

Certain hydrolyzed formulas reduce the incidence of atopic dermatitis but not that of asthma: Three-year results of the German Infant Nutritional Intervention Study

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Background: Recommendations for primary prevention of allergic diseases in high-risk children include feeding with hydrolyzed formulas if breast-feeding is insufficient.

Objective: The primary objective of the German Infant Nutritional Intervention study was to investigate the allergy preventive effect of 3 hydrolyzed formulas compared with cow's milk formula in the first 3 years of life in a randomized, double-blind trial.

Methods: Between 1995 and 1998, 2252 newborns with atopic heredity were allocated to a group receiving cow's milk formula, partially or extensively hydrolyzed whey formula, or extensively hydrolyzed casein formula as a milk substitute for the first 4 months if breast-feeding was insufficient. Main outcome parameters were allergic manifestations, atopic dermatitis (AD), and asthma.

Results: After 3 years, 396 of 2252 children (17.6%) had dropped out. Breast-fed infants without formula feeding during the intervention (n = 889) were considered separately. A

significant reduction of the incidence of AD was achieved with the extensively hydrolyzed casein formula in the intention-to-treat (ITT; n = 1363) and per protocol (PP; n = 904) analyses (ITT: population odds ratio [95% CI], 0.67 [0.45-0.99]; PP: adjusted odds ratio (OR_{adj}), 0.53 [0.32-0.88]), and with the partially hydrolyzed whey formula in the PP analysis (ITT: population odds ratio, 0.76 [0.52-1.11]; PP:OR_{adj}, 0.60 [0.37-0.97]). None of the formulas reduced the incidence of asthma.

Conclusion: The risk for AD, but not for asthma, can be reduced with certain cow's milk hydrolyzates in high-risk infants when breast-feeding is insufficient.

Clinical implications: Early nutritional intervention in high-risk children has significant influence on the incidence of AD, but not of asthma. (J Allergy Clin Immunol ■■■■;■■■: ■■■-■■■.)

Key words: Birth cohort, randomized trial, cow's milk formula, hydrolyzed formula, breast-feeding, prevention, atopic dermatitis, asthma

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The increase in allergic diseases over the last decades has become a challenge for all physicians, especially for pediatricians working in primary prevention. Early contact to food allergens plays a major role for the development of sensitization and allergic manifestations in early infancy.¹ Therefore, allergen avoidance measures are the goal for primary allergy prevention. Consequently, the guidelines on infant nutrition recommend exclusive breast-feeding for 4 to 6 months. In case of insufficient breast feeding, a hypoallergenic formula is advised for infants with a genetically determined risk for allergies.^{2,3} However, the optimal extent of protein hydrolysis, partial or extensive, in cow's milk-based formulas needed to avoid sensitization and allergic manifestation and/or to induce tolerance is unknown.

In several studies, the allergy preventive potential of partially or extensively hydrolyzed formulas has been compared with regular cow's milk formula.⁴⁻⁹ However, most studies included only small numbers of infants, did not have strictly defined outcome parameters, and/or did not perform a head-to-head comparison of extensively and partially hydrolyzed formulas compared with cow's

Abbreviations used

AD:	Atopic dermatitis
AM:	Allergic manifestation
ARR:	Absolute risk reduction
CMF:	Cow's milk formula
eHF-C:	Extensively hydrolyzed casein formula
eHF-W:	Extensively hydrolyzed whey formula
GEE:	Generalized estimation equation
GINI:	German Infant Nutritional Intervention
ITT:	Intention to treat
NNT:	Number needed to treat
OR:	Odds ratio
pHF-W:	Partially hydrolyzed whey formula
POR:	Population odds ratio
PP:	Per protocol
RRR:	Relative risk reduction

milk formula. Therefore, it remains controversial which type of hydrolyzed formula is more beneficial to prevent the most common allergic manifestations, particularly atopic dermatitis (AD) and asthma.

The German Infant Nutritional Intervention (GINI) study was initiated to compare the allergy preventive effect of 3 hydrolyzed formulas with a standard cow's milk formula as the only substitute to breast-feeding in high-risk children in the first 4 months of life. This prospective trial is by far the largest study in this field, and the only one that was sponsored by a governmental grant and therefore is independent of industry involvement. Recently we reported the results of the study at 1 year of age on early manifestations excluding those of the respiratory tract.¹⁰ Here, we present the follow-up data at 3 years of age, including the effect on the development of asthma.

METHODS

The GINI trial is a prospective, randomized, double-blind intervention study that follows the development of atopic manifestations in a cohort of 2252 infants with single (1 parent and/or sibling) or biparental heredity for atopy. Details of design, recruitment, and follow-up of the study have been described previously.¹⁰ At birth, children were randomly allocated to 1 of 3 hydrolyzed infant formulas or a regular cow's milk formula (partially hydrolyzed whey [pHF-W; Beba-HA], extensively hydrolyzed whey [eHF-W; HIPP-HA (at that time identical with Nutrilon Pepti)], extensively hydrolyzed casein formula [eHF-C; Nutrainingen], standard cow's milk formula [CMF; Nutrilon Premium]), which should be the only milk substitute to breast-feeding if needed during the first 16 weeks of life (intervention period).¹⁰

Exclusive breast-feeding for the first 4 months with the introduction of solid foods postponed to after the end of the fourth month was recommended. Parents were asked to keep weekly diaries to record milk feeding characteristics and time of introduction and diversity of solids.

At the end of the intervention period, infants were separated according to their feeding regimen. Only results of infants who were fed study formula (interventional arm) were relevant for the main questions; breast-fed infants who did not receive study formula (observational arm) were not relevant but were analyzed separately.

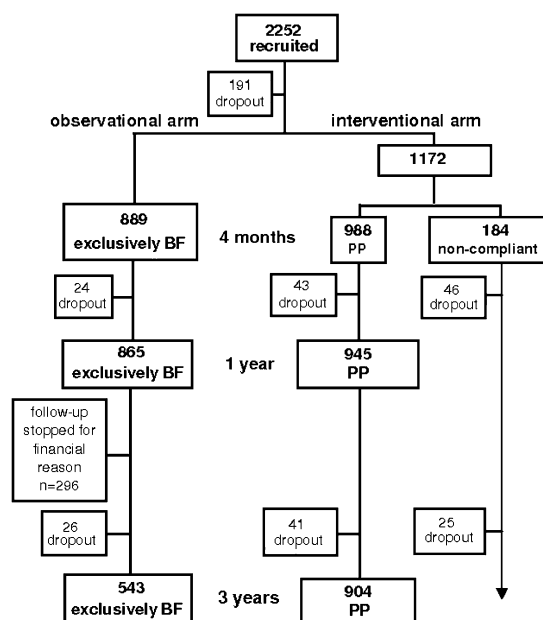


FIG 1. GINI trial profile from birth to 3 years. PP analysis in children of the interventional arm at 4 month and 1 and 3 years. The ITT analysis (N = 1363) included the 191 early dropouts and all children of the interventional arm (N = 1172). The observational arm included all children who were exclusively breast-fed for 4 months (BF).

Written informed consent was obtained from both parents. The study was approved by the local ethics committees.

Outcome parameters

The clinical diagnosis of allergic manifestation (AM) at 3 years included AD, urticaria, food allergy with manifestation in the gastrointestinal tract as previously defined,¹⁰ and asthma. Asthma was first diagnosed in the third year and considered when parents reported ≥ 3 episodes of wheezing or nighttime cough without infection, or regular use of asthma medication for obstructive symptoms (β_2 -agonists, ipratropiumbromide, inhaled or systemic steroids, dinitrochromoglycate, theophylline, or leukotriene inhibitors).

Statistics

Details on the sample size calculation were given previously, and the power calculation was based on children who received study formula.¹⁰ Two ITT analyses were performed: first, on all randomized children (n = 2252), and second, after exclusion of the 889 breast-fed infants in the observational arm. The second one seems to be the more meaningful analysis because the outcomes of the infants in the observational arm were not relevant for the main study questions. To model longitudinal data with missing outcome caused by loss to follow-up, generalized estimation equations (GEEs) were used, and as results, population odds ratios (PORs) are reported.^{11,12} Per protocol (PP) analysis was performed in all infants fed with study formula within the first 4 months (interventional arm) who were compliant with the milk feeding recommendations and followed until 3 years of age. In this fixed cohort population, the risk of a disease was estimated by simple cumulative method. The cumulative incidence was calculated as the proportion of new cases diagnosed during the observation period to disease-free subjects at the beginning. Period prevalence was estimated as the proportion of the number of cases observed anytime during the targeted follow-up period to the size (N) of the followed population.

TABLE I. Results of the ITT analyses: PORs from marginal logistic models using GEE by study formula in comparison with cow's milk feeding

	CMF	pHF-W POR (95% CI)	eHF-W POR (95% CI)	eHF-C POR (95% CI)
All infants excluding exclusively breast-fed infants from the observational arm; completed 12-month follow-up, n = 1083; completed 3-year follow-up, n = 1017				
No. of followed children (N = 1363)	356	335	334	338
AM* period prevalence, first year (n = 144)	1	0.80 (0.51-1.24)	0.93 (0.62-1.41)	0.63 (0.40-1.01)
Period prevalence, third year (n = 192)	1	0.89 (0.57-1.37)	0.99 (0.65-1.51)	0.70 (0.44-1.11)
Cumulative incidence, birth to 3 years (n = 312)	1	0.87 (0.64-1.19)	1.03 (0.77-1.40)	0.80 (0.58-1.09)
AD period prevalence, first year (n = 130)	1	0.74 (0.46-1.18)	0.90 (0.59-1.39)	0.54 (0.32-0.89)
Period prevalence, third year (n = 86)	1	0.52 (0.28-0.97)	0.78 (0.45-1.38)	0.53 (0.28-1.00)
Cumulative incidence, birth to 3 years (n = 206)	1	0.76 (0.52-1.11)	0.99 (0.69-1.41)	0.67 (0.45-0.99)
Asthma period prevalence, third year (n = 111)	1	1.30 (0.75-2.27)	1.37 (0.79-2.36)	0.93 (0.51-1.69)
All infants including exclusively breast-fed infants from the observational arm; completed 12-month follow-up, n = 1948†; completed 3-year follow-up, n = 1560†				
No. of followed children (N = 2252)	556	557	559	580
AM* period prevalence, first year (n = 242)	1	0.90 (0.64-1.27)	0.97 (0.69-1.35)	0.72 (0.51-1.03)
Period prevalence, third year (n = 299)	1	0.88 (0.62-1.25)	1.06 (0.75-1.49)	0.63 (0.43-0.92)
Cumulative incidence, birth to 3 years (n = 518)	1	0.94 (0.73-1.20)	1.08 (0.85-1.37)	0.82 (0.64-1.06)
AD period prevalence, first year (n = 216)	1	0.88 (0.61-1.26)	1.00 (0.70-1.41)	0.65 (0.44-0.96)
Period prevalence, third year (n = 134)	1	0.63 (0.38-1.03)	0.87 (0.55-1.37)	0.52 (0.31-0.88)
Cumulative incidence, birth to 3 years (n = 348)	1	0.90 (0.67-1.22)	1.09 (0.82-1.45)	0.78 (0.57-1.06)
Asthma period prevalence, third year (n = 168)	1	1.20 (0.76-1.88)	1.29 (0.82-2.00)	0.83 (0.51-1.36)

FA-GIT, Food allergy with manifestation in the gastrointestinal tract.

Boldface indicates a significant effect.

*Defined by any of AD, FA-GIT, urticaria for the first 3 years, and obstructive airways disease in the third year only.

†See Fig 1.

Effects were analyzed by means of multiple logistic regression models. Adjusted odds ratios (ORs) with 95% CIs were calculated. Sex and the remaining variables of the backward stepping procedure for each of the interesting outcomes, separately, were chosen for adjustment.¹⁰ Potential risk factors were defined as those with significant ($P < .10$) influence on the disease in the univariate analyses. Length of breast-feeding was additionally considered as a potential confounder. For estimation of the clinical benefit of the different hydrolyzates, we calculated the relative risk reduction (RRR), the absolute risk reduction (ARR), and the number needed to treat (NNT) to avoid 1 case of AD.

Statistical analyses were performed by using the Statistical Analysis System (SAS) for Windows, Release 8.2 (SAS Institute, Cary, NC).

RESULTS

Study population

From 1995 to 1998, a total of 2252 newborns were recruited, of whom 60.5% (n = 1363) qualified for the intervention part and 39.5% (n = 889) formed the observational part of the study.

The total dropout rate in the first year was 13.5% (304/2252), and after 3 years, 17.6% (396/2252; Fig 1). Major reasons for dropouts were personal problems in the families, nutritional problems of the infant, and change of residency outside the study region, being equally distributed between the study groups at 1 year¹⁰ and at 3 years.

From the 1363 infants in the intervention part, 1172 (86%) completed the intervention period of 4 months, of whom 988 followed the milk feeding protocol, whereas 184 were considered noncompliant as previously described.^{10,13} The 1-year follow-up was completed for 945 compliant infants, of whom 41 children dropped out in the second and third year with no difference between formula groups: 11 (CMF), 12 (pHF-W), 8 (eHF-W), 10 (eHF-C). The remaining 904 children formed the basis for the PP analysis at 3 years to answer the main question of the study.

Baseline sociodemographic and feeding characteristics of the 4 study groups, including time of first introduction of formula and duration of formula feeding,¹⁰ were comparable.

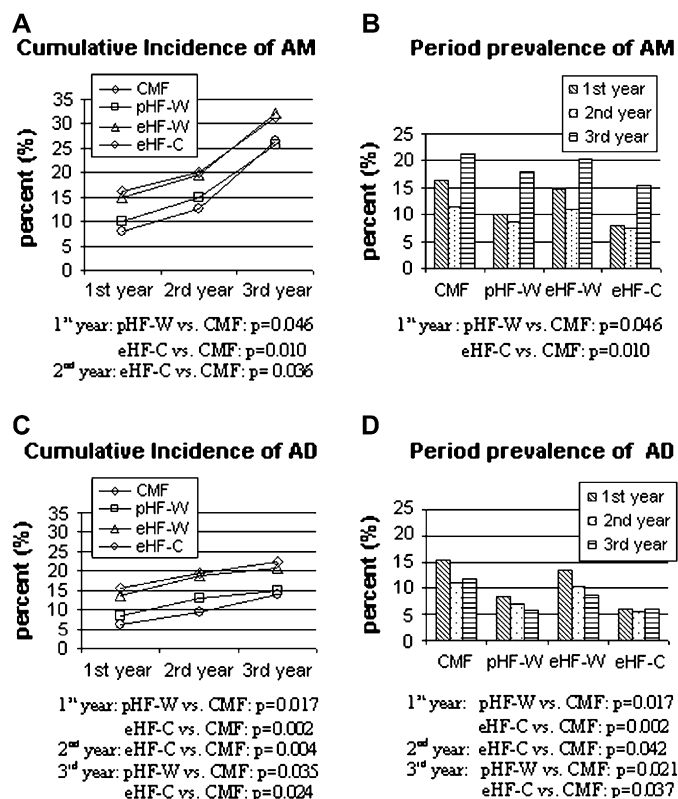


FIG 2. Crude cumulative incidence and period prevalence of AM (A, B) and of AD (C, D) in the 4 study groups during the first 3 years. Results of the per protocol analysis.

ITT analysis

The main ITT analysis at 3 years included 1363 children (2252 except 889 breast-fed infants; Fig 1). The proportion of missing outcome information because of dropouts at all examination times was equal in the 4 randomized groups (statistically tested, data not shown). In the first 3 years, 312 children developed at least 1 AM, $\frac{2}{3}$ of the cases presented with AD ($n = 206$), $\frac{1}{3}$ presented with asthma ($n = 111$), and only few children had more than 1 AM (Table I). During the first 3 years, a preventive effect could be observed for AD only. Compared with CMF, eHF-C showed a significantly reduced period prevalence at 1 and 3 years, and also 3-year incidence of AD (OR [95% CI]: 0.67 [0.45-0.99]; Table I). pHF-W demonstrated a significant reduction of the period prevalence of AD at 3 years, but the effect on the 3-year incidence for AD (24%) and for AM (13%) failed to reach significance (Table I).

Table I shows the results of the ITT analysis of all 2252 randomized children. The inclusion of infants from the observational arm slightly diluted the results of the main ITT analysis.

PP analysis

The PP analysis included 904 children (Fig 1). Because dropouts and noncompliant children were excluded from this analysis, the effects are stronger than in the ITT

analysis. The mean cumulative incidence for AM increased from 12.3% in the first to 29% in the third year of life; the corresponding data for AD were 10.8% and 18.1%. In the third year of life, asthma was the most prevalent allergic manifestation (mean, 11.1%). The period prevalence of AD had declined in mean from 10.8% in the first year of life to 8.6% and 8.05% in the second and third years, respectively.

Fig 2 depicts the results for the different study formulas. It shows that the effect of pHF-W and eHF-C on AM and AD develops in the first year and is carried on until 3 years, whereas the incidence of new cases in the second and third year is similar in the 4 study groups (Fig 2, A and C). The relatively steep increase in the cumulative incidence of AM in the third year is a result of the addition of asthma to the overall diagnosis of AM at 3 years (Fig 2, A and B). The prevalence of AD declines in all study groups; eHF-C was significantly reduced at all 3 time points and pHF-W at 1 and 3 years (Fig 2, D).

Table II highlights the results for the different hydrolyzed formulas compared with CMF for the main outcome parameters after adjustment for relevant confounders. The prevalence of asthma was not affected by any of the 3 hydrolyzed formulas. However, the significant disease reduction of AD found in the 1-year results¹⁰ could be confirmed at 3 years in the eHF-C-fed infants for the cumulative incidence and for the period prevalence.

TABLE II. Results of the PP analysis (N = 904): risk of developing AMs by study formula and adjusted ORs by logistic regression in comparison with cow's milk feeding

	N	CMF 245	pHF-W 229	eHF-W 230	eHF-C 200
AM*					
Period prevalence, first year	Cases (%)	40 (16.3)	23 (10.0)	34 (14.8)	16 (8.0)
	Adj† OR (95% CI)	1	0.57 (0.33-0.99)	0.85 (0.51-1.41)	0.43 (0.23-0.80)
Period prevalence, third year	Cases (%)	52 (21.2)	41 (17.9)	47 (20.4)	31 (15.5)
	Adj† OR (95% CI)	1	0.81 (0.51-1.28)	0.93 (0.60-1.46)	0.66 (0.40-1.09)
Cumulative incidence, birth to 3 years	Cases (%)	77 (31.4)	59 (25.8)	74 (32.2)	53 (26.5)
	Adj† OR (95% CI)	1	0.76 (0.50-1.13)	1.01 (0.68-1.49)	0.76 (0.50-1.16)
AD					
Period prevalence, first year	Cases (%)	38 (15.5)	19 (8.3)	31 (13.5)	12 (6.0)
	Adj§ OR (95% CI)	1	0.49 (0.27-0.88)	0.81 (0.48-1.36)	0.33 (0.17-0.66)
Period prevalence, third year	Cases (%)	29 (11.8)	13 (5.7)	20 (8.7)	12 (6.0)
	Adj§ OR (95% CI)	1	0.46 (0.23-0.90)	0.68 (0.37-1.25)	0.46 (0.23-0.93)
Cumulative incidence, birth to 3 years	Cases (%)	55 (22.5)	34 (14.9)	48 (20.9)	28 (14.0)
	Adj§ OR (95% CI)	1	0.60 (0.37-0.97)	0.87 (0.56-1.37)	0.53 (0.32-0.88)
Asthma					
Period prevalence, third year	Cases (%)	25 (10.2)	28 (12.2)	29 (12.6)	19 (9.5)
	Adj OR (95% CI)	1	1.14 (0.64-2.05)	1.25 (0.70-2.22)	0.92 (0.48-1.74)

GIT, Gastrointestinal tract.

Boldface indicates a significant effect.

*Defined by any of AD, GIT, urticaria for the first 3 years, and obstructive airways disease in the 3rd year only.

†Adjusted for family history of AD and asthma, sex, passive smoking in the third year.

‡Adjusted for family history of AD and asthma, sex, maternal smoking in the first year.

§Adjusted for family history of AD, sex, and maternal smoking in the first year.

||Adjusted for family history of asthma, sex, maternal smoking in the first year, pets in household, and study region.

TABLE III. PORs from marginal logistic models using GEE by study formula in comparison with cow's milk feeding, stratified by family history (FH) for AD or asthma: results of the ITT analysis

	pHF-W POR (95% CI)	eHF-W POR (95% CI)	eHF-C POR (95% CI)
All infants excluding exclusively breast-fed infants from the observational arm; completed 12-month follow-up, n = 1083; completed 3-year follow-up, n = 1017			
No AD in FH			
N (867)	223	198	210
Cumulative incidence of AD, birth to 3 years (n = 106)	0.65 (0.38-1.11)	0.81 (0.48-1.37)	0.78 (0.47-1.30)
AD in FH			
N (496)	112	136	128
Cumulative incidence of AD, birth to 3 years (n = 100)	0.91 (0.53-1.59)	1.10 (0.66-1.81)	0.53 (0.29-0.98)
No asthma in FH			
N (963)	231	238	242
Period prevalence of asthma, third year (n = 70)	1.10 (0.53-2.28)	1.50 (0.76-2.95)	1.17 (0.56-2.41)
Asthma in FH			
N (400)	104	96	96
Period prevalence of asthma, third year (n = 41)	1.62 (0.68-3.85)	1.17 (0.46-2.93)	0.55 (0.18-1.69)

Boldface indicates a significant effect.

Also, the risk reduction with pHF-W remained significant for the cumulative incidence and the third year prevalence. No significant preventive effect was observed in children fed with eHF-W.

Only a small proportion of children randomized to each feeding group had received study formula as the only milk feeding during the first 4 months of life (5.0% to 7.6%; NS). The 3-year cumulative incidences of AD in these subgroups were as follows: CMF, 8 of 42 (19%); pHF-W,

3 of 31 (10%); eHF-W, 6 of 31 (19%); eHF-C, 2 of 29 (7%). For asthma, the figures were as follows: CMF, 4 of 42 (10%); pHF-W, 7 of 31 (23%); eHF-W, 9 of 31 (29%); eHF-C, 2 of 29 (7%); differences not tested because of the small group sizes).

Stratification for genetic risk factors

To test the exploratory hypothesis generated from the 1-year PP analysis that the genetic background modifies the

preventive potential of formulas,¹⁰ we performed additional stratified post hoc analyses with respect to a family history of eczema and asthma on the basis of the 1363 children included in the ITT analysis. In children with no eczema in the family history ($n = 867$), we observed a (nonsignificant) risk reduction of AD with the 3 hydrolyzates (pHF-W, 35%; eHF-W, 19%; eHF-C, 22%). In contrast, in the 496 children with eczema in their family, the risk for developing AD was reduced only with eHF-C (OR, 0.55; $P = .04$). Stratification with respect to asthma showed that eHF-C had a considerable reduction of asthma in children with a positive family history for asthma ($n = 400$; OR, 0.55; NS; Table III). The respective PP analysis confirmed these results, showing even more pronounced differences of the formula effects depending on the phenotype in the family: if the family history for AD is positive, eHF-C reduces AD significantly (adjusted OR, 0.44; $P = .05$), whereas in children without AD in the family, pHF-W is effective (adjusted OR, 0.45; $P < .05$).

NNT

On the basis of the ITT analysis, the RRRs for eHF-C and pHF-W were 29% and 23%, respectively; the ARR decreased to 5.0% for eHF-C and to 4.0% for pHF-W. On the basis of the PP analysis, the adjusted RRR was 38% for eHF-C and 34% for pHF-W, and corresponding values for the ARR were 8.5% and 7.6%, respectively. The mean NNT calculated from the main ITT analysis was similar for eHF-C and pHF-W: 20 versus 25, respectively, and 12 versus 13 according to the PP analysis. In the subgroup of children with a family history for AD, however, the mean NNT (from ITT analysis) to avoid 1 case of AD was 11 for eHF-C compared with 51 in children who received pHF-W.

DISCUSSION

The 3-year results of this large-scale, prospective, randomized, double-blind trial clearly confirm the concept that the risk for AD but not for early asthma can be reduced by nutritional intervention in infants at high risk for allergic diseases. The strength of the preventive effect seems to depend on the type of formula used as well as on the compliance with the feeding recommendations in the first 4 months of life. Children who were supplemented with either eHF-C or pHF-W instead of normal CMF had AD significantly less often. The preventive effect developed in the first year and persisted into the third year, indicating real disease reduction rather than postponement of disease onset.

The GINI study has several major strengths compared with previous randomized, double-blind nutritional intervention trials in high-risk infants.^{4,6,8,14-16} The large scale and the independence from industry support make it a unique study. Compared with other studies, we had more strictly defined endpoints and very intense monitoring with weekly diaries during the first 6 months of life to assess symptoms, feeding characteristics, and violation of the protocol.^{10,13} For logistic reasons in a

large study like GINI, we, like others,^{15,17} randomized children at birth rather than at weaning and provided the parents with the blinded study formula to avoid the feeding of another formula than the study formula. We anticipated that possible feeding differences would be equalized between the study groups because of the large number of children. The power calculation took the high rate of exclusive breast-feeding in Germany into account. Although the duration of breast-feeding was generally unpredictable, our randomization procedure did not influence the equal distribution of breast-feeding (variable duration until start of formula feeding) and thus the dose of formula protein given to the children between the 4 formula groups during the intervention period. In addition, the proportion of compliance with recommendations for solid food introduction was similar in the study groups (not shown). The main drawback of the randomization process at birth rather than at weaning is the high number of dropouts during the first 4 months of life ($n = 191$; Fig 1), which may also include exclusively breast-fed infants. This procedure also made it necessary to perform 2 types of ITT analyses.

Although it remains controversial whether breast-feeding reduces the risk for allergy in high-risk infants,^{5,18,19} breast-feeding is the gold standard for infant nutrition. It was therefore not the goal of our study to question this gold standard and show that hydrolyzates are worse or better. Instead, we wanted to evaluate, in case of formula feeding (for whatever reason), which formula would be the best alternative to reduce the risk for AMs.

The design of our study took this into consideration, because breast-feeding for the first 4 months was recommended.

Although the primary objective of the study was the prevention of any allergic disease, we concentrated on AD and asthma in our final analyses. Allergic rhinitis is very rare within the first 3 years of life, but will be considered as an endpoint at the 6-year follow-up. The incidence of food allergy with and without gastrointestinal manifestations was very low in our study compared with others.^{14,16} Our endpoint definitions included the proof of association between clinical symptoms and suspected allergens by double-blind placebo-controlled challenges. This turned out to be a major flaw of the study, because many parents did not agree to the challenge procedures requiring hospital admission. Therefore, it is very likely that we have underreported the prevalence of food allergy including cow's milk protein allergy, as well as of allergic urticaria.

The GINI study could not confirm the preventive effect of hydrolyzed formulas on early wheezing that was reported in previous studies using the same pHF-W or eHF-C.^{14,16} Again, this may be related to our strict definition of asthma, which tried to distinguish between allergic asthma and infant wheeze. However, our results are in line with trials that showed no effect of the nutritional intervention on asthma in children older than 18 months unless concomitant environmental cointerventions were implemented.^{20,21} Because asthma is more a disease of children

older than 3 years, we may have more meaningful data at the 6-year follow-up, when lung function tests will be performed.

The lack of effect of the eHF-W used in this study is not understood. This particular formula has never been studied previously for its allergy preventive effect. Halken et al¹⁵ investigated a different eHF-W (Prophylac, ALK Laboratories A/S, Hørsholm, Denmark) and found it equally as preventive as eHF-C. According to findings in the literature, we can only speculate that the hydrolyzing process of the eHF-W in our study may result in the persistence or occurrence of some antigenic or loss of tolerogenic activity.²²⁻²⁶ This would confirm findings from *in vitro* studies that the degree of hydrolysis, the resulting molecular weight, and the protein source have little predictive value on the immunogenic or allergenic effect and thus on the clinical outcome.²²⁻²⁶

Therefore, only those formulas should be used and recommended for allergy prevention that have been proven efficacious in clinical trials.

Although the PP analysis proved the preventive effect, the ITT analysis better reflects the real-life situation, when mothers and others caregivers might not be entirely compliant with the milk feeding recommendations. As expected, the results in the ITT analysis are somewhat weaker, and only feeding eHF-C revealed a significant reduction of AD compared with CMF over the 3-year period. However, the period prevalence in the third year of life remained significantly reduced for both eHF-C and pHF-W. Considering the much higher cost of eHF-C compared with pHF-W, the cost/benefit ratio seems to be in favor of the pHF-W. However, the cost/benefit calculation may differ in certain subgroups. Children with a family history for AD benefit most from eHF-C (Table III). This is indeed the first study to suggest that the allergic phenotype in the family rather than a biparental family history modifies the effect of nutritional intervention and may be considered when deciding which hydrolyzate should be given. Because these results are derived from a post hoc analysis, they are hypothetical. However, the discovery of phenotype-specific susceptibility genes^{27,28} supports our hypothesis and suggests that in future studies, stratification should be based on the allergic phenotype in the family.

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