PROBIOTIC SUPPLEMENTATION IN PREGNANCY, LACTATION AND/OR INFANCY, AND RISK OF ALLERGIC SENSITISATION OR ALLERGIC DISEASE

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1. Probiotics and risk of allergic outcomes – summary of interventions and findings

Probiotics are traditionally defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. Synbiotics are defined as a combination of probiotic and prebiotic administered to the same individual. In this analysis we included studies of any microbial intervention, whether live or heat-killed, given either alone (=probiotic) or in combination with a prebiotic (=synbiotic). We included heat-killed microbes for two reasons. First observational studies exploring the hygiene hypothesis have found relationships between both live microbial exposures, and non-live microbial components, and allergic outcomes. Second there is a lack of good understanding of the mechanisms through which probiotics might prevent allergic outcomes, and while microbes may need to be live for some health indications of probiotics, it is unclear whether this is the case when they are used for the prevention of allergic outcomes. We planned to undertake subgroup/stratified analyses for meta-analyses which included >5 studies, and where relevant to include probiotic/synbiotic intervention as a subgroup. We planned to assess publication bias using Funnel plots and Egger's test where there were ≥10 studies in a meta-analysis. Due to the significant number of studies and participants included in intervention trials of reasonable quality, we did not analyse the very small number of observational studies which we identified reporting probiotic intake in relation to allergic outcomes, in keeping with the hierarchical approach outlined in the review protocols. In total we identified two high quality systematic reviews in our July 2013 literature search – data were extracted from these reviews, and included in relevant sections of this report. In our updated search on 26th February 2017, we identified three further high quality systematic reviews – the findings of these reviews are referred to in the Conclusions section of this report. In total we identified 28 original trials (27 RCT, 1 CCT) investigating the effect of 30 different probiotic interventions during infancy and/or pregnancy on allergic outcomes.

Interventions used

Characteristics of studies are shown in Table 1, and interventions used are summarised in Table 2. Below is a brief description of the intervention for each original study:

The **Abrahamsson** study (1) used 1 x 10^8 CFU/day freeze-dried *Lactobacillus reuteri* (strain American Type Culture Collection 55730; BioGaia AB, Stockholm, Sweden), suspended in

three-quarters refined coconut oil and one-quarter refined peanut oil containing cryo-protective components. This was given to pregnant mothers from week 36 until delivery, and then to the infants until 12 months of age. The **Allen** study (2) administered 2 strains of lactobacilli and 2 strains of bifidobacteria to pregnant mothers from week 36 and to their offspring until six months of age. The study by **Boyle** and colleagues (3) used 1.8 x 10^{10} colony forming units (cfu)/day of *L. rhamnosus* GG (LGG; American Type Culture Collection 53103; Dicofarm, Italy) each morning from 36 weeks gestation until delivery. The Cabana study used 10^{10} cfu/day of LGG to infants for the first 6 months (4). The Chien study used B. breve M-16V (7.5x10^{8}CFU/100ml) for the first 4 months to infants, within a formula milk, with added prebiotic (5). The **De Leon** study (6) used lactobacillus/bifidobacterium strains given daily for 4 months to infants or their breastfeeding mothers. The **Dotterud** study (7) used 250 mL probiotic low fat fermented milk, for 4 months, from 36 weeks prenatally to 3 months of age while breastfeeding (i.e. mother only). The probiotic milk, Biola (Tine BA, Oslo, Norway), contained LGG, *Bifidobacterium animalis* subsp. lactis Bb-12 (Bb-12) and *L. acidophilus* La-5 (La-5), equalling 5 x 10^{10} cfu of LGG and Bb-12, and 5 x 10^{9} of La-5 per day for its entire shelf life. The **Enomoto** study (8) used 5 x 10^{9} cfu *B. longum* BB536 (ATCC BAA-999) and 5 x 10^{9} cfu *B. breve* M-16V given to pregnant women from 36 weeks gestation then for 6 months to the infant. The **Huurre** study (9) used 1 x 10^{10} cfu/day each of LGG (ATCC 53103, Valio Ltd, Helsinki, Finland) and *B. lactis* Bb12 (Chr. Hansen, Horsholm, Denmark). The **Kalliomaki** study (10) used 2 x 10^{10} cfu of LGG (Valio Ltd; Helsinki, Finland) daily for 2–4 weeks before expected delivery and 6 months after birth (to mothers if breastfeeding, or to infants if not). The **Kim** study (11) used a mixture of *B. bifidum* BGN4 (1.6 x 10^{9} cfu), *B. lactis* AD011 (1.6 x 10^{9} cfu), and *L. acidophilus* AD031 (1.6 x 10^{9} cfu) (Bifido Inc., Hongchungun, Korea) daily from 8 weeks before expected delivery to 3 months after delivery to mother, and from 4 to 6 months to infant. The **Kopp** study (12) used 2 capsules containing 5 x 10^{9} cfu/day of LGG (American type culture collection 53103) by Infectopharm, Heppenheim, Germany. Mothers consumed this from 2-4 weeks before delivery until 6 months after birth. The **Kukkonen** study (13) used a probiotic during the last 2-4 weeks of pregnancy – LGG (ATCC 3103), 10^{10} cfu/day; *L.rhamnosus* LC705 (DSM 7061), 1010 cfu/day; *B. breve* Bb99(DSM 13692), 4 x 10^{8} cfu/day; and *Propionibacterium freudenreichii* ssp. shermanii JS(DSM 7076), 4 x 10^{9} cfu/day (Valio, Helsinki, Finland). Infants then received the same probiotics with 20 drops of syrup containing 0.8 g GOS prebiotic daily for 6 months. The **Lau** study used heat-killed

Escherichia coli Symbio DSM 17252 and *E faecalis* Symbio DSM 16440 4.5-13.5 x 10^7 cfu/day to the infant only, from 5 weeks age to 7 months age. The **Lodinová-Žádníková** study (14) gave 0.8 x 10^9 cfu *E. coli* 3 times per weeks to infants from <48 hours age to 4 weeks (Dyntec. Co. (Terezín, Czech Republic)). The Lundelin study used L. rhamnosus GG, B. lactis, L. paracasei ST11, B.longum BL999 for mothers and infants (15). In the study of **Morisset** and colleagues (16), participants were fed a fermented formula without live bacteria (FWLB), given from birth -or weaning- to 12 month of age. During breastfeeding, mothers ingested the same formula as their child. In the study of **Niers** (17), pregnant mothers during the last 6 weeks of pregnancy and their infants for 12 months, were fed 1 x 10^9 cfu each of *B. bifidum* W23, B. lactis W52 and *Lactococcus lactis* W58 (Ecologic Panda, Winclove Bio Industries B.V. In the **Ou** study (18), the authors used LGG (ATCC 53103; 1 x 10^{10} cfu/day; Valio Ltd.) beginning from 24 weeks gestation (second trimester) of pregnancy until delivery. After delivery, LGG was administered exclusively to breastfeeding mothers or to non-breastfeeding neonates, where it was mixed with water and given by spoon for 6 months. In the **Prescott** study (19), infants were fed 3 x 10^9 cfu/day *L. acidophilus* LAVRI-A1 in maltodextrin (Probiomics, Sydney, Australia) for six months. In the **Rautava 2006** study (20), authors used an infant formula (Enfamil, Mead Johnson Nutritionals, Evansville, IN) supplemented with 1 x 10^{10} cfu of both LGG and *B. lactis* Bb-12 (Chr. Hansen, Hoersholm, Denmark), given to infants daily until 12 months of age. The same group (**Rautava 2012**) investigated the effect of probiotics in a separate intervention (21), using *L. rhamnosus* LPR (CGMCC 1.3724) and *B. longum* BL999 (ATCC: BAA-999) [Nestle S.A.] at 1 x 10^9 cfu, each given daily as a sachet diluted in a glass of water. The study of **Roze** (22) used infant formula containing a synbiotic - *L. rhamnosus* LCS-742 and *B. longum* subsp infantis M63, and a 96% galactooligosaccharides (GOS)/ 4% fructooligosaccharides (FOS) prebiotic. The formula was also enriched with bovine a-lactalbumin, using whey protein concentrate, and was fed to infants for the first 6 months. The study of **Scalabrin** (23) used Nutramigen plus LGG at 10^8 cfu per gram of formula powder, given to infants for 1 year. In the study of **Soh** (24), the authors used a cow's milk-based infant formula supplemented with *B. longum* BL999 (BB536, Morinaga, Japan) 1 x 10^7 cfu/g and *L. rhamnosus* LPR (CGMCC 1.3724) 2 x 10^7 cfu/g, initiated within 12 hours of life for the first six months. The study of **Van der Aa** (25) used an extensively hydrolyzed whey-based formula (Nutrilon Pepti; Nutricia, Netherlands) with synbiotics for 12 weeks. The synbiotic contained Immunofortis at 8g/L, and *B. breve* M-6V (Morinaga Milk Co, Ltd., Tokyo, Japan) 1.3 x 10^9 cfu/100 ml. The study

of **West** (26) combined a daily intake of cereals with 1 x 10^8 cfu of strain LF19 per serving (Semper AB, Stockholm, Sweden) during weaning, from 4 to 13 months of age. The study of **Wickens** (27) used 6 x 10^9 cfu/day *L rhamnosus* HN001 or 9 x 10^9 cfu/day *B animalis* subsp lactis HN019, delivered in a freeze dried capsule (Fonterra Cooperative Group, Auckland, New Zealand). Capsule powder was given to the infant either undiluted or mixed with water, breast milk, or formula and given with a teaspoon. Mothers took the capsules from 35 weeks gestation until the end of the breastfeeding period or up to 6 months post-partum, whilst infants took it from 2-16 days of birth until 2 years of age.

Populations and Outcomes assessed

Outcomes studied were allergic sensitisation (total IgE, specific IgE and skin prick test (SPT)), food allergy, AD, allergic rhinitis, and wheeze/recurrent wheeze. Overall 6000 infants were randomly or non-randomly allocated to an intervention arm. Nineteen studies were in infants at high risk of allergic disease. 17 studies were carried out in Europe, 9 in Asia-Pacific and 2 in the USA. The definitions of diseases varied across studies but with few exceptions,studies used commonly accepted criteria for these definitions.

Overall findings

Overall the quality of evidence was moderate - there was a low or unclear risk of bias in most studies, although approximately a quarter of studies were considered to be at high risk of conflict of interest bias due to direct industry involvement. Overall we found MODERATE level evidence (-1 inconsistency) that probiotics can prevent atopic AD ie AD with associated positive skin prick test or specific IgE test (11 studies, 12 interventions; 3000 participants RR 0.78; 95% CI 0.65 to 0.92; I^2=0%). We found MODERATE level evidence (-1 inconsistency) that probiotics can prevent *all* AD (19 studies, 21 interventions; 4700 participants; RR 0.78; 95% CI 0.68 to 0.90; I^2=61%) in children ≤ 4 years old. The majority of the evidence in these positive meta-analyses came from studies of high risk infants i.e. those with a positive family history of allergic disease (10 of 12 interventions for atopic AD; 17 of 21 interventions for *all* AD).

We found LOW level evidence (-1 indirect outcome; -1 imprecision) that probiotics can prevent allergic sensitisation to cow's milk, but no evidence that probiotics or synbiotics prevent allergic sensitisation to other allergens or prevent clinical cow's milk allergy.

We found no evidence for persistence of the effect on atopic AD or *all* AD beyond age 4 years, and no evidence that probiotics prevent other allergic outcomes.

Table 1 Characteristics of included studies evaluating probiotic supplementation and allergic outcomes

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Pelucchi (28)	14 RCT (1417 participants)	SR	-	Pregnant or lactating women or their infants; any probiotic(s) versus no probiotic	all	Up to age 12	AD, IgE-associated AD
Tang (29)	11 RCT (1007 participants)	SR	-	Pregnant or lactating women or their infants; probiotic versus no probiotic	high	All	AD, asthma, allergic sensitisation to any food
Abrahamsson 2007 (1) Abrahamsson 2013 (30)	117/ 115	RCT	Sweden	Probiotic Pregnant women (week 36) and infants (for 12 months)	high	2, 7	AD (Seymour), Wheeze (single, or ≥2 episodes), ARC (watery discharge ≥2 times with same allergen), Allergic sensitisation (SPT common allergens)
Allen 2012 (2) Allen 2014 (31)	220/ 234	RCT	UK	Probiotic Pregnant women (week 36) and infants (for 6 months)	high	2	AD (DD), Allergic sensitisation (SPT common allergens, CM, Egg), Wheeze (unclear), ARC (unclear), Food Allergy (parent report)
Boyle 2011 (3)	125/ 125	RCT	Australia	Probiotic Pregnant women (week 36)	high	1	AD (UK Working party criteria), Wheeze (wheeze + loose API), Allergic sensitisation (SPT common allergens)
Cabana, 2015 (4)	93/ 92	RCT	USA	Probiotic Infants (for 6 months)	high	2	Wheeze (unclear); AD (unclear)

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Chien, 2016 (5)	Unclear – outcome reported in 45 (synbiotic), 39 (prebiotic), 45 (control)	RCT	Singapore	Prebiotic & Synbiotic scGOS/lcFOS (0.8g/100ml) and B. breve M-16V (7.5x108CFU/100ml), or scGOS/lcFOS (0.8g/100ml), or control formula from birth to 4 months, in mixed fed infants born by elective Caesarean	unclear	0.4	AD (unclear)
De Leon 2007 (6) Simon 2007 (32)	Total = 33	RCT	Philippines	Probiotic for 4 months to infants or to their breastfeeding mothers	high	0.5	AD (unclear) Allergic sensitisation (Total IgE)
Dotterud 2010 **(7)** **Simpson 2015** (33)	211/ 204	RCT	Norway	Probiotic Mothers only (36 weeks gestation to 3 months after birth)	normal	2	AD (UK Working party criteria), Wheeze (≥3 episodes + ICS), ARC (DD), Allergic sensitisation (SPT common allergens)
Enomoto 2014 (8)	130/36	CCT	Japan	Probiotic Pregnant women (week 36) and infants (for 6 months)	normal	1.5	AD (Hanifin and Rajka), Wheeze (physician assessment), ARC (physician assessment)
Huurre 2008 (9)	72/ 68	RCT	Finland	Probiotic Infants (for 6 months)	high	1	AD (Hanifin and Rajka), Allergic sensitisation (SPT common allergens)

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Kalliomaki 2001 (34) Kalliomaki 2003 (10) Kalliomaki 2007 (35) Rautava 2002 (36)	77/ 82	RCT	Finland	Mothers and infants; from 2–4 weeks before expected delivery and 6 months of age	high	2	AD (relapsing itchy lesions with typical location), Wheeze (symptoms + ICS), ARC (symptoms with allergen exposure), Food Allergy (CMA by DBPCFC), Allergic sensitisation (Total IgE and SPT/sIgE to common allergens)
Kim 2010 (11)	57/ 55	RCT	Korea	Probiotic, pregnant women and infants from 4 to 6 months	high	1	AD (Hanifin and Rajka), Allergic sensitisation (Total IgE and sIgE to common allergens)
Kopp 2008 (12)	54/ 51	RCT	Germany	Probiotic Mothers (2-4 weeks before birth until 3 months post birth) and infants (months 4-6)	high	2	AD (UK Working party criteria), Wheeze (≥5 episodes), Allergic sensitisation (Total IgE and sIgE to common allergens)
Kukkonen 2007 (13) Kuitunen 2009 (37) Kukkonen 2011(38)	610/ 613	RCT	Finland	Synbiotic Pregnant women (2-4 weeks before delivery) and infants up to 6 months	high	2, 5	AD (UK Working party criteria), Wheeze (≥2 episodes + interval symptoms), ARC (symptoms + sensitisation), Allergic sensitisation (Total IgE and SPT/sIgE to common allergens)

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Lau 2012 (39)	303/ 303	RCT	Germany	Probiotic Infant from 5 weeks up to 7 months age	high	2	AD (Hanifin and Rajka), Allergic sensitisation (Total IgE and sIgE)
Lodinová-Žádníková 2010 (40)	56/ 57	RCT	Czech Republic	Probiotic Infants - birth to age 4 weeks	high	1	AD (unclear), Food allergy (unclear), Wheeze (unclear) Allergic sensitisation (Total IgE and sIgE to common allergens)
Lundelin, 2016 (15) Luoto, 2014 (41)	31, 31, 32	RCT	Finland	Probiotic Pregnant women and infants	normal	1	Wheeze (ISAAC); ARC ISAAC); AD (ISAAC); FA (unclear)
Morisset 2008 (16)	59/ 56	RCT	France	Probiotic Infant – from birth or weaning, to age 1 year	high	1	Food allergy (CMA by physician assessment) Allergic sensitisation (sIgE to cow's milk)
Niers 2009 **(17)** **Gorissen, 2014 (42)**	78/ 78	RCT	Netherlands	Probiotic Pregnant women during the last 6 weeks of pregnancy and their infants until age 1 year	high	2	AD (modified ECRHS) Allergic sensitisation (Total IgE and SPT/sIgE to common allergens) AR (ISAAC) Wheeze (physician assessment), Food allergy (physician assessment), lung function (FEV1)

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Ou 2012 (18)	95/ 96	RCT	Taiwan	Probiotic Pregnant women (third trimester) and then breastfeeding mothers, or directly to infants, until age 6 months	high	3	AD (ISAAC), Wheeze (ISAAC), ARC (ISAAC), Allergic sensitisation (sIgE to common allergens)
Taylor 2007 (43), Prescott 2008 (44) Jensen 2012 (termed Taylor 2012 in some meta-analyses) (45)	115/ 111	RCT	Australia	Probiotic, infants until 6 months	high	1, 2.5, 5	AD (DD), Food allergy (any food - physician assessment), Wheeze (DD), ARC (symptoms + sensitisation), Allergic sensitisation (SPT common allergens)
Rautava 2006 (20)	38/ 43	RCT	Finland	Probiotic Infant formula; infants until age 1 year	normal	1	AD (Hanifin and Rajka), Food allergy (CMA by DBPCFC) Allergic sensitisation (SPT food allergens)
Rautava 2012 (21)	82/ 78	RCT	Finland	Probiotic Infants fed daily until age 1 year	high	2	AD (Hanifin and Rajka), Allergic sensitisation (SPT common allergens)
Roze 2012 (22)	48/ 49	RCT	France	Synbiotic Infants (first 6 months)	normal	0.5	AD (UK Working party criteria)
Scalabrin 2009 (46) Scalabrin 2014 (47) Scalabrin 2017 (48)	95/ 95	RCT	USA	Probiotic Infants (first 12 months)	normal	0.4, 5	Allergic sensitisation (sIgE to common allergens), AD (unclear), Wheeze (unclear), ARC (unclear), Food Allergy (unclear)

Study	N Intervention / Control	Study Design	Country	Intervention & Population studied	Disease risk	Age at outcome (years)	Outcomes reported
Soh 2009 (49) Loo 2014 (50)	127/ 126	RCT	Singapore	Probiotic Cow's milk-based infant formula supplemented with Probiotic; infants up to 6 months of age	high	1	AD (Seymour), Allergic sensitisation (Total IgE and SPT/sIgE to common allergens) Food allergy (physician assessment), AR (physician assessment)
Van der Aa 2010 (51)	46/ 44	RCT	Netherlands	Synbiotic Whey-based formula combined with Synbiotic, for 3 months	high	1	Wheeze (≥3 episodes), Allergic sensitisation (Total IgE)
West 2009 (26) West 2013 (52)	89/ 90	RCT	Sweden	Probiotic To infant from 4 until 13 months	normal	1, 8-9	AD (itchy rash with typical distribution, or DD), Wheeze (DD), ARC (DD), Allergic sensitisation (Total IgE and sIgE to common allergens) Food allergy (physician assessment)
Wickens 2008 (27) Wickens 2012 (53) Wickens 2013 (54)	341/ 171	RCT	New Zealand	Probiotic To pregnant women (35 weeks gestation to end up of BF or 6 months post-partum) and infants from 2-16 days of birth to 2 years	high	2, 4, 6	AD (UK Working party criteria), Wheeze (ISAAC), ARC (ISAAC), Allergic sensitisation (SPT common allergens)

Seymour criteria and UK working party criteria are both modifications of the Hanifin and Rajka criteria. AR: Allergic Rhinitis. ARC: Allergic Rhinoconjunctivis. DD doctor's diagnosis; SPT skin prick test; sIgE specific IgE; RCT randomised controlled trial; CCT controlled clinical trial;

ISAAC International Study of Asthma and Allergies in Childhood; ICS inhaled corticosteroids; ECRHS European Community Respiratory Health Survey; API Asthma Predictive Index

Table 2 Probiotic(s) and daily dose used in intervention trials of probiotics/synbiotics for primary prevention of allergic outcomes

First Author & Publication Year	Intervention
Abrahamsson 2007 **(1)**	1 x 10^8 cfu/day freeze-dried L reuteri (strain American Type Culture Collection 55730)
Allen 2012 **(2)**	6.5 x 10^9 cfu/day L. salivarius CUL61, 1.25 x 10^9 cfu/day L. paracasei CUL08, 1.25 x 10^9 cfu/day B. animalis subsp. Lactis CUL34, 1.25 x 10^9 cfu/day B. bifidum CUL20
Boyle 2011 **(3)**	1.8 x 10^{10} cfu/day L. rhamnosus strain GG (ATCC 53103)
Dotterud 2010 **(7)**	250 mL probiotic milk with L. rhamnosus strain GG (ATCC 53103), B. animalis subsp. lactis Bb-12 and L. acidophilus La-5
Cabana, 2015 (4)	Lactobacillus GG from birth to 6 months to infants at 10^{10} cfu/day
Chien, 2016 (5)	Infant formula supplemented with scGOS/lcFOS (0.8g/100ml) and B. breve M-16V (7.5x108CFU/100ml), or formula with scGOS/lcFOS (0.8g/100ml), or control formula from birth until 4 months
Enomoto 2014 **(8)**	5 x 10^9 cfu B. longum BB536 (ATCC BAA-999) and 5 x 10^9 cfu B. breve M-16V
Huurre 2008 **(9)**	1 x 10^{10} cfu/day each of L. rhamnosus strain GG (ATCC 53103) and B. lactis Bb12
Kalliomaki 2001 **(10, 34-36)**	2 x 10^{10} cfu L. rhamnosus strain GG (ATCC 53103)
Kim 2010 **(11)**	B. bifidum BGN4 [1.6 x 10^9 cfu], B. lactis AD011 (1.6 x 10^9 cfu), and L. acidophilus AD031 (1.6 x 10^9 cfu)
Kopp 2008 **(12)**	2 capsules containing 5 x 10^9 cfu/day L. rhamnosus strain GG (ATCC 53103)

First Author & Publication Year	Intervention
Kuitunen 2009 **(37)**	5 x 10^9 cfu L. rhamnosus strain GG (ATCC 53103), 5 x 10^9 cfu L rhamnosus LC705 (DSM 7061), 2 x 10^8 cfu B. breve Bb99(DSM 13692), 2 x 10^9 cfu Propionibacterium freudenreichii ssp. shermanii JS(DSM 7076). Infants received 1 capsule with 20 drops of syrup containing 0.8 g GOS daily for 6 months.
Lau 2012 **(39)**	Heat-killed E coli Symbio DSM 17252 and E faecalis Symbio DSM 16440 4.5-13.5 x 10^7 cfu/day
Lodinová-Žádníková 2010 **(40)**	0.8 x 10^9 cfu E. coli 3 times weekly to infant, from <48 hours age to 4 weeks
Lundelin, 2016 (15) **Luoto, 2014 (41)**	L. rhamnosus GG, B. lactis, L. paracasei ST11, B.longum BL999 given to pregnant women and their infants
Morisset 2008 **(16)**	Fermented formula without live bacteria (FWLB)
Niers 2009 **(17)**	1 x 10^9 cfu each of B. bifidum W23, B. lactis W52 and Lc. lactis W58
Ou 2012 **(18)**	L. rhamnosus strain GG (ATCC 53103) 1 x 10^{10} cfu/day
Rautava 2006 **(20)**	Infant formula supplemented with 1 x 10^{10} cfu L. rhamnosus strain GG (ATCC 53103) and B. lactis Bb-12
Rautava 2012 **(21)**	L. rhamnosus LPR (CGMCC 1.3724) and B. longum BL999 (ATCC: BAA-999) at 1 x 10^9 cfu each daily
Roze 2012 **(22)**	Extensively hydrolysed casein based formula, plus L. rhamnosus strain GG (ATCC 53103) at 10e8 cfu per gram of formula powder
Scalabrin 2009 **(46)**	Extensively hydrolysed casein based formula, plus L. rhamnosus strain GG (ATCC 53103) at 10e8 cfu per gram of formula powder
Simon 2007 **(32)**	L./B. strains
Soh 2009 **(49)**	At least 60 mL (9.26 g) a day of cow's milk-based infant formula supplemented with [B. longum BL999 (BB536) 1 x 10^7 cfu/g and L. rhamnosus LPR (CGMCC 1.3724) 2 x 10^7 cfu/g
Prescott 2008 **(44)**	3 x 10^9 cfu/day L acidophilus LAVRI-A1

First Author & Publication Year	Intervention
Van der Aa 2010 **(51)**	Extensively hydrolyzed whey-based formula with synbiotics [B. breve M-6V (1.3 x 10^9 cfu/100 ml and 90% scGOS / 10% lcFOS (Immunofortis), 0.8 g/100 ml]
West 2009 **(26)**	1 x 10^8 cfu/serving L.paracasei LF19 per serving fed to infant from 4 to 13 months age
Wickens 2008 **(27)**	6 x 10^9 cfu/day L rhamnosus HN001 or 9 x 10^9 cfu/day B animalis subsp lactis HN019

2. Probiotics and allergic sensitisation

Twenty-four studies reported the effect of probiotics on allergic sensitisation in over 5000 participants. Studies reported skin prick test (SPT) or specific IgE to common allergens, SPT to food allergens, and total IgE. Children's age at time of outcome measurement ranged between 4 months and 7 years old – as in other parts of this project, allergic sensitisation data were combined for all ages, due to limited data available when age-groups were analysed separately. Assessment bias was low in 85% of studies, and over half had a low risk of selection or attrition bias. Approximately a quarter of studies were considered to have a high risk of conflict of interest (Figure 1).

Fourteen studies (16 interventions) reported AS to any allergen. There was no evidence that probiotics reduce the prevalence of AS to any one of a panel of common allergens (Figure 2), with low statistical heterogeneity. Subgroup analyses showed no evidence of different treatment efficacy according to features of the intervention, population or risk of bias (Table 4). We found no evidence of publication bias (Figure 3). Similarly analysis of AS to aeroallergen or any food (Figures 4 and 5) did not show any evidence of a treatment effect, and subgroup analyses showed no important subgroup differences (Tables 5 and 6). We found no evidence for publication bias in the analysis of 'sensitisation to any food' as an outcome (Figure 6).

Analysis of allergic sensitisation to specific foods showed some evidence that sensitisation to cow's milk may be reduced by probiotics (Figure 7) but not egg or peanut (Figures 8 and 9). Subgroup analyses for milk and egg allergy showed no evidence of different efficacy according to features of the intervention, population or risk of bias (Tables 7 and 8). It is worth noting that 7 of 8 studies included in meta-analysis of cow's milk sensitisation were considered to be at high/unclear overall risk of bias, and 5 of 8 at high/unclear risk of conflict of interest.

Four studies (~2000 participants) which reported geometric mean total IgE could not be pooled due to extreme statistical heterogeneity, but the studies tended to show reduced total IgE in the probiotic compared to control group (Figure 10). However ten further studies (also ~2000 participants) which couldn't be presented on a forest plot due to the nature of outcome

data reported, all showed no significant difference in total IgE between probiotic and control group (11, 12, 17, 18, 26, 32, 39, 46, 51, 54).

Four studies reported some data which could not be included in meta-analyses. Huurre and colleagues (9) found no effect of probiotic supplementation with L.rhamnosus on risk of positive SPT to any food at age 1 year (OR 0.92; 95% CI 0.45, 1.9; p=0.83). Rautava (2006) found no statistically significant differences in the percentage of children having a positive SPT to any food (p=0.84) (20). Scalabrin and colleagues (46) found no effect on sensitisation to cow's milk using sIgE (p=0.63). Finally Kalliomaki and colleagues (10) reported allergic sensitisation at 2 years (shown in Figure 2), but also reported no effect on AS-any at ages 4 and 7 (35). Gorrisen (42) reported outcomes from the trial of Niers (17) at 6 years, and found no difference between groups in total IgE, specific IgE or skin prick test response to common allergens. Simpson reported outcomes from the trial of Dotterud at 6 years, and found no difference between groups in specific IgE or skin prick test response to common allergens.

Overall we found LOW (-1 indirect outcome; -1 imprecision due to low event numbers and borderline statistical significance) evidence that probiotics reduce allergic sensitisation to cow's milk, but no evidence that probiotics or synbiotics reduce allergic sensitisation to other allergens.

Figure 1 Risk of bias in intervention studies of probiotics and allergic sensitisation

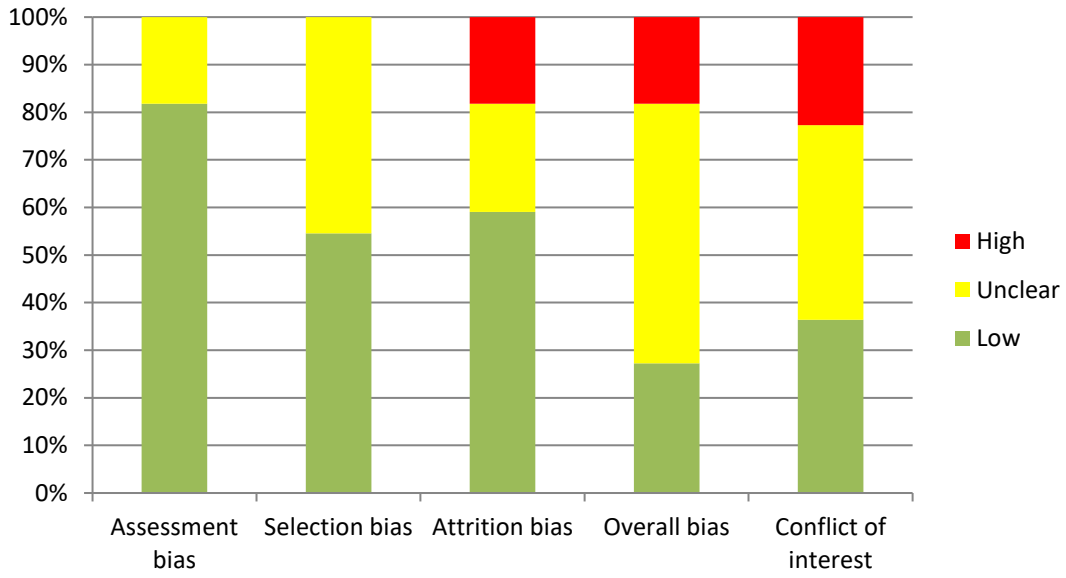


Table 3 Findings from a high quality systematic review identified in the 07/13 search

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)	I^2
Tang (29)	AS-Food	1826 (7)	**RR 0.95 [0.80, 1.12]**	19

Figure 2 Probiotics and risk of AS to any allergen

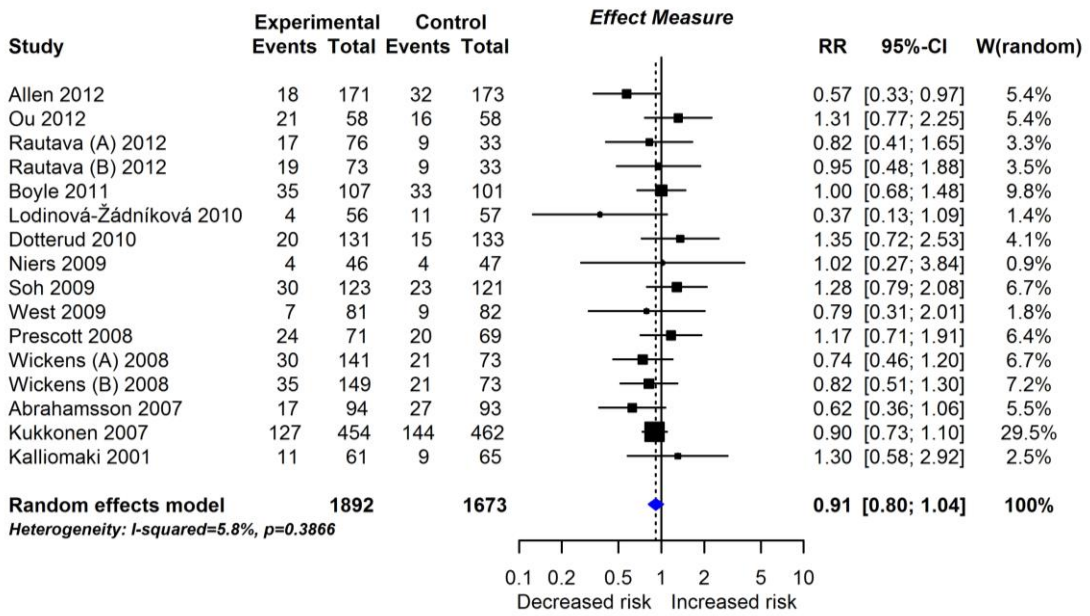
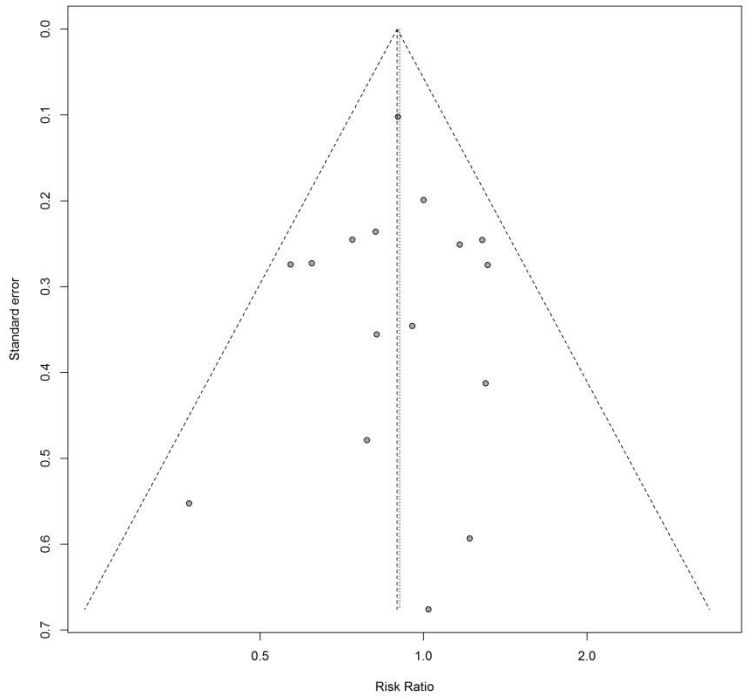


Table 4 Subgroup analyses of effect of probiotics on risk of allergic sensitisation to common allergen

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	14	0.90 [0.76; 1.07]	16	0.92
Risk of disease – Normal	2	0.94 [0.45; 1.94]	0	
Method of assessment – sIgE	3	0.82 [0.39; 1.69]	56	0.80
Method of assessment – SPT	13	0.90 [0.79; 1.02]	0	
Type of Intervention – Probiotic	15	0.91 [0.77; 1.06]	4	0.95
Type of Intervention – Synbiotic	1	0.90 [0.73; 1.10]	--	
Type of Probiotic – L.rhamnosus	9	0.96 [0.83; 1.10]	0	0.15
Type of Probiotic – Other	7	0.77 [0.60; 0.99]	14	
Timing – Postnatal only	4	0.98 [0.64; 1.50]	38	0.62
Timing – Pre +/-Post-natal	12	0.88 [0.77; 1.00]	0	
*Postnatal Administration – Infant only	8	0.85 [0.67; 1.07]	33	0.65
*Postnatal Administration – Other	7	0.97 [0.78; 1.21]	0	
Overall risk of bias – High/Unclear	10	0.90 [0.73; 1.11]	29	0.96
Overall risk of bias – Low	6	0.90 [0.72; 1.11]	0	
Conflict of interest – High/Unclear risk	8	0.90 [0.71; 1.14]	35	0.93
Conflict of interest – Low risk	8	0.91[0.74; 1.11]	0	

*no postnatal administration in study of Boyle, 2011 – hence only 15 interventions included in this analysis

Figure 3 Risk of publication bias: probiotics and AS to any allergen



Egger's test p = 0.84

Figure 4 Probiotics and risk of AS to any aeroallergen

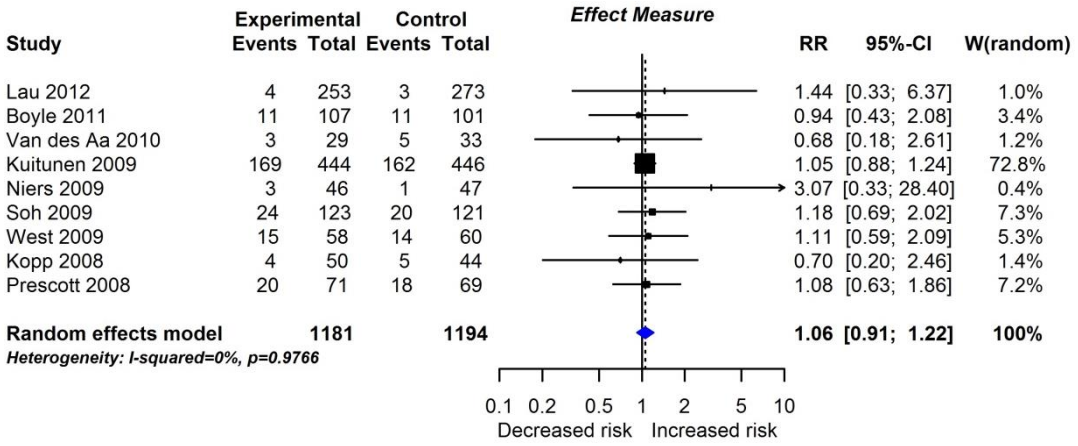


Figure 5 Probiotics and risk of AS to any food

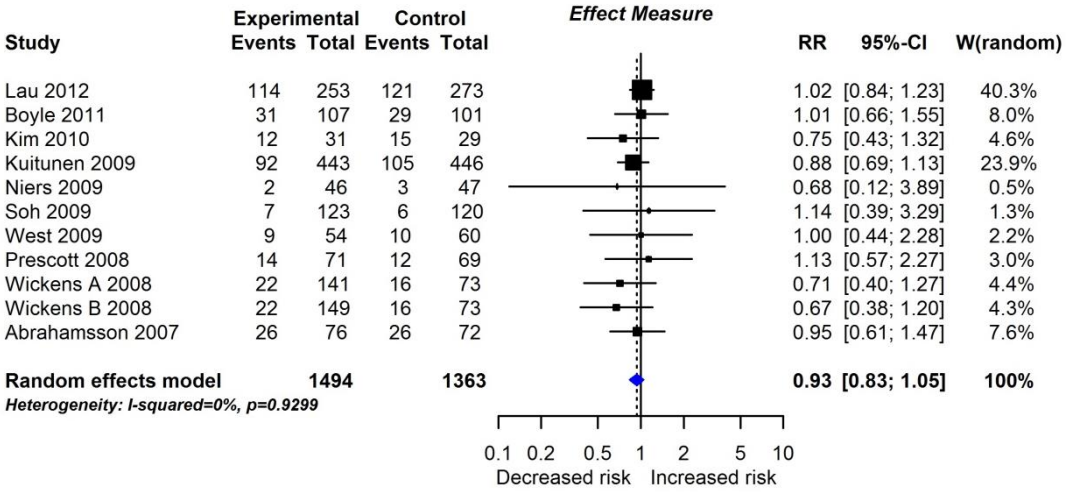


Table 5 Subgroup analyses of effect of probiotics on risk of allergic sensitisation to aeroallergen

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	8	1.06 [0.91-1.22]	0	0.88
Risk of disease – Normal	1	1.11 [0.59-2.09]	-	
Method of assessment – sIgE	4	1.00 [0.61; 1.63]	0	0.70
Method of assessment – SPT	5	1.12 [0.80; 1.57]	0	
Type of Intervention – Probiotic	8	1.10 [0.83; 1.46]	0	0.50
Type of Intervention – Synbiotic	1	0.68 [0.18; 2.61]	--	
Type of Probiotic – L.rhamnosus	5	1.05 [0.90-1.23]	0	0.86
Type of Probiotic – Other	4	1.10 [0.69-1.75]	0	
Timing – Postnatal only	5	1.11 [0.81-1.51]	0	0.74
Timing – Pre +/-Post-natal	4	1.04 [0.88-1.23]	0	
*Postnatal Administration – Infant only	7	1.07 [0.92-1.24]	0	0.78
*Postnatal Administration – Other	1	0.70 [0.20-2.46]	-	
Overall risk of bias – High/Unclear	6	1.06 [0.91-1.24]	0	0.71
Overall risk of bias – Low	3	0.95 [0.51-1.74]	0	
Conflict of interest – High/Unclear risk	3	0.95 [0.51-1.74]	0	0.71
Conflict of interest – Low risk	6	1.06 [0.91-1.24]	0	

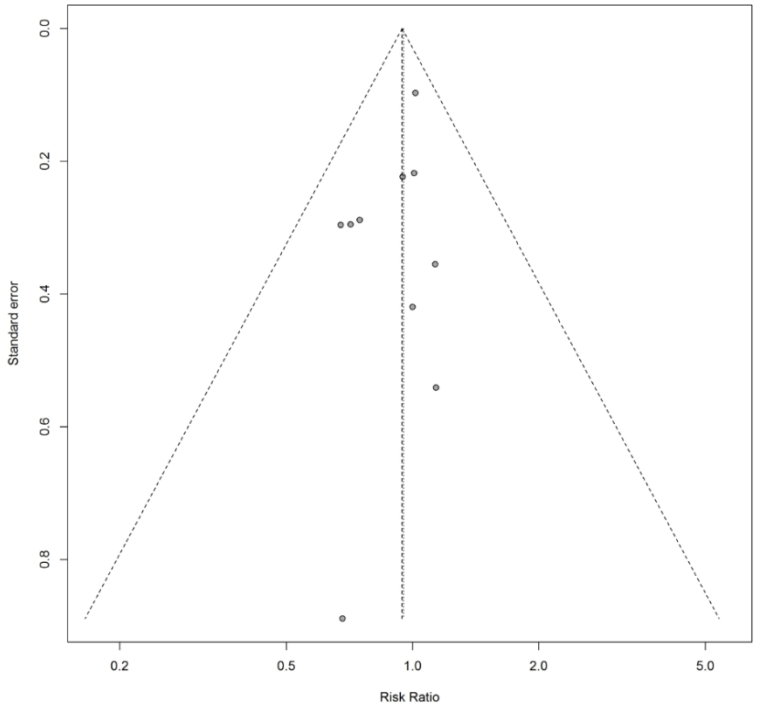
*no postnatal administration in study of Boyle, 2011 – hence only 8 interventions included in this analysis

Table 6 Subgroup analyses of effect of probiotics on risk of allergic sensitisation to any food

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	10	0.93 [0.83-1.05]	0	0.87
Risk of disease – Normal	1	1.00 [0.44-2.27]	-	
Method of assessment – sIgE	4	0.98 [0.83; 1.15]	0	0.49
Method of assessment – SPT	7	0.88 [0.68; 1.14]	0	
Type of Intervention – Probiotic	11	0.95 [0.83; 1.09]	0	--
Type of Intervention – Synbiotic	0	--	--	
Type of Probiotic – L.rhamnosus	5	0.90 [0.74-1.09]	0	0.61
Type of Probiotic – Other	6	0.96 [0.82-1.12]	0	
Timing – Postnatal only	4	1.02 [0.86-1.22]	0	0.15
Timing – Pre +/-Post-natal	7	0.86 [0.73-1.01]	0	
*Postnatal Administration – Infant only	7	0.97 [0.85-1.11]	0	0.22
*Postnatal Administration – Other	3	0.71 [0.51-0.99]	-	
Overall risk of bias – High/Unclear	7	0.90 [0.75-1.09]	0	0.64
Overall risk of bias – Low	4	0.96 [0.82-1.12]	0	
Conflict of interest – High/Unclear risk	6	0.95 [0.83-1.09]	0	0.62
Conflict of interest – Low risk	5	0.88 [0.68-1.14]	0	

*no postnatal administration in study of Boyle, 2011 – hence only 10 interventions included in this analysis

Figure 6 Risk of publication bias: probiotics and AS to any food allergen



Egger's test p = 0.22

Figure 7 Probiotics and risk of AS to CM

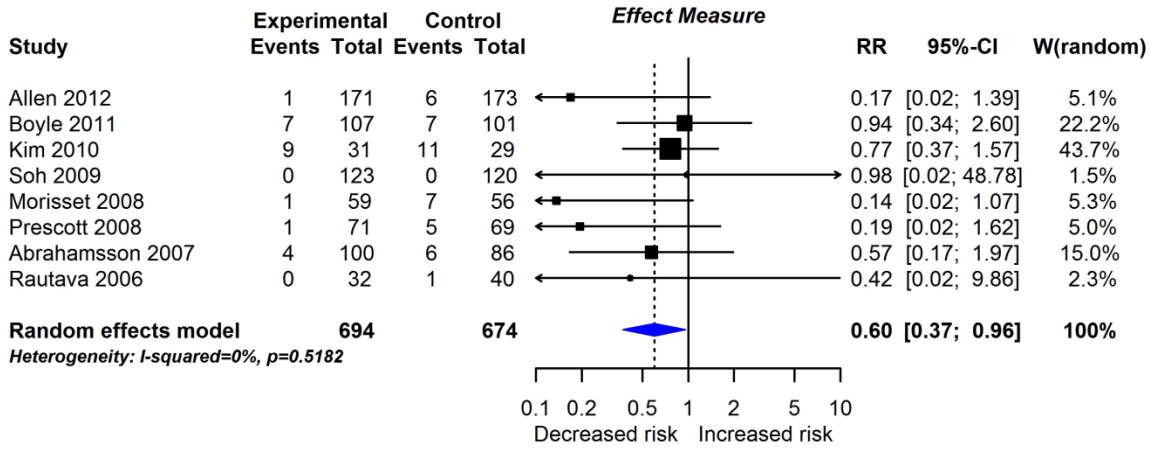


Figure 8 Probiotics and risk of AS to egg

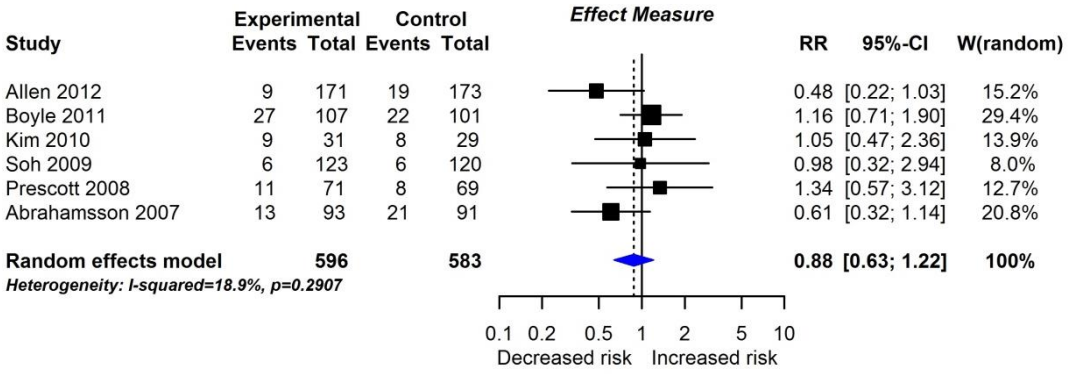


Figure 9 Probiotics and risk of AS to peanut

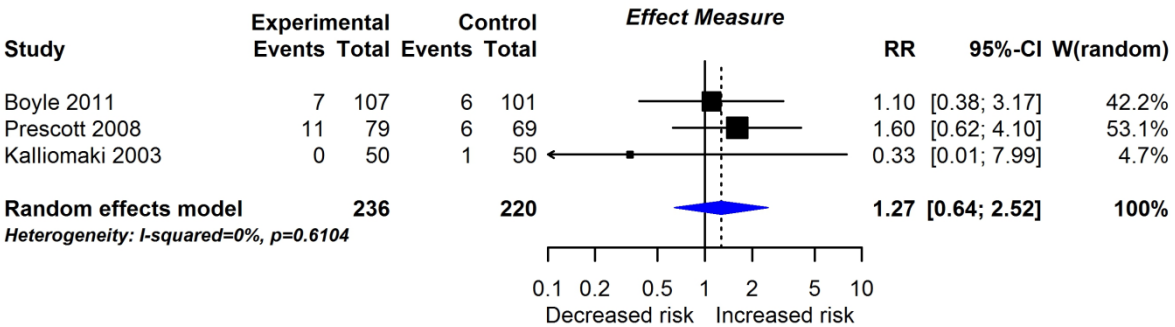


Table 7 Subgroup analyses of effect of probiotics on risk of allergic sensitisation to cow's milk

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	7	0.60 [0.36; 0.98]	2	0.82
Risk of disease – Normal	1	0.42 [0.02; 9.86]	--	
Method of assessment – sIgE	2	0.41 [0.07; 2.33]	63	0.74
Method of assessment – SPT	6	0.57 [0.29; 1.10]	0	
Type of Intervention – Probiotic	8	0.60 [0.37; 0.96]	0	--
Type of Intervention – Synbiotic	0	--	--	
¶Type of Probiotic – L.rhamnosus	3	0.88 [0.35; 2.24]	0	0.26
¶Type of Probiotic – Other	4	0.56 [0.30; 1.04]	6	
Timing – Postnatal only	4	0.23 [0.06; 0.81]	0	0.11
Timing – Pre +/-Post-natal	4	0.70 [0.42; 1.17]	0	
*Postnatal Administration – Infant only	5	0.38 [0.16; 0.93]	0	0.40
*Postnatal Administration – Other	2	0.41 [0.07; 2.33]	63	
Overall risk of bias – High/Unclear	7	0.53 [0.31; 0.90]	0	0.32
Overall risk of bias – Low	1	0.94 [0.34; 2.56]	--	
Conflict of interest – High/Unclear risk	5	0.55 [0.29; 1.01]	6	0.69
Conflict of interest – Low risk	3	0.68 [0.28; 1.63]	0	

¶the study of Morisset, 2008 did not name the probiotic given, hence only 7 interventions included in this analysis

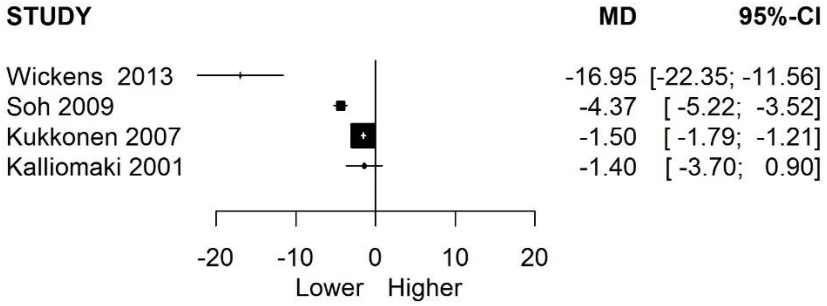
*no postnatal administration in study of Boyle, 2011 – hence only 7 interventions included in this analysis

Table 8 Subgroup analyses of effect of probiotics on risk of allergic sensitisation to egg

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	6	0.88 [0.63; 1.22]	19	--
Risk of disease – Normal	0	--	--	
Method of assessment – sIgE	1	1.05 [0.47; 2.36]	0	0.65
Method of assessment – SPT	5	0.85 [0.57; 1.25]	32	
Type of Intervention – Probiotic	6	0.88 [0.63; 1.22]	19	--
Type of Intervention – Synbiotic	0	--	--	
Type of Probiotic – L.rhamnosus	2	1.13 [0.72; 1.77]	0	0.23
Type of Probiotic – Other	4	0.77 [0.49; 1.20]	29	
Timing – Postnatal only	2	1.19 [0.61; 2.33]	0	0.33
Timing – Pre +/-Post-natal	4	0.80 [0.52; 1.22]	41	
*Postnatal Administration – Infant only	4	0.73 [0.47; 1.14]	19	0.37
*Postnatal Administration – Other	1	1.05 [0.47; 2.36]	--	
Overall risk of bias – High/Unclear	5	0.78 [0.53; 1.13]	10	0.21
Overall risk of bias – Low	1	1.16 [0.71; 1.90]	--	
Conflict of interest – High/Unclear risk	4	0.67 [0.46; 0.99]	0	0.06
Conflict of interest – Low risk	2	1.21 [0.79; 1.85]	0	

*no postnatal administration in study of Boyle, 2011 – hence only 6 interventions included in this analysis

Figure 10 Probiotics and total IgE



3. Probiotics and risk of food allergy

Eleven intervention trials (1167 participants, 580 randomised to probiotics) assessed the effect of supplementation with probiotics on risk of developing food allergy. Interventions lasted 6-12 months postnatally. One study was carried out in Australia, one in the USA and 9 in Europe. Four studies had a normal disease risk, whilst the other 7 were carried out in high risk infants. Children's age at the time of outcome measurement ranged between 1 and 6 years. Three studies measured allergy to cow's milk, using either DBPCFC (Kalliomaki and Rautava), or physician assessment (Morisset). The other studies measured food allergy to any food, mainly using a physician's assessment, relying on a combination of a suggestive history and positive allergy test.

Risk of bias was generally unclear (Figure 11). There was a low risk of assessment and attrition bias in over 60% of studies. There was a high risk of conflict of interest in almost 30% of studies.

We found no evidence that probiotic supplementation reduces the risk of any food allergy at age ≤4 years or age 5 to 14 years (Figures 12 and 13), and no evidence that probiotics reduce the risk of having cow's milk allergy at age ≤4 years (Figure 14). Subgroup analysis showed no evidence that specific subgroups have different outcome with respect to any food allergy at age 5 to 14 years (Table 9).

The data from Prescott (19) at age 2.5 years old could not be combined with other studies in meta-analysis. They reported no effect of probiotics on odds of food allergy (OR 0.83; 95% CI 0.33 – 2.20). In an analysis including data from Luoto, together with other probiotic intervention studies, Lundelin (15) found no significant difference in food allergy between probiotic and placebo groups.

Overall we found no evidence that probiotics influence risk of food allergy.

Figure 11 Risk of bias in intervention studies of probiotics and food allergy

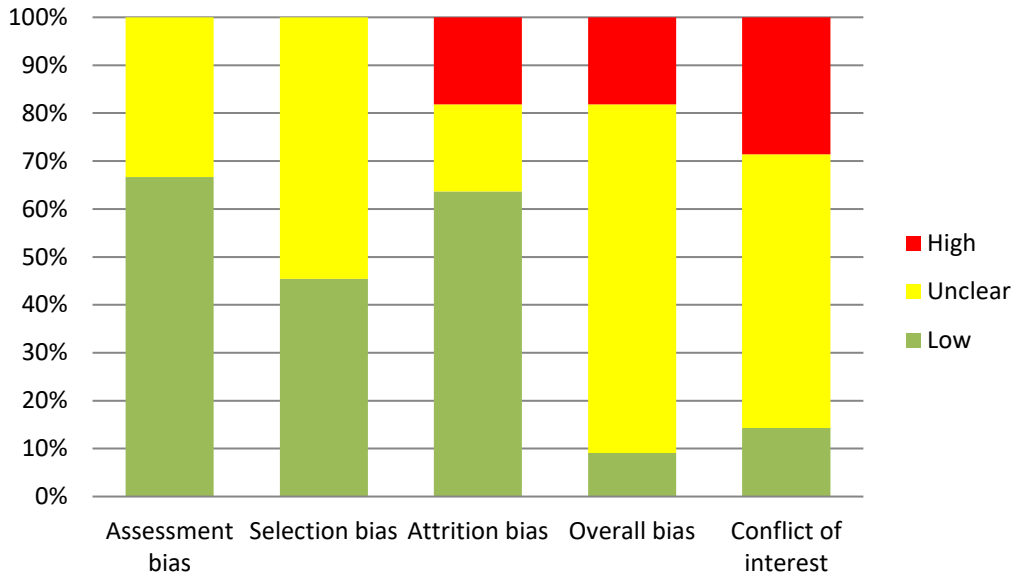


Figure 12 Probiotics and risk of any food allergy at age ≤ 4 years old

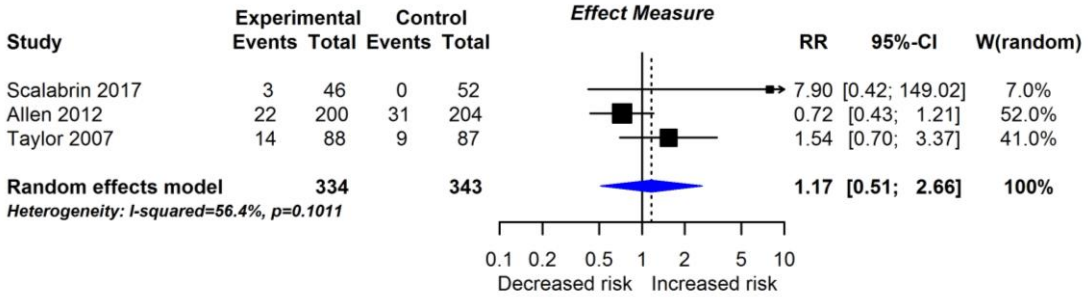


Figure 13 Probiotics and risk of any food allergy at age 5-4 years old

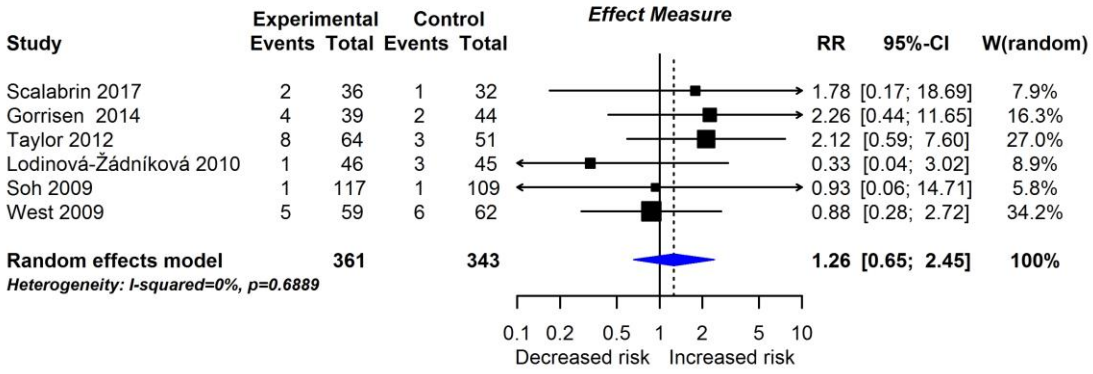
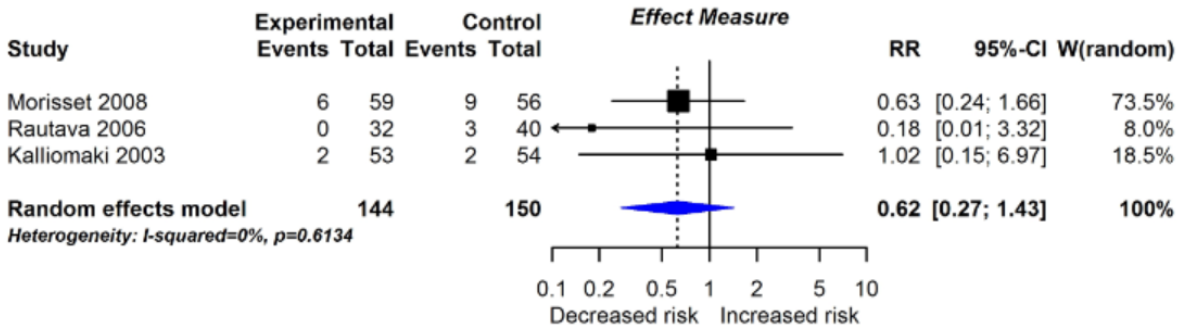


Table 9 Subgroup analyses of effect of probiotics on risk of any food allergy at age 5 to 14 years

	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Risk of disease – High	4	1.49 [0.63; 3.57]	0	0.56
Risk of disease – Normal	2	1.00 [0.36; 2.77]	0	
Type of Intervention – Probiotic	6	1.26 [0.65; 2.45]	0	--
Type of Intervention – Synbiotic	0	--	--	
Type of Probiotic – L.rhamnosus	3	0.99 [0.38; 2.58]	0	0.55
Type of Probiotic – Other	3	1.52 [0.55; 4.18]	14	
Timing – Postnatal only	5	1.13 [0.55; 2.32]	0	0.45
Timing – Pre +/-Post-natal	1	2.26 [0.44; 11.65]	--	
Postnatal Administration – Infant only	5	1.13 [0.55; 2.32]	0	0.45
Postnatal Administration – Other	1	2.26 [0.44; 11.65]	--	
Overall risk of bias – High/Unclear	6	1.26 [0.65; 2.45]	0	--
Overall risk of bias – Low	0	--	--	
Conflict of interest – High/Unclear risk	4	1.21 [0.42; 3.51]	0	0.93
Conflict of interest – Low risk	2	1.30 [0.55; 3.08]	4	

Figure 14 Probiotics and risk of CMA at age ≤ 4 years old



4. Probiotics and risk of AD

One systematic review (13 trials, 3000 participants) evaluated AD (28). They reported significantly reduced AD and atopic AD, with low statistical heterogeneity, and did not identify important subgroup differences.

Twenty-six original intervention trials (25 RCT; 1 CCT) evaluated over 6000 participants allocated to probiotic or control treatment with AD as an outcome. Sixteen studies were carried out in Europe, 2 in USA and 8 in Asia-Pacific. Seven studies were carried out in infants with normal risk of AD, 18 in infants at high risk of AD and in one study this was unclear. Age at time of outcome measurement ranged between 4 months and 7 years. Fourteen studies used Hanifin & Rajka or modifications of this method for outcome assessment, 5 used doctor diagnosis of AD and others used different assessment methods or (for 5 studies) method of outcome assessment was unclear. The overall risk of bias was low or unclear in over 80% of studies based on assessment, selection and attrition bias, however over 30% of studies had a high risk of conflict of interest due to direct industry involvement in the trial (Figure 15).

Probiotics reduced AD risk at age ≤4 years (Figure 16 – RCT) with high statistical heterogeneity (I^2=61%). In the CCT of Enomoto (8) there was significantly reduced AD risk at age 18 months in probiotic versus control group (Figure 17), despite a significant imbalance at randomisation with increased risk factors for allergic disease in the probiotic group. There was no evidence of publication bias in these two meta-analyses (Figure 18; Egger's test p=0.12). Subgroup analyses showed no clear evidence that one subgroup had different efficacy to another, however there was some evidence that postnatal administration to mother during lactation is more effective than infant supplementation alone during the postnatal period (p=0.016) – high statistical heterogeneity remained in this subgroup analysis. Probiotics also reduced risk of atopic AD at age ≤4 years (Figure 19), with no statistical heterogeneity (I^2=0%) and no evidence of publication bias (Figure 20). Subgroup analyses did not identify any important subgroup differences (Table 11).

We found no evidence that probiotics reduce AD or atopic AD risk at age 5-14 years (Figures 21 and 22) with moderate and no statistical heterogeneity respectively, and no evidence for

important subgroup differences in analysis of all AD (Table 12) or publication bias (Figure 23).

A further five studies were not eligible for meta-analysis. Huurre (9) reported reduced AD, but this was not statistically significant (9.7% probiotic, 17.6% control; p=0.13). De Leon (6, 32) found no difference at age 6 months (45% probiotic, 56% control). Scalabrin reported no difference in AD by age 5, but did not present numerical data. In an analysis including data from Luoto, together with other probiotic intervention studies, Lundelin found no significant difference in food allergy between probiotic and placebo groups. In the study of Chien 3 participants in the synbiotic group, 9 in the prebiotic and 10 in the control group developed eczema by 3 months. The difference between synbiotic and other groups, adjusted for family history, was reported as statistically significant P<0.05.

Overall we found MODERATE level evidence (-1 inconsistency between age ≤4 and age 5-14 findings) that probiotics can prevent atopic AD and MODERATE level evidence (-1 inconsistency between studies i.e. high statistical heterogeneity) that probiotics can prevent *all* AD in children ≤ 4 years old. The majority of the evidence in these positive meta-analyses came from studies of high risk infants i.e. those with a positive family history of allergic disease. So although in subgroup analyses we found no evidence that outcomes differed according to disease risk, our view is that these conclusions should only be seen as relevant for infants at high risk of AD.

Figure 15 Risk of bias in intervention studies of probiotics and AD

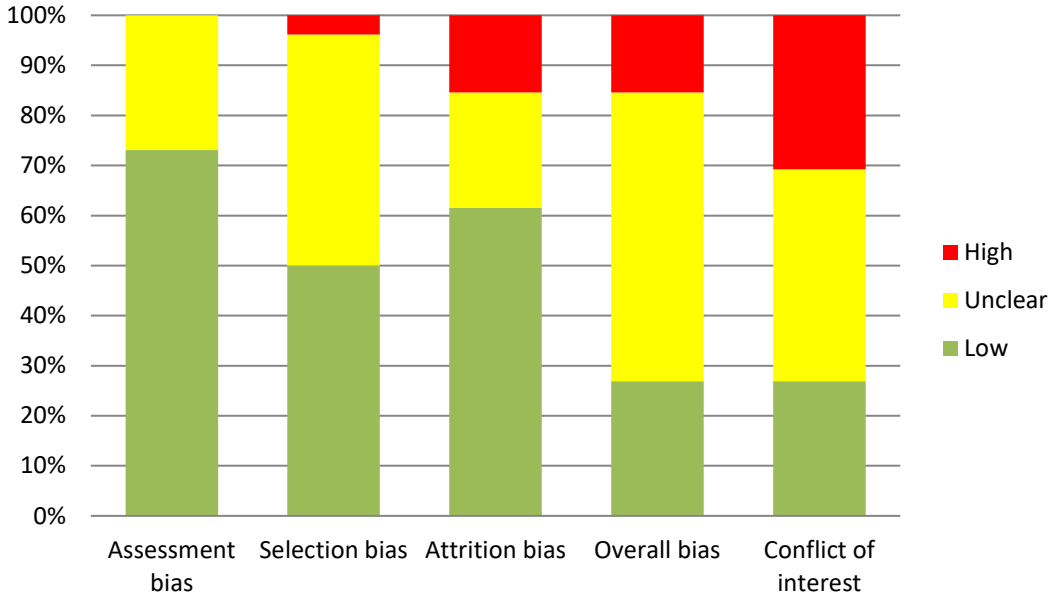


Table 10 Findings from the previous high quality systematic review found in 07/13 search

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)	I^2
Pelucci (28)*	AD	3092 (13)	**RR 0.79 [0.71, 0.88]**	24
	IgE-associated AD	2711 (10)	**RR 0.80 [0.66, 0.96]**	32
	AD (high risk infants)	(12)	**RR 0.80 [0.70, 0.91]**	24
	AD (normal/low risk infants)	(2)	RR 0.35 [0.06, 2.01]	49
	AD (Hanifin and Rajka criteria)	(6)	RR 0.80 [0.61, 1.06]	49
	AD (UK working party criteria)	(5)	**RR 0.78 [0.67, 0.90]**	0
	AD (parent reported)	(2)	RR 0.70 [0.47, 1.04]	26
	AD at < 2 years	(6)	**RR 0.78 [0.65, 0.93]**	40
	AD at ≥ 2 years	(7)	**RR 0.79 [0.65, 0.95]**	1

* The authors also undertook meta-regression to examine the effect of pre/postnatal/combined treatment, treatment of mother/child/both, duration of treatment,

treatment dose, single versus multiple probiotic treatment, location of trial and apparent conflict of interest and found no significant effect for any of these factors.

Figure 16 Probiotics and risk of AD at age ≤ 4 years - RCT

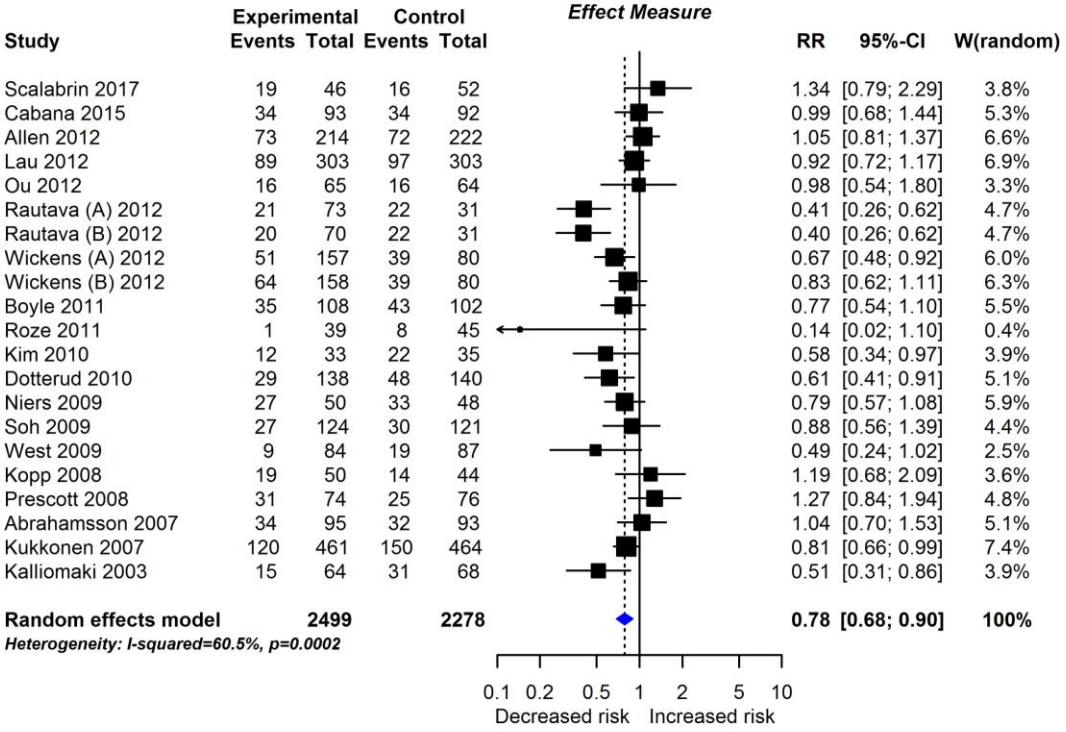


Figure 17 Probiotics and risk of AD at age ≤ 4 years - CCT

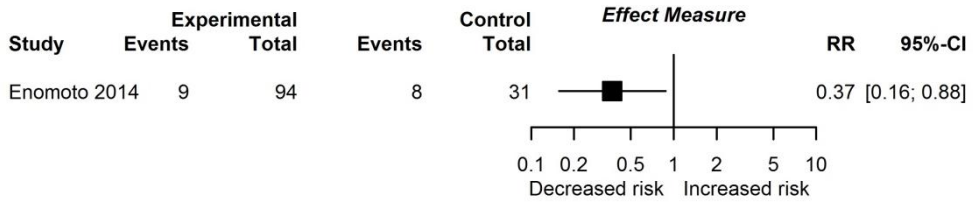
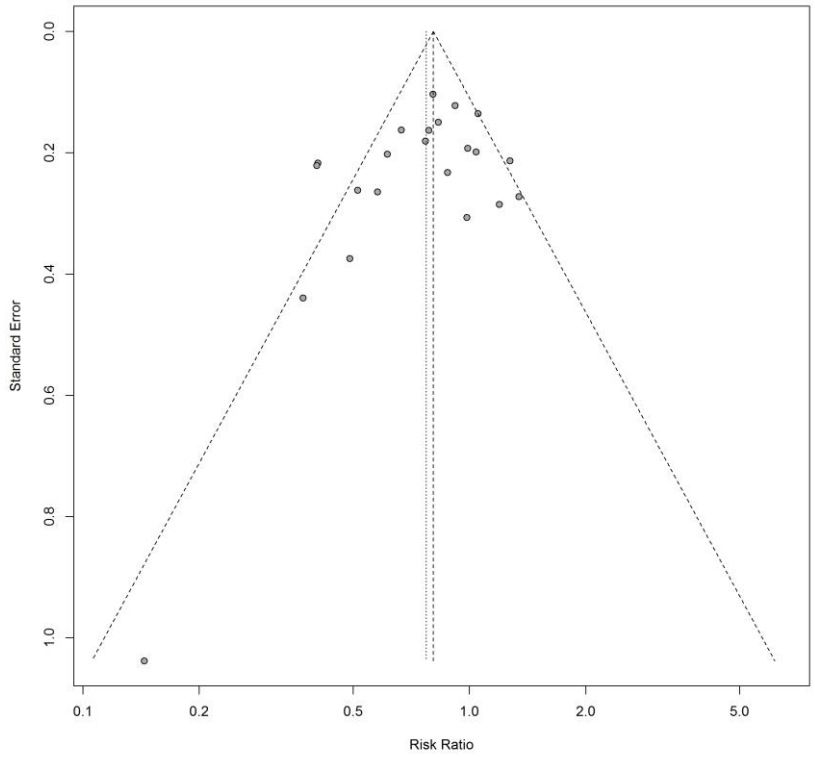


Table 10 Subgroup analyses of probiotics and risk of AD at age ≤ 4 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Type of Probiotic – L.rhamnosus	13	0.75 [0.62-0.89]	55	0.42
Type of Probiotic – Other	8	0.84 [0.68-1.03]	67	
Type of Intervention – Probiotic	19	0.79 [0.68; 0.91]	62	0.51
Type of Intervention – Synbiotic	2	0.46 [0.09; 2.27]	64	
Timing – Postnatal only	7	0.95 [0.76-1.20]	42	0.06
Timing – Pre +/-Post-natal	14	0.73 [0.62-0.86]	62	
*Postnatal Administration – Infant only	11	0.93 [0.81-1.06]	31	0.016
*Postnatal Administration – Other	9	0.64 [0.51-0.80]	59	
Risk of disease – High	17	0.80 [0.69-0.92]	61	0.58
Risk of disease – Normal	4	0.55 [0.38-0.80]	69	
Overall risk of bias – High/Unclear	12	0.88 [0.76-1.02]	43	0.06
Overall risk of bias – Low	9	0.67 [0.53-0.85]	69	
Conflict of interest – High/Unclear risk	14	0.86 [0.76-0.98]	37	0.10
Conflict of interest – Low risk	7	0.66 [0.49-0.88]	74	

*no postnatal administration in study of Boyle, 2011 – hence only 18 interventions included in this analysis

Figure 18 Risk of publication bias: probiotics and AD at age ≤4



Egger's test p = 0.12

Figure 19 Probiotics and risk of atopic AD at age ≤ 4 years

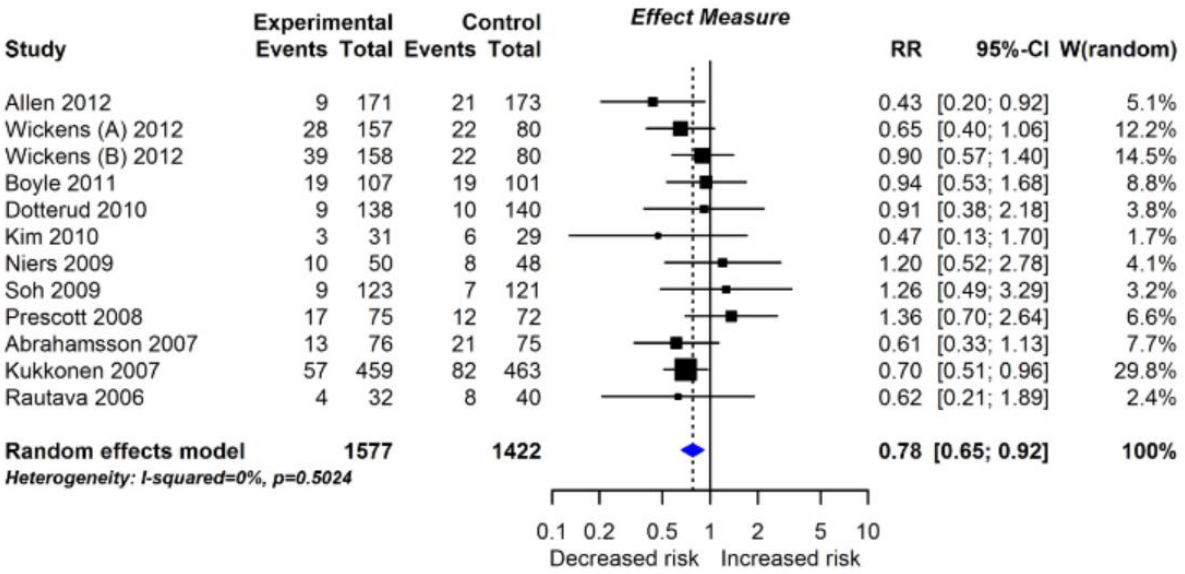
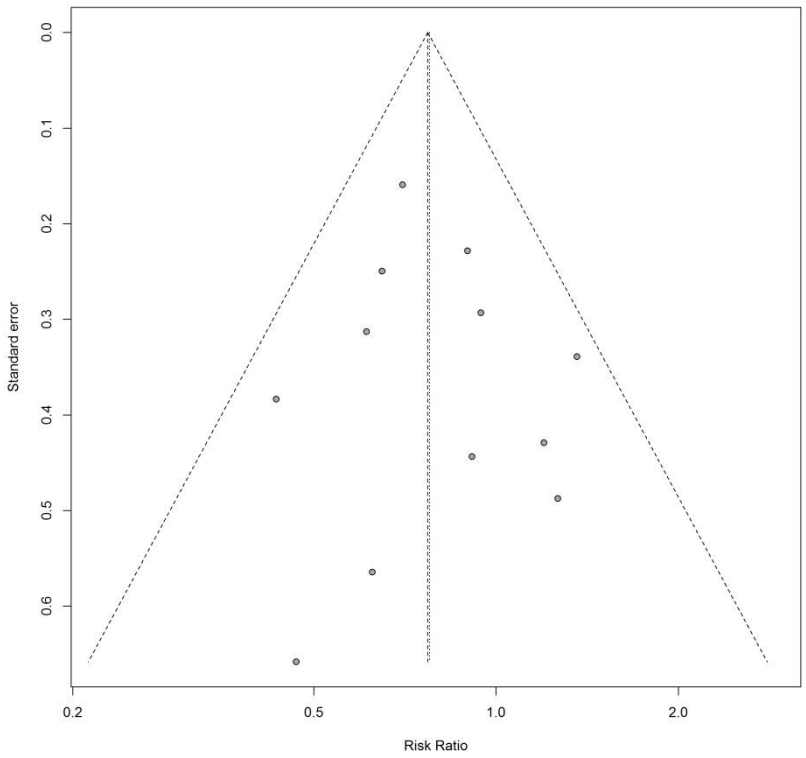


Figure 20 Risk of publication bias: probiotics and atopic AD at age ≤4



Egger's test p = 0.70

Table 11 Subgroup analyses of probiotics and risk of atopic AD at age ≤ 4 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Intervention – Probiotics	11	0.81 [0.66-0.99]	0	0.45
Intervention – Synbiotics	1	0.70 [0.51-0.96]	-	
Type of Probiotic – L.rhamnosus	6	0.75 [0.60-0.94]	0	0.38
Type of Probiotic – Other	6	0.80 [0.56-1.13]	34	
Timing – Postnatal only	3	1.15 [0.70-1.87]	0	0.10
Timing – Pre +/-Post-natal	9	0.73 [0.61-0.88]	0	
*Postnatal Administration – Infant only	7	0.78 [0.58-1.05]	27	0.93
*Postnatal Administration – Other	4	0.77 [0.57-1.04]	0	
Risk of disease – High	10	0.78 [0.64-0.95]	10	0.97
Risk of disease – Normal	2	0.79 [0.40-1.57]	0	
Overall risk of bias – Low	4	0.79 [0.60-1.05]	0	0.96
Overall risk of bias – High/Unclear	8	0.78 [0.60-1.01]	16	
Conflict of interest – High/Unclear risk	7	0.71 [0.57-0.90]	0	0.27
Conflict of interest – Low risk	5	0.87 [0.67-1.12]	0	

*no postnatal administration in the study of Boyle, 2011 – hence only 11 interventions included in this analysis

Figure 21 Probiotics and risk of AD at age 5-14 years

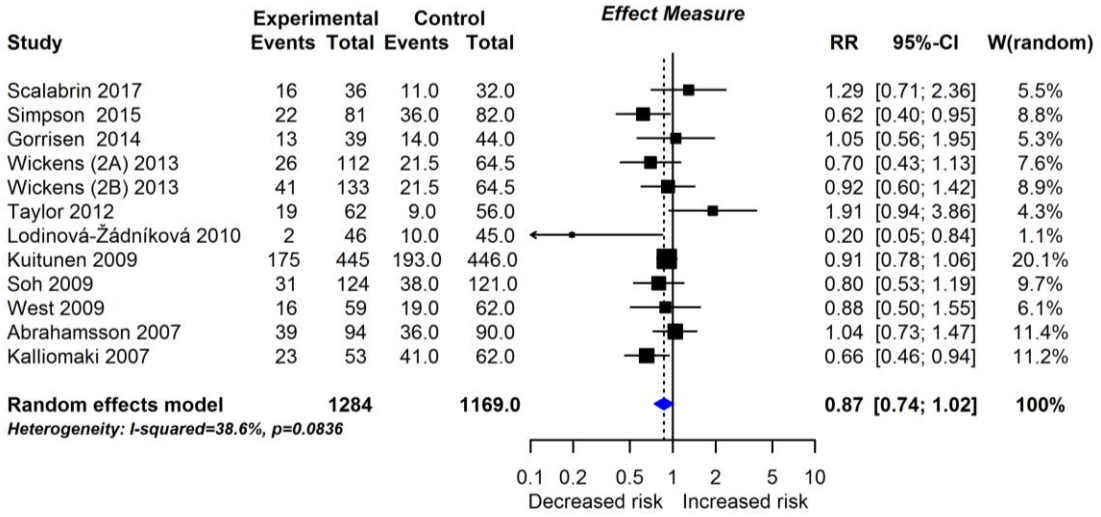


Figure 22 Probiotics and risk of atopic AD at age 5-14 years

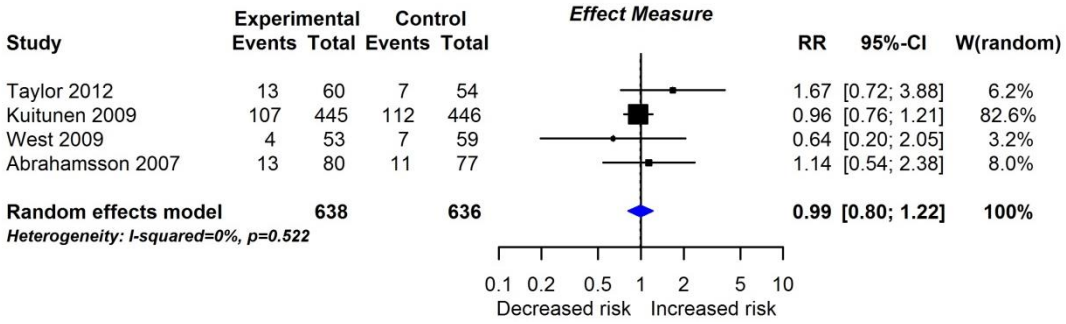
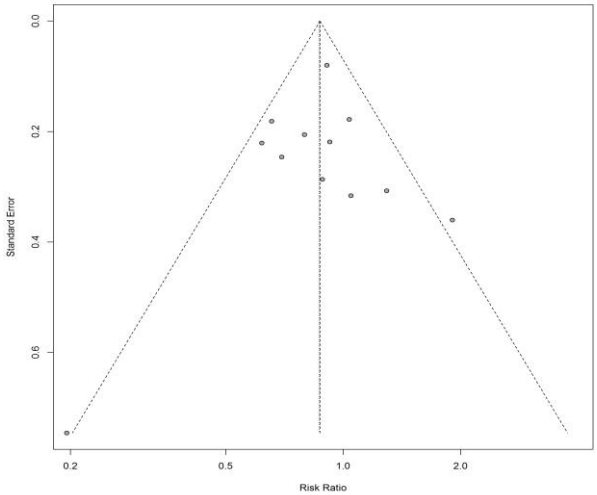


Figure 23 Risk of publication bias: probiotics and AD at age 5 to 14 years



Egger's test p = 0.73

Table 12 Subgroup analyses of probiotics and risk of AD at age 5-14 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Type of Probiotic – L.rhamnosus	7	0.82 [0.70-0.95]	19	0.28
Type of Probiotic – Other	5	1.02 [0.70-1.47]	51	
Type of Intervention – Probiotic	11	0.86 [0.70; 1.05]	43	0.67
Type of Intervention – Synbiotic	1	0.91 [0.78; 1.06]	-	
Timing – Postnatal only	5	0.96 [0.61-1.52]	60	0.58
Timing – Pre +/-Post-natal	7	0.84 [0.73-0.97]	18	
Postnatal Administration – Infant only	7	0.97 [0.77-1.21]	43	0.08
Postnatal Administration – Other	5	0.74 [0.61-0.90]	0	
Risk of disease – High	10	0.87 [0.74-1.03]	35	0.98
Risk of disease – Normal	2	0.87 [0.42-1.78]	74	
Overall risk of bias – High/Unclear	10	0.88 [0.73-1.06]	47	0.69
Overall risk of bias – Low	2	0.82 [0.59-1.12]	0	
Conflict of interest – High/Unclear risk	8	0.84 [0.69-1.01]	43	0.51
Conflict of interest – Low risk	4	0.96 [0.67-1.37]	45	

5. Probiotics and risk of allergic rhinitis or conjunctivitis

Fourteen intervention trials (13 RCT; 1 CCT – in total 15 interventions; 4450 participants) reported allergic rhinitis (AR) or allergic rhinoconjunctivitis (ARC) – here analysed together as 'allergic rhinitis'. No studies reported allergic conjunctivitis as an outcome. Eight studies were carried out in Europe, one in USA and five Asia-Pacific. Five studies were carried out in infants with normal risk of allergic disease, whilst the other nine were in children at high risk. Age at outcome assessment varied between 1 and 9 years. Two studies defined allergic rhinitis according to specific symptoms, 4 were based on previous Dr-diagnosis or physician assessment during the trial, 2 studies combined symptoms and having 1 or more positive SPTs, and four studies based the diagnosis on ISAAC questionnaires; two studies didn't report the method of outcome assessment. Risk of bias was similar to other analyses, with a low overall risk of bias in <10%, unclear in the majority, and high in over 35%. (Figure 24).

There was no evidence that probiotics reduce risk of AR at age ≤4 (Figure 25) with low statistical heterogeneity. There was also no evidence for an effect at age 5-14 (Figure 26) with no statistical heterogeneity, and no evidence of publication bias (Figure 27). Subgroup analyses did not identify a subgroup with different outcomes (Tables 13 and 14).

Enomoto (8) reported no cases of ARC in either active (n=94) or control (n=31) group at 18 months age. In an analysis including data from Luoto, together with other probiotic intervention studies, Lundelin found no significant difference in allergic rhinitis between probiotic and placebo groups.

Overall we found no evidence that probiotics influence risk of allergic rhinitis, and data were lacking for allergic conjunctivitis.

Figure 24 Risk of bias in intervention studies of probiotics and allergic rhinitis

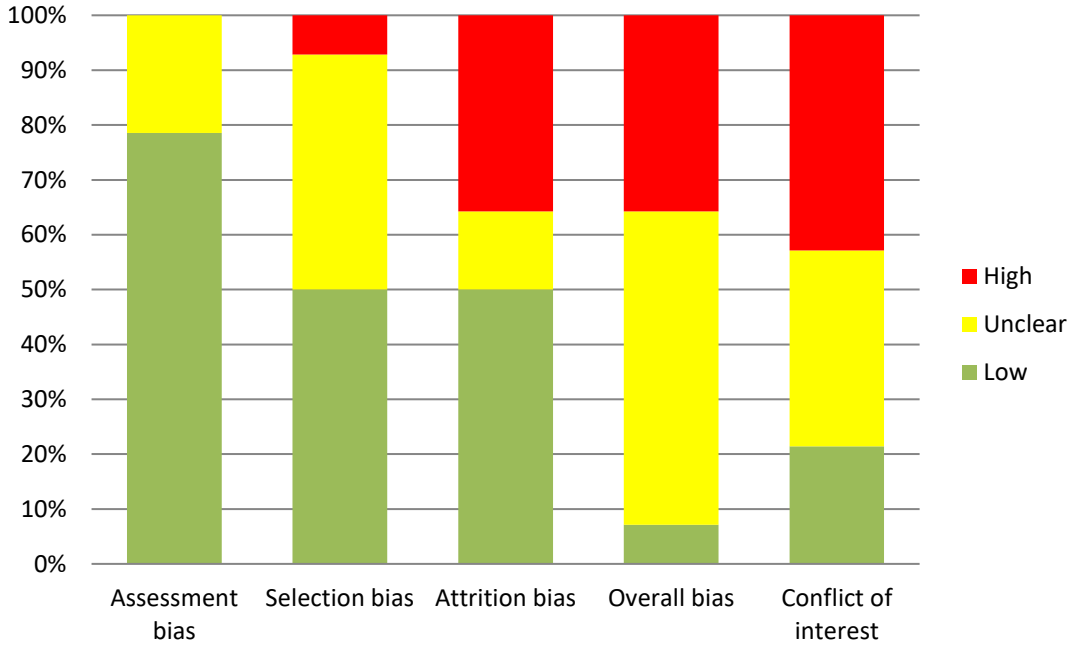


Figure 25 Probiotics and risk of allergic rhinitis at ≤ 4 years

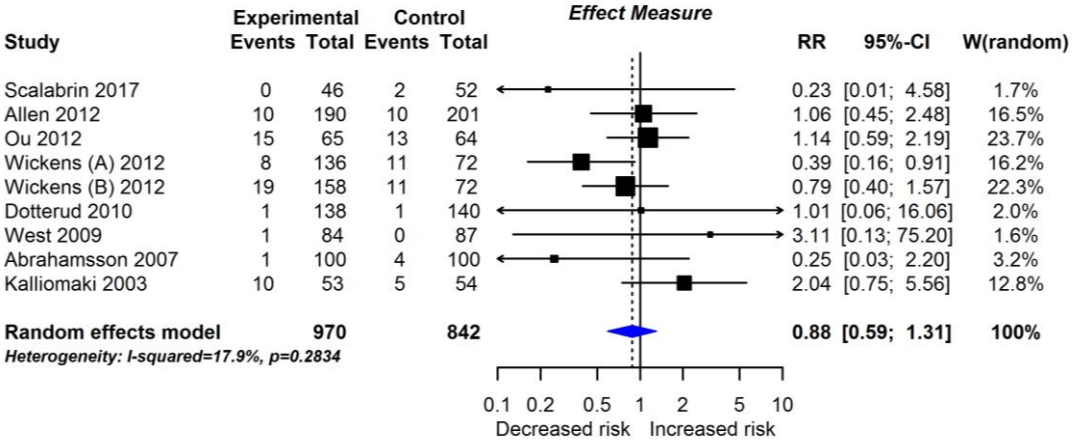


Figure 26 Probiotics and risk of allergic rhinitis at age 5-14 years

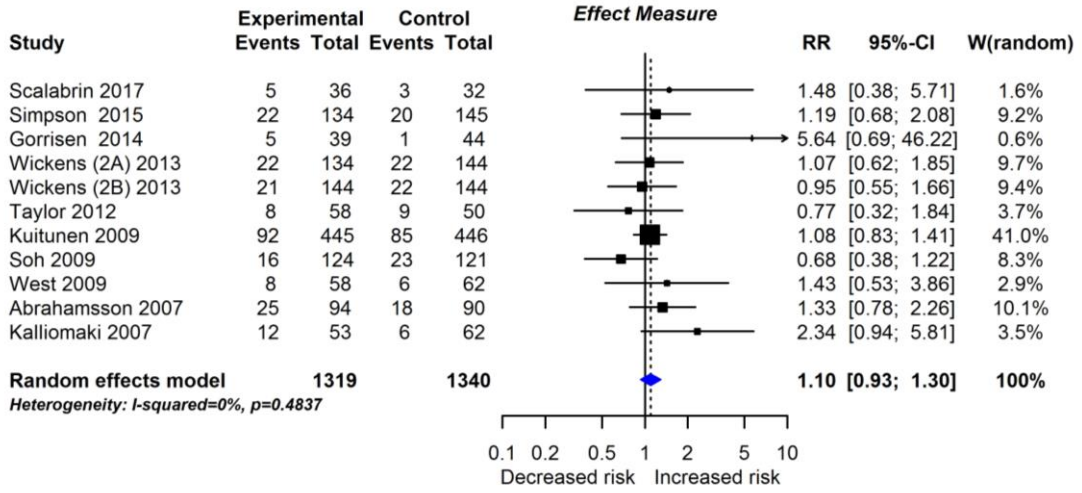
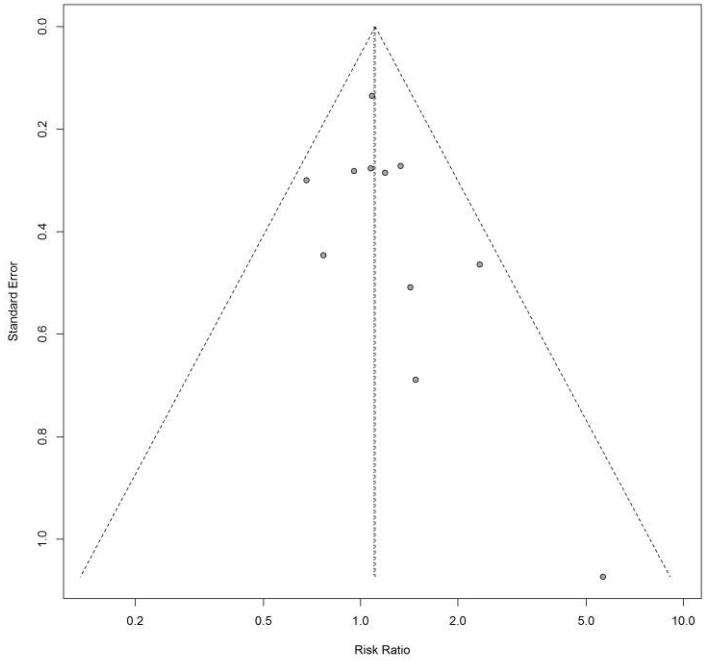


Figure 27 Risk of publication bias: probiotics and AR at age 5 to 14 years



Egger's test p = 0.22

Table 13 Subgroup analyses of probiotics and risk of allergic rhinitis at age ≤ 4 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Type of Intervention – Probiotic	9	0.81[0.59; 1.31]	18	--
Type of Intervention – Synbiotic	0	--		
Type of Probiotic – L.rhamnosus	6	0.86 [0.30-2.42]	47	0.94
Type of Probiotic – Other	3	0.82 [0.49-1.38]	0	
Timing – Postnatal only	2	0.79 [0.06-10.38]	27	0.99
Timing – Pre +/-Post-natal	6	0.80 [0.44-1.45]	47	
Postnatal Administration – Infant only	4	0.86 [0.41-1.82]	0	0.94
Postnatal Administration – Other	5	0.83 [0.39-1.74]	51	
Risk of disease – High	6	0.87 [0.55-1.40]	40	0.99
Risk of disease – Normal	3	0.86 [0.16-4.79]	0	
Overall risk of bias – Low	2	0.58 [0.29-1.16]	38	0.10
Overall risk of bias – High/Unclear	7	1.15 [0.74-1.78]	0	
Conflict of interest – High/Unclear risk	6	1.13 [0.73-1.76]	0	0.15
Conflict of interest – Low risk	3	0.62 [0.32-1.21]	23	

Table 14 Subgroup analyses of probiotics and risk of allergic rhinitis at age 5-14 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Type of Intervention – Probiotic	10	1.11 [0.89; 1.40]	12	0.88
Type of Intervention – Synbiotic	1	1.08 [0.83; 1.41]	--	
Type of Probiotic – L.rhamnosus	7	1.10 [0.90; 1.33]	0	0.94
Type of Probiotic – Other	4	1.12 [0.74; 1.68]	20	
Timing – Postnatal only	4	0.86 [0.56; 1.30]	0	0.19
Timing – Pre +/-Post-natal	7	1.16 [0.96; 1.39]	0	
Postnatal Administration – Infant only	6	1.06 [0.86; 1.30]	0	0.45
Postnatal Administration – Other	5	1.23 [0.87; 1.74]	20	
Risk of disease – High	8	1.08 [0.86; 1.36]	22	0.54
Risk of disease – Normal	3	1.27 [0.80; 2.00]	0	
Overall risk of bias – Low	2	1.01 [0.69; 1.49]	0	0.62
Overall risk of bias – High/Unclear	9	1.14 [0.91; 1.42]	13	
Conflict of interest – High/Unclear risk	7	1.17 [0.89; 1.54]	27	0.50
Conflict of interest – Low risk	4	1.01 [0.72; 1.41]	0	

6. Probiotics and risk of wheeze

One systematic review was identified in our July 2013 search. The study of Tang (29) included 5 trials and over 1500 participants, and concluded that probiotics do not reduce risk of wheezing prior to age 5 years (Table 15).

In our own systematic review we identified 18 intervention studies (17 RCT; 1 CCT; in total 19 interventions; 4950 participants) investigating the effect of probiotic supplementation on risk of wheeze. Five studies were from Asia-Pacific countries, two from USA, eleven from Europe. Age at time of outcome assessment ranged between 1 and 9 years old. In four studies the definition used for asthma was prior doctor diagnosis or study physician assessment, in 7 asthma was defined according to whether the child had had from 1 to 3 episodes of wheeze, accompanied sometimes by other symptoms; three studies used the ISAAC definition of wheeze, and in four studies the definition was unclear. Overall risk of bias was low in just over 20%, and unclear in over half of studies. Over one third of studies were considered to be at high risk of conflict of interest due to direct industry involvement in the trial (Figure 28).

We found no evidence that probiotics reduce risk of wheeze or recurrent wheeze at age ≤4 years (Figure 29 – RCT; Figure 31 – CCT; Figure 32– recurrent wheeze) or at 5-14 years (Figures 33 and 35), with low/moderate and no statistical heterogeneity respectively, and no evidence of publication bias for the analysis of wheeze at age ≤4 years or age 5-14 years (Figures 30 and 34).

Subgroup analyses (Table 16-19) demonstrated that the single synbiotic trial showed a positive effect, whereas the trials of probiotics without prebiotic showed no effect on wheeze at age ≤4 (test for subgroup difference p=0.02). The synbiotic trial also differed from other trials in the inclusion criteria of eczema and SCORAD >15 at enrolment. No other consistent subgroup differences were identified.

In an analysis including data from Luoto, together with other probiotic intervention studies, Lundelin found no significant difference in asthma between probiotic and placebo groups - OR 0.55 (0.24, 1.25) P=0.15.

Four studies reported measures of lung function. Abrahamsson reported no difference in forced expiratory volume in 1 second (FEV1) as % predicted at age 7 (Figure 36), and meta-analysis of 3 studies showed no difference in FEV1 reversibility after administration of bronchodilator (Figure 37). Abrahamsson and Wickens both reported FEV1 as % of forced vital capacity (FVC) – in Abrahamsson the median FEV1 as % of FVC was 87 (IQR 83.5, 95) in the intervention group, 88.5 (84.4, 96) in the control group. In the study of Wickens neither probiotic group showed a significant difference in FEV1 as % of FVC – mean difference compared with control group was -1.5% (95% CI -3.7, 0.8) for L. rhamnosus HN001, and -1.2 (-3.4, 0.9) for B. animalis HN019. Gorissen reported 'all spirometry measures were essentially equal in both groups', without presenting specific data.

Overall we found no evidence that probiotics influence risk of wheeze, recurrent wheeze or lung function.

Figure 28 Risk of bias in intervention studies of probiotics and wheeze

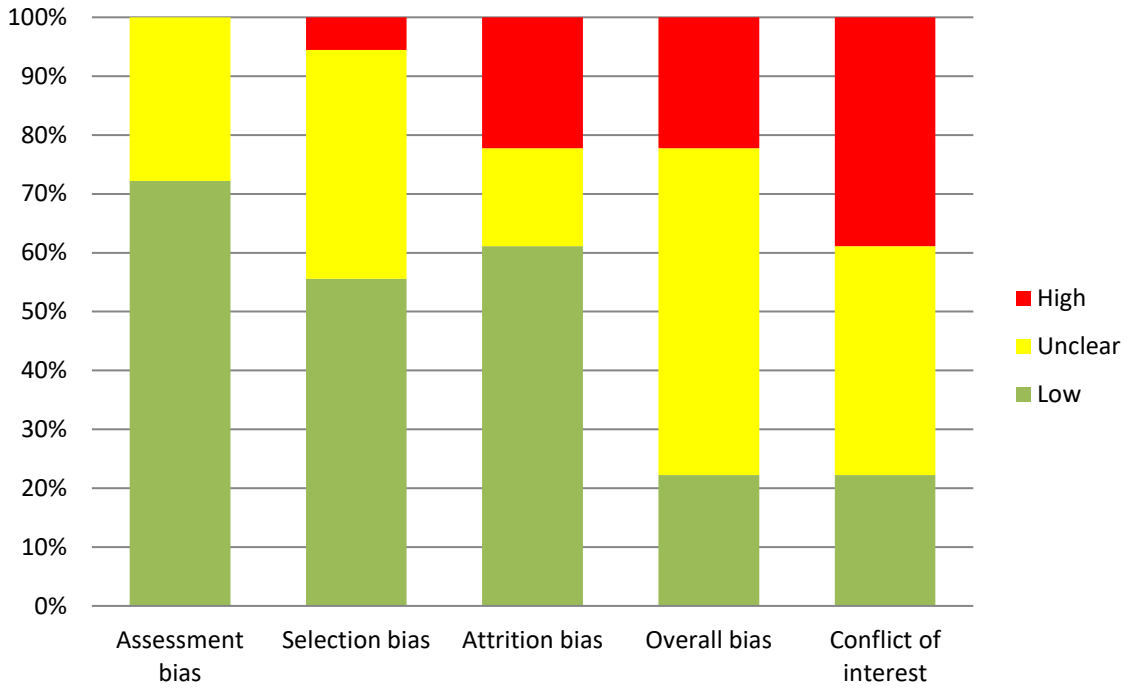


Table 15 Findings from the previous high quality systematic review found in 7/13 search

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)	I^2
Tang (29)	Wheeze (under 5 years)	1536 (5)	**RR 0.93 [0.71, 1.21]**	0

Figure 29 Probiotics and risk of any wheeze at age ≤ 4 years – RCT

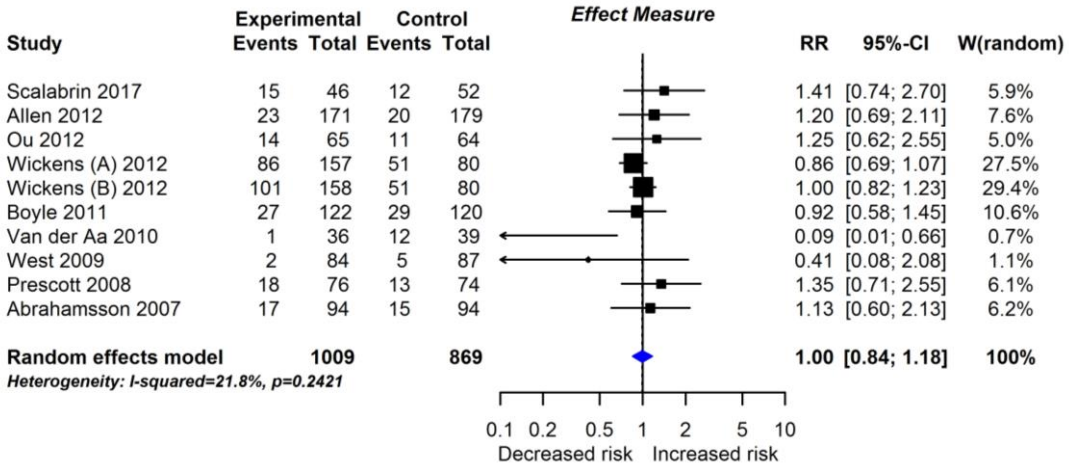
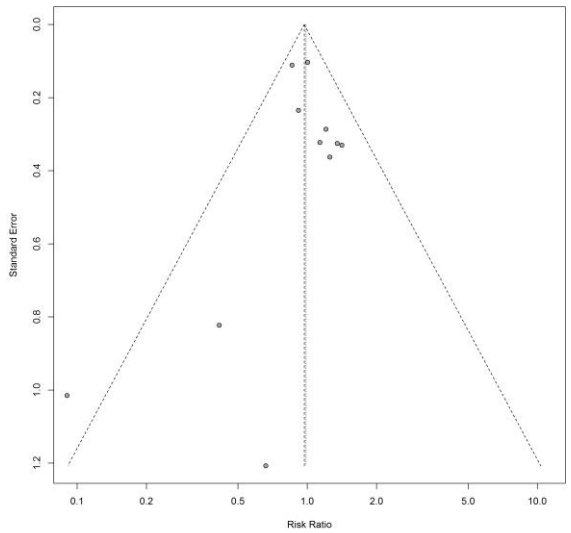


Figure 30 Risk of publication bias: probiotics and wheeze at age ≤ 4 years



Egger's test p = 0.73

Figure 31 Probiotics and risk of any wheeze at age ≤ 4 years - CCT

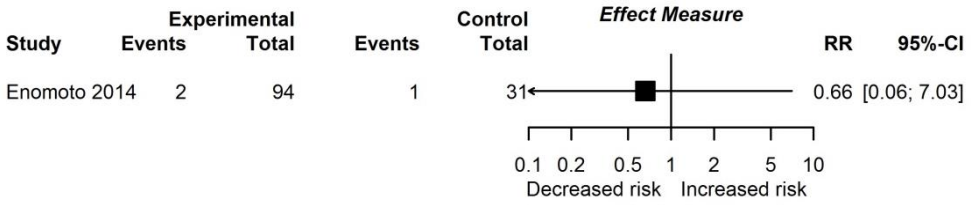


Figure 32 Probiotics and risk of recurrent wheeze at age ≤ 4 years

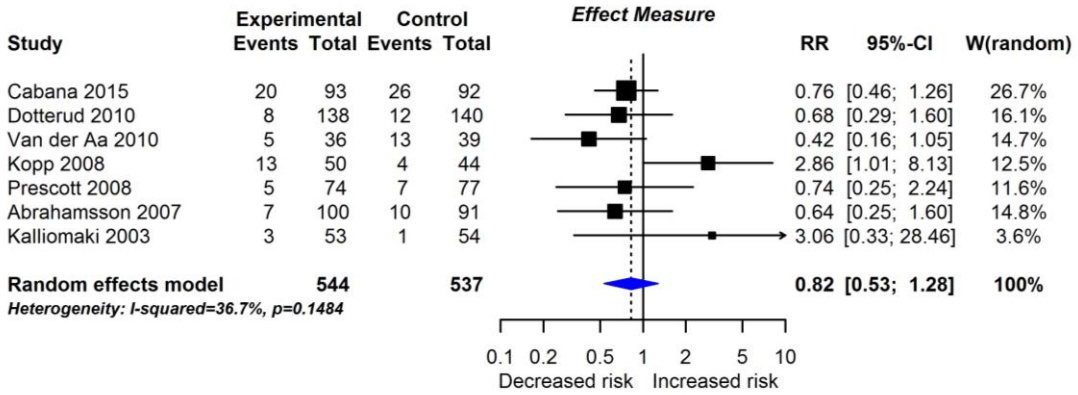


Table 16 Subgroup analyses of probiotics and risk of wheeze at age ≤ 4 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Intervention – Probiotics	9	0.98 [0.87; 1.12]	0	0.02
Intervention – Synbiotics	1	0.09 [0.01; 0.66]	-	
Type of Probiotic – L.rhamnosus	5	0.92 [0.76; 1.10]	0	0.47
Type of Probiotic – Other	5	1.05 [0.76; 1.46]	43	
Timing – Postnatal only	4	0.77 [0.31; 1.89]	68	0.62
Timing – Pre +/-Post-natal	6	0.96 [0.84; 1.10]	0	
*Postnatal Administration – Infant only	6	1.06 [0.68; 1.63]	45	0.88
*Postnatal Administration – Other	3	0.95 [0.82; 1.09]	0	
Risk of disease – High	8	0.98 [0.83; 1.17]	24	0.97
Risk of disease – Normal	2	0.96 [0.31; 2.98]	49	
Overall risk of bias – High/Unclear	6	1.22 [0.92; 1.61]	0	0.11
Overall risk of bias – Low	4	0.89 [0.69; 1.16]	56	
Conflict of interest – High/Unclear risk	5	1.11 [0.71; 1.72]	45	0.50
Conflict of interest – Low risk	5	0.94 [0.82; 1.08]	0	

*no postnatal administration in the study of Boyle, 2011 – hence only 7 interventions included in this analysis

Table 17 Subgroup analyses of probiotics and risk of recurrent wheeze at age ≤ 4 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Intervention – Probiotics	6	0.92 [0.58-1.46]	32	0.13
Intervention – Synbiotics	1	0.42 [0.17-1.05]	-	
Type of Probiotic – L.rhamnosus	4	1.14 [0.56-2.33]	56	0.13
Type of Probiotic – Other	3	0.57 [0.32-1.00]	0	
Timing – Postnatal only	3	0.67 [0.45-1.02]	0	0.25
Timing – Pre +/-Post-natal	4	1.16 [0.51-2.65]	54	
Postnatal Administration – Infant only	4	0.67 [0.46-0.97]	0	0.16
Postnatal Administration – Other	3	1.55 [0.50-4.76]	60	
Risk of disease – High	6	0.87 [0.51-1.49]	46	0.63
Risk of disease – Normal	1	0.68 [0.29-1.60]	0	
Overall risk of bias – Low	2	1.07 [0.16-7.13]	86	0.71
Overall risk of bias – High/Unclear	5	0.75 [0.52-1.08]	0	
Conflict of interest – High/Unclear	6	0.85 [0.51-1.42]	47	0.83
Conflict of interest – Low	1	0.74 [0.25-2.24]	-	

Figure 33 Probiotics and risk of any wheeze at age 5-14 years

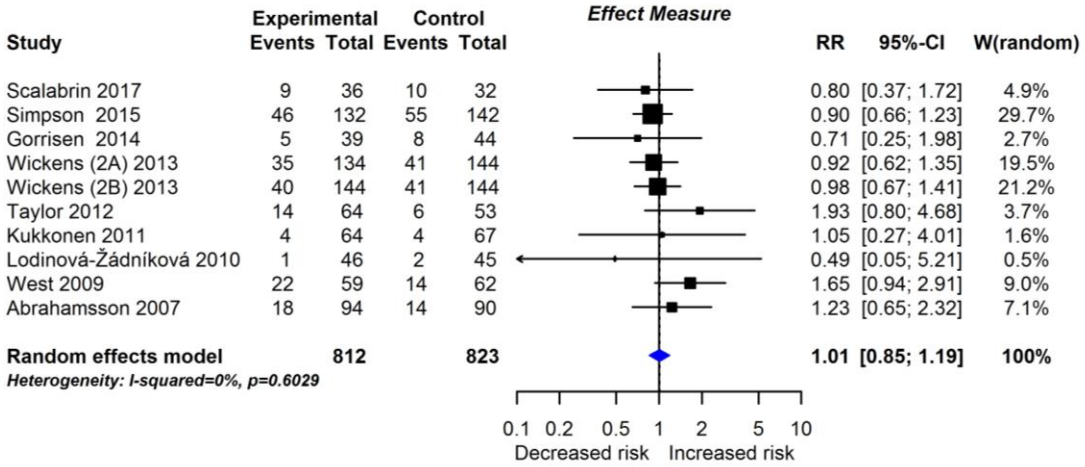
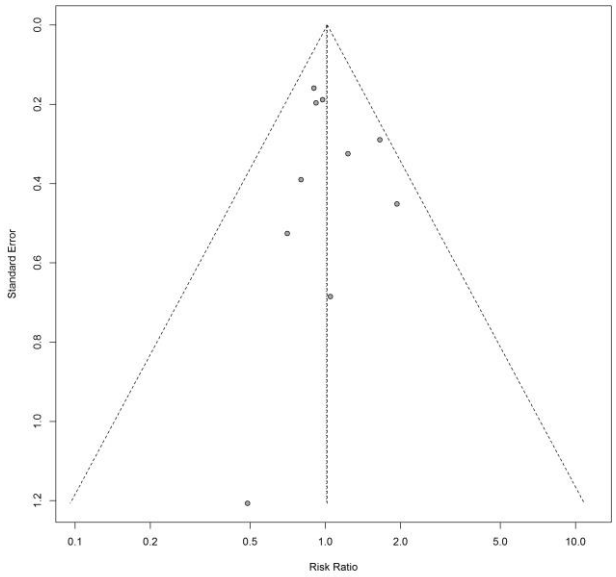


Figure 34 Risk of publication bias: probiotics and wheeze at age 5-14 years



Egger's test p = 0.68

Figure 35 Probiotics and risk of recurrent wheeze at age 5-14 years

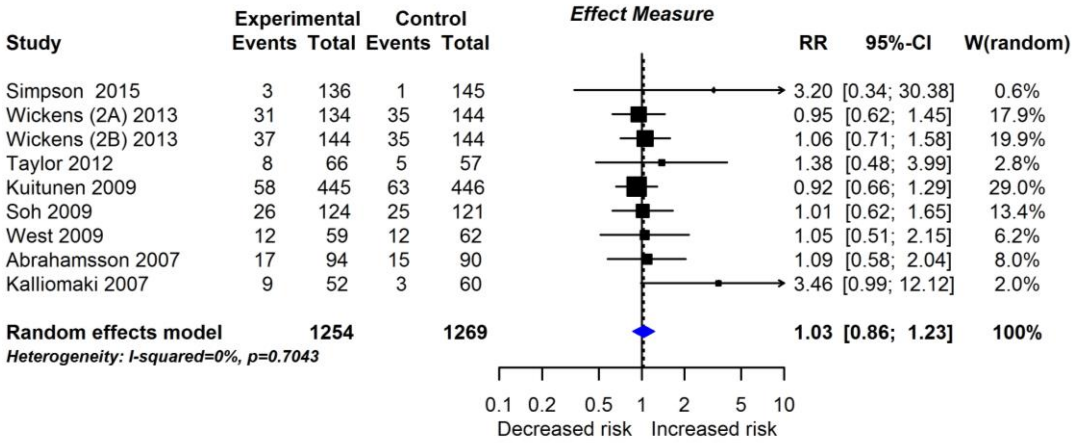


Table 18 Subgroup analyses of probiotics and risk of wheeze at age 5-14 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Intervention – Probiotics	9	1.01 [0.85-1.19]	0	0.95
Intervention – Synbiotics	1	1.05 [0.27-4.01]	-	
Type of Probiotic – L.rhamnosus	5	0.97 [0.79-1.21]	0	0.66
Type of Probiotic – Other	5	1.06 [0.80-1.41]	0	

Timing – Postnatal only	4	1.33 [0.84-2.11]	17	0.18
Timing – Pre +/-Post-natal	6	0.94 [0.78-1.14]	0	
Postnatal Administration – Infant only	6	1.30 [0.94-1.80]	0	0.08
Postnatal Administration – Other	4	0.92 [0.75-1.12]	0	
Risk of disease – High	8	1.08 [0.87-1.33]	0	0.28
Risk of disease – Normal	2	0.88 [0.66-1.18]	0	
Overall risk of bias – Low	2	0.95 [0.73-1.24]	0	0.56
Overall risk of bias – High/Unclear	8	1.05 [0.84-1.31]	0	
Conflict of interest – High/Unclear	6	0.92 [0.72-1.18]	0	0.29
Conflict of interest – Low	4	1.15 [0.84-1.57]	38	

Table 19 Subgroup analyses of probiotics and risk of recurrent wheeze at age 5-14 years

Subgroups compared	Number of studies	RR [95% CI]	I^2 (%)	P for between groups difference
Intervention – Probiotics	8	1.08 [0.87-1.34]	0	0.43
Intervention – Synbiotics	1	0.92 [0.66-1.29]	-	
Type of Probiotic – L.rhamnosus	6	1.01 [0.81-1.26]	2	0.70
Type of Probiotic – Other	3	1.09 [0.79-1.51]	0	
Timing – Postnatal only	3	1.07 [0.73-1.55]	0	0.87
Timing – Pre +/-Post-natal	6	1.03 [0.83-1.27]	4	
Postnatal Administration – Infant only	5	1.00 [0.79-1.26]	0	0.50
Postnatal Administration – Other	4	1.18 [0.78-1.78]	35	
Risk of disease – High	8	1.03 [0.86-1.23]	0	0.32
Risk of disease – Normal	1	3.20 [0.34-30.38]	-	
Overall risk of bias – Low	2	1.00 [0.75-1.35]	0	0.82
Overall risk of bias – High/Unclear	7	1.05 [0.84-1.32]	0	
Conflict of interest – High/Unclear	5	1.08 [0.79-1.47]	21	0.83
Conflict of interest – Low	4	1.03 [0.79-1.34]	0	

Figure 36 Probiotics and lung function at age 5-14 (FEV1<80% predicted)

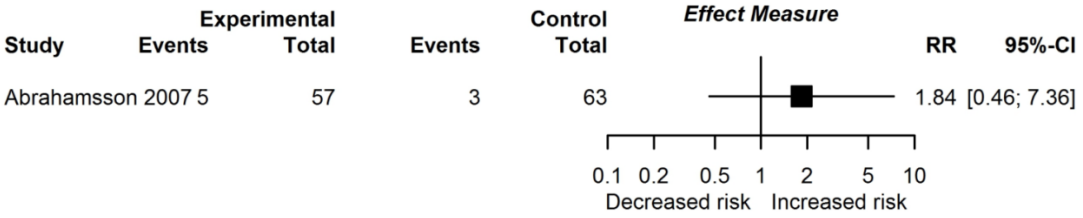
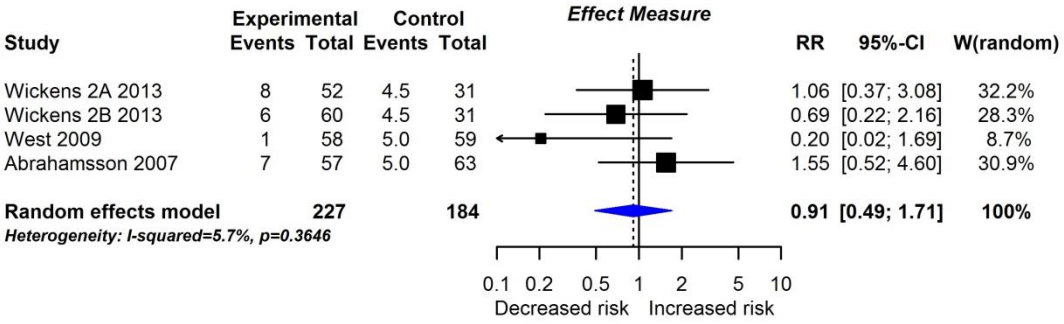


Figure 37 Probiotics and lung function at age 5-14 (FEV1 reversibility >12%)



Conclusions

In this systematic review of probiotic supplementation during pregnancy/lactation/infancy, (either as a probiotic alone or as part of a symbiotic) and risk of allergic outcomes, we found evidence that probiotics reduce the risk of AD or atopic AD, and allergic sensitisation to cow's milk. The positive findings for AD/atopic AD were not supported in analyses of longer term follow up data from a smaller number of trials at age 5-14. The positive finding for allergic sensitisation to cow's milk was not supported by data for allergic sensitisation to other allergens, nor by data for clinical cow's milk allergy. For the outcomes allergic rhinitis, food allergy and wheeze, there was no evidence that probiotics impact on disease risk. For allergic conjunctivitis and autoimmune disease, data were lacking.

In the analysis of AD, there was high statistical heterogeneity. Subgroup analysis identified that postnatal supplementation of mother during lactation may be important for a beneficial effect, and the data were predominantly from studies of infants at high risk of AD due to family history of allergic disease. In the analysis of atopic AD, there was no statistical heterogeneity. In the analysis of allergic sensitisation to cow's milk there was no statistical heterogeneity, but the number of events was low, and this led to high imprecision and borderline statistical significance.

In the systematic review of Pelucchi (28), which we included in our overview of systematic reviews in 2013, the authors also found reduced AD risk in children supplemented with probiotics (RR 0.79; 95%CI 0.71 – 0.88), with less statistical heterogeneity than we found (I^2=24%). For atopic AD they found RR 0.80 (95% CI 0.66 – 0.96), this time with more statistical heterogeneity than we found (I^2=31.5%). Also included in our overview Tang found no effect of probiotic supplementation on risk of allergic sensitisation to food in children (RR 0.95; 95% CI 0.80 – 1.12).

Our updated search on 26th February 2017 identified several new systematic reviews of probiotics or synbiotics for prevention of allergic outcomes. R-AMSTAR scoring identified 3 high quality reviews (Dick; Elazab; Azad) and a recent international guideline and systematic review (Fiocchi), which together found the following:

i. Fiocchi 2015 (55) in a World Allergy Organization systematic review and position paper have recommended the use of probiotics for preventing AD in high risk pregnancies/infants – for pregnant and lactating women, and directly to their infant. This is based on very low grade evidence.

ii. The review of Dick 2014 (56) covered a wide range of dietary influences on the development of childhood asthma. They cited the negative finding of Kukkonen 2011, but did not identify the other studies included in our systematic review.

iii. Elazab 2013 (57) found no evidence that probiotics prevent wheeze, but did find evidence for a protective effect on specific allergic sensitisation with borderline statistical significance. They also found evidence for reduced total IgE, but not in the context of primary prevention. The finding for specific sensitisation was statistically significant for studies which included a prenatal component to the intervention.. We did not find clear evidence for a subgroup difference in allergic sensitisation according to timing of probiotic intervention. Taken together our findings and the findings of Elazab suggest that a small effect (<20% risk reduction) of probiotics on risk of allergic sensitisation cannot be confidently excluded at this stage, and further research is warranted if a small reduction in incidence of allergic sensitisation is considered an important intervention goal.

iv. Azad and colleagues published a systematic review on probiotic supplementation and risk of wheeze, asthma or lower tract respiratory infections subsequent to our overview of systematic reviews and found no evidence of a protective effect of probiotics on this outcome (risk ratio 0.97; 95% CI 0.87 – 1.09; I^2=0%), nor on doctor diagnosed asthma (risk ratio 0.99; 95% CI 0.81 – 1.21; I^2=0%) (58). Azad 2013 found no evidence that probiotics prevent asthma (RR 0.99 95% CI 0.81, 1.21 I^2=0) or wheeze.

Two further systematic reviews had R-AMSTAR scores below 30, but were nevertheless reasonably comprehensive, and came to similar conclusions to ours. A systematic review by Mansfield identified 27 publications corresponding to 16 trials, and reported a protective effect of probiotic exposure for AD (RR 0.74; CI 0.67 – 0.82) (59). Dang 2013 (60) identified 18 trials of prebiotics, probiotics or synbiotics for preventing AD. We identified 31 trials (29 with AD as an outcome measure). Dang reported similar conclusions to us – probiotics/synbiotics reduce AD at age <2. They did not review later outcomes, and found no effect on allergic sensitisation.

Overall, our systematic review on probiotics and allergic outcomes provides evidence of a protective effect of these supplements against AD and atopic AD in high risk children ≤ 4 years old, but not beyond this age. Our data are consistent with other recent systematic reviews which did not include all the studies identified in our review.

Conclusion:

Probiotics/synbiotics reduce risk of AD in the first 4 years: grade of evidence MODERATE (-1 inconsistency i.e. statistical heterogeneity)

Probiotics/synbiotics reduce risk of atopic (IgE-associated) AD in the first 4 years: grade of evidence MODERATE (-1 inconsistency with age 5-14 outcome).

Probiotics may reduce risk of allergic sensitisation to cow's milk: grade of evidence LOW (-1 indirectness; -1 imprecision).

Further research is required in order to confirm whether probiotics reduce risk of allergic sensitisation.

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