



Probiotics and prebiotics in preventing food allergy and eczema

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Purpose of review

To describe the current literature on clinical trials of probiotics for eczema and food allergy prevention in view of recent new approaches and long-term follow-ups.

Recent findings

Attempting allergy prevention by probiotic administration has been most successful when assessing atopic eczema, the most prevalent allergic disease at an early age. More than half of the published studies demonstrate a decrease in eczema prevalence until 2 years, whereas the remaining studies fail to show an effect. Effects have been most consistent with combined prenatal and direct postnatal supplementation of the infant and appear strain-specific, with *Lactobacillus rhamnosus* most often showing an effect. Prenatal-only and postnatal-only studies often fail to show effects. Recent long-time follow-ups have shown promising but not consistent results. A very recent follow-up of a large well conducted cohort shows that long-term effects of eczema prevention persists until age 4 and prevention of respiratory allergies might also be possible.

Summary

Prevention of eczema with probiotics seem to work until age 2 years and extended effects until 4 years have been shown in high-risk for allergy cohorts. Effects are strain-specific, with *L. rhamnosus* showing the most consistent effects especially when combining pre and postnatal administration.

Keywords

allergy prevention, eczema, food allergy, *Lactobacillus rhamnosus*, probiotic

INTRODUCTION

The increase in allergic diseases has been linked to the relative lack of microbial stimulation [1], especially in early childhood when the permeability of the gut is higher [2] and the gut immune system is not fully developed [3]. A recent understanding is the coevolution of the human species and the metagenome [4]. The diversity of the microbiome and its contribution to the development of allergic and autoimmune diseases has gained much attention [5]. The body's largest immune system residing in the gut is complexly stimulated by the gut microbiome, which is considered central when evaluating the hygiene hypothesis, now rephrased as the microflora hypothesis of allergic diseases [6,7]. New molecular techniques enable broader analysis of microbiota and the microbiome.

Development of oral tolerance requires contacts with microbes [8]. A low diversity of gut microbiota during the first months has been associated with development of atopic eczema [9,10]. Mice reared in germ-free environments do not develop tolerance,

but this can be reconstituted with the administration of bifidobacteria [11]. Further, less lactobacilli and bifidobacteria have been shown in the gastrointestinal tract of infants developing allergy later [12,13]. This led to the probiotic concept.

Supplementing microbes using probiotics, health-promoting nonpathogenic bacteria in an attempt to prevent allergies is a well tolerated alternative [14–16]. Twenty-three randomized, placebo-controlled intervention studies regarding the clinical effect of probiotic supplementation on development of allergy and eczema in particular have been published. Eczema is the most prevalent allergic disease in early childhood and fairly easy to diagnose reliably using well defined validated

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KEY POINTS

- The majority of probiotic allergy prevention studies show a decrease in eczema frequency until age 2 years.
- The most consistent effect is from combined pre and infant postnatal supplementation.
- The effect is strain-specific, with *Lactobacillus rhamnosus* showing the most consistent effect.
- A recent long-term follow-up until 4 years shows encouraging allergy preventive effects.

criteria and a reliable marker of allergic disease being a significant risk factor for developing respiratory allergies later [17]. Many studies also report on the prevention of food allergy, but its prevalence is significantly less than that of eczema. Around 60% of the studies show a favourable effect decreasing the risk of eczema during the first years of life. The remaining studies fail to show an effect. Most investigators have chosen high risk for allergy cohorts to study the probiotic preventive capacity. This review highlights recent work on prevention of eczema and food allergy using probiotics. Since the publication of earlier reviews on prevention and treatment of allergic diseases [18,19], several large prevention studies have been published that are the focus of this review.

CLINICAL PROBIOTIC STUDIES ON PREVENTION OF ECZEMA AND FOOD ALLERGY

The main probiotic prevention studies are summarized in Table 1 [20–28,29,30–32,33,34–42]. In the largest cohort reported ($n=1223$), supplementing pregnant women from week 36 with a mixture of four probiotics [*Lactobacillus rhamnosus* GG (LGG), *L. rhamnosus* LC705, bifidobacterium lactis Bb12 and propionibacterium] and infants receiving the same probiotics and a prebiotic oligosaccharide from birth to 6 months with 925 infants followed until age 2 years after showed a 20% reduction of eczema [32.3 to 26.0%, odds ratio (OR) 0.69 (0.52–0.93), $P=0.015$] and a 30% reduction of atopic eczema [17.7 to 12.4%, OR 0.61 (0.42–0.90), $P=0.012$] compared with the placebo group [25]. Long-term follow-up until age 5 of 891 infants showed no effect in reducing eczema or any allergic disease in the whole cohort, but a significantly diminished cumulative incidence of IgE-associated eczema and food-specific IgE-sensitization in caesarean-delivered children

(17% of the cohort) [26]. They showed a delayed colonization with bifidobacteria compared with vaginally delivered children, which was corrected with probiotic supplementation. A good retention of children was shown, with 88% attending at the 5-year visit. The second largest cohort from New Zealand is unique in comparison of two different probiotic strains. Pregnant women ($n=474$) were treated with *Lactobacillus rhamnosus* HN001, bifidobacterium animalis subsp lactis HN019 or placebo 1 month prenatally and until 6 months to the breastfeeding mother and directly to infants from birth until 2 years. A 50% reduction of eczema in the lactobacillus group [26.8 vs. 14.8%, hazard ratio 0.51 (0.30–0.85)], but no change in the bifidobacteria group was found [32]. The study highlights the importance of the bacterial strain; not every probiotic strain is efficient. The probiotic intervention was prenatal combined with postnatal both to the lactating mother and directly to the infant and with a longer intervention than in most studies. Very recently, their 4-year follow-up was reported [33] showing sustained eczema reduction with *L. rhamnosus*. Interestingly, this is also the first study to show a reduction in respiratory allergies with less rhinoconjunctivitis, indicating that by preventing early onset eczema, it is possible to stop the atopic march. These two largest cohorts show an eczema preventive effect from *L. rhamnosus* alone or in a mixture with other strains, but not all studies do so.

Some studies used postnatal-only probiotic supplementations. In an Australian study, *Lactobacillus acidophilus* or placebo was administered from birth to 6 months in 231 newborns. Their long-term follow-up study until 5 years has just been published in which no significant difference in prevalences of eczema, food allergy or respiratory allergies were found [29] consistent with earlier reported 1 [27] and 2.5 years [28] of follow-up. Another postnatal-only study by Soh *et al.* [35] in Asian infants stated that infants were given *Bifidobacterium longum* and *L. rhamnosus* during 6 months in two logs lower concentrations than other studies, and they found no allergy-preventive effects. Nonhydrolyzed fermented milk with or without heat-killed *Bifidobacterium breve* and *Streptococcus thermophilus* was given from birth until 1 year and children followed at 4, 12 and 24 months. No difference in cow's milk allergy prevalence was found, but decreased positive skin prick test to cow's milk and incidence of digestive and respiratory potentially allergic events emerged [43]. Hence, postnatal-only supplementation appears less effective in allergy prevention.

All aforementioned studies assessed allergy-preventive capacity of probiotics in high risk for allergy cohorts. Three studies used unselected

Table 1. Main probiotic prevention studies

Ref.	Population active, placebo	Probiotic and daily dose	Intervention prenatal	Postnatal ^a	Follow-up, years	Result for eczema
Kalliomaki <i>et al.</i> [20]	FHA+ 159 randomized, 132 completed A = 64 P = 68	<i>Lactobacillus rhamnosus</i> GG (LGG) 2×10^{10}	1 month	6 months to BF mother or infant if not BF (56%)	2	RR of eczema 0.51 [0.32–0.84] in probiotic vs. placebo
Kalliomaki <i>et al.</i> ^b [21]	107 completed A = 53 P = 54				4	RR of eczema 0.57 [0.33–0.97]
Kalliomaki <i>et al.</i> ^b [22]	116 completed A = 53 P = 62				7	RR of eczema 0.64 [0.45–0.92]
Rautava <i>et al.</i> [23]	FHA+ 62 randomized, 57 completed A = 27, P = 30	LGG 2×10^{10}	2–4 weeks	3 months BF mother only	2	RR of eczema 0.32 [0.12–0.85]
Rautava <i>et al.</i> [24]	FHA+ 81 randomized, 72 completed A = 32, P = 40	LGG 1×10^{10} , <i>B. lactis</i> Bb12 1×10^{10}	No	From start of infant formula to 12 months	1	NS eczema decrease 20 to 13% in placebo vs. probiotic group
Kukkonen <i>et al.</i> [25]	FHA+ 1223 randomized, 925, completed A = 461 P = 464	LGG: 5×10^9 , <i>L. rhamnosus</i> LC705: 5×10^9 , <i>B. breve</i> Bb99: 2×10^8 , <i>propionibacterium freundi</i> : 2×10^9 mothers $2 \times$ dose	1 month	6 months	2	OR of eczema 0.69 [0.52–0.93] and of IgE+eczema 0.61 [0.42–0.90]
Kuitunen <i>et al.</i> [26]	891 completed A = 445 P = 446				5	No difference in eczema in whole cohort; OR 0.43 [0.19–0.95] in probiotic caesarean delivered
Taylor <i>et al.</i> [27]	FHA+ 226 randomized, 178 completed A = 89 P = 89	<i>L. acidophilus</i> 3×10^9	No	6 months	1	No eczema difference between groups; more IgE+ eczema in probiotic group (26 vs. 14%), P = 0.045
Prescott ^d <i>et al.</i> [28]	153 completed A = 77, P = 76				2.5	No eczema difference between groups
Jensen ^d <i>et al.</i> [29]	123 completed (54%) A = 66, P = 57				5	No eczema difference between groups
Abrahamsson <i>et al.</i> [30]	FHA+ 232 randomized, 188 completed A = 95 P = 93	<i>L. reuteri</i> 1×10^8	1 mo	12 months	2	Eczema no difference, less IgE+ eczema 2nd year in probiotic group (8 vs. 20%), P = 0.02
Kopp <i>et al.</i> [31]	FHA+ 105 randomized, 94 completed A = 50 P = 44	LGG 1×10^{10}	1 month	0–3 months BF mother only, 3–6 months direct to infant	2	No eczema difference between groups
Wickens <i>et al.</i> [32]	FHA+ 512 randomized, 446 completed A1 = 144 A2 = 152 P = 150	<i>L. rhamnosus</i> HN001 6×10^9 , <i>B. animalis</i> HN019 9×10^9	1 month	Until 6 months if BF + direct to infants 2 years	2	HR 0.51 (.30–.85) of eczema in lactobacillus group; no difference to placebo in bifidogroup

Wickens ^a <i>et al.</i> [33 [■]]	425 completed A1 = 136, A2 = 146, <i>P</i> = 143	4	HR 0.57 [0.39–0.83] of eczema in lactobacillus group; no difference to placebo in bifido group
Huurre <i>et al.</i> [34]	Unselected 171 randomized, 140 completed A = 72 <i>P</i> = 68	1	No significant eczema difference between groups
Soh <i>et al.</i> [35]	FHA + 253 randomized, 245 completed A = 124 <i>P</i> = 121	1	No significant eczema difference between groups
West <i>et al.</i> [36]	Unselected 179 randomized, 171 completed A = 84 <i>P</i> = 87	1	Eczema lower in probiotic 11% vs. placebo 22%, <i>P</i> < 0.05
Niers <i>et al.</i> [37]	FHA + 156 randomized, 98 completed A = 50 <i>P</i> = 48	2	Parent reported eczema lower at 3 mo, later no difference between groups
Dotterud <i>et al.</i> [38]	Unselected 415 randomized, 278 completed A = 138 <i>P</i> = 140	2	OR of eczema 0.51 [0.30–0.87] in probiotic group vs. placebo
Kim <i>et al.</i> [39]	FHA + 112 randomized, 68 completed A = 33 <i>P</i> = 35	1	Less eczema in probiotic 36% vs. placebo 62%, <i>P</i> = 0.029
Boyle <i>et al.</i> [40]	FHA + 250 randomized, 210 completed A = 108 <i>P</i> = 102	1	No significant eczema difference between groups
Rautava <i>et al.</i> [41]	FHA + 241 randomized, 205 completed A1 = 62, A2 = 73, <i>P</i> = 70	2	OR of eczema 0.17 [0.08–0.35] in A1 and 0.16 [0.08–0.35] in A2
Ou <i>et al.</i> [42]	FHA + 191 randomized, 128 completed A = 65, <i>P</i> = 63	3	No significant eczema difference between groups

FHA, family history of atopy positive; HR, hazard ratio; OR, odds ratio; RR, relative risk.

^aProbiotic directly to the child, if not otherwise specified.

^bSame cohort as Kalliomäki 2001 ref [20].

^cSame cohort as Kukkonen 2007 ref [25].

^dSame cohort as Taylor 2007 ref [27].

^eSame cohort as Wickens 2008 ref [32].

cohorts. An easy-to-implement approach was used in a Swedish study [36], in which supplementation with *Lactobacillus* F19 during weaning from 4 to 13 months resulted in halved eczema frequencies at 13 months. In a Norwegian study [38], a probiotic mixture (LGG, *L. acidophilus* La-5 and *Bifidobacterium animalis*) given 1 month prenatally and 3 months to the breastfeeding mother showed less atopic eczema in the children at 2 years in the actively treated group [OR 0.51 (0.30–0.87)]. Supplementing the mother pre and postnatally without infant supplementation can possibly work and would be an easy way of supplementation. Boyle *et al.* [40] assessed whether prenatal administration without supplementing infants would suffice for allergy prevention. Using LGG from 36 weeks of gestation until delivery had no effect on eczema prevalence by age 1 year, however. A recent study evaluated the effects of maternal supplementation of *L. rhamnosus* LPR and *B. longum* BL999, *Lactobacillus paracasei* ST11 and BL999 or placebo 2 months before delivery and during breastfeeding from birth to 2 months. Eczema risk very efficiently decreased in both probiotic groups until 2 years [OR 0.17; 95% confidence interval (CI) 0.08–0.35, $P < 0.001$ and 0.16; 95% CI 0.08–0.35, $P < 0.001$, respectively] [41]. This study shows an effect from two combinations of bifidobacteria and lactobacilli, an unusual finding in probiotic studies. In a similar study, LGG or placebo was given to atopic mothers from the second trimester of pregnancy. After delivery, LGG was given to the breastfeeding mother or to nonbreastfeeding infants for 6 months. No effects on prevalences of allergic diseases including eczema were detected. However, the mothers' own allergic disease symptoms were relieved [42].

Taken together, prenatal maternal supplementation appears important for allergy-preventive effects, leading to faster infant colonization, but prenatal-only supplementation seems insufficient [40]. Further changes in the breastmilk composition can be important for the preventive effects [40,44–46].

Two studies have evaluated the eczema-preventing effect of prebiotics. Moro supplemented with a galacto-oligosaccharide (GOS)/fructo-oligosaccharide (FOS) vs. maltodextrin in extensively hydrolysed formula in high-risk infants from birth to 6 months showed a significantly reduced risk of eczema at 6 months in the GOS/FOS group (9.8%; 5.4–17.1 vs. 23.1%; 16.0–32.1, $P = 0.014$) [47], an effect that was sustained until 2 years [48]. An increase in faecal bifidobacteria was evident in the GOS/FOS group [47]. A multicentre study from five European countries randomized 830 low-risk for allergy infants to receive a regular formula with or without

prebiotics before the age of 2 months. At 1 year, the prevalence of atopic dermatitis was 44% lower in the prebiotic group [49].

SYSTEMATIC REVIEWS ON PROBIOTICS FOR ALLERGY PREVENTION

Several systematic reviews addressing probiotics for allergy prevention have been published and a more analytical approach was used in two meta-analyses [50,51]. A recent review summarized the publications on probiotics and prebiotics for preventing allergic disease including six randomized controlled studies. It concluded that an effect on development of eczema could be supported, with the strongest effect when supplementation started prenatally, in which seven out of 10 studies showed a decrease in eczema frequency until 2 years [OR for eczema 0.76 (95% CI 0.64–0.91) and atopic (IgE-associated) eczema 0.70 (95% CI 0.56–0.88)] [51]. However, due to the heterogeneity of study design using different populations in diverse environments, various strains and study designs, especially time and length of intervention, it is difficult to perform stringent meta-analyses and hence conclusions should be cautious.

In summary, results from studies on primary prevention of allergies using probiotics should be limited to used strain(s) and time (pre and/or postnatal) and length of intervention as well as populations (high-risk, normal risk) and setting (hygienic conditions in study environment). The use of prebiotics should also be taken into account.

MECHANISMS OF ACTION IN ALLERGY PREVENTION

The prenatal exposure to a farming environment has also pointed to the importance of prenatal exposure for allergy-preventive effect [52]. By colonizing the mother prenatally, the transfer of favourable bacteria to the infant starts during birth. Also, immunomodulation of the mother and changes in her breastmilk composition could benefit the infant with regard to allergy development [45,46]. It appears that the prenatal immunomodulation is insufficient for a change in the child's immunologic response to the nonallergic phenotype and needs to be followed by stimulation of the infant's gut immune system, preferably directly to the infant.

The preventive mechanism by which probiotics operate might be the modification of the gut microbiota and immunomodulation. In-vitro and in-vivo immunologic effects have been shown from probiotic administration [53,54]. We showed an inverse association of C-reactive protein (CRP)

and development of eczema. Probiotics induced a low-grade inflammation characterized by increased IgE, IgA, interleukin (IL)-10 and CRP [53]. We propose that a chronic low-grade inflammation may be the link between probiotics and development of allergic diseases similar to the inflammation induced by people with helminth infestation. Probiotic administration has resulted in demonstrable changes in the levels of the given strains in faecal samples in reported studies and supplementation has been successful in all studies [25–27,31,35,37] in which colonization has been reported. However, there is no good evidence for a permanent colonization of the supplemented probiotic in infants or children and in adults given probiotics, which can be found in faeces only for weeks after stopping the intervention [55]. A short prenatal supplementation of LGG modulated the infants' intestinal colonisation with *Bifidobacteria* towards that of a healthy breastfed infant [56] but did not affect microbial diversity [57]. Administering only one or few probiotic bacteria cannot affect the gut microbial diversity. Further, supplying one bacteria leads to bacterial antigen exposure of the host's immune system, that after a specific mucosal IgA-response develops, diminishes [58]. Pakistani children have a higher turnover of *Escherichia coli* strains than Swedish children [59]. An interesting approach would be to constantly change the supplemented probiotic bacteria to achieve a stronger and long-lasting immune stimulation. This would be a surrogate for the diminished microbial diversity in our westernized societies.

CONCLUSION

No proven effective way of primary prevention of allergic disease has been found, despite intensive research on environmental and dietary factors assessed, including breastfeeding, maternal diets and dietary restrictions, during pregnancy and lactation [60]. The most promising allergy-preventive alternative is administration of probiotic bacteria. However, giving recommendations on allergy prevention is difficult because the studies have used different probiotic strains and timing [61]. The majority of studies have evaluated eczema as the main outcome rather than food or other allergies. There is a growing body of evidence that primarily *L. rhamnosus* strains can be effective in preventing eczema. Recent studies show that an effect can be seen until at least 2 years, a good result already, and further some new studies show a longer effect until 5 years. By preventing development of food allergy and eczema, it is hoped that stopping the allergic march would be possible. Combined pre and direct

infant postnatal supplementation has demonstrated most consistent effects. Choosing the most effective strains or combination of strains and the mode and length of the supplementation needs to be settled. We still need long-time follow-ups of the rigorous large preferably multicentre studies. We have seen in-vivo immunologic actions related to administration of probiotics, one attractive mechanism relating to low-grade inflammation, but we still have a lack of understanding of the mechanisms behind the allergy-preventive effects afforded by probiotic bacteria. There is also a potential for prebiotics in allergy prevention, but more studies are needed. There is a variation among probiotic studies related to several factors, including probiotic strain/combination of strains, dose, duration, host factors such as allergy risk profile, mode of delivery and type of feeding.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 319).

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