Supplementation with Probiotics in the First 6 Months of Life Did Not Protect against Eczema and Allergy in At-Risk Asian Infants: A 5-Year Follow-Up

Evelyn X.L. Loo^a Genevieve V. Llanora^b Qingshu Lu^{c, d} Marion M. Aw^{a, b}
Bee Wah Lee^{a, b} Lynette P. Shek^{a, b}

^aDepartment of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, ^bUniversity Children's Medical Institute, National University Hospital, ^cDepartment of Biostatistics, Singapore Clinical Research Institute, and ^dCenter for Quantitative Medicine, Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore

Key Words

Allergy · Probiotics · Eczema

Abstract

Background: Healthy gut microflora is essential for oral tolerance and immunity. A promising approach to preventing allergic diseases in genetically at-risk infants is to introduce administration of probiotics early in life when their immune system is still relatively immature. **Objective:** In this follow-up study, we aim to determine if early-life supplementation with strains of probiotics has any long-term effect on allergic outcomes. **Methods:** We analyzed the charts and electronic databases of the PROMPT (Probiotics in Milk for the Prevention of Atopy Trial) study cohort. This cohort consisted of 253 infants at risk for allergy who were administered cow's milk supplemented with or without probiotics from the first day of life to the age of 6 months. The cohort was then followed up until the children were 5 years old and clinical outcomes were assessed. **Results:** Of the 253 children recruited into the study, 220 (87%) completed the follow-up. At the age of 5 years, there were no significant differences between the groups in the proportion of children who had developed any asthma, allergic rhinitis, eczema, food allergy and sensitiza-

tion to inhalant allergens. Similar growth rates were observed in both groups. **Conclusions:** The supplementation of probiotics in early childhood did not play a role in the prevention of allergic diseases. **Clinical/Key Message:** Early-life supplementation with probiotics did not change allergic outcomes at 5 years of age.

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Introduction

We previously reported that feeding with cow's-milk formula supplemented with probiotics [*Bifidobacterium longum* (BL999) and *Lactobacillus rhamnosus* (LPR)] in the first 6 months of life in a cohort of Asian infants at risk for allergic disease did not prevent eczema or allergen sensitization in the first year of life [1]. Here, we report on the long-term effects on allergic outcomes at the age of 5 years.

Briefly, the subjects were randomized to receive a commercially available cow's-milk formula supplemented with or without probiotics from birth to 6 months of age. At follow-up visits from 1 month to 5 years of age, subjects were assessed for allergic outcomes. Diagnoses of

Table 1. Comparison of incidence of atopic diseases by year up to the age of 5 years

Clinical characteristics, n (%)	Probiotic (n = 124)	Placebo (n = 121)	RR (95% CI)	p value
Ever had eczema	(n = 124)	(n = 121)		
By year 1	26 (21.0)	30 (24.8)	0.8 (0.5–1.3)	0.543
By year 2	27 (21.8)	32 (26.4)	0.8 (0.5–1.3)	0.456
By year 3	30 (24.2)	32 (26.4)	0.9 (0.6–1.4)	0.769
By year 4	30 (24.2)	35 (28.9)	0.8 (0.6–1.3)	0.470
By year 5	31 (25.0)	38 (31.4)	0.8 (0.5–1.2)	0.320
Ever had asthma	(n = 124)	(n = 121)		
By year 1	4 (3.2)	4 (3.3)	1.0 (0.2–3.8)	1.000
By year 2	11 (8.9)	11 (9.1)	1.0 (0.4–2.2)	1.000
By year 3	15 (12.1)	13 (10.7)	1.1 (0.6–2.3)	0.842
By year 4	20 (16.1)	17 (14.0)	1.1 (0.6–2.1)	0.722
By year 5	26 (21.0)	25 (20.7)	1.0 (0.6–1.7)	1.000
Ever had allergic rhinitis	(n = 124)	(n = 121)		
By year 1	1 (0.8)	1 (0.8)	1.0 (0.1–15.4)	1.000
By year 2	2 (1.6)	3 (2.5)	0.7 (0.1–3.8)	0.681
By year 3	5 (4.0)	4 (3.3)	1.2 (0.3–4.4)	1.000
By year 4	9 (7.3)	8 (6.6)	1.1 (0.4–2.8)	1.000
By year 5	16 (12.9)	23 (19.0)	0.7 (0.4–1.2)	0.223
Ever had food allergy since year 3	(n = 117)	(n = 109)		
By year 3	1 (0.9)	0	NA	1.000
By year 4	1 (0.9)	0	NA	1.000
By year 5	1 (0.9)	1 (0.9)	1.1 (0.1–17.0)	1.000
Sensitization to inhalant allergens				
At year 2 test	(n = 118)	(n = 111)		
Any sensitization	20 (16.9)	19 (17.1)	1.0 (0.6–1.8)	1.000
Der p	18 (15.3)	19 (17.1)	0.9 (0.5–1.6)	0.723
Blo t	5 (4.2)	6 (5.4)	0.8 (0.2–2.5)	0.763
Der f (not done)	NA	NA	NA	NA
At year 5 test	(n = 112)	(n = 108)		
Any sensitization	55 (49.1)	57 (52.8)	0.9 (0.7–1.2)	0.593
Der p	46 (41.1)	51 (47.2)	0.9 (0.6–1.2)	0.415
Blot t	37 (33.0)	41 (38.0)	0.9 (0.6–1.2)	0.483
Der f	44 (39.3)	47 (43.5)	0.9 (0.7–1.2)	0.584

asthma, allergic rhinitis and eczema were made by pediatricians in the research team, and were based on a detailed history and clinical examination at yearly visits; food allergy was diagnosed by a history of convincing symptoms of food allergy and the presence of IgE allergen sensitization. Questionnaires were also administered at each visit to record potential sources of environmental exposure to allergens such as day-care, number of siblings, use of antibiotics, tobacco smoke and pets.

Of the 253 subjects who were recruited into the study, 245 (97%) (124 receiving probiotics and 121 receiving placebo) completed at least 1 follow-up assessment, 231 (91%) completed follow-up until the age of 2 years and 220 (87%) until the age of 5 years. Compared to published

studies, this is the largest cohort to have completed a follow-up to the age of 5 years. There were no significant differences in the baseline demographics and family history of allergic disease between the subjects who completed the follow-up and those who were lost to follow-up. For those who completed the 5-year follow-up, the probiotic and placebo groups did not differ significantly with regard to environmental factors. The proportion of subjects who had had any eczema since birth was similar in the probiotic and placebo groups (see table 1). Eczema severity was also similar, with a mean SCORAD (Scoring Atopic Dermatitis) score of 16.9 in the probiotic group and 15.3 in the placebo group ($p = 0.295$). There were also no significant differences between the probiotic group

and the placebo group in the proportion of subjects who had developed asthma (defined by 3 episodes of wheeze) or allergic rhinitis (see table 1). The proportion of subjects who had experienced any food allergy ($p = 1.000$) as well as those sensitized to dust-mite allergens (*Dermatophagoides pteronyssinus*, *Blomia tropicalis* or *D. farinae*, $p = 0.593$) was also similar in the 2 groups. The growth rates as well as the rate of weight ($p = 0.660$) and height ($p = 0.996$) gain were similar in the 2 groups.

It was noted that a large number of subjects (208/226 or 92%) continued to consume probiotics of their own accord in the form of milk formula/food/supplements with probiotics at a frequency of at least once a week for at least 1 year from the age of 2 years. Incidentally, this practice was statistically associated with a reduced incidence of asthma and allergic rhinitis at the age of 5 years. Calculations of relative risk (RR) were made with adjustment for a subject's treatment group, i.e. probiotics or placebo. A diagnosis of asthma was made in 36 of 208 (17.3%) subjects who had a weekly consumption of probiotics compared with 8 of 18 (44.4%) who did not receive probiotics [adjusted RR 0.4 and 95% confidence interval (CI) 0.2–0.7]. Allergic rhinitis was diagnosed in 32 of 208 (15.4%) with a regular consumption of probiotics and in 7 of 18 (38.9%) subjects not receiving probiotics (adjusted RR 0.4 and 95% CI 0.2–0.8). The incidence of asthma was found to be associated with duration of feeding with probiotics ($p = 0.002$), but this was not observed for allergic rhinitis, eczema and allergen sensitization (data not shown). However, the possibility that these observations may in part have been confounded by reverse causality cannot be excluded. Those with symptomatic allergic rhinitis and asthma may have been less proactive in their consumption of probiotics. In addition, there was no reduction noted in the rate of eczema (RR 0.8 and 95% CI 0.3–1.9, $p = 0.543$) or the sensitization to dust-mite allergens ($p = 0.154$) with regular consumption of probiotics.

Healthy gut microflora is essential for oral tolerance and immunity. A promising approach to preventing allergic diseases in genetically at-risk infants is to introduce probiotics to them early in life when their immune system is still relatively immature [2]. However, whether or not probiotics indeed have a beneficial effect in the prevention of allergic diseases remains controversial. Some studies have shown the prevention of eczema [2, 3] while others do not find a reduction in allergic outcomes [4]. In addition, very few studies have looked at the long-term effects of probiotics on allergic diseases [5]. It is critical to report the long-term effects of early-life supplementation with probiotics, as respiratory allergies such as asthma,

allergic rhinitis and sensitization to inhalant allergens often manifest later in life.

In our cohort, early supplementation in the first 6 months of life with probiotics did not change allergic outcomes at 5 years of age. Other studies using different bacterial strains have also demonstrated no effect; for example, early-life supplementation with *Lactobacillus acidophilus* was not found to exhibit long-term protective effects on allergic outcomes [5]. In contrast, the study by Kalliomaki et al. [6] showed a significantly decreased cumulative risk for the development of eczema with the use of the *L. rhamnosus* GG strain in a group of children in their first 7 years compared to a group receiving a placebo. The protective effect of *L. rhamnosus* in decreasing the cumulative prevalence of eczema was also reported in another study [3]. A possible reason for the protective effects observed by some groups could be the inclusion of prenatal supplementation as well as the dose of probiotics administered. Protective effects could also be attributed to specific bacterial strains [3]; the 2 bacterial strains we used in our study may have had a possible antagonistic effect [7]. We also did not observe any difference in growth rate with the use of probiotics; this is in line with a pooled analysis of previous trials which showed no significant differences in birth weight, length and BMI between infants who received *Bifidobacterium lactis*-supplemented infant formula and those that did not [8]. Interestingly, our study suggests that later and long-term probiotic supplementation could reduce the risk of allergic diseases. Another study recently reported that infants who received probiotic supplementation between 2 and 16 days after birth until 2 years of age had a significantly lower cumulative prevalence of eczema by the age of 4 years [9].

In conclusion, early-life supplementation with probiotics did not change allergic outcomes in children at the age of 5 years.

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