Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants

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Background: Most infants developing atopic dermatitis have a low risk for atopy. Primary prevention of atopic dermatitis is difficult.

Objective: To assess the effect of supplementation of an infant and follow-on formula with prebiotic and immunoactive oligosaccharides on the occurrence of atopic dermatitis in the first year of life.

Methods: Healthy term infants from 5 European countries with low atopy risk were recruited before the age of 8 weeks, either having started with formula feeding or being on full breast-feeding (breast-feeding group). Formula-fed infants were randomized to feeding with a regular formula containing a specific mixture of neutral oligosaccharides and pectin-derived acidic oligosaccharides (prebiotic formula group) or regular formula without oligosaccharides (control formula group).

Results: A total of 414 infants were randomized to the prebiotic group and 416 infants to the control group. A total of 300 infants were followed in the breast-feeding group. Up to the first birthday, atopic dermatitis occurred in significantly fewer infants from the prebiotic group (5.7%) than from the control group (9.7%; $P = .04$). The cumulative incidence of atopic dermatitis in the prebiotic group was in the low range of the breast-feeding group (7.3%). In a Cox regression model, the rate of atopic dermatitis was significantly lower by 44% in the prebiotic group versus the control group ($P = .04$). The number needed to prevent 1 case of atopic dermatitis by supplementation of prebiotics was 25 infants.

Conclusion: Formula supplementation with a specific mixture of oligosaccharides was effective as primary prevention of atopic dermatitis in low atopy risk infants. (J Allergy Clin Immunol 2010;126:791-7.)

Key words: *Oligosaccharides, atopic dermatitis, infant, primary prevention, prebiotics*

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Atopic dermatitis (AD) is the most common chronic skin disease in children, with a rising prevalence of about 10% currently in many industrialized countries.[1,2] The peak incidence is in the first year of life.[3] Although generally not life-threatening and in most cases transient,[3] the itchy inflammation of the skin can cause considerable emotional stress and skin damage. Genetic factors play a major role in the development of AD.[4-6] A positive family history for atopic disorders is the strongest predictor for the development of AD and allows targeting of a high-risk population for primary prevention measures.[7] The majority of children who express atopic disease, however, comes from families with a negative family history. [8]

Primary prevention of AD in infants at low risk for AD is difficult. Benefits of nutritional allergen avoidance during the first 4 to 6 months of life, either by exclusive breast-feeding or by feeding of certain formula without intact cow milk protein, are modest and largely limited to infants from families with a positive history of allergy.[9-11] Mite aeroallergen avoidance did not prevent AD in a randomized controlled study.[12]

Because there is a broad consensus that the intestinal microbiota plays an important physiological role in the postnatal development of the immune system, many attempts have been made to influence the intestinal microbiota and herewith the occurrence of atopic manifestations by dietary interventions. A heavily marketed strategy for primary prevention is dietary supplementation of potentially beneficial bacteria (probiotics) as a tool to redirect the immune system away from atopy. A pioneering placebo-controlled study in high-risk families with perinatal supplementation of the mothers' and infants' diet with *Lactobacillus GG* demonstrated a reduced prevalence of early AD in children.[13] In a recent study of infants at high risk of atopy, perinatal supplementation with *Lactobacillus rhamnosus* (but not with *Bifidobacterium animalis subsp lactis*) reduced the cumulative prevalence of eczema by age 2 years.[14] Further controlled trials in infants at high risk for atopy failed to demonstrate a preventive effect of probiotics on the emergence of AD.[15-17] Trials in infants at low risk for AD are lacking.

The probiotic approach adds to a spectrum of hundreds of species in the gut flora only 1 or 2 species that happened to be a

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Abbreviations used
AD: Atopic dermatitis
BG: Breast-feeding group
CG: Control group
lcFOS: Long chain fructo-oligosaccharides
pAOS: Pectin-derived oligosaccharides
PG: Prebiotics group
scGOS: Short chain oligosaccharides
SCORAD: Scoring Atopic Dermatitis
TARC: Thymus and activation-regulated chemokine

marker of a microbiota associated with fewer allergies. The prebiotic approach aims at fertilization of the intestinal ecosystem in a way that the microbiota profile turns toward healthy commensals. Oligosaccharides contribute about 10% of the solid components of human milk and exert prebiotic function. Previous data in infants at elevated risk for development of atopy demonstrate that a specific mixture of synthetic neutral prebiotic oligosaccharides reduces the incidence of AD up to age 2 years by 51%.[18,19] To come even closer to the functional composition of human milk, pectin-derived acidic oligosaccharides (pAOS) have been added. There is experimental evidence in mice that adding pAOS to a diet supplemented with short chain oligosaccharides (scGOS)/long chain fructo-oligosaccharides (lcFOS) results in better attenuation of a proallergic T_H2-type immune response than scGOS/lcFOS alone.[20]

In this study, we evaluated whether supplementation of an infant and follow-on formula with prebiotic and immunoactive oligosaccharides reduces the occurrence of AD in the first year of life. To answer this question, we investigated the effect of a formula supplemented with a specific mixture of scGOS, lcFOS, and pAOS designed functionally to imitate human milk oligosaccharides in a population of weaned infants at low risk for atopy. These infants are from a study with the primary aim to evaluate the effect of these oligosaccharides on the incidence of fever episodes.

METHODS

Study design

The study was performed as a double-blind, placebo-controlled, randomized prospective nutritional intervention study. As reported elsewhere, the primary endpoint of the study was to elucidate whether formula feeding supplemented with a specific mixture of neutral and acidic oligosaccharides reduces the incidence of fever episodes in healthy term-born infants during the first year of life (Multicentric Infection Prevention Study (MIPS); Margriet van Stuivenberg, June 2010, unpublished data).

The main endpoint of the analysis in this article was the occurrence of AD up to the first birthday, which was included in the study protocol as a prespecified secondary parameter of efficacy. We hypothesized that formula supplementation with a specific mixture of scGOS/lcFOS/pAOS reduces the incidence and severity of AD and prevents early allergic sensitization to food allergens.

The study was registered in the German Clinical Trials Register (registration code DRKS 00000201).

Participating centers

Participating study centers were the Beatrix Children's Hospital in Groningen, The Netherlands; the Schwarzach Hospital in Schwarzach, Austria; the University Children's Hospital in Zurich, Switzerland; the Mangiagalli Hospital in Milan, Italy; the Macedonio Melloni Hospital in Milan, Italy; the Charité-Universitätsmedizin Berlin in Berlin, Germany; and the Spedali Civili Hospital in Brescia, Italy. The institutional ethics committees of all study centers approved the study protocol.

Patient recruitment

Parents with babies in their first 8 weeks of life from the region of the participating centers were informed about the study and asked for their consent. Parents were asked to call back only if they were interested in the study. Infants were included in the study before the postnatal age of 8 weeks.

Inclusion criteria

We included healthy, term infants (gestational age 37-42 weeks) with a normal birth weight (> 10th percentile and < 90th percentile for gestational age according to locally applicable growth charts), age up to 8 weeks when entering the study, without a positive history of allergic disease (hay fever, asthma or AD) of any parent or sibling and without a metabolic disorder requiring a special diet.

Exclusion criteria

Exclusion criteria included mothers with hepatitis B, HIV, or group B streptococcal infection during pregnancy; mothers taking antibiotics during breast-feeding; infants with known congenital or postnatal diseases that could interfere with the study; and study prefeedings of the infants that could interfere with the study.

Procedures

At the start of the study, the parents indicated whether the mother was intending to provide either exclusive breast-feeding until at least 4 months of age or to give formula feeding only. Mothers were encouraged to breast-feed the infant for at least 4 months and preferably 6 months. The local study team asked mothers for their consent to participate in the study and to be randomized to 1 of the 2 formula groups only if they could not or did not fully breast-feed their infants and had fed at least 1 bottle of formula before. Only infants of mothers who indicated before the eighth week after birth that they would provide only formula feeding at least during the first 4 months of age were randomized. In case of insufficient breast-feeding, the only substitute or supplement was the randomized study formula throughout the study.

Infants of mothers who indicated they would provide full breast-feeding were included in the breast-feeding group (BG). This group served as the nonrandomized reference group. If mothers could not provide enough breast milk any longer, a formula available on the local market was offered.

Randomization to 1 of the 2 formula groups was performed immediately after study entry. Randomization was performed stratified according to study center. Time-balanced randomization was performed with the software RANCODE professional 3.6 (idv Data Analysis and Planning, Gauting, Germany) with a random permuted block size of 4. The hospital pharmacist only had a copy of the randomization list with the actual treatment allocation. The parents, the study physicians, and the study nurses were unaware of the group allocation. The tins and the milk powder looked and smelled identical.

Infants randomized to the prebiotics group (PG) received a regular nonhydrolyzed cow's milk–based formula to which a specific mixture of neutral scGOS and lcFOS, ratio 9:1 (IMMUNOFORTIS, Nutricia Cuijk BV, Cuijk, The Netherlands; 85 weight percent), and specific pAOS (15 weight percent), was added (data to be published elsewhere). The total amount of oligosaccharides was 8g/L with 6.8g/L neutral and 1.2g/L pAOS. Infants randomized to the control group (CG) received a similar regular nonhydrolyzed cow's milk–based formula without added oligosaccharides. For both groups, starter formula was provided during the first 6 months of life; thereafter, follow-on formula was offered. Infants randomized to the PG continued to receive the oligosaccharides in the follow-on formula. It was advised to all participating mothers not to start weaning from either exclusive breast-feeding or formula feeding before the age of 4 months. All study formula were manufactured and provided by Danone Research (at the time the study was conducted, NUMICO), Cuijk, The Netherlands.

Ethics

Written informed consent was obtained from all parents before randomization. All participating centers obtained approval of their local ethical review board.

Observation period

The observation period was until the age of 1 year. Every 2 weeks (after the age of 16 weeks, every 4 weeks), contact was made with the parents, either by home visits, clinic visit, or phone calls. During these interviews, data about the onset of AD or any other symptoms and about any prescribed drugs were collected. To help accuracy of recall, parents kept a symptom and therapy diary.

At study entry, 2, 4, 6, and 12 months of life, infants were clinically examined at the study centers and checked for symptoms of AD. If parents gave their additional informed consent for venous blood sampling of their child, blood samples were taken at the ages of 6 and 12 months.

Outcomes

Atopic dermatitis was diagnosed according to standard criteria based on the typical morphology and distribution of skin lesions, pruritus, and chronicity (duration at least 14 days and/or chronically relapsing).[21] The date of AD onset was retrieved on the basis of diary and case report forms entries during the hospital or home visits after validation of AD by a study physician. For assessing the severity of AD we applied a widely accepted scoring system (Scoring Atopic Dermatitis [SCORAD] index score).[22]

Serum samples were stored at –20°C until analysis. All sera were screened with a fluorescence immunoassay (CAP FEIA; Phadia, Freiburg, Germany) for the presence of specific IgE to hen's egg and cow's milk. An IgE titer of ≥0.7 kU/L was considered a positive test result.

Recent studies indicated that the T_H2-specific thymus and activation-regulated chemokine (TARC) is a useful, organ-selective, objective marker of AD disease severity.[23-25] Therefore we added TARC as an outcome parameter after start of the trial. TARC serum levels were analyzed by ELISA. The limit of detection of the TARC ELISA was 40 pg/mL. All samples below this limit of detection were given the result 40×0.5 = 20 pg/mL.

Statistical analysis

All statistical analyses were performed with SAS, Version 9 (SAS Institute, Cary, NC). A P value of <.05 was assumed to indicate statistical significance in all tests. All analyses were performed with stratification per center unless numbers were too small or a center effect was not expected (eg, laboratory parameters).

The analyses were performed by using the full analysis set—that is, an intention-to-treat analysis. This set consisted of all children who had been randomized in the PG or the CG or had been included in the BG (nonrandomized). The size of this sample had been calculated for the primary endpoint of MIPS.

Baseline demographic data were reported as median and interquartile ranges (continuous variables) or percentages (categorical variables). They were compared by using stratified linear regression, Cochran-Mantel-Haenszel tests, or nonparametric stratified Wilcoxon tests as appropriate for continuous and categoric variables.

The main endpoint was occurrence of AD up to the first birthday. Eczema-free survival was defined as the length of time from randomization to the first occurrence of eczema. For patients who left the study without AD, eczema-free survival was conservatively defined as the time from randomization to the last date on which the patient was known to be free of eczema (censored observations). Eczema-free survival was analyzed by using Kaplan-Meier analysis. Furthermore, Cox proportional hazard regression analysis was used to examine possible confounding factors in incidence of AD.

Study group differences in serum levels of TARC were assessed via a repeated measurement mixed model including study group as fixed effect, week as the repeating factor, and study group by week interaction, and including infant as random effect. Two-sided tests were performed using an α level of 5%. TARC levels were log-transformed by using a basis of 10 before entering into the model. The estimated marginal means and 95% CIs were back-transformed, resulting in geometric means and geometric means ratios.

RESULTS

Study population

From July 2005 to December 2006, a total of 1187 infants were screened. Fifty-seven of these infants were not enrolled. A total of 1130 infants participated and were randomized into 1 of the 2 study groups or were fully breast-fed and in the BG. The intention-to-treat population was composed of 414 infants in the PG, 416 infants in the CG, and 300 infants in the BG. The trial profile is shown in Fig 1. During the observation period, 129 patients (11%) dropped out (PG, n = 53; CG, n = 42; BG, n = 34). Twenty-seven percent of the recruited infants were fully breast-fed for at least 4 months and ranged from 2% to 43% in the study centers (Table I). The baseline characteristics and demographics of the infants are summarized per group in Table II. There was good comparability between the formula groups. The observation period ended in December 2007.

Occurrence of AD

Atopic dermatitis occurred in significantly fewer infants receiving the prebiotic formula (5.7%; SE, 1.2%) than in infants receiving the control formula without prebiotics (9.7%; SE, 1.5%; P = .04) up to their first birthday. Concomitantly, the cumulative incidence of AD among infants from the PG was in the low range of infants from the BG (7.3%; SE, 1.6%). Among infants with AD in their first year of life, the median time until expression of AD was similar in the PG (15.1 weeks; range, 5.1-49 weeks) and in the CG (16.8 weeks; range, 4.4-50.6 weeks) but longer in the BG (22.5 weeks; range, 4.4-50.3 weeks).

For a further comparison of study groups, the time to first occurrence of AD was modeled over the entire study period, using a Cox regression model. Parent's educational level was used as an indicator of social status to control for baseline risk of atopy in newborn infants. The final model included the following covariates: study group, sex, pets at home, total number of children in household, father's educational level, and age at introduction to solid food. The model indicates that the rate of AD is significantly lower by 44% in the PG versus the CG (Wald χ^2, 4.268; P = .04) and similarly low in the PG and the BG. Accordingly, the eczema-free survival rate as the main efficacy outcome was higher in the PG than in the CG (Fig 2). The number needed to treat to prevent 1 case of AD, calculated as 100 divided by the difference in the percentage of AD cases at 52 weeks of age, was 25 infants (PG vs CG, 95% CI, 13-386).

If the total number of children in the household increases by 1, the rate of AD significantly decreases by 31% (P = .02). Infants of fathers with postsecondary education have a 105% higher rate of AD than those with only secondary education (P = .006; Table III).

Severity of AD

There was a tendency toward less severe AD at the first birthday among the infants affected in the PG (n = 8; median SCORAD score, 8; range, 3-25) than in the CG (n = 16; median SCORAD score, 12; range, 2-59; P = .08). Similarly, the worst individual eczema among infants who had AD ever was not significantly different between the PG (n = 22; median SCORAD score, 16; range, 3-66) and the CG (n = 39; median SCORAD score, 13; range, 2-68; P = .713). Corticosteroid ointment was applied in 16 patients (3.9%) from the PG and in 40 patients (9.6%) from the CG (P = .001).

TARC

At age 26 weeks, mean serum levels of TARC were significantly lower among infants who remained free from AD

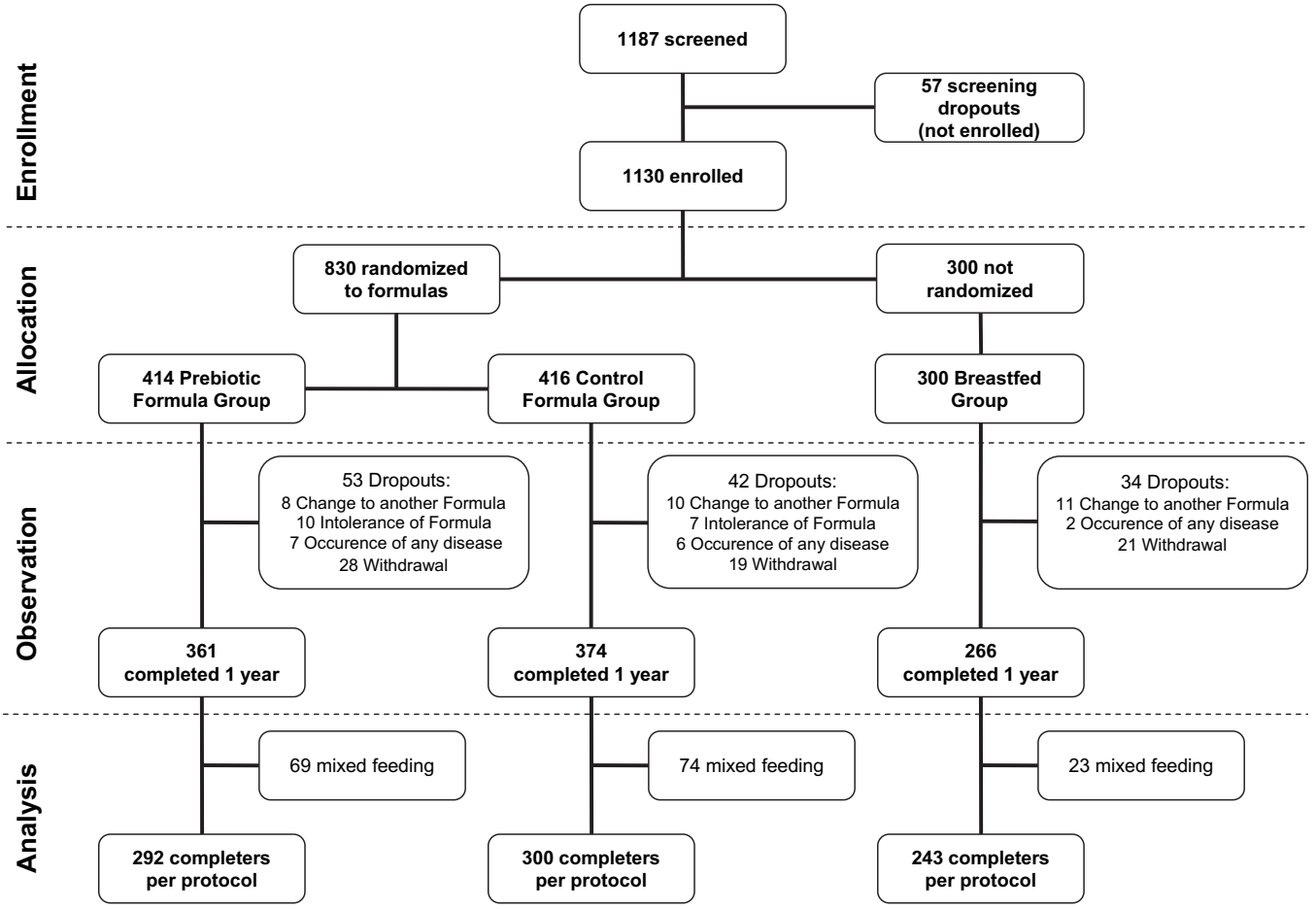


FIG 1. Trial profile.

TABLE I. Infants per study group by study site

Study site	Prebiotic formula	Control formula	Breast-feeding	Site total
Berlin (Germany)	46	45	52	143
Brescia (Italy)	39	42	55	136
Groningen (The Netherlands)	80	85	42	207
Milan I (Italy)	66	66	23	155
Milan II (Italy)	73	69	3	145
Schwarzach (Austria)	52	52	77	181
Zurich (Switzerland)	58	57	48	163
Total	414	416	300	1130

(199 pg/mL; 95% CI, 174-228 pg/mL) than among infants who expressed AD (338 pg/mL; 95% CI, 234-488 pg/mL; $P = .004$). This difference was less pronounced at the first birthday when mean TARC levels were 205 pg/mL (95% CI, 176-240 pg/mL) among infants who remained free from AD and 254 pg/mL (150-428 pg/mL) among infants who expressed AD ($P = .46$). Corresponding to the SCORAD index score, TARC serum levels were similar in all groups (Table IV).

IgE

There were no statistical significant differences in regard to allergic sensitization to hen's egg or to cow's milk between groups (Table IV).

DISCUSSION

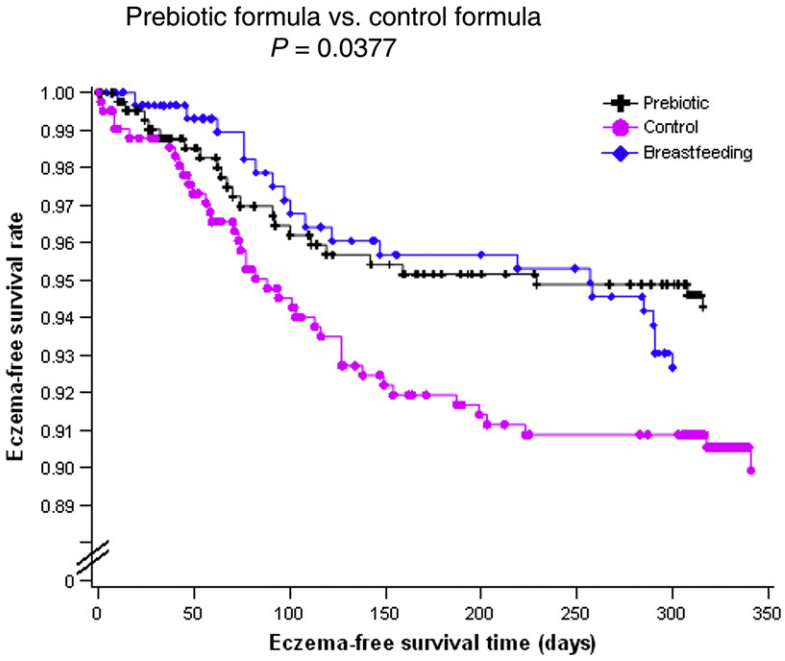
This trial shows that supplementation of infant formula/follow-on formula with a specific prebiotic mixture of scGOS/lcFOS/pAOS reduces the incidence of AD up to the first birthday in infants at low risk for atopy by 44% compared with the control group and down to a level similar to that of fully breast-fed infants. The severity of AD, however, was not affected significantly.

A novelty of our study is the low atopy risk strata as the target population. Primary prevention in infants at low AD risk is crucial because on a population level, most children who develop AD come from families without a positive family history.[8] Given the high prevalence of AD in many industrialized countries, it would be most interesting to learn whether the preventive effect of a specific mixture of prebiotics on the occurrence of AD observed in this study means just delay of AD development or whether the effect persists beyond the first birthday. If the latter were true, primary prevention of AD by a specific mixture of scGOS/lcFOS/pAOS would be an important achievement from a public health perspective.

The number of patients planned for each study group of our trial was calculated to detect a preventive effect of formula supplementation with scGOS/lcFOS/pAOS on the incidence of fever episodes. This limitation of our analysis does not affect the conclusions because the outcomes for its predefined hypotheses were coherent and statistically significant. In accordance with the

TABLE II. Baseline demographic characteristics of the infants per study group

Characteristic	Prebiotic formula (n = 414)	Control formula (n = 416)	Breast-feeding (n = 300)
Age at inclusion (d), median (25th-75th percentile)	30 (20-42)	32 (21-45)	50 (36-54)
Male sex, proportion (%)	220/414 (53.1%)	200/416 (48.1%)	134/300 (44.7%)
Birth weight (g), median (25th-75th percentile)	3277 (2965-3610)	3320 (2930-3625)	3437 (3110-3677)
Gestational age in completed weeks, median (25th-75th percentile)	39 (38-40)	39 (38-40)	40 (39-40)
Cesarean section, proportion (%)	153/414 (37.0%)	144/416 (34.6%)	53/300 (17.7%)
Smoking mother, proportion (%)	79/413 (19.1%)	81/416 (19.5%)	21/300 (7.0%)
Probiotic intake by mother, proportion (%)	59/412 (14.3%)	70/415 (16.9%)	51/300 (17.0%)
Postsecondary education of the mother, proportion (%)	99/413 (24.0%)	112/416 (26.9%)	100/300 (32.4%)
Postsecondary education of the father, proportion (%)	104/403 (25.8%)	116/410 (28.3%)	103/299 (34.4%)
No. of children in household, median (25th-75th percentile)	2 (1-2)	2 (1-2)	2 (1-2)
Furry pets at home, proportion (%)	133/411 (32.4%)	150/413 (36.3%)	95/300 (31.7%)



Infants at risk

Prebiotic formula	413	386	372	365	351	348	342
Control formula	415	390	370	355	345	340	337
Breastfeeding	300	280	267	260	257	255	242

FIG 2. Time to first occurrence of atopic dermatitis. Two infants had a missing onset date of AD and were not included in the survival analysis.

results of previous safety trials,[26,27] formula supplementation with these prebiotics was safe among our study infants (Paola Roggero, February 2010, unpublished data).

The finding that prebiotic supplementation of the diet is effective in primary prevention of AD is paralleling earlier observations in high-risk infants that supplementation of hypoallergenic infant formula with a scGOS/lcFOS reduces the incidence of AD.[18,19] Other studies using hydrolysates or probiotic supplements as strategy for primary prevention of AD have been performed in high atopy risk populations, with variable results.[13-17] Compared with these studies, an effect size of a reduced incidence of AD of about 40% seems a favorable result.

TABLE III. Hazard ratios and 95% CIs for the incidence of AD

Factor	Hazard ratio (95% CI)	*P* value
Prebiotic formula (vs control formula)	0.560 (0.323-0.971)	.039
Full breast-feeding (vs control formula)	0.648 (0.370-1.135)	.130
Female sex (vs male)	0.655 (0.414-1.037)	.071
No furry pets at home (vs pets at home)	1.651 (0.969-2.814)	.066
Postsecondary education of the father (vs secondary education)	2.049 (1.233-3.405)	.006
Age of introduction to solid foods	1.007 (1.000-1.014)	.067
No. of children in household	0.689 (0.497-0.954)	.025

Estimates were obtained by using Cox regression analysis.

TABLE IV. Laboratory data per study group

	Prebiotic formula		Control formula		Breast-feeding		*P* value, prebiotic vs control	
	Age, 6 mo	Age, 12 mo	Age, 6 mo	Age, 12 mo	Age, 6 mo	Age, 12 mo	Age, 6 mo	Age, 12 mo
Samples	157	137	143	122	59	45		
Total serum IgE (kU/L), Least squares mean (95% CI)*	7.5 (6.7-8.5)	13.0 (11.0-15.4)	7.4 (6.6-8.3)	11.9 (10.2-13.8)	7.1 (5.9-8.6)	10.9 (8.2-14.5)	.800	.431
Sensitized to hen's egg (>0.7 kU/L) (%)	2.5	2.2	3.5	2.5	3.4	4.4	.741	1.000
Sensitized to cow's milk (>0.7 kU/L) (%)	1.3	5.1	0	5.7	1.7	2.2	.499	1.000
Serum TARC (pg/mL), Least squares mean (95% CI)†	227 (189-253)	218 (176-271)	204 (164-253)	233 (186-292)	180 (132-246)	166 (112-246)	.461	.680

*Serum levels of total IgE were obtained from a repeated measurement mixed model including study group as fixed effect, week as the repeating factor, and study group by week interaction, and including infant as random effect.

†Serum levels of TARC were obtained from a repeated measurement mixed model including study group as fixed effect, week as the repeating factor, and study group by week interaction, and including infant as random effect. Levels were log-transformed before analysis by using a basis of 10. Values in the table are back-transformed to kU/L (IgE) and pg/mL (TARC). The number of sera for this analysis included at age 6 mo 138, 116, and 49 samples and at age 12 mo 128, 109, and 48 samples from the PG, the CG, and the BG, respectively.

The severity of the disease was not affected significantly in our study, as indicated by the SCORAD index. Similarly, serum levels of TARC did not differ significantly between groups. This finding is compatible with results from the earlier trial with scGOS/lcFOS, in which the severity of AD was not affected, either.[18,19] Prebiotics may be less effective once the disease has been established. A clinical trial looking at the therapeutic effect of these prebiotics for established AD has not been performed yet.

Allergic sensitization to allergens relevant in early life does not seem to be prevented by prebiotics. This finding is in accordance with results from earlier trials investigating probiotics that showed an effect on eczema but not on allergic sensitization.[13,28]

The neutral prebiotic oligosaccharides scGOS and lcFOS most likely act through selective growth promotion of a limited number of bacteria within the colonic microbiota that can improve host health.[29] In experimental models, addition of pAOS to a scGOS/lcFOS-supplemented diet enhanced upregulation of an antiallergic T_H1-type immune response in a dose-dependent fashion through mechanisms that may also include factors beyond selective growth promotion of microbiota.[20,30] To what extent the addition of pAOS to scGOS/lcFOS contributes to a clinical advantage in the primary prevention of AD in infants remains to be elucidated. The preventive effect in this study is similar to the effect in the previous study in high-risk infants without addition of pAOS.[18,19]

In regard to prevention of early AD, the data from our study support a general recommendation of breast milk as first choice for early infant nutrition. In cases in which sufficient breastfeeding is not warranted, a regular infant formula/follow-on formula supplemented with a specific mixture of scGOS/lcFOS/pAOS would be a promising alternative for infants at low risk for atopy. Most infants developing AD are expected to derive from this risk stratum. In this low atopy risk scenario, 25 infants would be needed to be treated to prevent AD in 1 infant during the first year of life.

In conclusion, this trial shows that formula supplementation with a specific mixture of scGOS/lcFOS/pAOS is effective as primary prevention of AD in infants from low atopy risk populations. We speculate that the effect persists beyond the first birthday and may even result in a reduced incidence of respiratory allergy later in life. Follow-up of our cohort is in progress to answer these questions.

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Clinical implications: Formula supplementation with a specific mixture of acidic and neutral oligosaccharides is effective as primary prevention of AD in infants from low atopy risk populations.

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