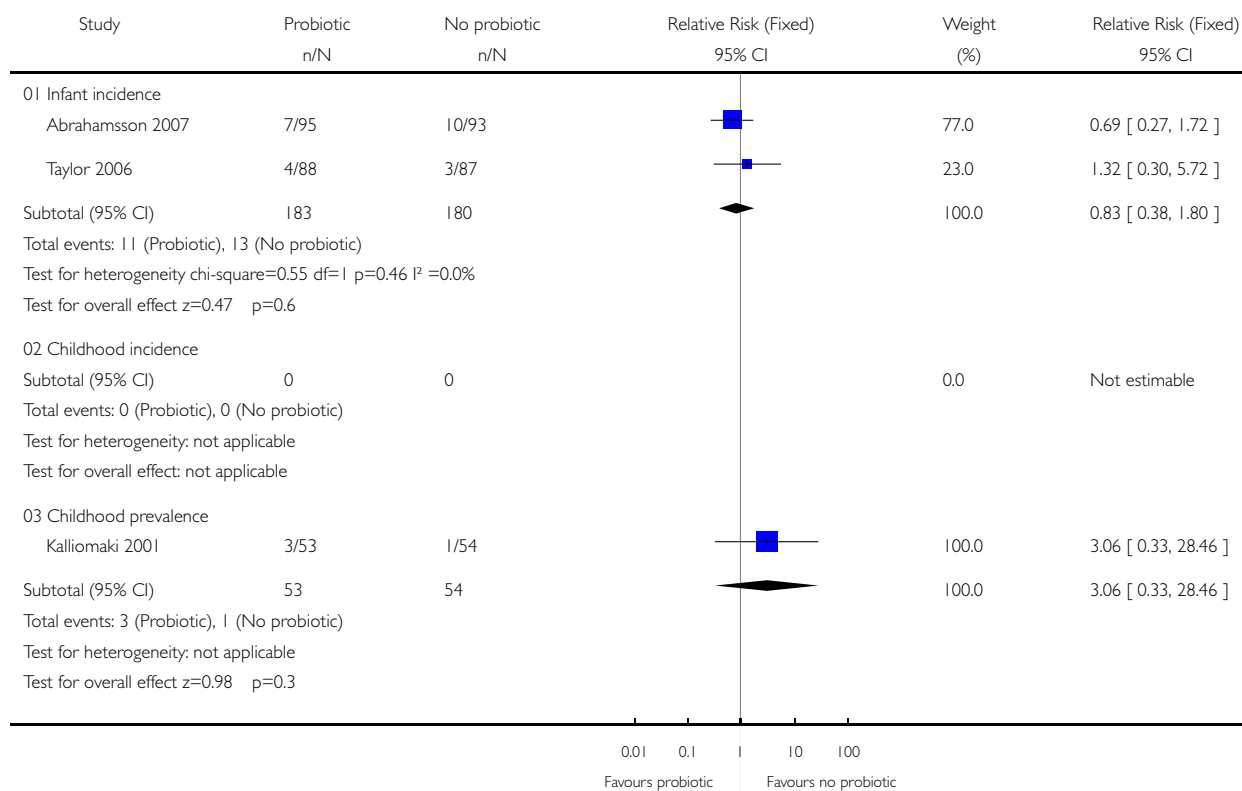


Analysis 01.04. Comparison 01 Probiotic versus no probiotic - all infants, Outcome 04 Asthma

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 01 Probiotic versus no probiotic - all infants

Outcome: 04 Asthma

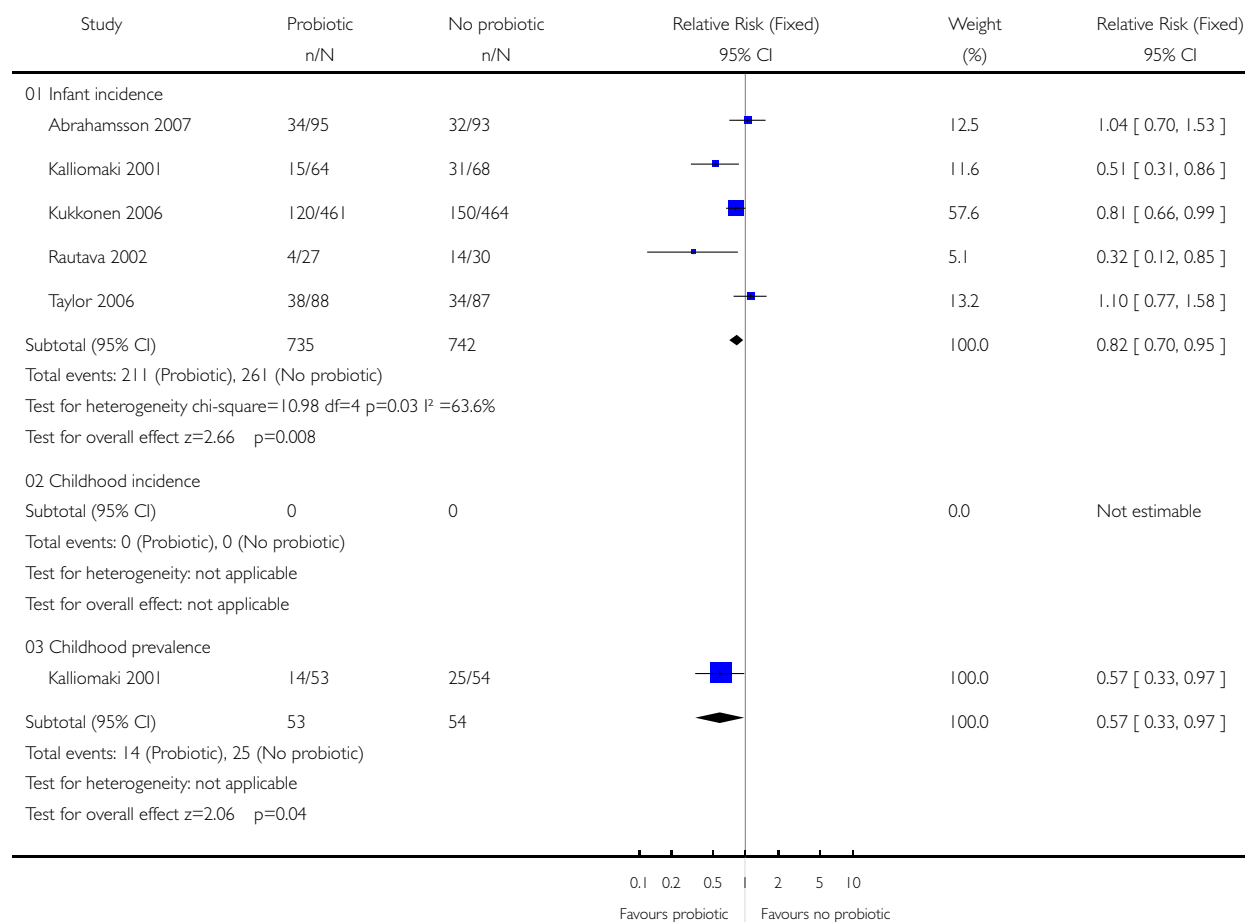


Analysis 01.05. Comparison 01 Probiotic versus no probiotic - all infants, Outcome 05 Eczema

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Comparison: 01 Probiotic versus no probiotic - all infants

Outcome: 05 Eczema

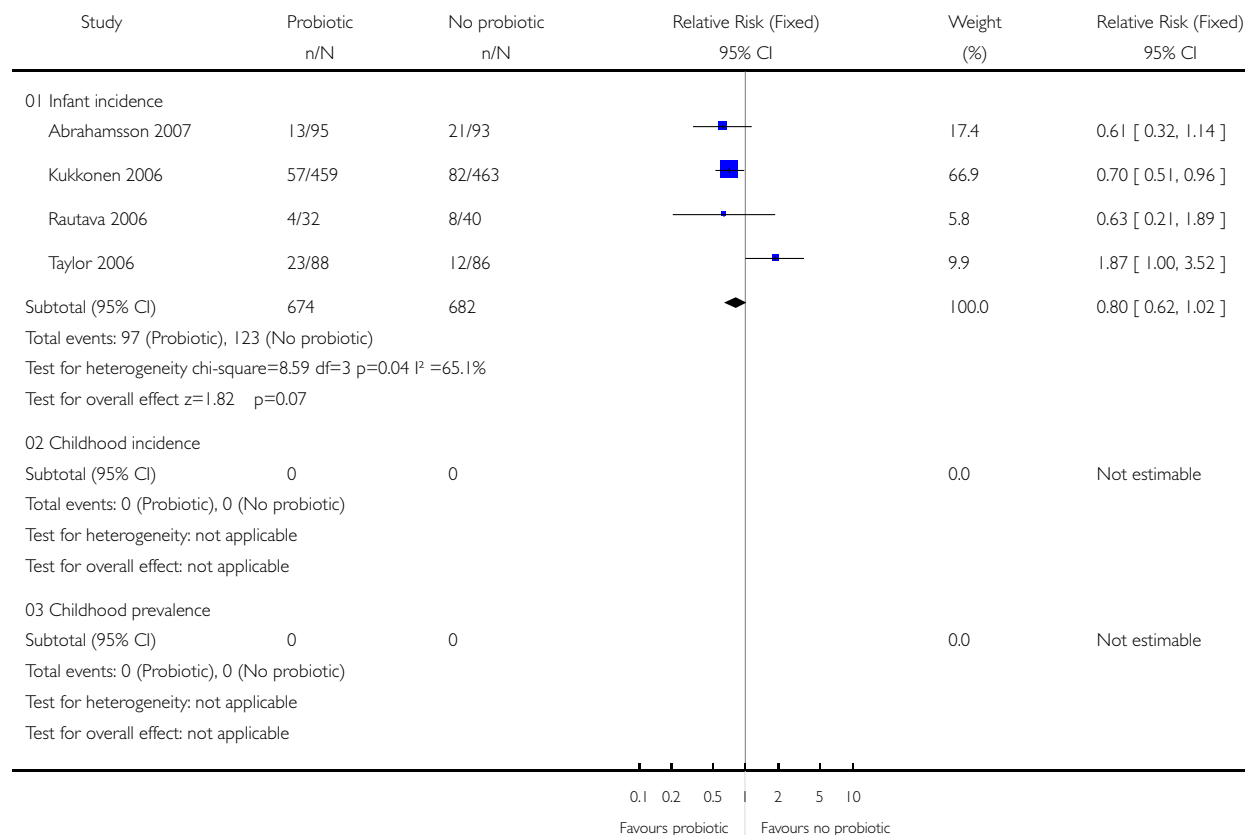


Analysis 01.06. Comparison 01 Probiotic versus no probiotic - all infants, Outcome 06 Atopic eczema

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Comparison: 01 Probiotic versus no probiotic - all infants

Outcome: 06 Atopic eczema

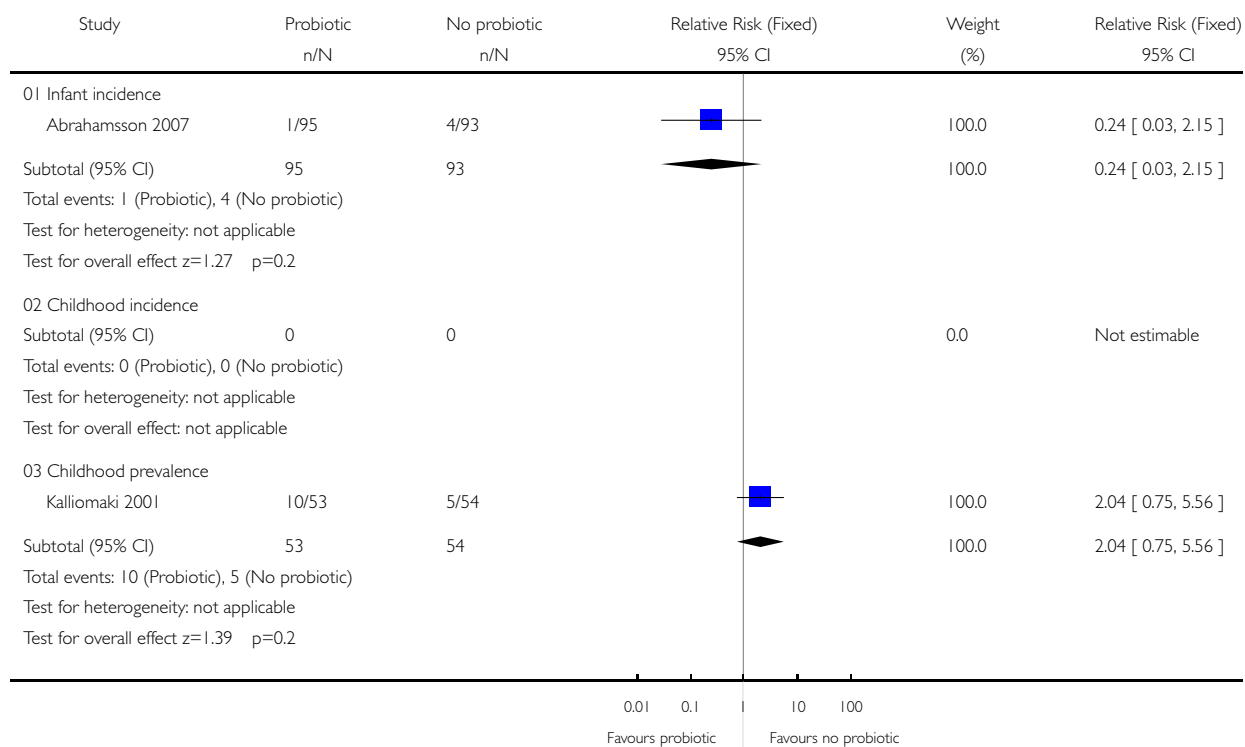


Analysis 01.07. Comparison 01 Probiotic versus no probiotic - all infants, Outcome 07 Allergic rhinitis

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Comparison: 01 Probiotic versus no probiotic - all infants

Outcome: 07 Allergic rhinitis

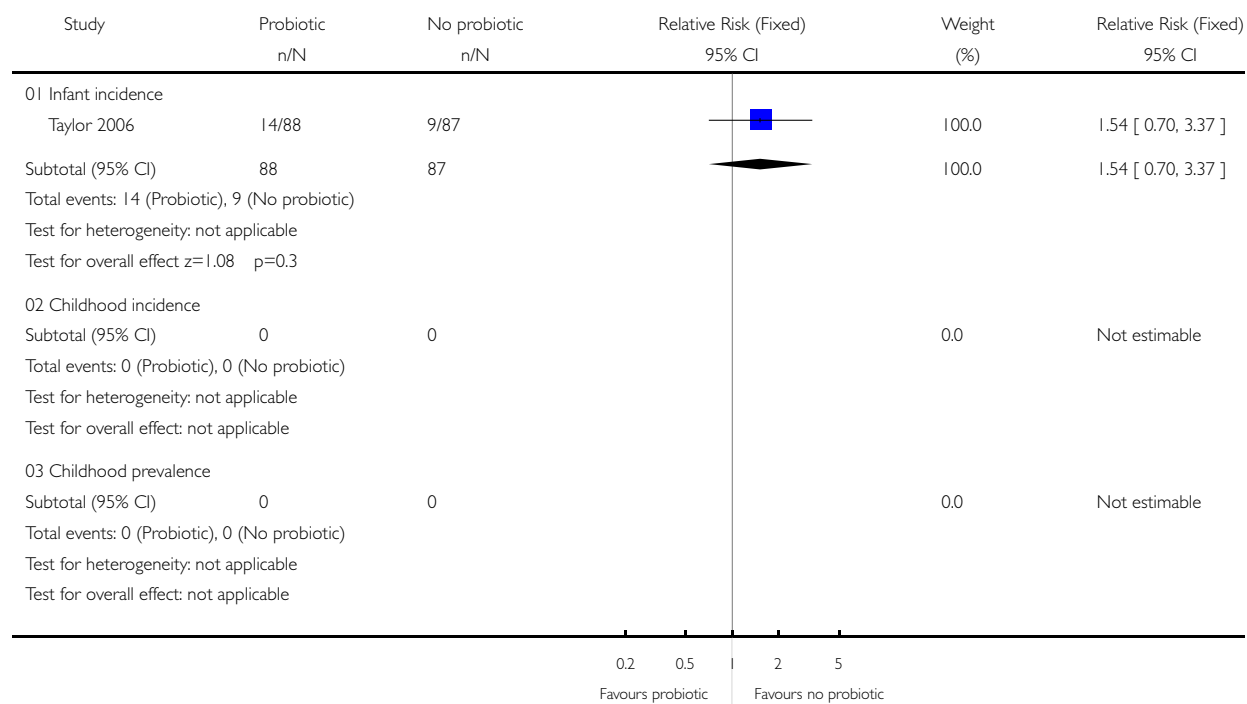


Analysis 01.08. Comparison 01 Probiotic versus no probiotic - all infants, Outcome 08 Food allergy

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 01 Probiotic versus no probiotic - all infants

Outcome: 08 Food allergy

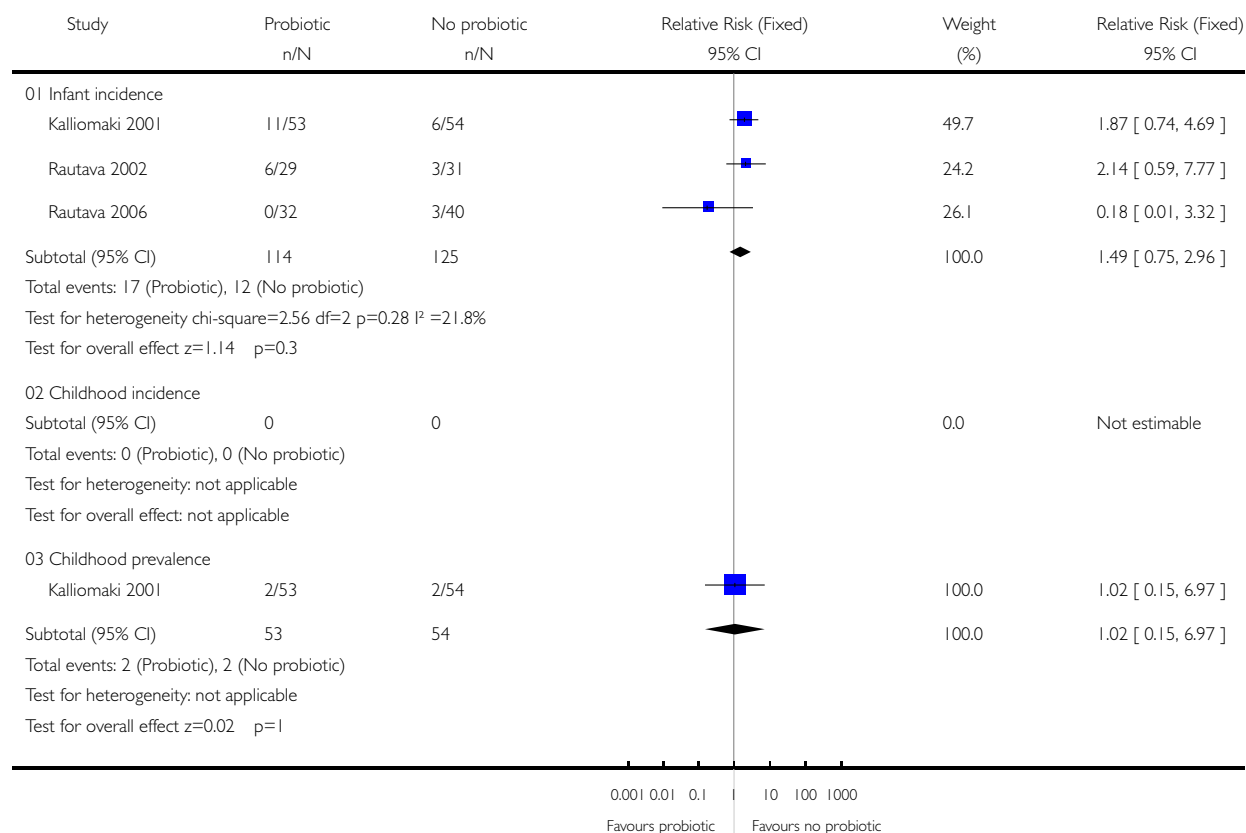


Analysis 01.09. Comparison 01 Probiotic versus no probiotic - all infants, Outcome 09 Cow's milk protein hypersensitivity

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 01 Probiotic versus no probiotic - all infants

Outcome: 09 Cow's milk protein hypersensitivity

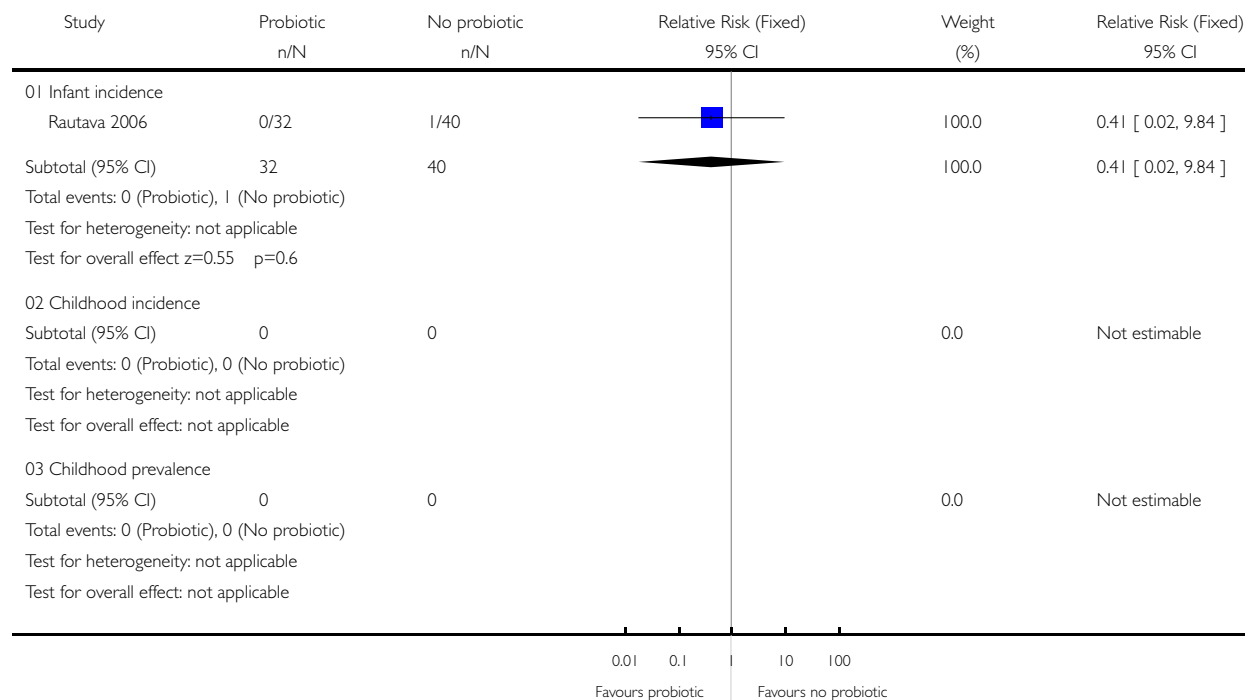


Analysis 01.10. Comparison 01 Probiotic versus no probiotic - all infants, Outcome 10 Cow's milk protein allergy

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Comparison: 01 Probiotic versus no probiotic - all infants

Outcome: 10 Cow's milk protein allergy

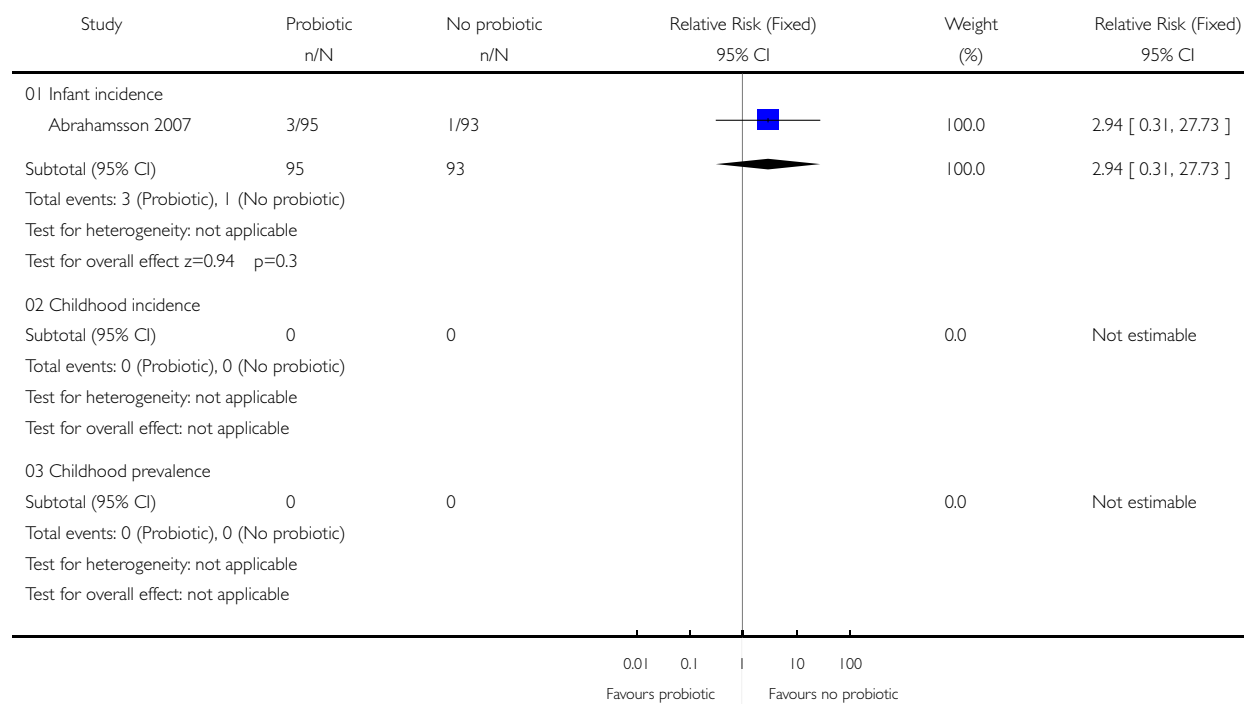


Analysis 01.11. Comparison 01 Probiotic versus no probiotic - all infants, Outcome 11 Urticaria

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 01 Probiotic versus no probiotic - all infants

Outcome: 11 Urticaria

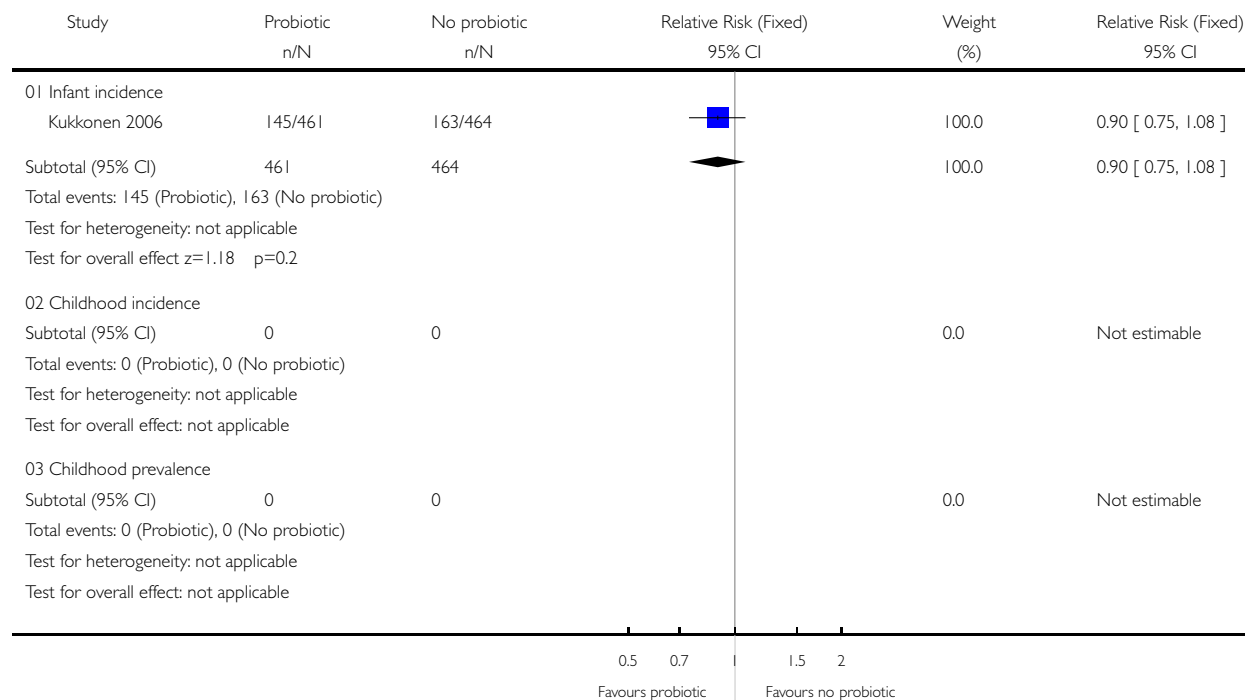


Analysis 02.01. Comparison 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity, Outcome 01 All allergic disease

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity

Outcome: 01 All allergic disease

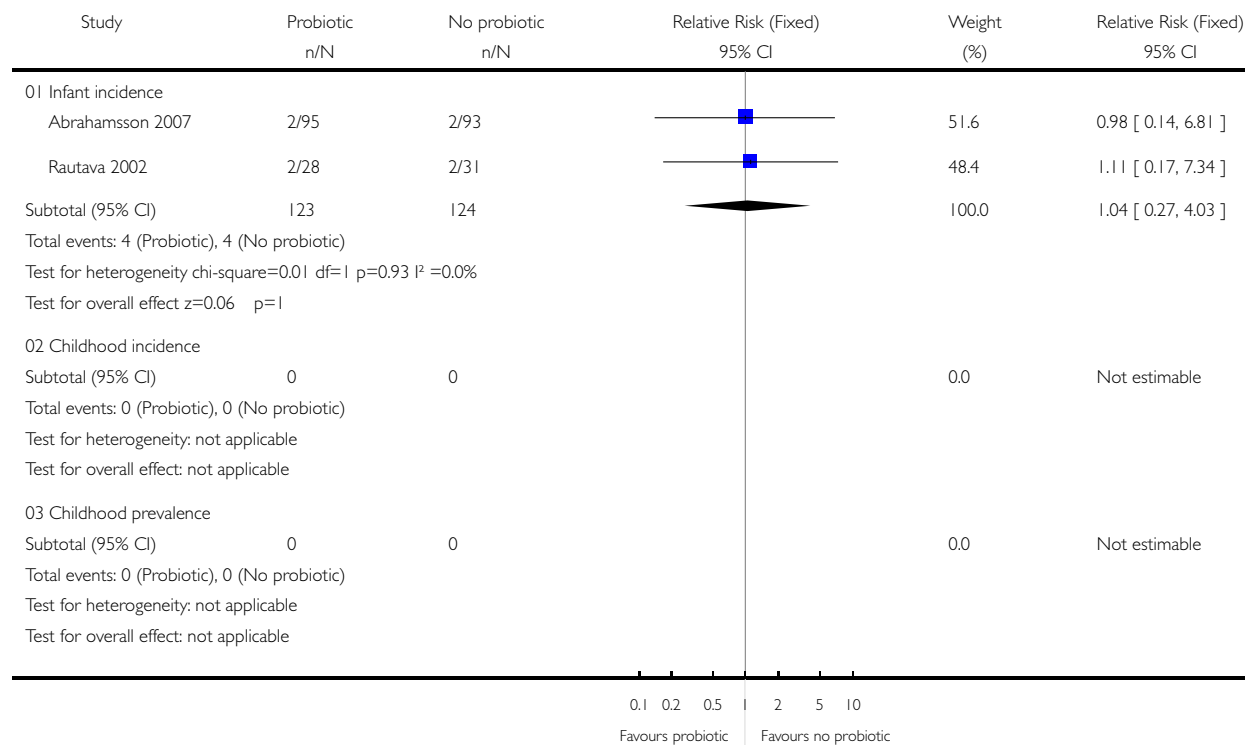


Analysis 02.02. Comparison 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity, Outcome 02 Food hypersensitivity (gastrointestinal symptoms)

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity

Outcome: 02 Food hypersensitivity (gastrointestinal symptoms)

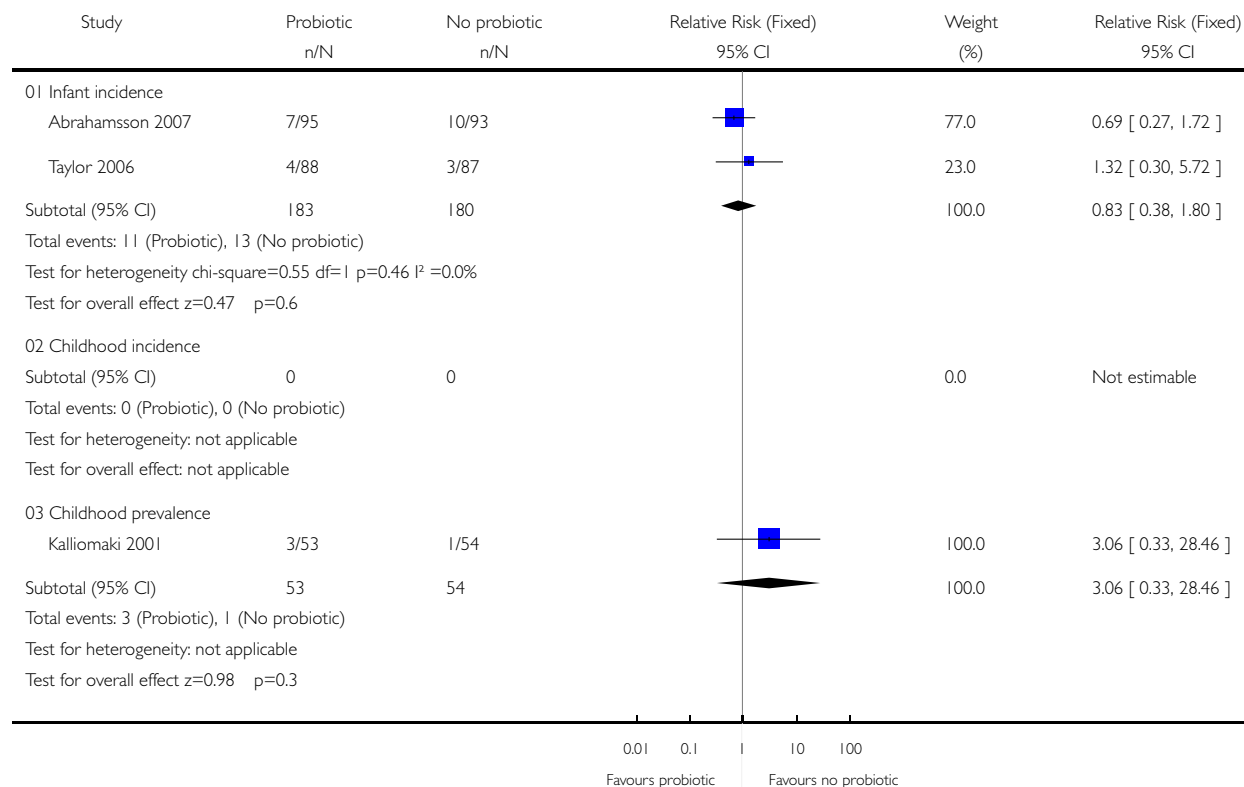


Analysis 02.03. Comparison 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity, Outcome 03 Asthma

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity

Outcome: 03 Asthma

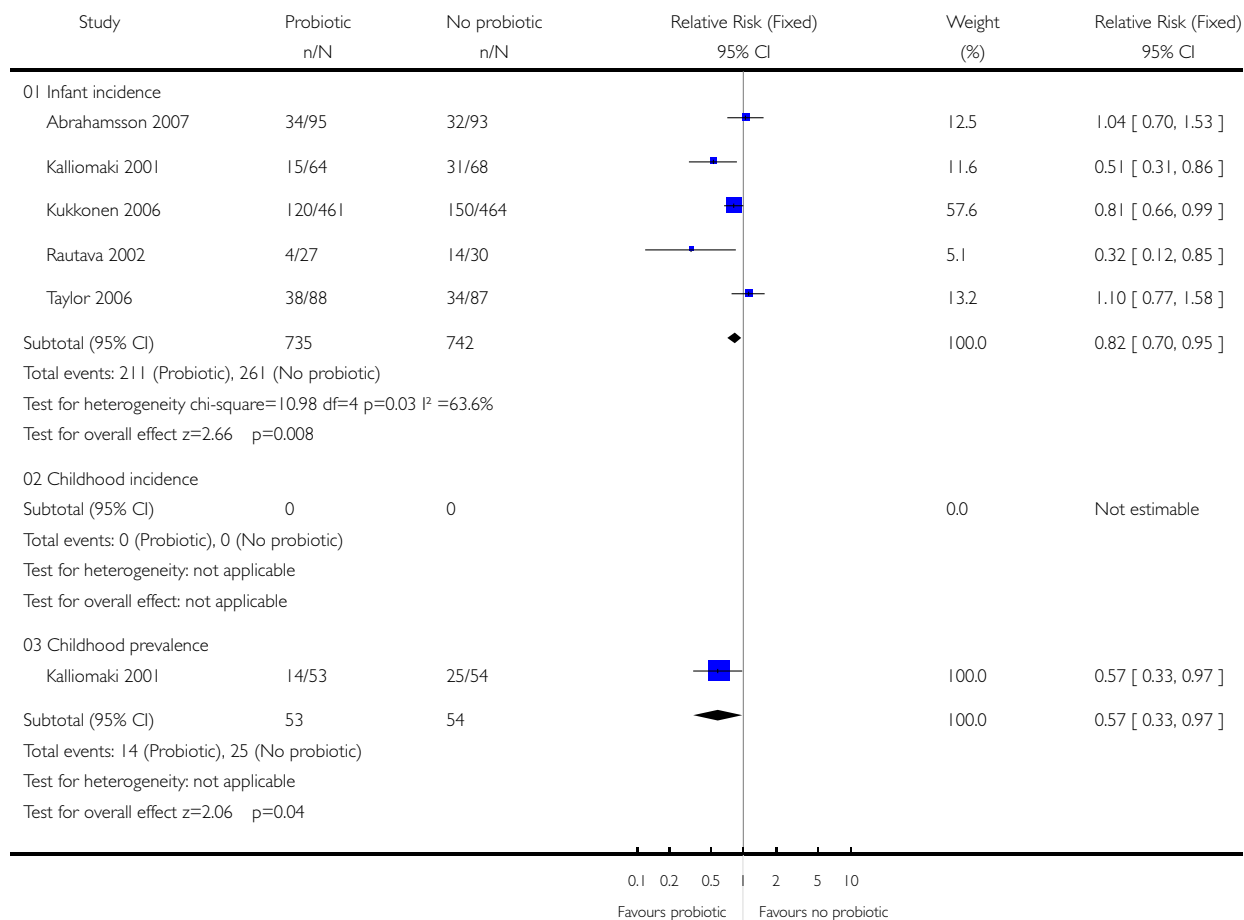


Analysis 02.04. Comparison 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity, Outcome 04 Eczema

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity

Outcome: 04 Eczema

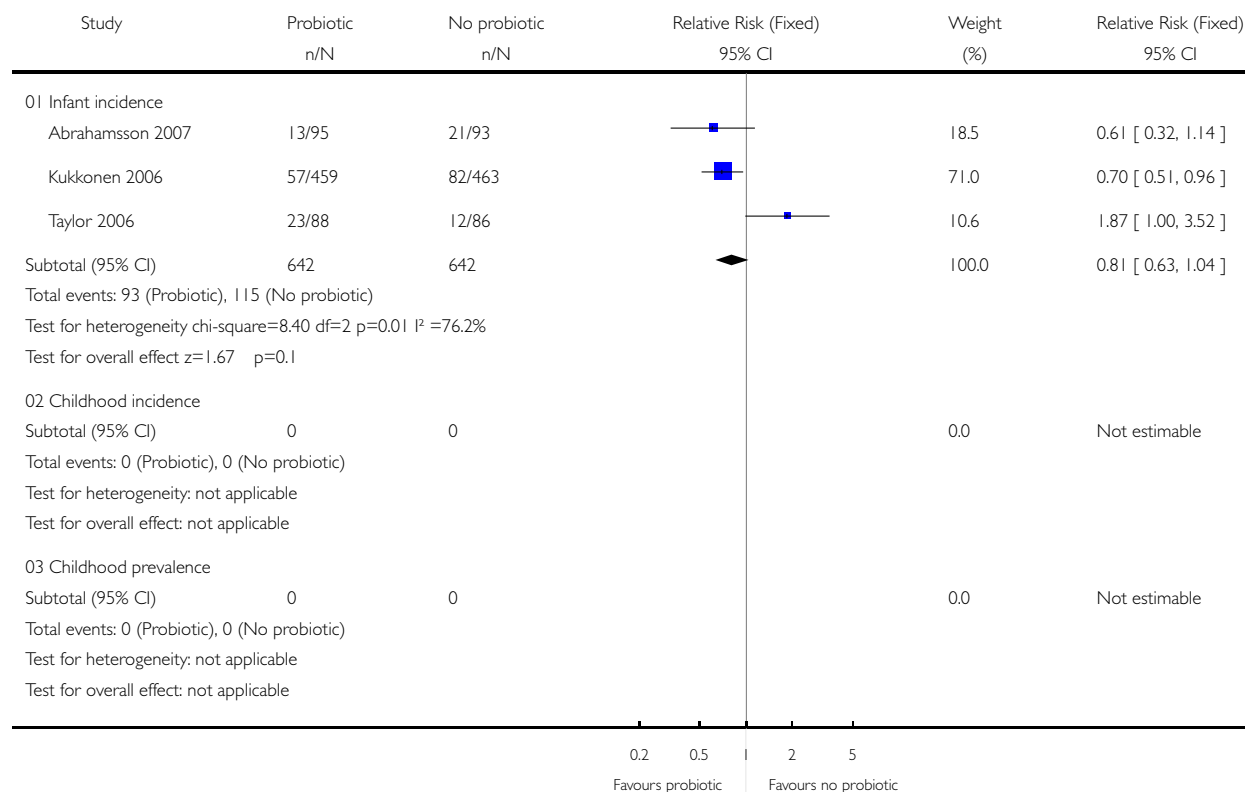


Analysis 02.05. Comparison 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity, Outcome 05 Atopic eczema

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity

Outcome: 05 Atopic eczema

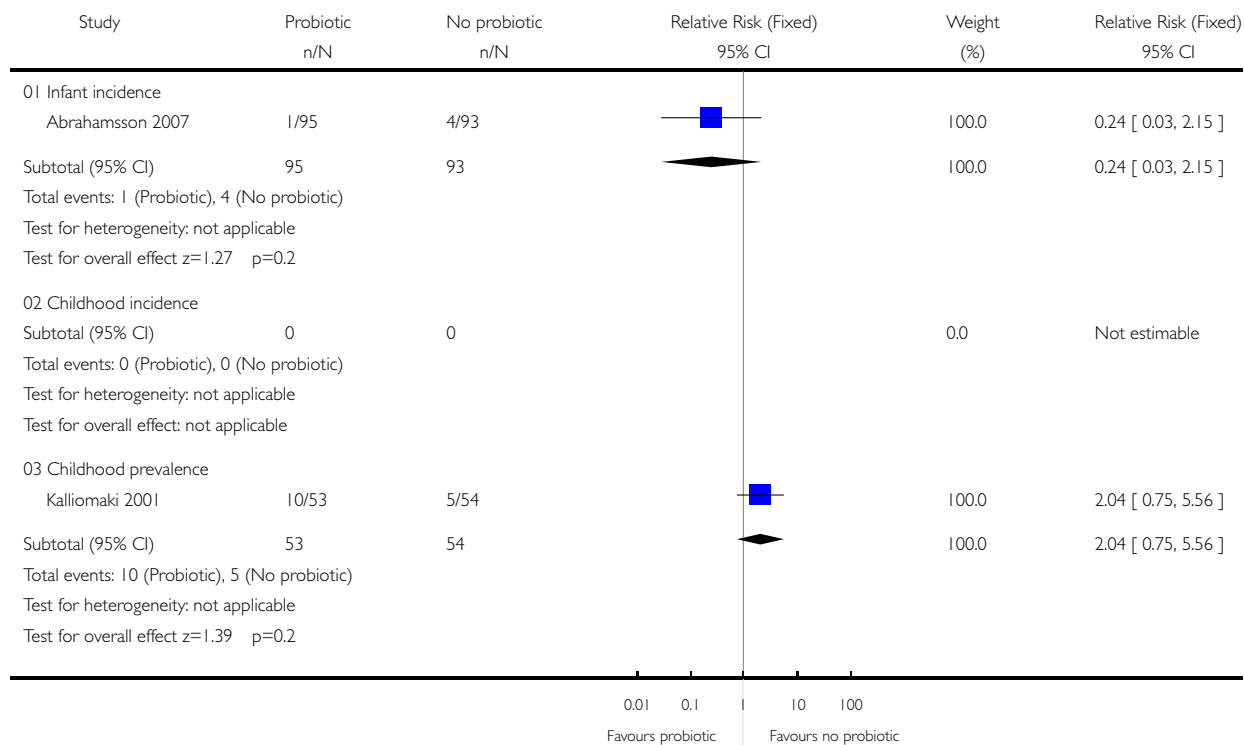


Analysis 02.06. Comparison 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity, Outcome 06 Allergic rhinitis

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity

Outcome: 06 Allergic rhinitis

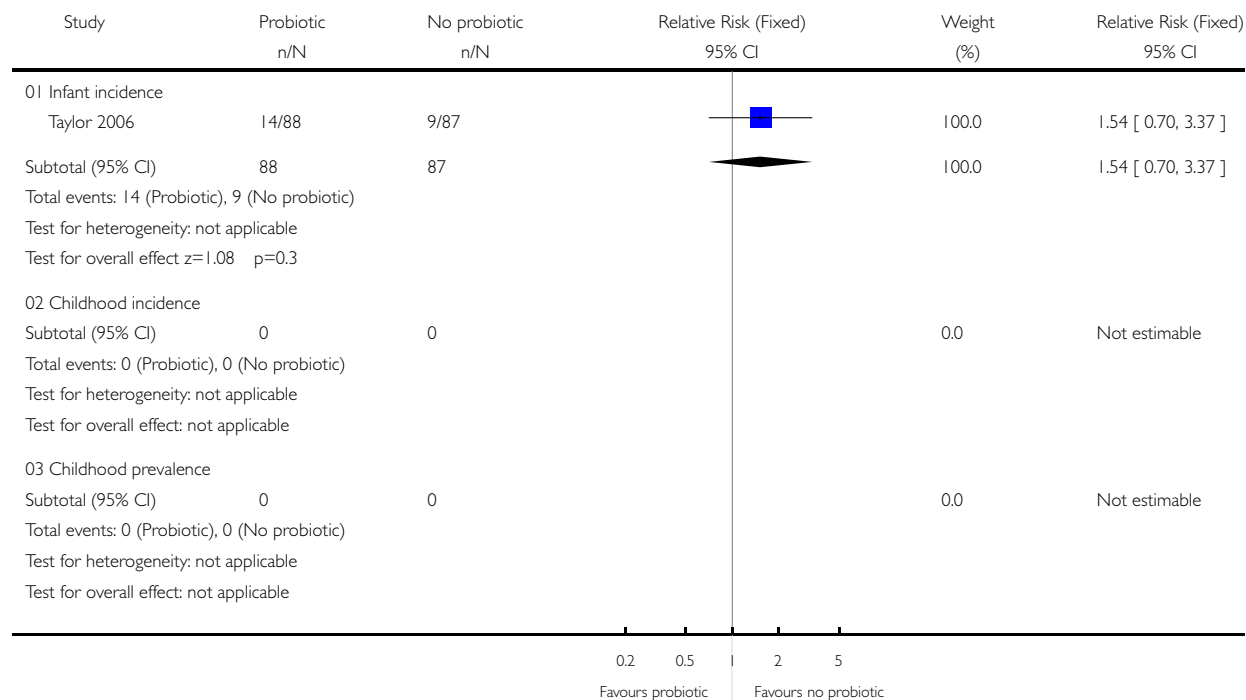


Analysis 02.07. Comparison 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity, Outcome 07 Food allergy

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity

Outcome: 07 Food allergy

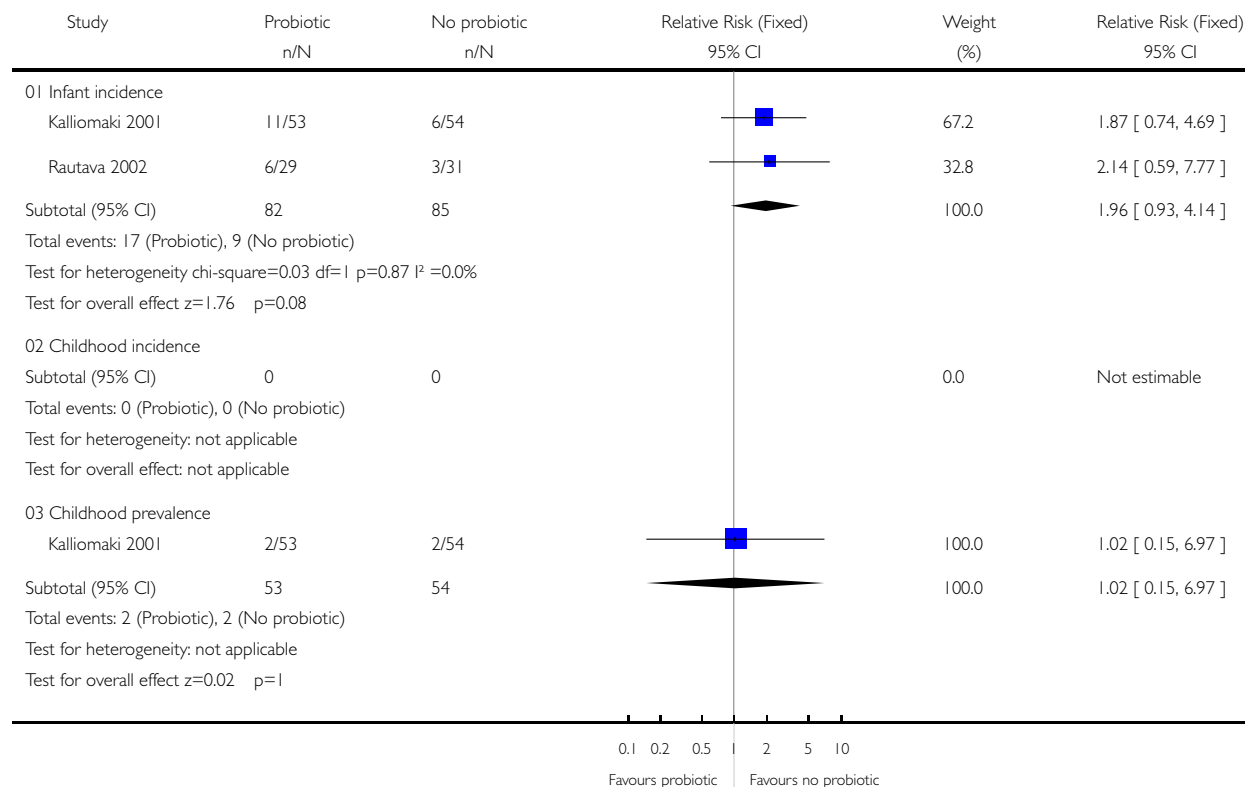


Analysis 02.08. Comparison 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity, Outcome 08 Cow's milk protein hypersensitivity

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity

Outcome: 08 Cow's milk protein hypersensitivity

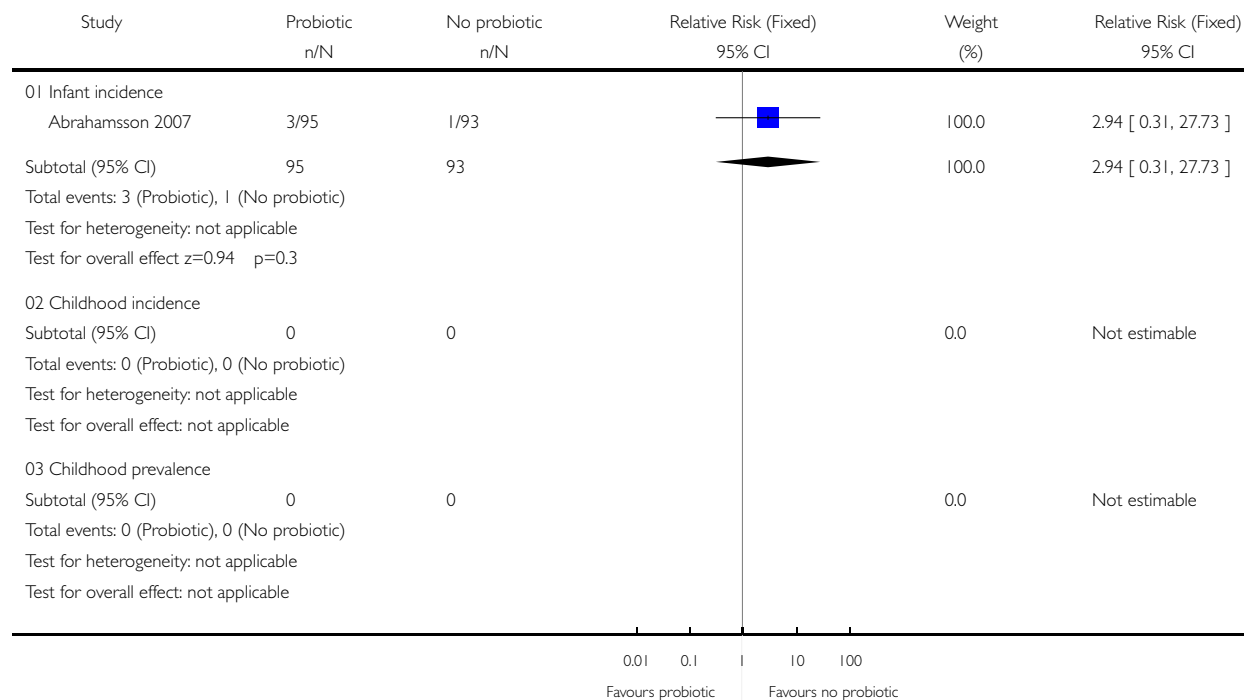


Analysis 02.09. Comparison 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity, Outcome 09 Urticaria

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 02 Probiotic versus no probiotic in infants at high risk of allergy or food hypersensitivity

Outcome: 09 Urticaria

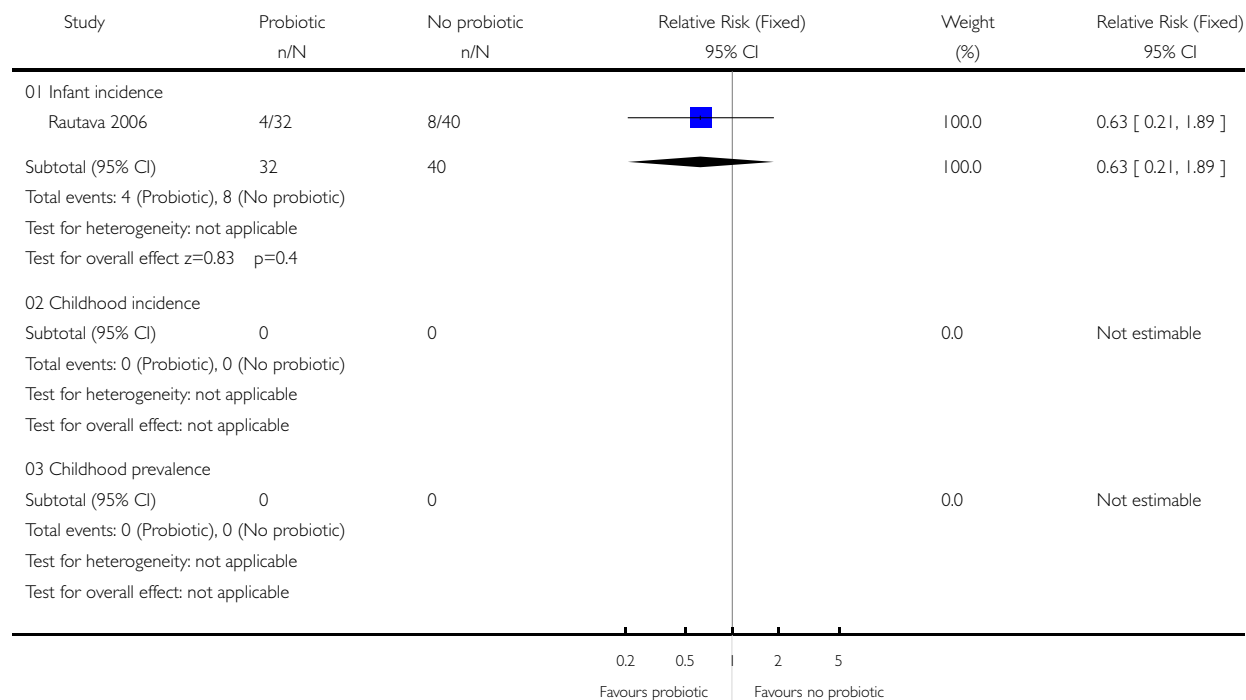


Analysis 03.01. Comparison 03 Probiotic versus no probiotic in infants not selected for risk of allergy or food hypersensitivity, Outcome 01 Atopic eczema

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 03 Probiotic versus no probiotic in infants not selected for risk of allergy or food hypersensitivity

Outcome: 01 Atopic eczema

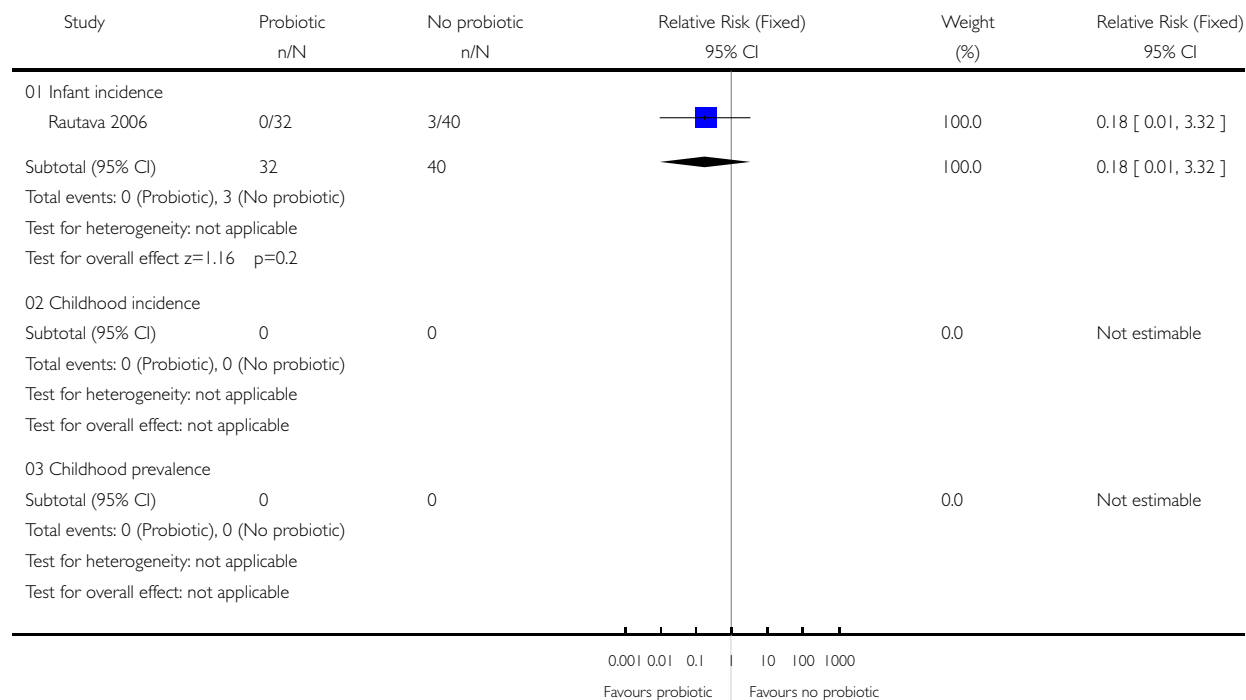


Analysis 03.02. Comparison 03 Probiotic versus no probiotic in infants not selected for risk of allergy or food hypersensitivity, Outcome 02 Cow's milk protein hypersensitivity

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 03 Probiotic versus no probiotic in infants not selected for risk of allergy or food hypersensitivity

Outcome: 02 Cow's milk protein hypersensitivity

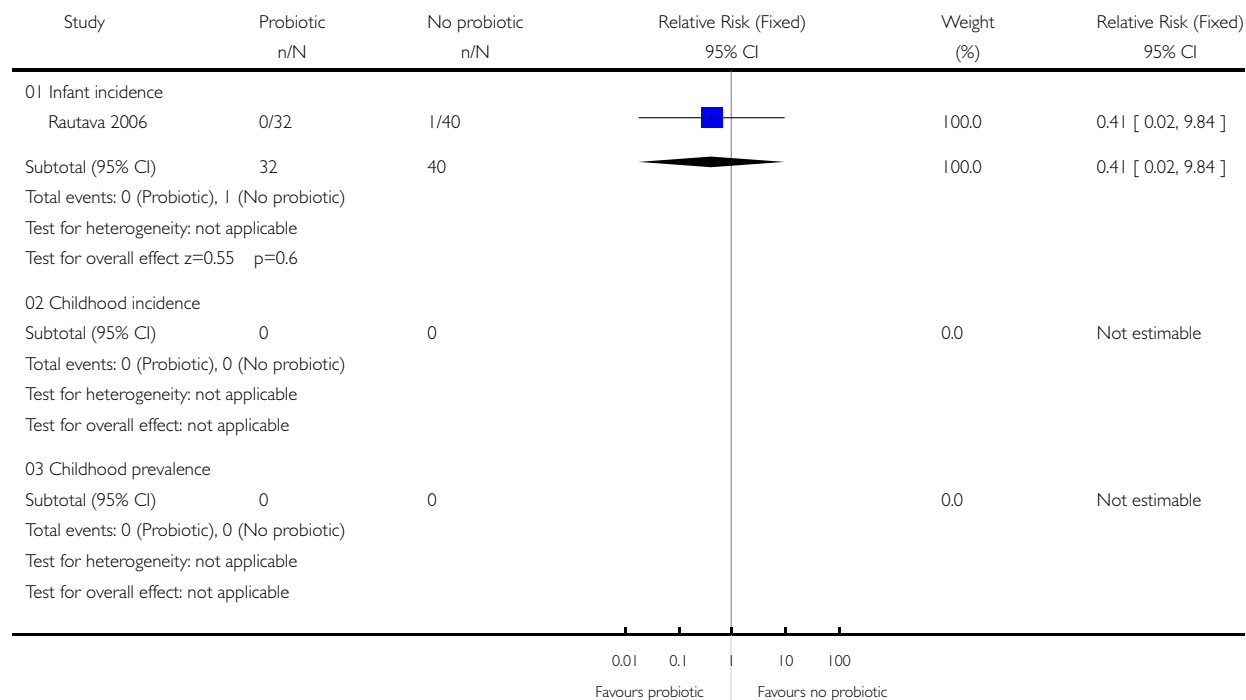


Analysis 03.03. Comparison 03 Probiotic versus no probiotic in infants not selected for risk of allergy or food hypersensitivity, Outcome 03 Cow's milk protein allergy

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 03 Probiotic versus no probiotic in infants not selected for risk of allergy or food hypersensitivity

Outcome: 03 Cow's milk protein allergy

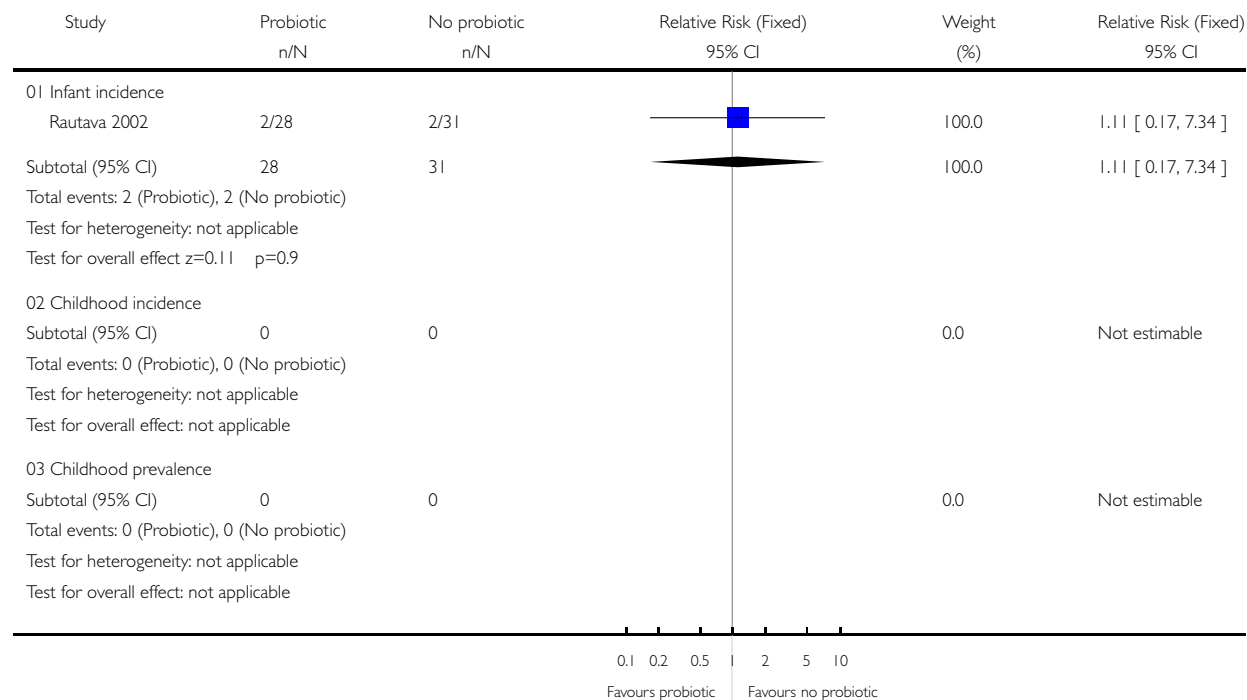


Analysis 04.01. Comparison 04 Probiotic versus no probiotic in infants fed exclusive human milk, Outcome 01 Food hypersensitivity (gastrointestinal symptoms)

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 04 Probiotic versus no probiotic in infants fed exclusive human milk

Outcome: 01 Food hypersensitivity (gastrointestinal symptoms)

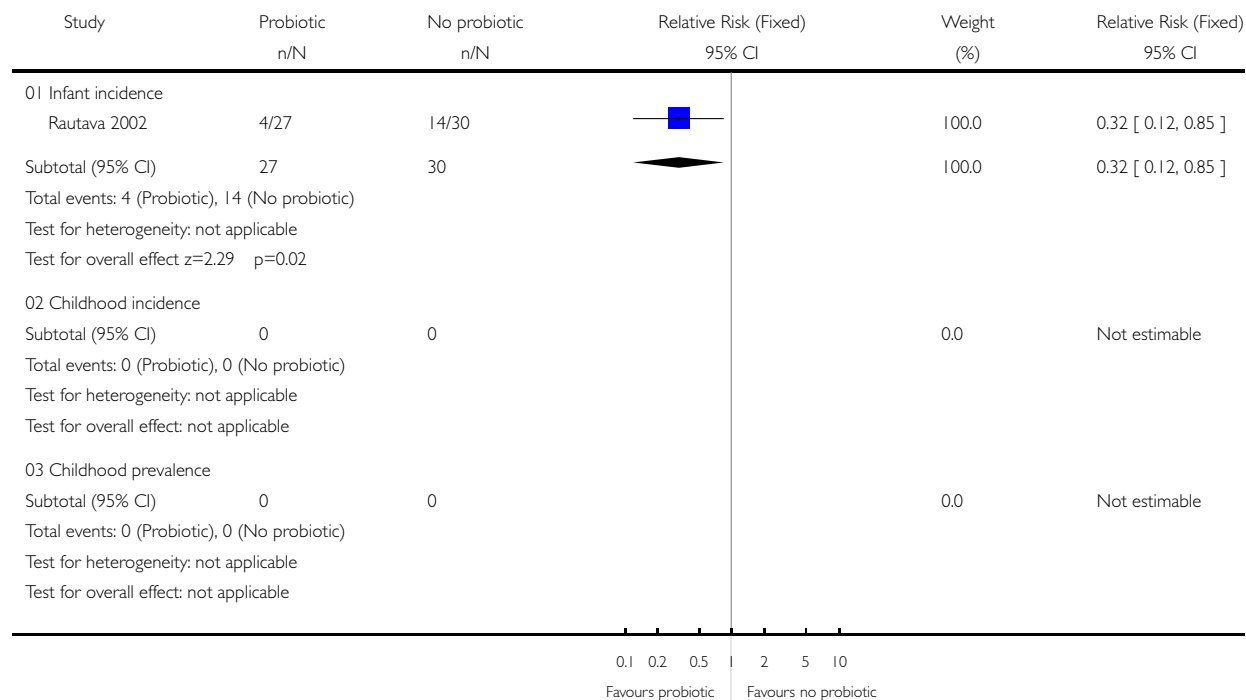


Analysis 04.02. Comparison 04 Probiotic versus no probiotic in infants fed exclusive human milk, Outcome 02 Eczema

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 04 Probiotic versus no probiotic in infants fed exclusive human milk

Outcome: 02 Eczema

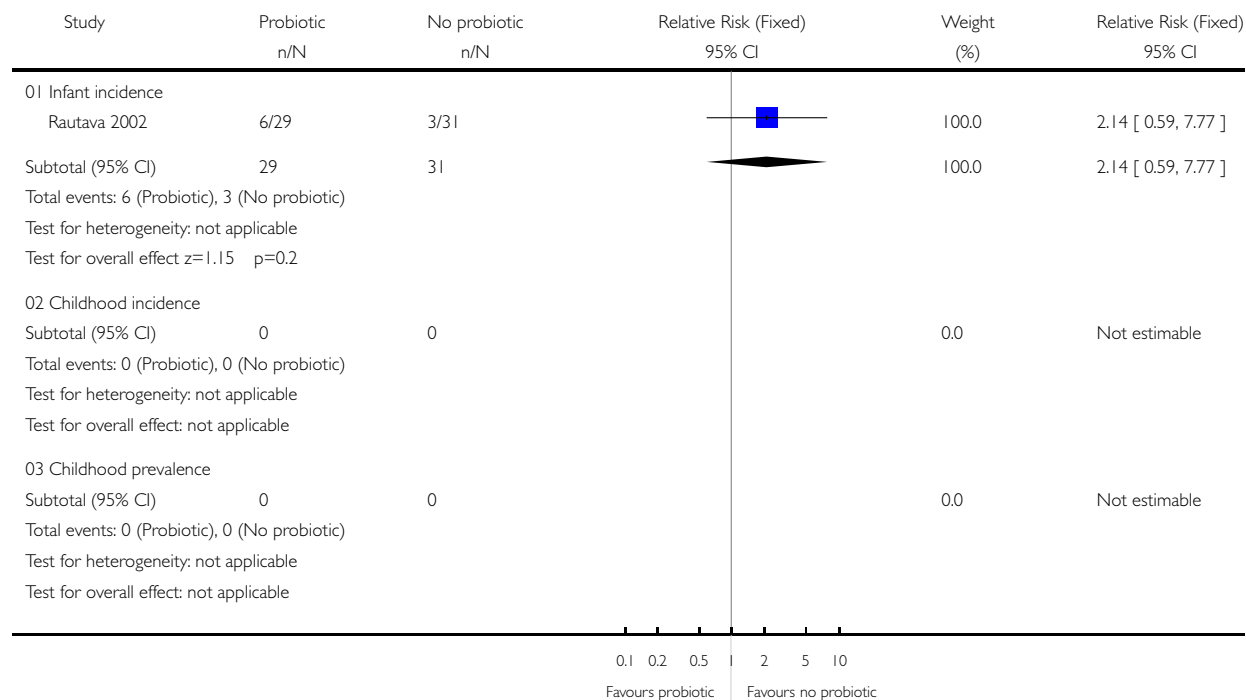


Analysis 04.03. Comparison 04 Probiotic versus no probiotic in infants fed exclusive human milk, Outcome 03 Cow's milk protein hypersensitivity

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 04 Probiotic versus no probiotic in infants fed exclusive human milk

Outcome: 03 Cow's milk protein hypersensitivity

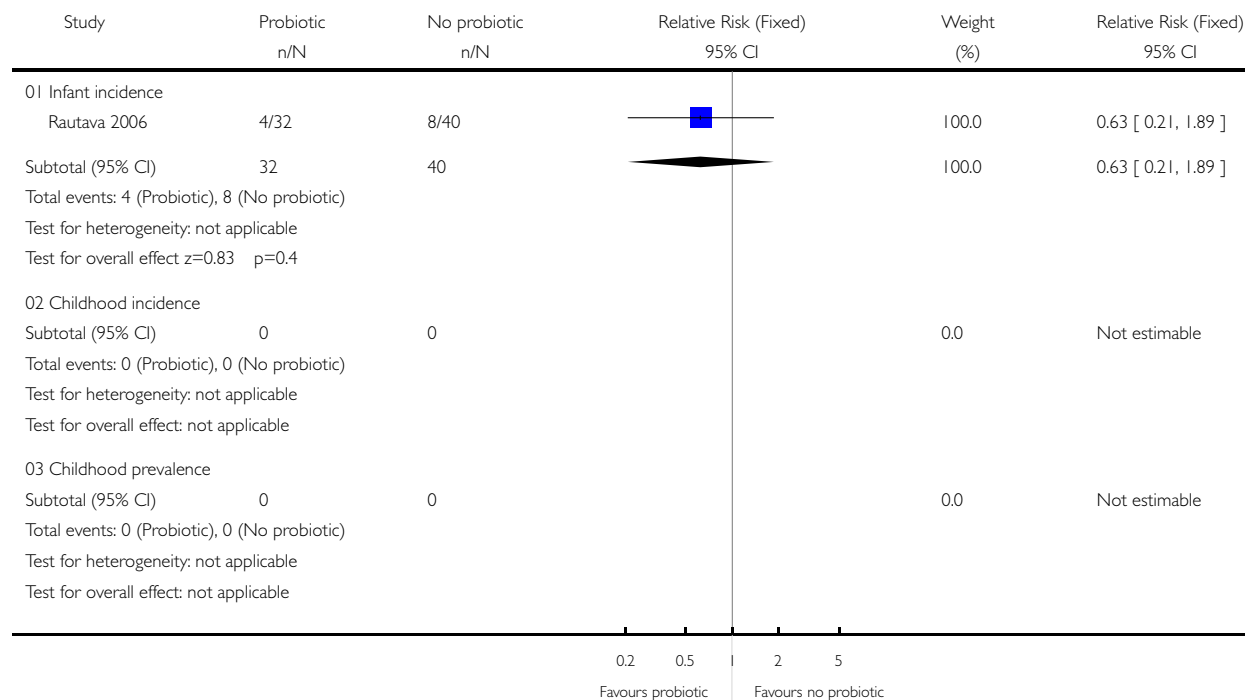


Analysis 05.01. Comparison 05 Probiotic versus no probiotic in infants fed cow's milk formula, Outcome 01 Atopic eczema

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 05 Probiotic versus no probiotic in infants fed cow's milk formula

Outcome: 01 Atopic eczema

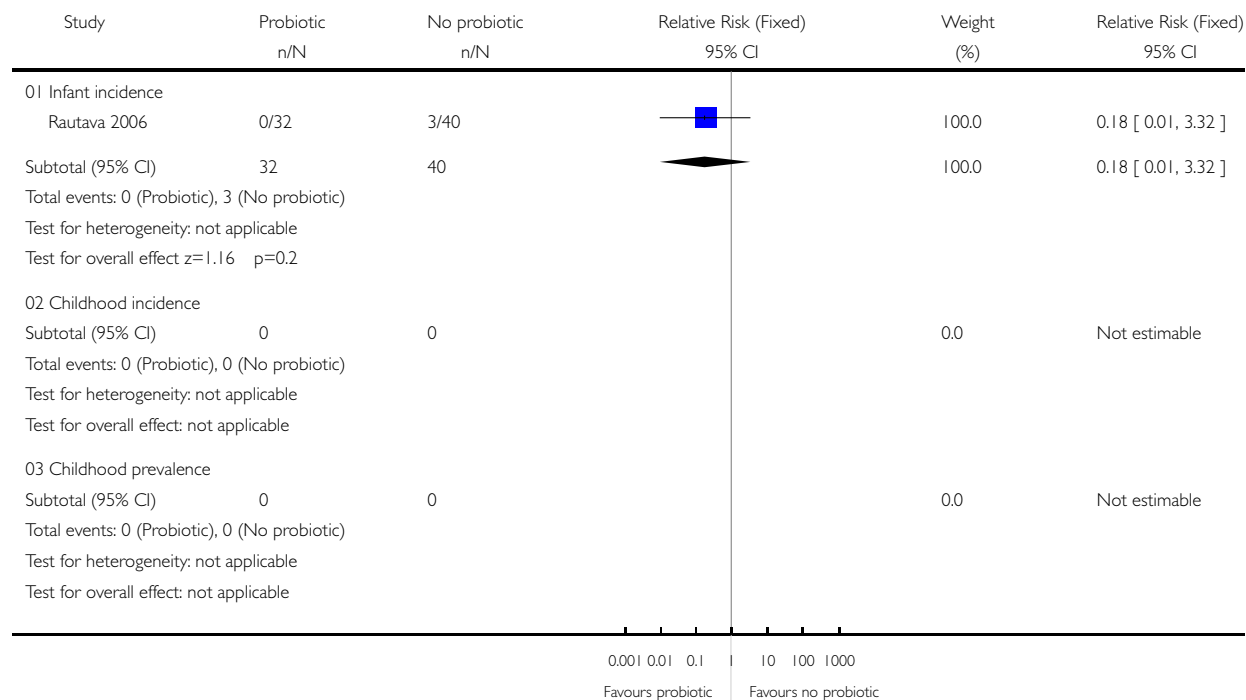


Analysis 05.02. Comparison 05 Probiotic versus no probiotic in infants fed cow's milk formula, Outcome 02 Cow's milk protein hypersensitivity

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 05 Probiotic versus no probiotic in infants fed cow's milk formula

Outcome: 02 Cow's milk protein hypersensitivity

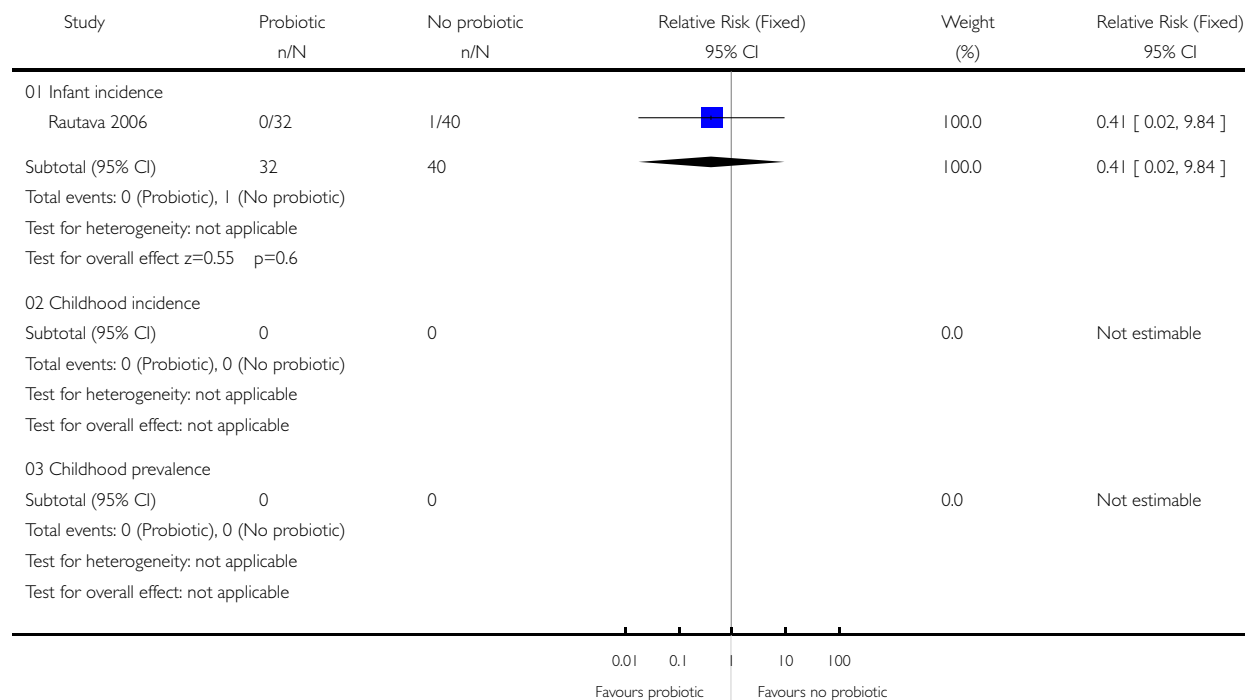


Analysis 05.03. Comparison 05 Probiotic versus no probiotic in infants fed cow's milk formula, Outcome 03 Cow's milk protein allergy

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 05 Probiotic versus no probiotic in infants fed cow's milk formula

Outcome: 03 Cow's milk protein allergy

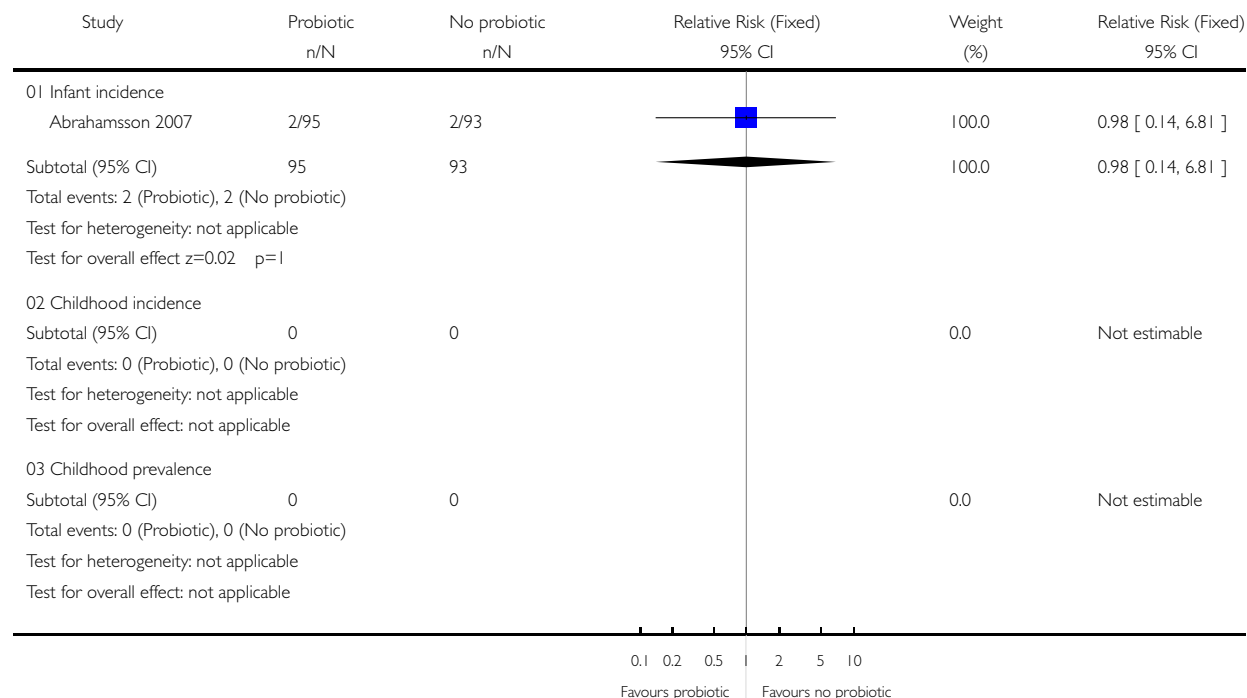


Analysis 06.01. Comparison 06 Probiotic versus no probiotic in infants fed a hydrolysed formula, Outcome 01 Food hypersensitivity (gastrointestinal symptoms)

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 06 Probiotic versus no probiotic in infants fed a hydrolysed formula

Outcome: 01 Food hypersensitivity (gastrointestinal symptoms)

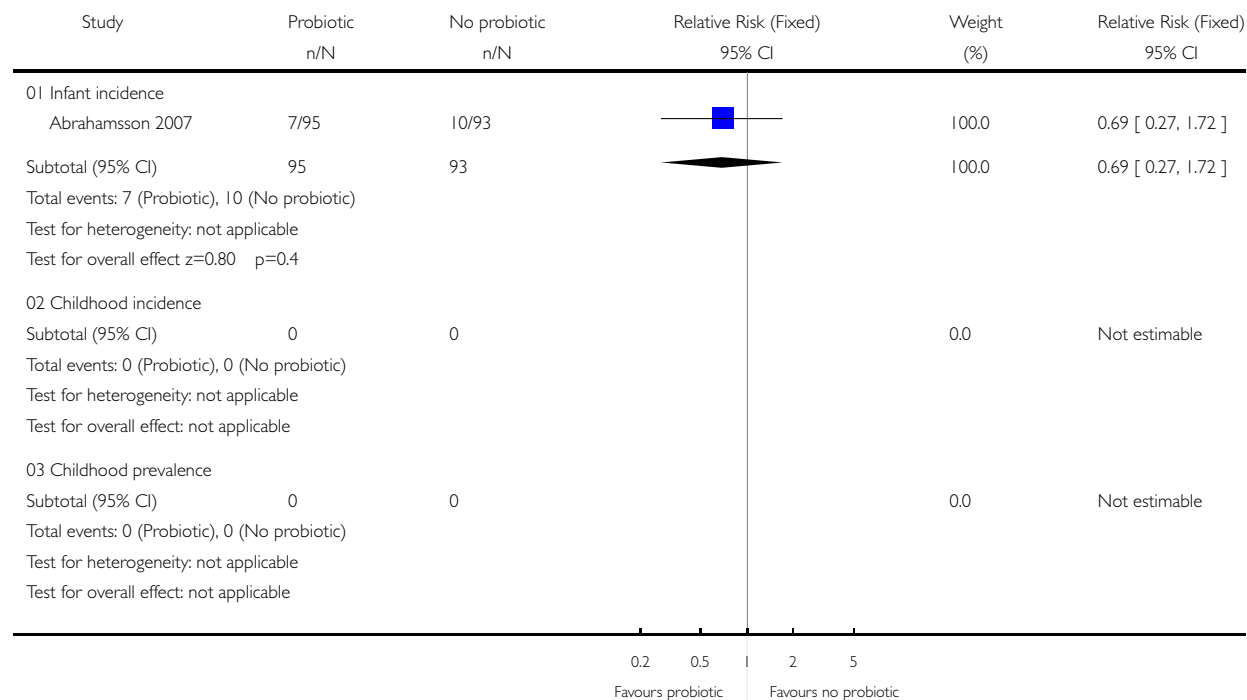


Analysis 06.02. Comparison 06 Probiotic versus no probiotic in infants fed a hydrolysed formula, Outcome 02 Asthma

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 06 Probiotic versus no probiotic in infants fed a hydrolysed formula

Outcome: 02 Asthma

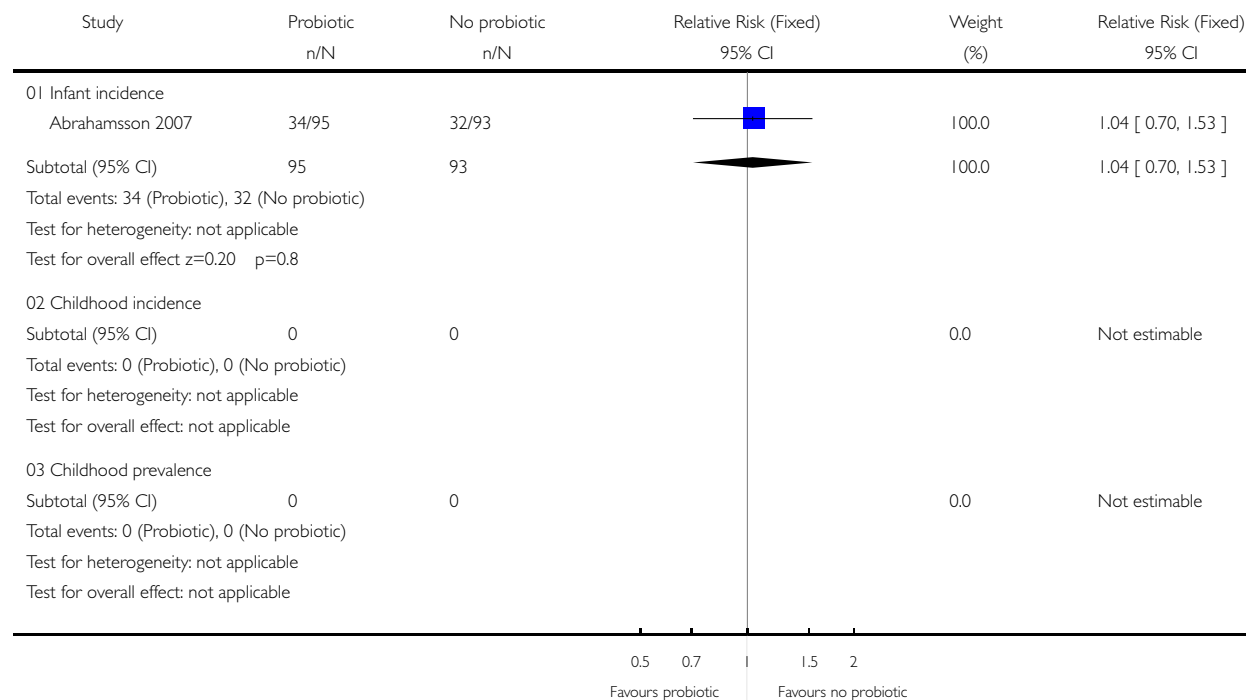


Analysis 06.03. Comparison 06 Probiotic versus no probiotic in infants fed a hydrolysed formula, Outcome 03 Eczema

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 06 Probiotic versus no probiotic in infants fed a hydrolysed formula

Outcome: 03 Eczema

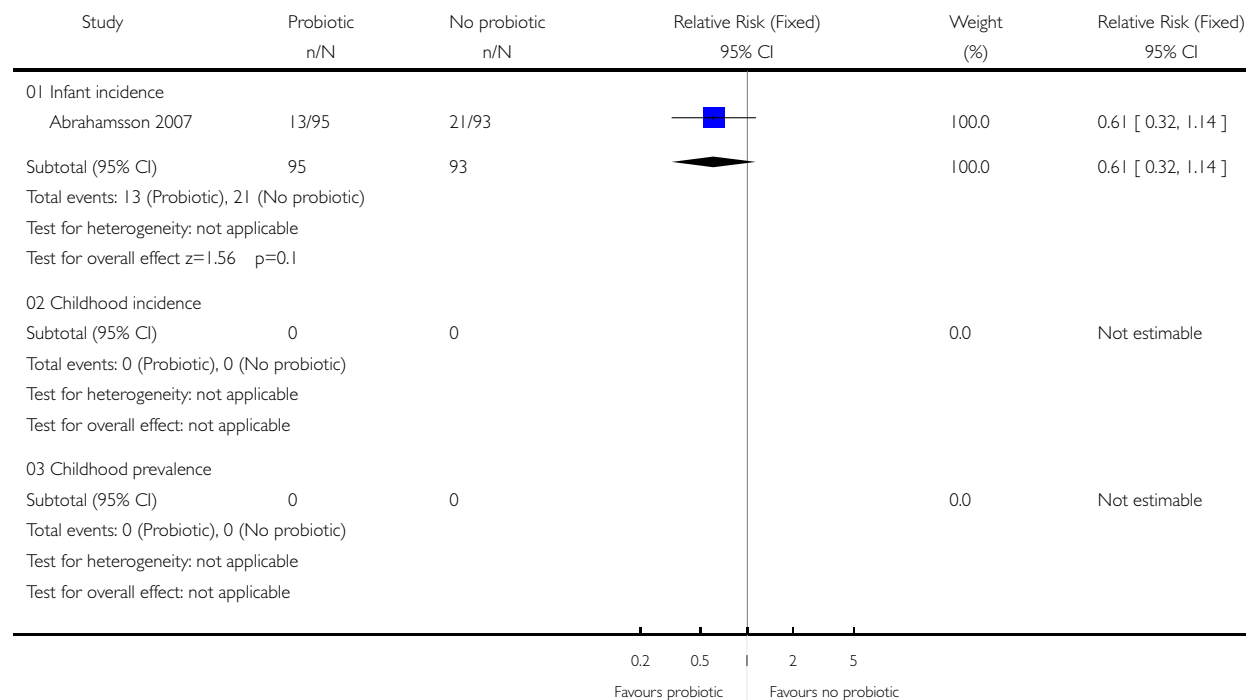


Analysis 06.04. Comparison 06 Probiotic versus no probiotic in infants fed a hydrolysed formula, Outcome 04 Atopic eczema

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 06 Probiotic versus no probiotic in infants fed a hydrolysed formula

Outcome: 04 Atopic eczema

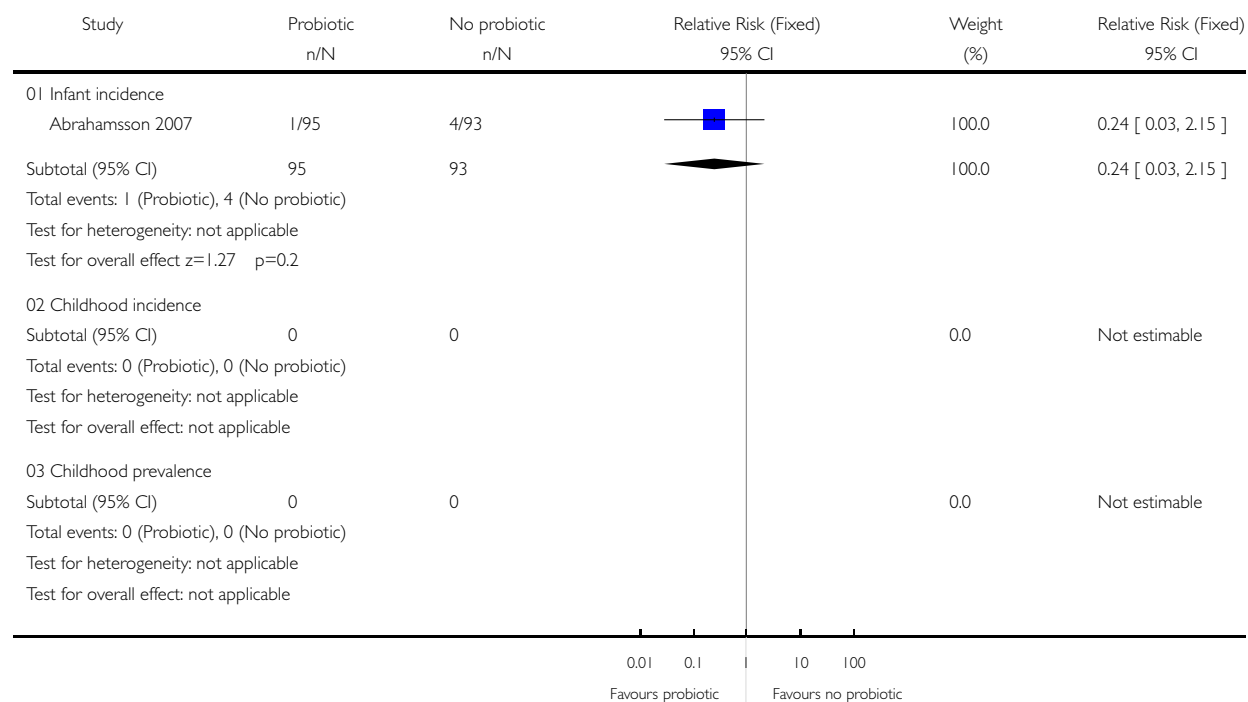


Analysis 06.05. Comparison 06 Probiotic versus no probiotic in infants fed a hydrolysed formula, Outcome 05 Allergic rhinitis

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 06 Probiotic versus no probiotic in infants fed a hydrolysed formula

Outcome: 05 Allergic rhinitis

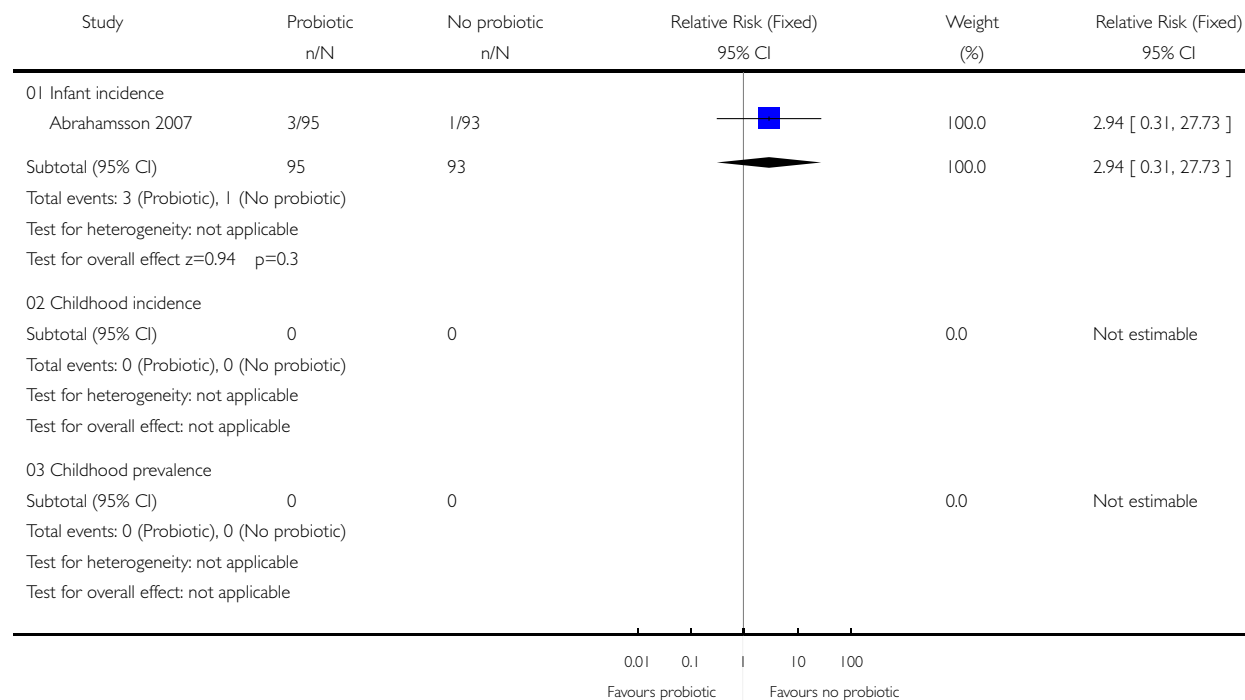


Analysis 06.06. Comparison 06 Probiotic versus no probiotic in infants fed a hydrolysed formula, Outcome 06 Urticaria

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 06 Probiotic versus no probiotic in infants fed a hydrolysed formula

Outcome: 06 Urticaria

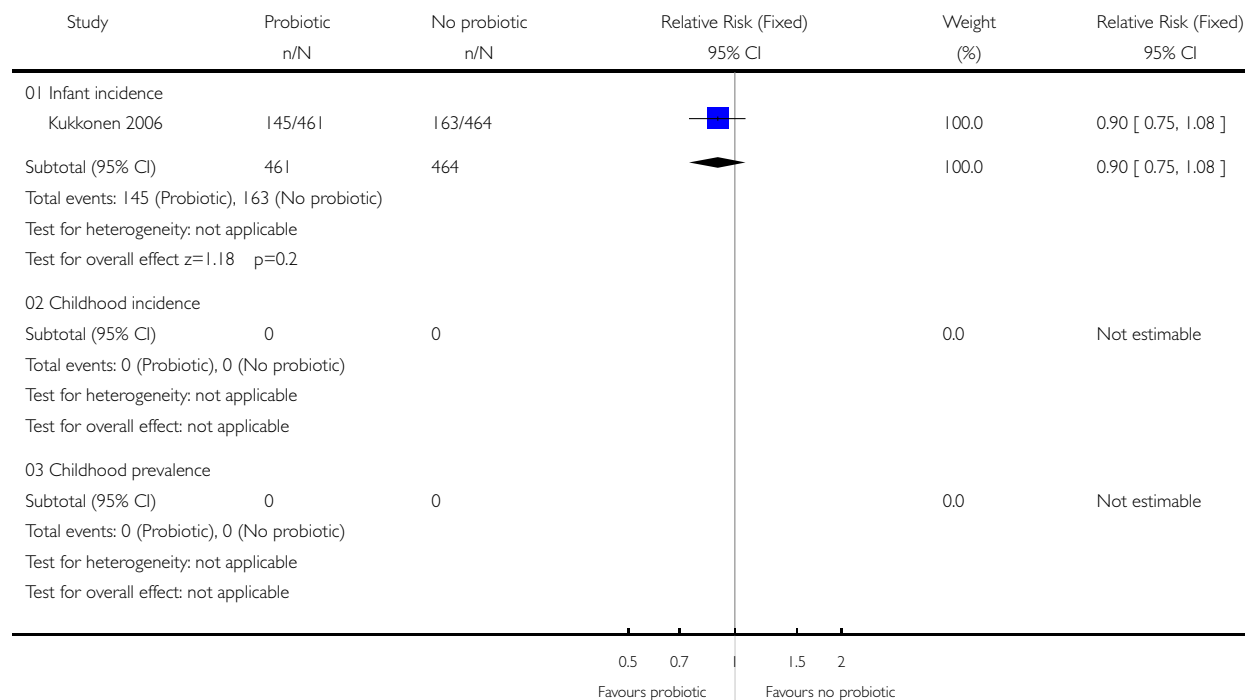


Analysis 07.01. Comparison 07 Probiotic with added prebiotic versus no probiotic, Outcome 01 All allergic disease

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Comparison: 07 Probiotic with added prebiotic versus no probiotic

Outcome: 01 All allergic disease

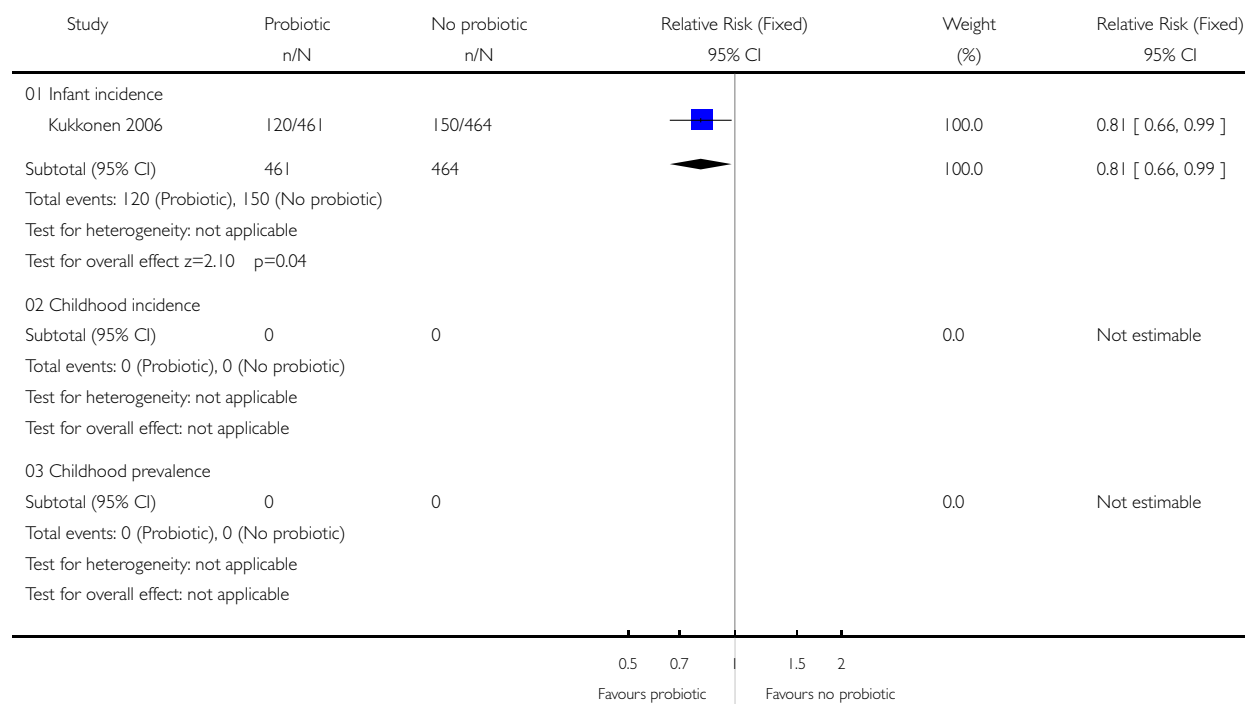


Analysis 07.02. Comparison 07 Probiotic with added prebiotic versus no probiotic, Outcome 02 Eczema

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 07 Probiotic with added prebiotic versus no probiotic

Outcome: 02 Eczema

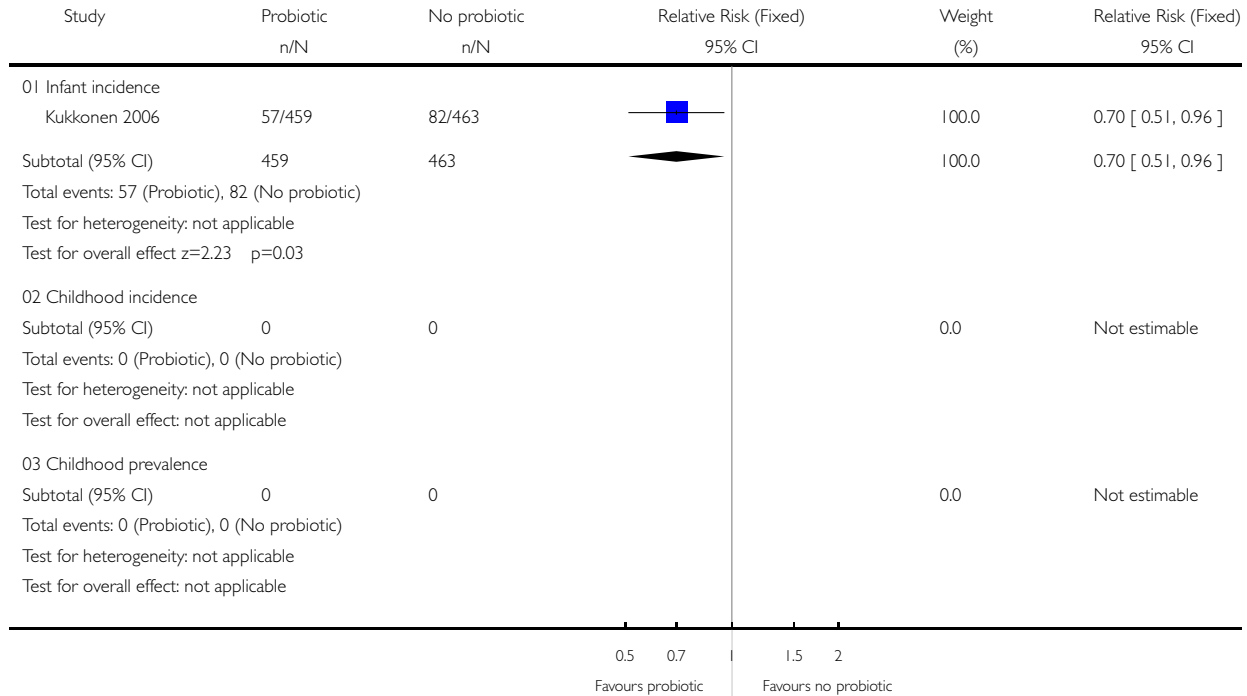


Analysis 07.03. Comparison 07 Probiotic with added prebiotic versus no probiotic, Outcome 03 Atopic eczema

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 07 Probiotic with added prebiotic versus no probiotic

Outcome: 03 Atopic eczema

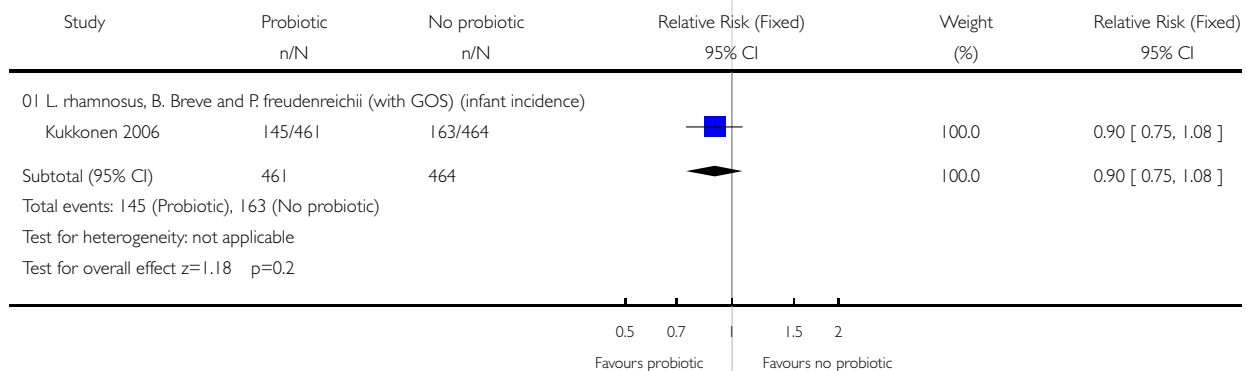


Analysis 08.01. Comparison 08 Specific probiotic versus no probiotic, Outcome 01 All allergic disease

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 08 Specific probiotic versus no probiotic

Outcome: 01 All allergic disease

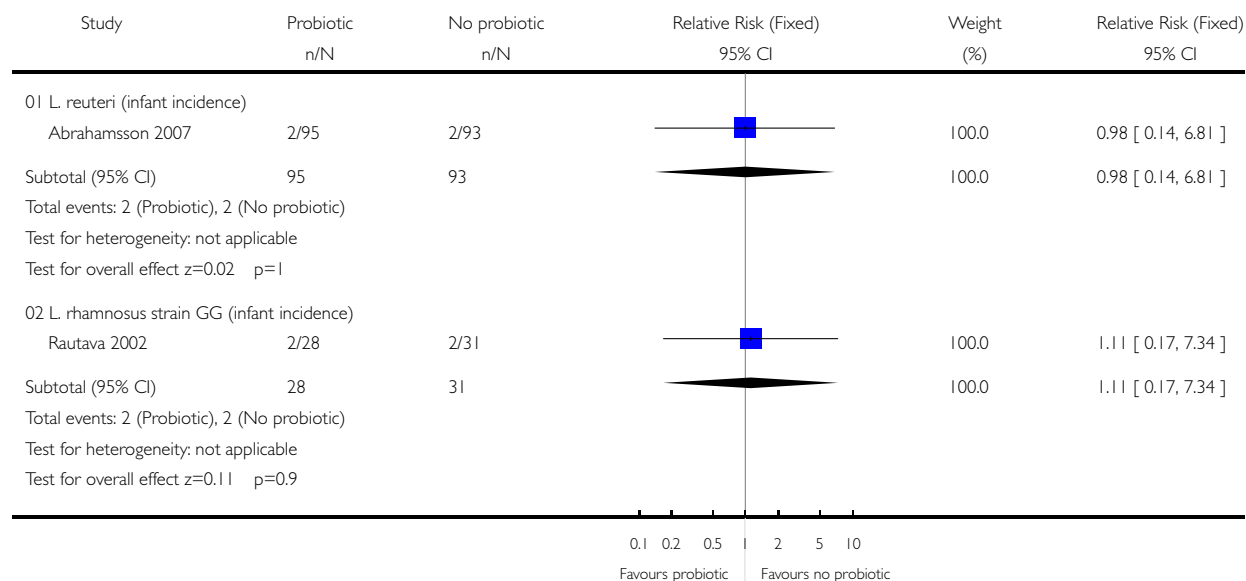


Analysis 08.02. Comparison 08 Specific probiotic versus no probiotic, Outcome 02 Food hypersensitivity (gastrointestinal symptoms)

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 08 Specific probiotic versus no probiotic

Outcome: 02 Food hypersensitivity (gastrointestinal symptoms)

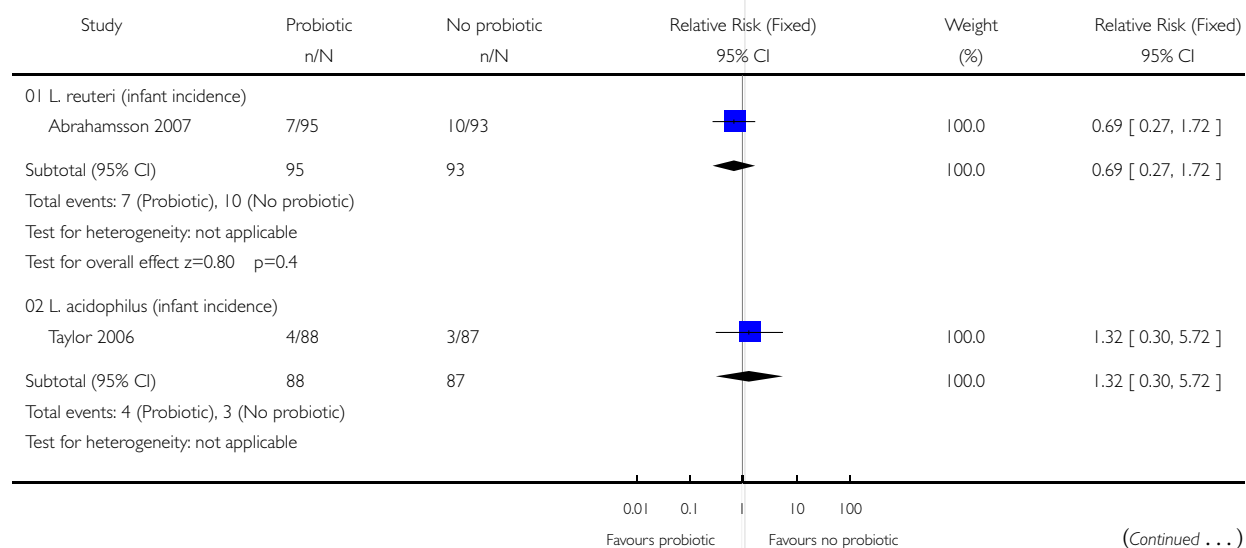


Analysis 08.03. Comparison 08 Specific probiotic versus no probiotic, Outcome 03 Asthma

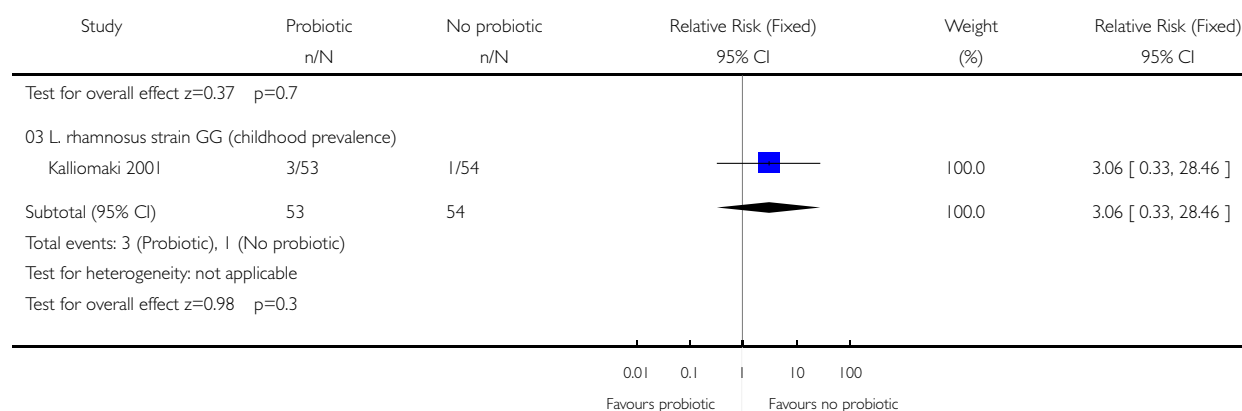
Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 08 Specific probiotic versus no probiotic

Outcome: 03 Asthma



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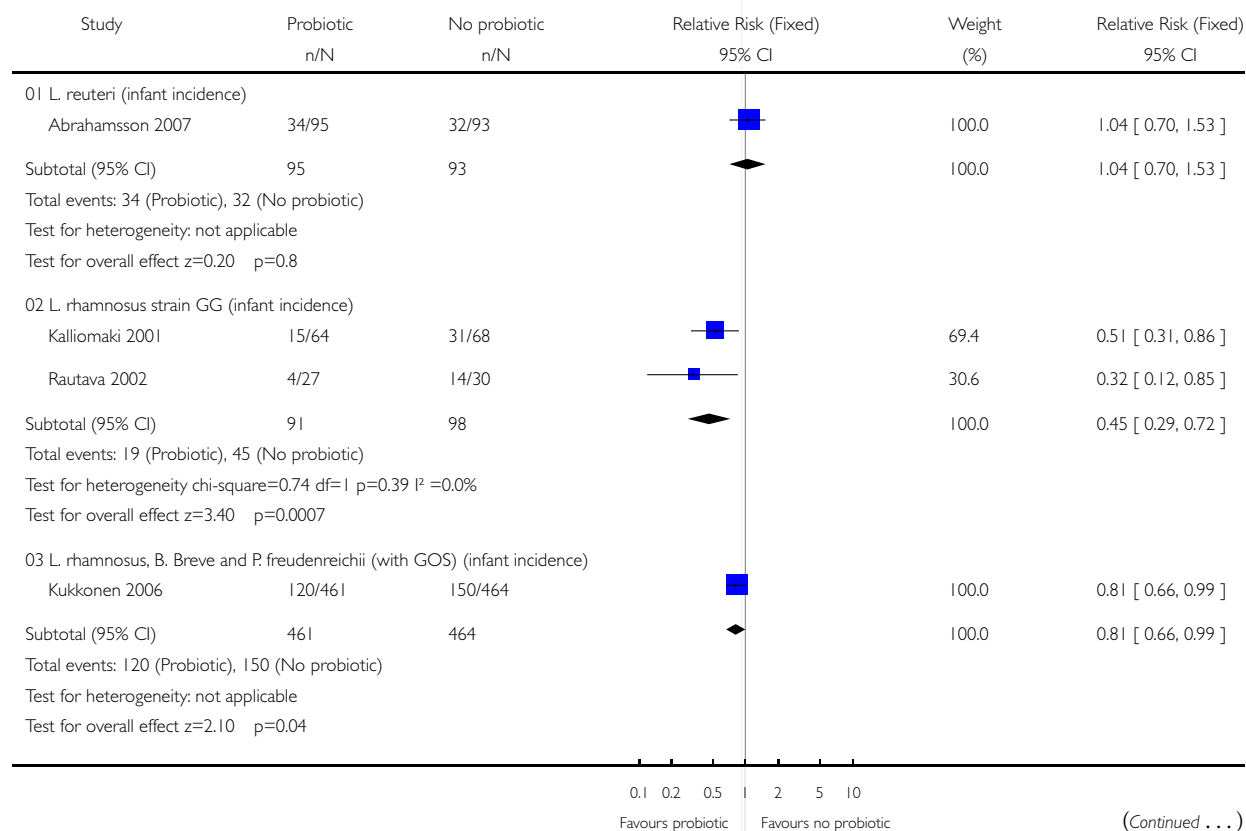


Analysis 08.04. Comparison 08 Specific probiotic versus no probiotic, Outcome 04 Eczema

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

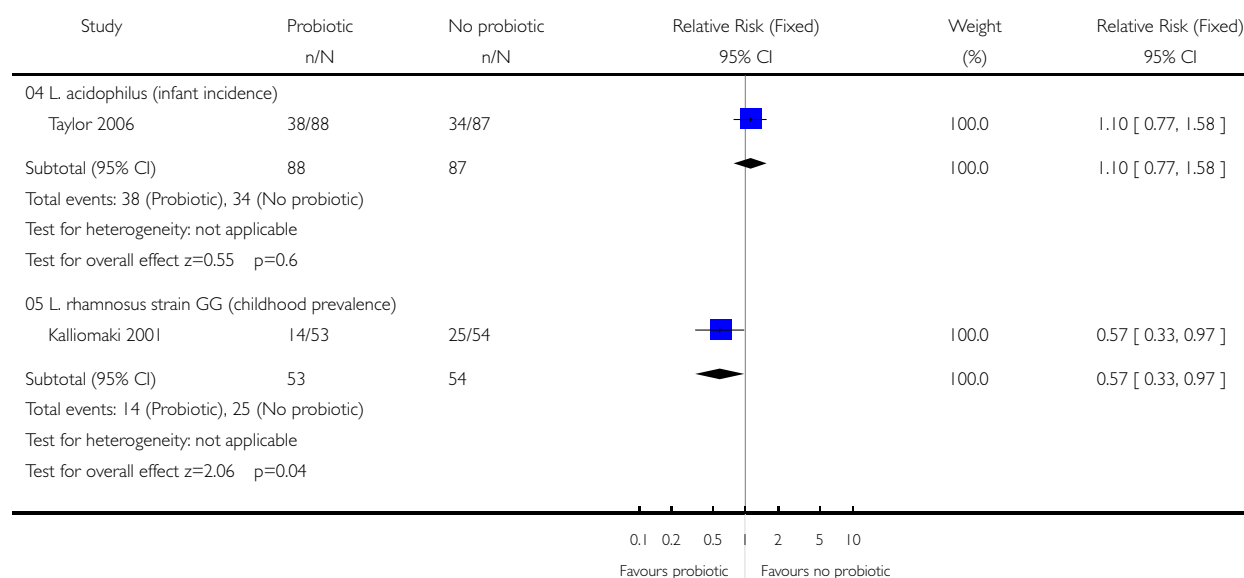
Comparison: 08 Specific probiotic versus no probiotic

Outcome: 04 Eczema



(Continued ...)

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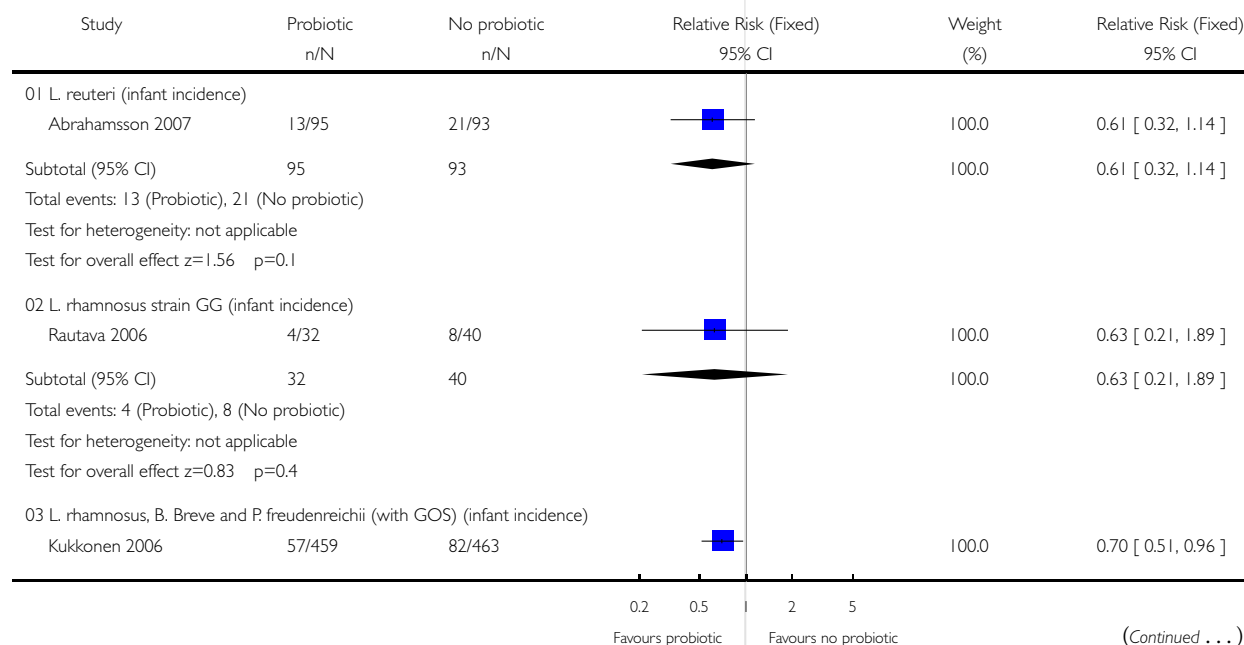


Analysis 08.05. Comparison 08 Specific probiotic versus no probiotic, Outcome 05 Atopic eczema

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

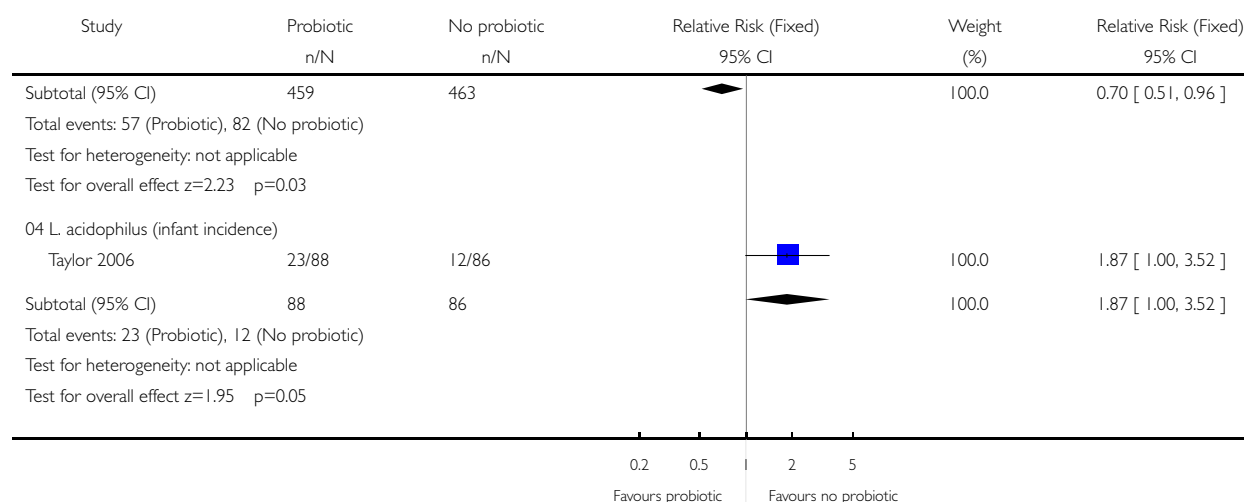
Comparison: 08 Specific probiotic versus no probiotic

Outcome: 05 Atopic eczema



(Continued ...)

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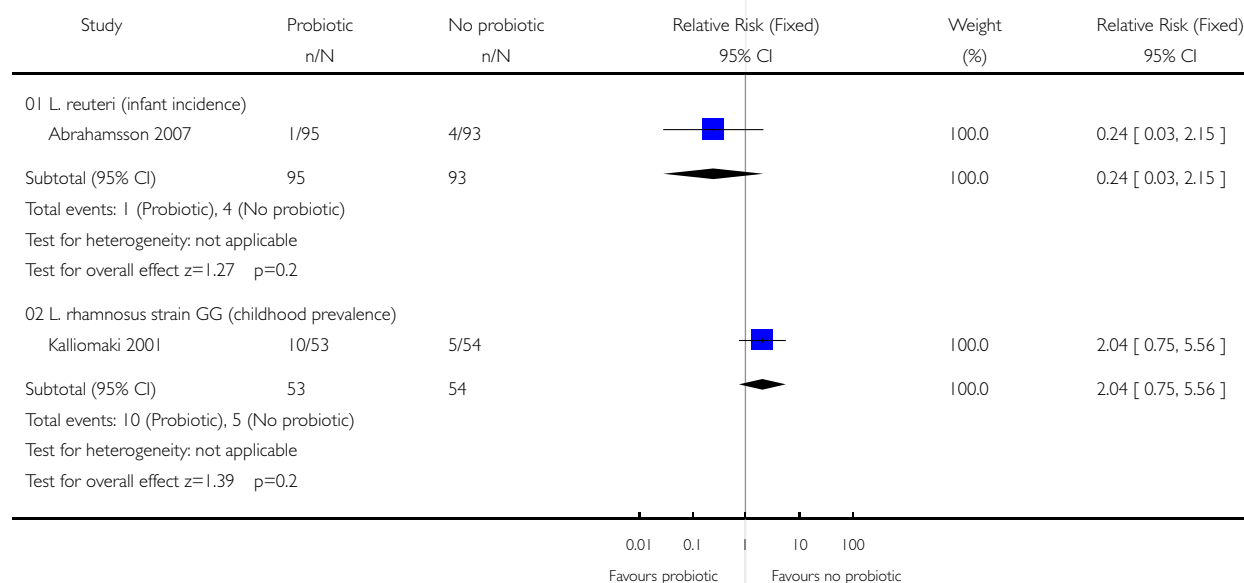


Analysis 08.06. Comparison 08 Specific probiotic versus no probiotic, Outcome 06 Allergic rhinitis

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 08 Specific probiotic versus no probiotic

Outcome: 06 Allergic rhinitis

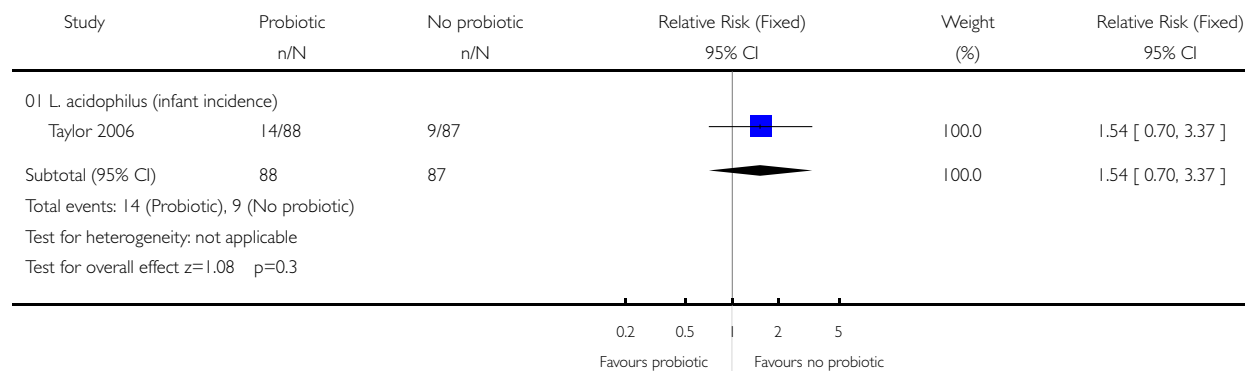


Analysis 08.07. Comparison 08 Specific probiotic versus no probiotic, Outcome 07 Food allergy

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 08 Specific probiotic versus no probiotic

Outcome: 07 Food allergy

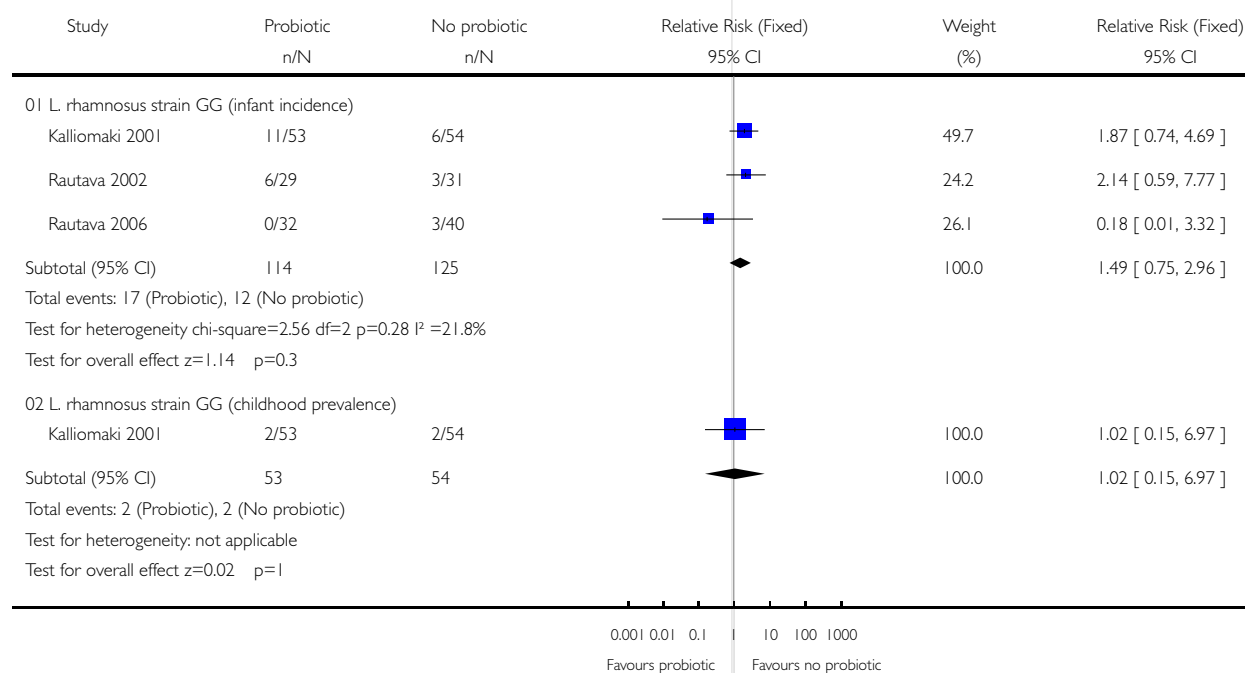


Analysis 08.08. Comparison 08 Specific probiotic versus no probiotic, Outcome 08 Cow's milk protein hypersensitivity

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 08 Specific probiotic versus no probiotic

Outcome: 08 Cow's milk protein hypersensitivity

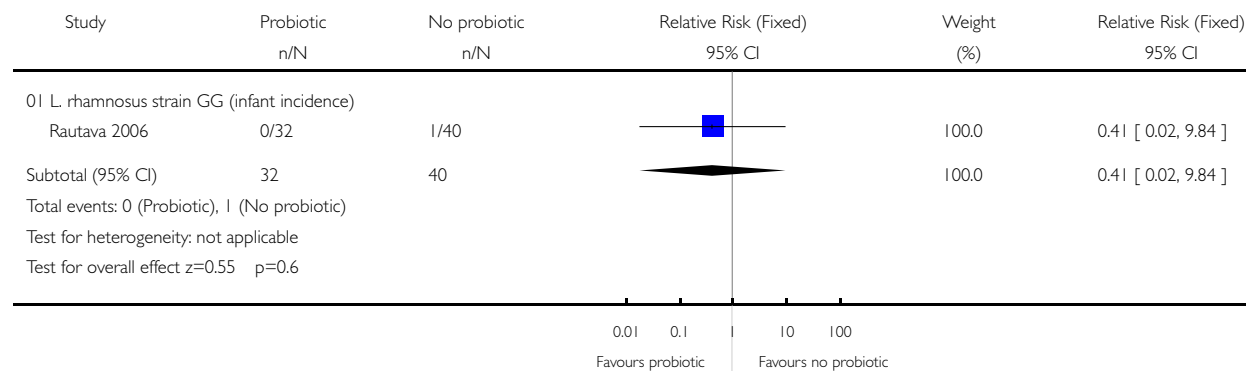


Analysis 08.09. Comparison 08 Specific probiotic versus no probiotic, Outcome 09 Cow's milk protein allergy

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 08 Specific probiotic versus no probiotic

Outcome: 09 Cow's milk protein allergy

**Analysis 08.10. Comparison 08 Specific probiotic versus no probiotic, Outcome 10 Urticaria**

Review: Probiotics in infants for prevention of allergic disease and food hypersensitivity

Comparison: 08 Specific probiotic versus no probiotic

Outcome: 10 Urticaria

