

Letter to the Editor

Immunoactive prebiotics transiently prevent occurrence of early atopic dermatitis among low-atopy-risk infants

To the Editor:

Atopic dermatitis (AD) frequently marks the start of an atopic march. The incidence is highest in the first year of life.¹ A positive family history for atopic disorders is the strongest predictor for the development of AD, but most children who express atopic disease come from families with a negative family history.² There is a consensus that the intestinal microbiota plays an important role in the postnatal development of the immune system and that its composition may influence the risk of AD development in infancy. Specific prebiotic oligosaccharides (OS) have been designed to functionally mimic human-milk OS and to skew the intestinal microbiota toward healthy commensals.³ Recently, we demonstrated that supplementation of infant diet with a specific mixture of prebiotic and immunoactive OS reduces AD occurrence in the first year of life by 44% in a low-atopy-risk population.⁴ Whether this effect persists beyond the first birthday is currently unknown. Here, we report follow-up results from this trial.

The study was performed as a double-blind, controlled, randomized prospective nutritional intervention study to investigate the effect of formula feeding supplemented with a specific mixture of OS on the incidence of febrile episodes.⁵ Occurrence of AD was included as a prespecified parameter of efficacy in the study protocol of the Multicentric Infection Prevention Study (MIPS I)⁴ and as main end point of the follow-up study (MIPS II).

Healthy term infants with a normal birth weight without a positive family history of atopic disease were included in MIPS I before postnatal age of 8 weeks. Infants from mothers who intended to provide exclusive breast-feeding for 4 months or more were included in the breast-feeding group (BG). Mothers who intended exclusive formula feeding were randomized. Infants randomized to the prebiotic formula group (PG) received a nonhydrolyzed cow milk-based formula supplemented with neutral short-chain galacto-OS and long-chain fructo-OS, ratio 9:1 (85 wt%), and specific pectin-derived acidic OS (15 wt%) up to age 12 months. The total amount of OS was 8 g/L. Infants randomized to the control formula group (CG) received a similar formula without added OS. Study formulas were manufactured and provided by Danone Nutricia Research (formerly NUMICO), Utrecht, The Netherlands.

Infants who participated in the original study⁴ were invited to MIPS II after age 2.5 years and observed until age 5 years. Children were clinically examined and checked for symptoms of AD at study entry and at 3, 4, and 5 years. Parent interview data about symptoms were collected every 3 months. To help accuracy of recall, parents kept a symptom diary. AD was diagnosed according to standard criteria.⁶ Severity of AD was assessed with the SCORing Atopic Dermatitis index score.⁷

All statistical analyses were performed with SAS (version 9; SAS Institute, Cary, NC). Written informed consent was obtained from all parents before randomization and follow-up. All participating centers obtained approval from their local ethical review board.

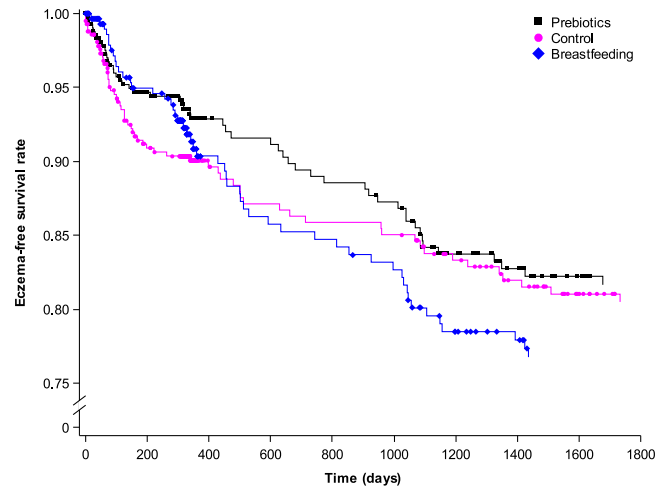


FIG 1. Kaplan-Meier curve for eczema-free survival (full analysis sample).

From the MIPS I study population, 232 (PG), 243 (CG), and 197 (BG) children were available for observation in the follow-up period (59% of the original population). At least 2 years of follow-up observation until the age of 5 years was completed by 172 (PG), 195 (CG), and 161 (BG) children. There were no statistically significant group differences in regard to age at inclusion (median, 36 months in all groups), sex, children in household, and educational level of the mother. Cesarean section was less prevalent in the BG (15%) than in the PG (37%) and the CG (37%).

The cumulative incidence of AD up to age 5 years was 18.2% (PG), 20.2% (CG), and 23.9% (BG). There was no significant group difference between PG and CG at 5 years or before. The cumulative incidence of AD up to age 5 years tended to be lower in the formula-fed groups (PG, 11.6%; CG, 11.9%) than in the nonrandomized BG (17.8%; PG vs BG, $P = .072$; CG vs BG, $P = .084$). Eczema-free survival rate as the main efficacy outcome parameter was not significantly different between groups (Fig 1). Few children with AD went into early remission after their first birthday (PG, 2.6%; CG, 3.7%; $P = .486$; BG, 4.1%) and few suffered persistently from AD (PG, 2.6%; CG, 2.9%; $P = .844$; BG, 4.6%). Afflicted from AD were 45 (PG), 49 (CG), and 49 (BG) children. Among them, the individually worst SCORing Atopic Dermatitis index score (median, range) was similar in all groups—PG 7 (0-47), CG 0 (0-48), $P = .080$; BG 9 (0-59)—as was use of corticosteroid ointment (PG, 7.8%; CG, 8.6%; $P = .726$; BG, 9.6%).

At 5 years, wheeze in the last 3 months was reported in 2.9% (PG), 4.1% (CG; $P = .903$), and 5.0% (BG) of the children. Parents of 19 children with wheeze reported colds ($n = 16$), physical activity ($n = 2$), house dust ($n = 1$), and grass ($n = 1$) as a causative factor. The incidence of doctor-diagnosed allergic diseases did not differ significantly between groups (Fig 2).

In the follow-up of our randomized controlled trial in low-atopy-risk children, we found no sustained statistically significant effect of immunoactive prebiotics added to infant diet against the occurrence of early AD at preschool age. This finding contrasts with results from a trial among high-atopy-risk

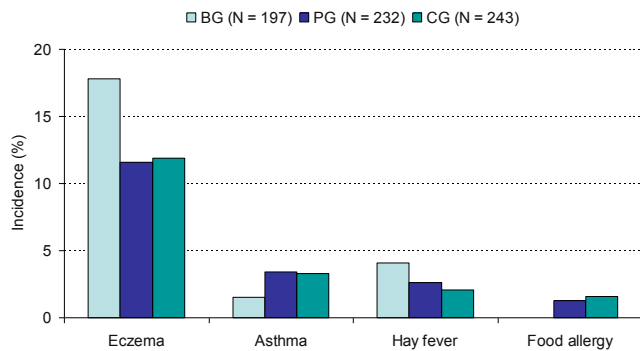


FIG 2. Incidence of doctor-diagnosed diseases (number of children).

children, in which supplementation of a hydrolyzed infant formula with neutral OS was associated with reduced occurrence of eczema beyond the first birthday.^{8,9} Hydrolyzed formula may be immunomodulatory by itself.^{E1} We did not offer hydrolyzed formula to the low-atopy-risk term infants in our study. Experimental data indicate that allergic inflammation may be better suppressed by the addition of acidic OS to neutral OS as used in our trial.^{E2,E3} An extrapolation of data from published studies in high-risk children thus seems difficult. Our data suggest that the preventive effect of immunoactive OS on eczema occurrence is transient in the low-atopy-risk strata.

The borderline inferior eczema-free survival in the BG compared with formula-fed children after the first year of life could not be explained by sociodemographic characteristics mentioned above. We speculate that lifestyle differences beyond the first birthday are operational. Given the multitude of beneficial effects of breast-feeding shown in many studies,^{E4} this circumstantial finding should not mislead to advocating formula feeding without need.

In addition, we did not find a protective effect of prebiotic supplement against the occurrence of early physician-diagnosed respiratory allergy. In the high-atopy-risk population, there was a protective effect against the occurrence of wheeze up to age 2 years,⁸ but not up to age 5 years.⁹ Wheeze in early infancy is commonly due to mucosal swelling induced by viral infection, whereas later in life allergic airway constriction becomes more important. In MIPS II, there were almost no reports of allergen-triggered wheeze. At preschool age, respiratory allergy played no significant role in our low-atopy-risk strata and we failed to show an effect of prebiotics on infection-triggered wheeze.

Recent experimental research indicates the protective potential of immunoactive prebiotics against the development of food allergy.^{E3} Perinatally administered probiotics in combination with galacto-OS had no statistically significant effect on food allergy in high-atopy-risk infants.^{E5} In our study, food allergy was a rare event (Fig 2) and the study was not designed to detect an effect on food allergy. Although a significant clinical problem, the incidence of food allergy among children is relatively low.^{E6} Accordingly, a rather high number needed to treat would be required for the prevention of early food allergy.

Trials testing the allergy-preventive potential of immunoactive prebiotics have been designed to improve immune development in formula-fed infants who lack breast-milk OS in their diet. Accordingly, supplementation of OS has been limited to the first

year of life in these trials.^{4,5,8,9,E5} Whether supraphysiologic duration of OS supplementation would have an allergy-preventive effect persisting beyond the first year is an interesting research question that has not been adequately studied yet.

In conclusion, there are indications that supplementation of infant diet in the first year of life with the immunoactive prebiotics tested here may have preventive potential against early AD, but the effect is not sustained in low-atopy-risk strata. As the number needed to treat was 25 infants in the MIPS trial, efforts have to be balanced against transient gains.

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