Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study

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Background: The long-term effect of nutritional intervention with hydrolysate infant formulas on allergic manifestations in high-risk children is uncertain.

Objective: We sought to investigate the effect of hydrolysate infant formulas on allergic phenotypes in children with family history of allergies at school age.

Methods: We analyzed data from participants of the prospective German Infant Nutritional Intervention study after 10 years of follow-up. At birth, children were randomly assigned to receive, for the first 4 months, one of 4 blinded formulas as breast milk substitute, if necessary: partially hydrolyzed whey formula (pHF-W), extensively hydrolyzed whey formula (eHF-W), extensively hydrolyzed casein formula (eHF-C), or standard cow's milk formula. Outcomes were parent-reported, physician-diagnosed allergic diseases. Log-binomial regression models were used for statistical analysis.

Results: The relative risk for the cumulative incidence of any allergic disease in the intention-to-treat analysis (n = 2252) was 0.87 (95% CI, 0.77-0.99) for pHF-W, 0.94 (95% CI, 0.83-1.07) for eHF-W, and 0.83 (95% CI, 0.72-0.95) for eHF-C compared with standard cow's milk formula. The corresponding figures for atopic eczema/dermatits (AD) were 0.82 (95% CI, 0.68-1.00), 0.91 (95% CI, 0.76-1.10), and 0.72 (95% CI, 0.58-0.88), respectively. In the per-protocol analysis (n = 988) effects were stronger. The period prevalence of AD at 7 to 10 years was significantly reduced with eHF-C in this analysis, but there was no preventive effect on asthma or allergic rhinitis.

Conclusion: The significant preventive effect on the cumulative incidence of allergic diseases, particularly AD, with pHF-W and eHF-C persisted until 10 years without rebound, whereas eHF-W showed no significant risk reduction. There is insufficient evidence of ongoing preventive activity at 7 to 10 years of age. (J Allergy Clin Immunol 2013;131:1565-73.)

Key words: *Birth cohort, double-blind randomized trial, nutritional intervention, cow's milk protein hydrolysate infant formulas, long-term allergy prevention*

Early nutritional intervention with cow's milk protein hydrolysate infant formulas (CMPHIFs) has shown a significant reduction of allergic manifestation in children with a family history for atopy.[1-8] Most of the studies demonstrated a preventive effect mainly on atopic eczema/dermatitis (AD)[6-8] but also on food allergy and early wheezing.[9-12] Because only a few studies could follow the children into school age, little is known about the long-term effects of early intervention with CMPHIFs on the persistence and development of allergic phenotypes at school age.[9,13,14]

Recently, we have shown that high-risk 6-year-old children have a reduced risk for AD but not for asthma or allergic rhinitis if they were fed in the first 4 months of life either exclusively or as a supplement to breast milk with one of 3 CMPHIFs, a partially hydrolyzed whey formula (pHF-W), an extensively hydrolyzed whey formula (eHF-W), or an extensively hydrolyzed casein formula (eHF-C), compared with standard cow's milk formula (CMF).[6] Although CMPHIFs are generally recommended for children at risk as a

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*Members of the GINIplus study group at 10 years are listed in the Online Repository.

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Abbreviations used

AD: Atopic eczema/dermatitis
AM: Allergic manifestation
aRR: Adjusted relative risk
CMF: Standard cow's milk formula
CMPHIF: Cow's milk protein hydrolysate infant formula
eHF-C: Extensively hydrolyzed casein formula
eHF-W: Extensively hydrolyzed whey formula
GEE: Generalized estimating equations
GINI: German Infant Nutritional Intervention
ISAAC: International Study on Asthma and Allergy in Childhood
ITT: Intention-to-treat
mITT: Modified intention-to-treat
NNT: Number needed to treat
pHF-W: Partially hydrolyzed whey formula
PP: Per protocol
RR: Relative risk

supplement for breast-feeding in the first 4 to 6 months in Europe, and pHF-W has been used recently in the United States,[15-17] this recommendation has been questioned for several reasons, such as lack of blinding; lack of double-blind, placebo-controlled food challenges; no effect on objective markers, such as specific IgE levels; lack of a universally accepted biologic mechanism to explain the effect[18]; and no or only modest evidence that allergic symptoms are truly prevented rather than only delayed.[18,19] One recent small study showed no preventive potential of pHF-W on AD,[20] and another study has favored introduction of CMF in the first 14 days of life for allergy prevention.[21] Because these 2 study results were based on small numbers, had severe limitations, or both,[22] we used the large dataset of the 10-year follow-up of the German Infant Nutritional Intervention (GINI) study to investigate the effect of early feeding with CMPHIFs on the allergic phenotypes of any allergic manifestation (AM), atopic eczema/dermatitis (AD), asthma, and allergic rhinitis at school age. Specifically, we were interested whether the previously observed preventive effect of the hydrolysate formulas on AD persists until school age and whether childhood asthma can be prevented by nutritional intervention through the oral route.

METHODS

Study design and population

The GINI study is an ongoing birth cohort study set up to investigate the preventive effect of different CMPHIFs in children with first-degree allergic heredity. Details of design, sample size, recruitment, outcome definitions, and follow-up have been published previously.[4-6] In brief, between September 1995 and July 1998, healthy term newborns were recruited at birth in 2 regions of Germany (rural Wesel and urban Munich). High-risk infants, who were defined as having at least 1 parent or biological sibling with a history of allergic disease, were selected by questionnaire (n = 2252). If the parents agreed to participate in the prospective, double-blind intervention trial, newborns were randomly allocated at birth by a computer-generated list to one of 3 hydrolyzed study formulas: pHF-W (Beba HA; Nestlé, Vevey, Switzerland); eHF-W (Hipp HA; Hipp, Pfaffenhofen, Germany, until 1999 on the German market and identical to Nutrilon Pepti, Nutricia/Numico, Zoetermeer, The Netherlands), and eHF-C (Nutramigen; Mead Johnson, Diezenbach, Germany) or CMF (Nutrilon Premium; Nutricia/Numico, Zoetermeer, The Netherlands) to be administered if breast-feeding needed to be supplemented or discontinued. Randomization was conducted stratified for uniparental or biparental allergic heredity and study region.[4] The infants were enrolled before any formula supplementation was necessary and at the latest at 14 days of age. Mothers were advised to feed the randomized formula as the only substitute to breast milk during the strict intervention period of 4 months, if necessary. The strict intervention period was defined as 16 weeks, although study formula was provided for 6 months. The aim was to avoid modification of the formula effect by solid foods. The study protocol was approved by local ethic committees, and written informed consent was obtained from all participating families. Ethics approval was repeated for the follow-up examinations at 6 and 10 years.

Follow-up examination

The follow-up examination at 10 years was divided into 2 steps. First, an International Study on Asthma and Allergy in Childhood (ISAAC) modified questionnaire[23] was sent to parents to collect information on health outcomes, allergic symptoms, physician's diagnosis of allergic diseases, and several covariates.[6] In a second step, all children were invited to the study center for physical examination and blood sampling.

Determination of outcomes and covariates by using questionnaires

The outcome of interest for this analysis was the cumulative incidence until 10 years and the period prevalence at age 7 to 10 years of parent-reported physician's diagnosis of any allergic manifestation (AM), which was defined by any of the following diseases: atopic eczema/dermatitis (AD), urticaria and food allergy/intolerance, asthma, and hay fever/allergic rhinitis.[24] The parents were asked the following: "Did a physician diagnose any of the following diseases during the 1st/2nd/3rd/4th/5th/6th/7th/8th/9th/10th year of life: […] asthma, allergic or atopic eczema/dermatitis, hay fever/allergic rhinitis, urticaria, food allergy? […]." A specific disease (asthma, eczema, or rhinitis) at school age was defined as present if, at 10 years, the parents reported a physician's diagnosis during the last 4 years, treatment in the last 12 months, or both for that specific disease.

The following covariates were reported at birth and regarded as potential confounders: sex; study region (Munich or Wesel); heredity of family allergy; family history of eczema, asthma, and hay fever; parental education (3 categories by years of schooling); and number of older siblings. Information on furry pets in the home was gathered yearly by using questionnaires, and passive tobacco smoke exposure was queried on and after the second year.

Symptoms of "wheezing" were defined by the ISAAC questions[25] as wheezing and whistling in the chest ever or in the last 12 months. Flexural rash was defined as an itchy rash that came and went for at least 6 months, affecting the elbow or knee bends, the front of the ankles, or the skin under the buttocks and around the neck, ears, or eyes. Symptoms of rhinitis were defined as a problem with sneezing or a runny or blocked nose without cold or flu accompanied by itchy-watery eyes. Parent-reported allergies were defined by using the following question: "Has your child ever had atopic dermatitis/atopic eczema, asthma, hay fever?"

Additionally, for asthma and eczema, age at the beginning and, if applicable, end of the symptoms and whether these symptoms were present at the time of the examination were queried.

Levels of specific IgE to the most common food and inhalant allergens were measured with the CAP System (Pharmacia, Freiburg, Germany) at the age of 10 years. We used the screening test "Kindernahrung" (FX5, children's food, containing hen's egg, milk protein, codfish, soybean, peanut, and wheat) and "Inhalation-mix" (SX1, containing *Dermatophagoides pteronyssinus*, rye, timothy grass, mugwort, birch pollen, *Cladosporium* species, and cat and dog dander). Single allergens were tested in the case of positive results. Additionally, we measured levels of specific IgE to ragweed. Sensitization was defined as positive if at least 1 specific IgE level was 0.35 kU/L or greater (ie, CAP class 1).

Statistics

Intention-to-treat (ITT) and per-protocol (PP) analyses were performed. The ITT population consisted of all primarily randomized children (n = 2252). Additionally, a modified intention-to-treat (mITT) analysis was done in which the population was restricted to those with certain or uncertain exposure to any study formula (n = 1615) by excluding all children who did

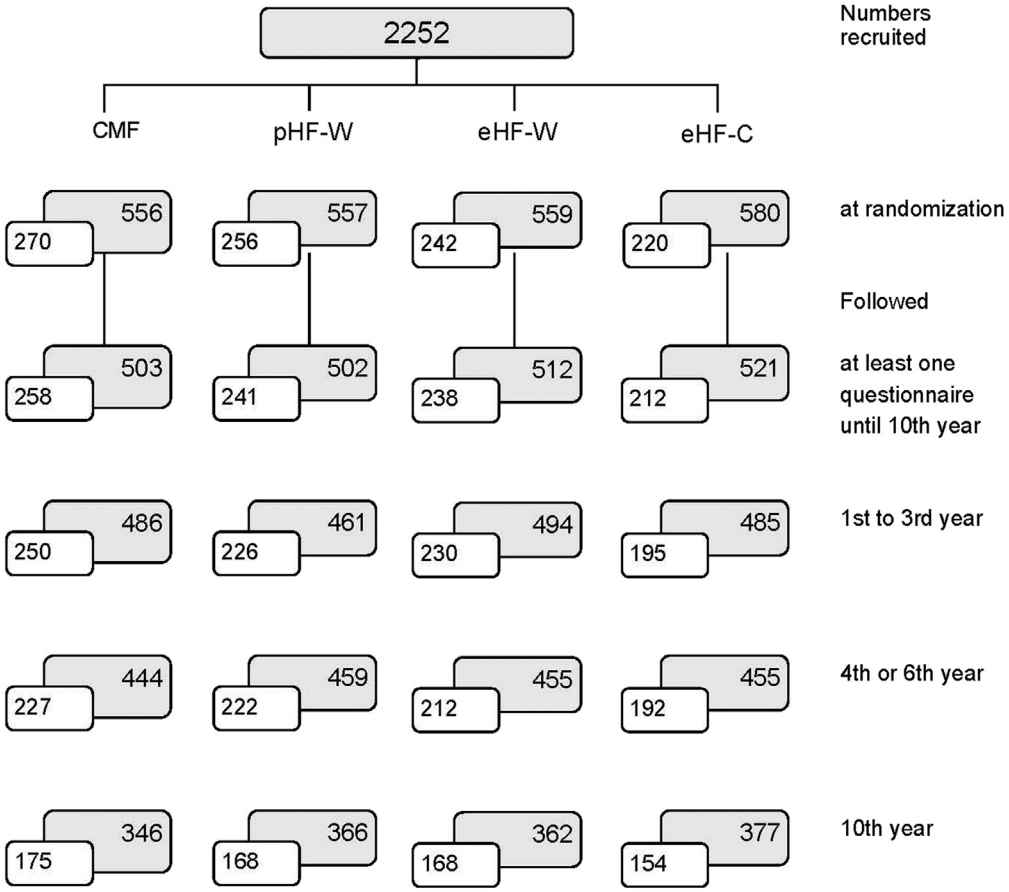

FIG 1. GINI study profile from birth to 10 years. Numbers of followed children in the ITT *(shaded boxes)* and the PP *(open boxes)* populations are shown.

not receive any study formula during the first 6 months of life because they were exclusively breast-fed. The PP analysis included all infants fed (fully or partially) with study formula within the first 4 months who were compliant with the study protocol.[26]

The risk of having 1 or more allergic diseases in a period (birth to 10 years) was expressed as the cumulative incidence, and the calculation was estimated by using the life-table method[27] based on the yearly parent-reported diagnoses in the first to tenth years. Generalized estimating equations (GEEs) models[28] were used to examine the potential influence of the study formulas (4 levels) on the cumulative incidence from birth to 10 years (binary outcome) in longitudinal analyses, assuming an autoregressive (first-order) correlation structure (selected by using quasi-likelihood goodness-of-fit criteria) to account for correlations between repeated measures over time. Weighted GEE models[29] were done as sensitivity analysis. The prevalence at school age (age, 7-10 years) was estimated as period prevalence in the participants of the 10-year follow-up and analyzed by using binomial regression models. Relative risks (RRs) with 95% CIs are given as results of the longitudinal and nonlongitudinal log-binomial models (PROC GENMOD with log-link and binomial distribution).

Family history of atopic eczema, hay fever, or asthma; heredity of family allergy; sex; and study region were included as covariates in PP and mITT analyses, and adjusted RRs were reported. Further covariates, such as parental education, number of older siblings, passive smoking exposure, and pets in the home, were not considered in the final models because their inclusion changed the effect estimates of the study formula on the outcome by less than 10%.

For comparisons of proportions in a descriptive manner, χ^2 tests were used. For analyses of participation, multiple logistic regression models were performed, partially including interaction (between study formula and early manifestation of AM or AD) as a product term, and odds ratios were provided. *P* values of less than .05 were considered statistically significant. *Post hoc* sample size calculation for the test of cumulative incidence from the first to tenth year of age between 2 groups was done with SAS-MACRO GEESIZE.[30] The baseline outcome and longitudinal pattern of outcome and nonresponse were expected based on observed data. Bernoulli variance, log-link function, and an autoregressive correlation matrix were used for the estimation of group sizes. Correlation between repeated measures of 0.8 to 0.9 was assumed. Approximately 181 to 214 subjects per group were needed with a 2-sided *P* value of .05 to detect an RR of 0.7 with 80% power.

Statistical analyses were done with the statistical software SAS for Windows (Release 9.2; SAS Institute, Cary, NC).

RESULTS

Study population and participation

Participation in the annual questionnaires up to 10 years is shown in Fig 1. The response to the 10-year questionnaire based on the total cohort at birth (ITT population, n = 2252) was 64.4% (62.2% to 65.7% in the 4 study groups) and 67.3% (64.8% to 70.0%) when based on the PP population (n = 988; there was no statistically significant difference between the groups by using the χ^2 test: $P = .642$ in the ITT population and $P = .512$ in PP population). A dropout rate of 21.9% in the ITT population and 23.5% in the PP population was observed between year 1, when we started with the annual questionnaires as a basis for the follow-up analyses, and year 10. The invitation to the clinical examination and blood sampling was followed by 65.5% of the ITT population and 65.6% of the PP population.

TABLE I. ITT analyses: cumulative incidence from 10-year follow-up and period prevalence at 7 to 10 years

	CMF	pHF-W	eHF-W	eHF-C
No. of followed children (n = 2252)	556	557	559	580
AM* cumulative incidence, birth to 10 y	63.1%	58.6%	59.9%	54.2%
RR (95% CI)	1	0.87 (0.77-0.99)	0.94 (0.83-1.07)	0.83 (0.72-0.95)
AM prevalence in 7th to 10th years (n = 1377)	34.3%	34.1%	35.0%	27.7%
RR (95% CI)	1	1.0 (0.81-1.23)	1.02 (0.83-1.26)	0.81 (0.64-1.01)
AD cumulative incidence, birth to 10 y	40.5%	35.3%	34.8%	29.3%
RR (95% CI)	1	0.82 (0.68-1.00)	0.91 (0.76-1.10)	0.72 (0.58-0.88)
AD prevalence in 7th to 10th years (n = 1389)	11.2%	13.2%	9.6%	8.2%
RR (95% CI)	1	1.18 (0.79-1.77)	0.86 (0.55-1.34)	0.74 (0.47-1.16)
Asthma cumulative incidence, 3-10 y	8.05%	11.4%	11.4%	8.9%
RR (95% CI)	1	1.56 (0.97-2.49)	1.58 (0.99-2.52)	1.08 (0.66-1.79)
Asthma prevalence in 7th to 10th years (n = 1407)	7.4%	9.3%	11.3%	6.3%
RR (95% CI)	1	1.26 (0.76-2.07)	1.53 (0.95-2.48)	0.85 (0.49-1.47)
Rhinitis cumulative incidence, 4-10 y	20.4%	18.9%	21.0%	18.7%
RR (95% CI)	1	0.95 (0.69-1.30)	0.93 (0.69-1.26)	0.92 (0.67-1.25)
Rhinitis prevalence in 7th to 10th years (n = 1393)	17.2%	14.7%	19.4%	14.0%
RR (95% CI)	1	0.85 (0.60-1.21)	1.13 (0.82-1.55)	0.82 (0.58-1.15)

RRs are from log-binomial models using the 3 different hydrolysate formulas in comparison with CMF.
*Defined as any of the following: physician-diagnosed AD, urticaria and food allergy/intolerance, asthma (start at third year), and rhinitis (start at fourth year).

Participation at 10-year follow-up

Lower participation at the 10-year follow-up examination was observed in children from Wesel (odds ratios from logistic regression: ITT population, 0.53 [95% CI, 0.44-0.63]; PP population, 0.63 [95% CI, 0.48-0.83]), in those with 2 and more siblings (ITT population, 0.74 [95% CI, 0.56-0.97]; PP population, 0.50 [95% CI, 0.33-0.76]), and in those with low parental education (ITT population: 0.41 [95% CI, 0.31-0.56]; PP population, 0.69 [95% CI, 0.45-1.05]; see Table E1 in this article's Online Repository at www.jacionline.org). Other individual characteristics did not modify the response in the different formula groups (nonsignificant interaction term in multiple logistic regression models).

Overall, a physician's diagnosis of AM or AD in the first 2 years had no clear influence on the response at 10 years but varied slightly over the study formula groups (see Table E2 in this article's Online Repository at www.jacionline.org). For the PP population, the response in early AM-free children was 67.1% to 72.2% but varied in children with early disease between 60.7% and 81.7% (67.0% in the CMF group, 60.7% in the pHF-W group, 81.7% in the eHF-W group, and 66.7% in the eHF-C group; statistical test of interaction between study formula and early manifestation of AM: $P = .07$ in the PP population). For the ITT population, results were 68.4% to 74.2% and 67.8% to 75.9%, respectively ($P = .25$, test for interaction; see Table E2).

ITT analysis

Table I depicts the cumulative incidence until 10 years and the prevalence at 7 to 10 years for AM, AD, asthma, and allergic rhinitis in the ITT analyses. The ITT population consists of all 2252 children primarily randomized, including all exclusively breast-fed children, 184 who were noncompliant with the milk feeding recommendations,[26] and 191 dropouts with unknown exposure (also considered noncompliant). The cumulative incidence of AM increased from 49.8% at 6 years to 59.9% at 10 years, the cumulative incidence of asthma increased from 5.0% to 9.9%, and the cumulative incidence of allergic rhinitis increased from 10.8% to 19.7%, whereas atopic eczema leveled off from 32.4% at 6 years of age to 35% at 10 years of age.

The RR for the cumulative incidence of AM was significantly reduced in the pHF-W and eHF-C groups by 13% and 17%, respectively, compared with the CMF group. This effect was primarily driven by the effect of the formulas on AD (pHF-W, 18% risk reduction; eHF-C, 28% risk reduction). The effect of eHF-W on AM and AD persisted at the previously described level, with reduction of less than 10%.[6] Very similar results were found with weighted GEE.

The hydrolysate formulas exerted no significant effect on the cumulative incidence of asthma and allergic rhinitis in comparison with CMF.

When excluding children from the analysis who were exclusively breast-fed for the first 6 months of life (mITT population, Table II), the pattern for the cumulative incidence of allergic disease was similar to the main analysis. For AM and AD, significant protective effects were observed for pHF-W and eHF-C. The asthma incidence was increased in the 3 hydrolyzed formula groups (by 29% to 49%, $P > .05$) compared with CMF, but for the 2 whey-based products, the effect on asthma was less in the mITT analysis (Table II) compared with the original ITT analysis (Table I).

The prevalence of AD at school age (7-10 years) decreased slightly from 11.4% at 4 to 6 years[6] to 10.5%, whereas the prevalence of asthma increased to 8.5% and that of allergic rhinitis increased to 16.3%. No significant differences exist for the prevalence of AD, asthma, and allergic rhinitis at 7 to 10 years between the study groups (Tables I and II).

PP analysis

The results of the PP analysis are shown in Table III and Fig 2. As in the previous analyses, at 3 and 6 years, the results in the PP analysis are generally stronger for AM and AD.[5,6] The cumulative incidence of AD (until 10 years total, 32.5%) is significantly (pHF-W and eHF-C groups) or marginally (eHF-W group)

TABLE II. mITT analysis (excluding children exclusively breast-fed for 6 months): cumulative incidence from 10-year follow-up and period prevalence at 7 to 10 years

	CMF	pHF-W	eHF-W	eHF-C
No. of followed children (n = 1615)	422	398	402	393
AM* cumulative incidence, birth to 10 y	62.8%	57.6%	57.8%	54.5%
RR (95% CI)	1	0.82 (0.70-0.96)	0.87 (0.75-1.02)	0.83 (0.70-0.97)
aRR† (95% CI)	1	0.81 (0.69-0.95)	0.86 (0.74-1.00)	0.83 (0.71-0.97)
AM prevalence in 7th to 10th years (n = 900)	35.2%	32.7%	32.4%	30.1
RR (95% CI)	1	0.93 (0.72-1.20)	0.92 (0.71-1.19)	0.86 (0.66-1.12)
aRR† (95% CI)	1	0.91 (0.72-1.16)	0.95 (0.75-1.22)	0.89 (0.69-1.15)
AD cumulative incidence, birth to 10 y	41.3%	33.5%	33.7%	27.9%
RR (95% CI)	1	0.77 (0.55-0.91)	0.85 (0.68-1.06)	0.69 (0.53-0.88)
aRR‡ (95% CI)	1	0.71 (0.56-0.89)	0.82 (0.66-1.03)	0.68 (0.53-0.87)
AD prevalence in 7th to 10th years (n = 914)	11.3%	11.0%	9.4%	9.0%
RR (95% CI)	1	0.97 (0.58-1.62)	0.83 (0.48-1.42)	0.79 (0.46-1.37)
aRR‡ (95% CI)	1	0.92 (0.56-1.52)	0.79 (0.46-1.32)	0.76 (0.45-1.30)
Asthma cumulative incidence, 3-10 y	8.4%	11.8%	10.6%	11.8%
RR (95% CI)	1	1.49 (0.86-2.58)	1.29 (0.74-2.27)	1.29 (0.74-2.24)
aRR§ (95% CI)	1	1.43 (0.83-2.49)	1.28 (0.73-2.24)	1.25 (0.73-2.15)
Asthma prevalence in 7th to 10th years (n = 926)	6.9%	9.1%	9.8%	7.6%
RR (95% CI)	1	1.30 (0.71-2.41)	1.41 (0.77-2.58)	1.09 (0.57-2.09)
aRR§ (95% CI)	1	1.30 (0.71-2.37)	1.47 (0.81-2.66)	1.08 (0.57-2.05)
Rhinitis cumulative incidence, 4-10 y	21.2%	20.5%	19.7%	20.5%
RR (95% CI)	1	0.99 (0.69-1.43)	0.85 (0.58-1.22)	0.98 (0.68-1.42)
aRR‖ (95% CI)	1	1.03 (0.72-1.47)	0.88 (0.61-1.26)	1.02 (0.71-1.46)
Rhinitis prevalence in 7th to 10th years (n = 917)	18.4%	15.5%	16.7%	15.5%
RR (95% CI)	1	0.84 (0.56-1.26)	0.91 (0.62-1.35)	0.84 (0.56-1.27)
aRR‖ (95% CI)	1	0.89 (0.60-1.32)	0.97 (0.66-1.43)	0.91 (0.61-1.35)

RRs and aRRs are from log-binomial models using the 3 different hydrolysate formulas in comparison with CMF.
*Defined as any of the following: physician-diagnosed AD, urticaria and food allergy/intolerance, asthma (start at third year), and rhinitis (start at fourth year).
†Adjusted for family history of AD, hay fever, and asthma; heredity of family allergy; sex; and study region.
‡Adjusted for family history of AD, heredity of family allergy, sex, and study region.
§Adjusted for family history of asthma, heredity of family allergy, sex, and study region.
‖Adjusted for family history of hay fever, heredity of family allergy, sex, and study region.

reduced by 23% to 42% in the formula groups compared with that seen in the CMF group. The cumulative incidence of asthma (total, 10.7%) ranged between 9.4% (CMF group) and 13.2% (pHF-W), but the risk estimates were not significantly different. The incidence of rhinitis (total, 19%) shows only marginal group differences (maximal, 2.3%; $P > .05$). The adjustment in the models did not change the findings substantially.

The prevalence of AD at school age, which has decreased to 8.7% in total, still revealed a significant risk reduction in children fed eHF-C (0.42; 95% CI, 0.19-0.92; Table III), whereas none of the formulas exerted any notable effect on the school-age prevalence of asthma (total, 8.9%) and rhinitis (total, 15.4%).

Sensitivity analyses with ISAAC outcomes

Results are shown in Tables E3 and E4. In the ITT analysis the direction and size of point estimates were in most cases similar for GINI outcomes and the analogous ISAAC outcomes. All analyses showed nonsignificant changes, with the exception of a consistent protective effect of eHF-C on both the GINI outcome cumulative incidence of AD and the ISAAC outcome of "Has your child ever had atopic eczema?" In PP analysis the adjusted RRs for the cumulative incidence of AD up to the age of 10 years (GINI study outcome) and for the ISAAC questions were almost identical, with slightly larger CIs for the ISAAC outcomes. The larger CIs result from the different estimation methods; for cumulative incidence, GEE models with data from multiple questionnaires were used versus simple regression models for ISAAC question at age 10 years with smaller sample size because of loss to follow-up.

When looking at the prevalence at school age, the associations between formula groups and the original GINI outcomes were also very similar to those using the ISAAC questions. Smaller concordance was found between the GINI cumulative incidence outcomes and the ISAAC questions on symptoms during the last 12 months.

Stratification by family history of AD

Stratification by family history of AD showed a significant risk reduction in the cumulative incidence of AD only in children with AD in their families. In the ITT population the risk reduction in children with AD in the family was significant for the pHF-W and eHF-C groups (27% and 35%, respectively) but not for the eHF-W group (15%). In children without a family history of AD, no significant risk reduction occurred (6%, 6%, and 23% for the pHF-W, eHF-W, and eHF-C groups, respectively).

In the PP analysis, compared with CMF, all 3 intervention formulas were effective at reducing the risk for AD in children with a family history of AD: pHF-W adjusted relative risk (aRR), 0.59 (95% CI, 0.40-0.88); eHF-W aRR, 0.64 (95% CI, 0.43-0.95);

TABLE III. PP analyses: cumulative incidence from 10-year follow-up and period prevalence at 7 to 10 years

	CMF	pHF-W	eHF-W	eHF-C
No. of followed children (n = 988)	270	256	242	220
AM* cumulative incidence, birth to 10 y	61.5%	55.5%	54.2%	50.1%
RR (95% CI)	1	0.80 (0.66-0.96)	0.83 (0.68-1.00)	0.72 (0.58-0.89)
aRR† (95% CI)	1	0.79 (0.66-0.95)	0.82 (0.68-0.99)	0.72 (0.59-0.89)
AM prevalence in 7th to 10th years (n = 620)	35.8%	30.8%	31.7%	25.7%†
RR (95% CI)	1	0.86 (0.63-1.18)	0.88 (0.65-1.20)	0.72 (0.51-1.01)
aRR† (95% CI)	1	0.86 (0.64-1.15)	0.87 (0.65-1.16)	0.73 (0.52-1.01)
AD cumulative incidence, birth to 10 y	40.2%	30.9%	31.9%	25.0%
RR (95% CI)	1	0.67 (0.51-0.90)	0.81 (061-1.07)	0.59 (0.42-0.81)
aRR‡ (95% CI)	1	0.67 (0.51-0.88)	0.77 (059-1.02)	0.58 (0.42-0.80)
AD prevalence in 7th to 10th years (n = 632)	11.5%	8.9%	8.8%	5.3%
RR (95% CI)	1	0.77 (0.40-1.48)	0.76 (0.40-1.47)	0.46 (0.21-1.03)
aRR‡ (95% CI)	1	0.70 (0.37-1.33)	0.65 (0.34-1.23)	0.42 (0.19-0.92)
Asthma cumulative incidence, 3-10 y	9.4%	13.2%	9.6%	11.0%
RR (95% CI)	1	1.50 (0.80-2.27)	1.01 (0.51-1.98)	0.97 (0.51-1.86)
aRR§ (95% CI)	1	1.43 (0.77-2.64)	1.00 (0.52-1.96)	0.94 (0.50-1.79)
Asthma prevalence in 7th to 10th years (n = 638)	7.7%	10.6%	10.2%	7.3%
RR (95% CI)	1	1.37 (0.69-2.73)	1.32 (0.66-2.66)	0.95 (0.44-2.05)
aRR§ (95% CI)	1	1.31 (0.67-2.58)	1.37 (0.69-2.71)	0.93 (0.44-1.99)
Rhinitis cumulative incidence, 4-10 y	18.9%	19.7%	19.7%	17.4%
RR (95% CI)	1	1.07 (0.69-1.66)	0.87 (055-1.36)	0.90 (0.56-1.45)
aRR‖ (95% CI)	1	1.08 (0.70-1.66)	0.87 (056-1.35)	0.93 (0.58-1.48)
Rhinitis prevalence in 7th to 10th years (n = 632)	16.0%	15.3%	17.0%	12.9%
RR (95% CI)	1	0.97 (0.58-1.59)	1.06 (0.65-1.73)	0.81 (0.47-1.39)
aRR‖ (95% CI)	1	0.98 (0.60-1.60)	1.07 (0.66-1.72)	0.87 (0.51-1.49)

Crude RRs and aRRs are from log-binomial models using the 3 different hydrolysate formulas in comparison with CMF.
*Defined as any of the following: physician-diagnosed AD, urticaria and food allergy/intolerance, asthma (past third year), and rhinitis (past fourth year).
†Adjusted for family history of AD, hay fever, and asthma; heredity of family allergy; sex; and study region.
‡Adjusted for family history of AD, heredity of family allergy, sex, and study region.
§Adjusted for family history of asthma, heredity of family allergy, sex, and study region.
‖Adjusted for family history of hay fever, heredity of family allergy, sex, and study region.

and eHF-C aRR, 0.60 (95% CI, 0.38-0.94). In contrast, in children with no family history of AD, only eHF-C was effective at reducing the risk for AD (aRR, 0.56 [95% CI, 0.36-0.89]); pHF-W (aRR, 0.74 [95% CI, 0.49-1.11]) and eHF-W (aRR, 0.92 [95% CI, 0.63-1.35) were not (data not shown).

Number needed to treat

The numbers needed to treat (NNTs) to prevent 1 case of AD calculated at 10 years for the pHF-W, eHF-W, and eHF-C groups were 11, 12, and 7, in the PP population; 13, 13, and 8 in the mITT population; and 19, 18, and 9 in the ITT population, respectively.

Sensitization

The consent to blood sampling was self-selective. Blood samples for specific IgE measurement at 10 years could be drawn in 949 children (response of 65.5% in the ITT population and 65.6% in the PP population). The response was 10% higher ($P < .001$) in children whose parents reported physician-diagnosed allergic disease at 7 to 10 years. No difference by diagnosis in the first 2 years was found.

Allergic sensitization, which was defined as at least 1 positive specific IgE level to one of the tested allergens, was 43.9% for inhalant allergens and 18.4% for food allergens in the ITT population and 47.5% and 19.0%, respectively, in the PP population. No significant differences were observed regarding sensitization among the 4 study groups (not shown).

DISCUSSION

The 10-year follow-up analysis of the GINI study allowed us to answer 2 main questions regarding the effect of early nutritional intervention with CMPHIFs on allergic disease in childhood.

First, feeding with the protein hydrolysate formulas pHF-W and eHF-C in the first 4 months of life has a preventive effect on the cumulative incidence of AD in high-risk children lasting until 10 years. This effect is heavily influenced by the observations in the first 6 years.[5,6] No effect was observed on AD of feeding eHF-W, with the exception of a significantly lower risk for AD at 6 years in the PP population.[6] On the basis of the results of the ITT population for the period prevalence at 7 to 10 years of age, there is insufficient evidence of ongoing preventive activity. At the same time, we have no evidence for an ensuing rebound effect (ie, a disproportionally higher incidence of AD during school age [7-10 years]), which has often been hypothesized by critics.[18]

Second, feeding a CMPHIF compared with CMF has neither a preventive effect on asthma and allergic rhinitis nor such an effect on specific sensitization. A trend toward higher asthma incidence in the hydrolyzed formula groups in the ITT population but not in

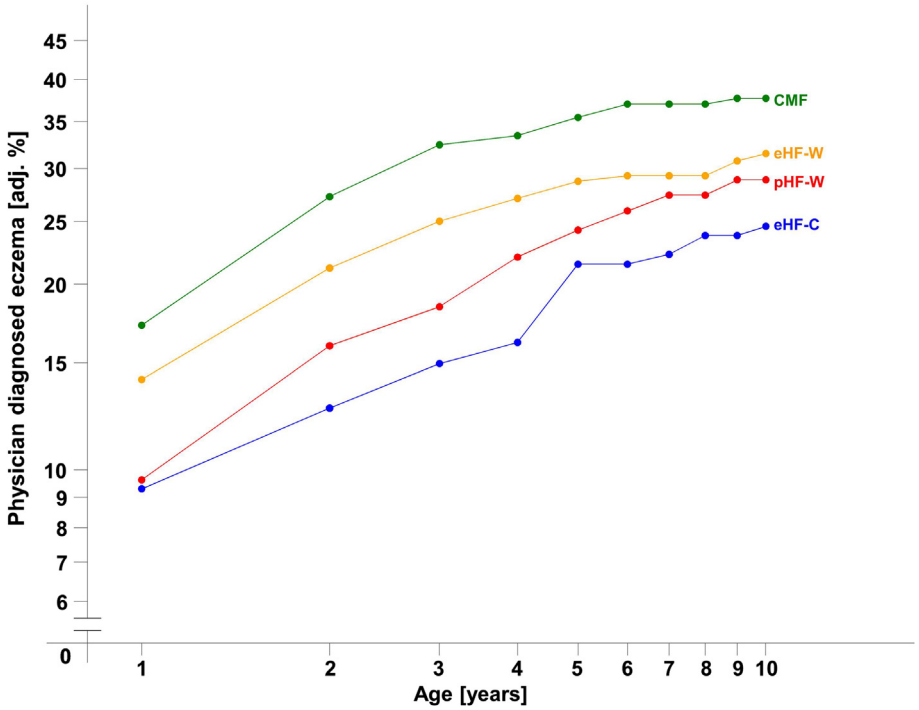

FIG 2. Adjusted cumulative incidence of parent-reported physician-diagnosed eczema in PP population. The incidence was adjusted for sex, body mass index at birth, parental education, siblings at birth, study region, maternal smoking during pregnancy and/or during the child's first 4 months, smoking in the presence of the child during the child's first 4 months, furry pets in the home during the child's first year of life, and mother's age at birth.

the PP population needs to be reinvestigated after an extended observation period.

The dimension of the effect of the hydrolysate formulas for the cumulative incidence of AM and AD is similar to the 6-year results,[6] with generally stronger effects in the PP and mITT populations compared with the ITT population. In addition to ITT and PP populations, we analyzed an mITT population (n = 1615) excluding all children who were fully breast-fed for the first 6 months and therefore did not receive any study or other formula during this period. These nonexposed children would have never been included in one of the intervention arms if randomization could have been performed at the time the mother decided to start formula feeding, but we had to randomize the children already before discharge from the maternity unit. The mITT is a meaningful additional analysis, but in contrast to the ITT analysis, it is a nonrandomized observational comparison because the excluded subjects were self-selected, and the results have to be interpreted with some caution. In the PP population the prevalence of AD at age 7 to 10 years is still significantly reduced with eHF-C, whereas pHF-W and eHF-W showed only a trend. However, in the ITT population we found no evidence for ongoing preventive activity of the formulas at 7 to 10 years.

In view of the recommendations to use CMPHIFs for allergy prevention, the severity of prevented AD and cost-effectiveness should be considered. Although there were no significant differences in the prevalence of AD between the study groups at the age of 7 to 10 years (ITT population), the preventive effect of pHF-W and eHF-C on AD in the first 3 years was not restricted to mild-or-moderate cases only, but an important risk reduction could also be achieved for severe AD cases (SCORAD score >21.5; 39% reduction in the pHF-W group and 52% reduction in the eHF-C group, data not shown). Considering the high incidence of severe AD (3.7% in the first year and 7% until 3 years) and its detrimental effects on the child's quality of life, as well as that of the family, this risk reduction carries a high public health effect.

For children who actually received the formula (PP population), the NNT was still rather low at the age of 10 years. The lowest NNT is always seen with eHF-C (6 at 3 and 6 years and 7 at 10 years), but this formula is also the most expensive one. In a recent cost-effectiveness calculation study of the GINI results up to age 6 years, eHF-C and pHF-W were almost equally cost-effective or even cost-saving in preventing AD in high-risk children.[31]

The analysis of the 10-year follow-up did not confirm the finding of the *post hoc* analysis at 3 years that pHF-W is especially effective on AD in children with no family history of AD.[5] Overall, the protective effect was seen regardless of family history but tended to be stronger if there was at least 1 first-degree family member with AD. However, the precision of the estimates is low because sometimes the size of the subgroups was only 52 to 64 children. It should be mentioned that the composition of pHF-W and eHF-C has been changed recently, with reduction of the protein concentration and supplementation with probiotics and long-chain polyunsaturated fatty acids. However, according to information of the 2 respective companies, the quality of the hydrolysates remained unchanged. The currently commercially available eHF-W (HIPP HA) has also been changed, but the composition is beyond our knowledge.

None of the hydrolysate formulas used in the GINI study had a preventive effect on asthma, wheezing, allergic rhinitis, or

sensitization. Studies that showed an effect on asthma at age 7 to 10 years have used mixed interventions of hydrolysate formulas and inhalant allergen avoidance measures.[13,14] Because of the high proportion of virally induced, nonallergic obstructive airway diseases[31,32] at preschool age, it was *a priori* decided to diagnose allergic asthma first at the age of 3 years,[5] and therefore we did not compare our results with those of studies that claimed an effect on "asthma" in the first 3 years.[11,12] The observed prevalence of asthma from 7 to 10 years of 8.9% in the PP population (and 8.5% in the ITT population) is comparable with the physician's diagnosis standard used by other studies.[33-36]

However, the trend in the ITT population toward a higher cumulative incidence of asthma in the hydrolysate groups compared with the CMF group (Table I) raises the question as to the mechanism of action of the hydrolysate formulas, the characteristics of the study population, or both. We therefore searched for an explanation and performed several sensitivity analyses. The mITT analysis found the increased risk for asthma was at least partly reduced, indicating that some of the effect shown, particularly in the eHF-W group, was due to fully breast-fed infants who were never exposed to the study formula. Another explanation could have been an uneven distribution of risk factors for asthma in the family history. However, in spite of increasing numbers of dropouts over the years, the distribution of AD, asthma, and allergic rhinitis (uniparental and biparental heredity) was at no time point significantly different in the study groups (data not shown). Other unmeasured risk factors for asthma or residual confounding leading to increased risk estimates cannot be excluded; however, they would have been relevant for children in the CMF group as well. We cannot exclude that families with a child with early AD take secondary preventive or therapeutic measures, which might have an effect on the incidence of asthma. We have no evidence that early exposure to intact CMP induces oral tolerance[20,21] or that oral tolerance induction is inhibited by hydrolysates because in the PP analysis 2 of the 3 hydrolysate formulas had a similar cumulative incidence of asthma compared with the CMF. We are not aware of data showing preventive effects on one allergic manifestation, in this case AD, and the opposite effect on another, in this case asthma. Altogether, we have no plausible explanation for our findings at this time. However, the unexpected and unexplained trend toward higher asthma incidence in the ITT population will be further investigated in the ongoing 15-year follow-up examination.

To our knowledge, the GINI study is the only randomized clinical trial in the field of allergy prevention using different CMPHIFs that has been followed for 10 years. However, this study has several limitations.

One of the main problems with long-term studies is the increasing dropout rate over time. This is a major limitation of our study. We carefully investigated whether participation at 10 years was biased by a nonrandom dropout. Several factors were identified that, similar to 6-year results, significantly decreased participation, such as living in Wesel, lower level of parental education, and more than 2 siblings, but they were not different between the formula groups.

On the other hand, early manifestation of atopic disease possibly influences the participation differently across the formula groups, especially in the PP population. The higher participation of children with early manifestation of AD in the eHF-W group (see Table E2) might bias the results toward a higher risk for cumulative incidence of AD or asthma and might explain, in part, our findings in this particular group. The opposite can occur for the pHF-W group, in which the preventive effect can be overestimated because of the lower participation of children with early disease. However, the cumulative incidence figures might not have been biased because these are much more heavily weighted by the results from earlier follow-up.

The study had to be unblinded after the 3-year follow-up examination to fulfill the study agreement with the German Ministry of Health as the primary sponsor. This fact has been criticized because of the potential for biased parent-reported outcomes after age 3 years. However, the outcome is parent-reported physician's diagnosis, and the physician's diagnosis at school age does not depend on the type of formula fed during infancy. Therefore we believe it is rather unlikely that unblinding has caused an essential bias.

There is still no universally accepted biologic mechanism to explain the allergy-preventive effects of CMPHIFs.[18] Unfortunately, we did not collect any parameters in blood or stool that could help to understand the mechanism. However, our data suggest that the effect on AD is not mediated through a reduction in sensitization. However, the data should be interpreted with caution because the consent to blood sampling was self-selective, with a response of 65.5%, and not independent from actual allergic diseases.

The major strength of the GINI study is the long-term longitudinal follow-up on 1450 children and the independence from industry.

In conclusion, the 10-year follow-up of the GINI study showed that the hydrolysate formulas pHF-W and eHF-C have a preventive effect on the cumulative incidence of eczema but not on asthma, allergic rhinitis, or sensitization to common food allergens or aeroallergens in high-risk children up to age 10 years. The present recommendation to use hydrolysate formulas in high-risk infants as a supplement to breast-feeding, if necessary, is supported by our results because the preventive effect seen in the first years of life is not compensated by a rebound effect until 10 years. There is insufficient evidence for ongoing preventive activity at 7 to 10 years. The recommendation should be restricted to hydrolysate formulas with proved efficacy. The unexpected tendency toward higher asthma incidence in the ITT population but not in the PP population needs to be further investigated in the ongoing 15-year follow-up examination.

We thank the children and their families for continuous participation and the GINIplus study teams for their excellent work.

Clinical implications: Our results support the present recommendation to use certain CMPHIFs in high-risk infants to reduce the risk for atopic eczema but not for respiratory allergies.

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GINIPLUS STUDY GROUP AT 10 YEARS

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TABLE E1. Relation between possible factors and participation (in percentages) at 10 years expressed as adjusted odds ratios (multiple logistic regression model*)

	ITT population (n = 2252)			PP population (n = 988)		
	No.	Percent	aOR* (95% CI)	No.	Percent	aOR* (95% CI)
Total	1451	64.4	—	665	67.3	—
Study formula						
CMF	346	62.2	1	175	64.8	1
pHF-W	366	65.7	1.13 (0.88-1.45)	168	65.6	0.95 (0.66-1.37)
eHF-W	362	64.8	1.10 (0.86-1.41)	168	69.4	1.17 (0.80-1.70)
eHF-C	377	65.0	1.10 (0.86-1.41)	154	70.0	1.26 (0.85-1.86)
Family history of AD						
No	875	64.0	1	426	68.1	1
Yes	576	65.2	1.09 (0.91-1.32)	239	66.0	1.00 (0.75-1.35)
Family history of asthma						
No	1038	64.5	1	478	68.3	1
Yes	413	64.2	0.95 (0.78-1.15)	187	64.9	0.82 (0.61-1.10)
Double heredity of family allergy						
No	991	63.2	1	464	66.2	1
Yes	460	67.2	1.02 (0.84-1.24)	201	70.0	1.10 (0.81-1.50)
Study region						
Munich	841	72.2	1	336	73.5	1
Wesel	610	56.1	0.53 (0.44-0.63)	329	62.0	0.63 (0.48-0.83)
Sibling						
0-1	1309	65.6	1	609	69.4	1
≥2	142	55.5	0.74 (0.56-0.97)	56	50.9	0.50 (0.33-0.76)
Education						
Middle/high	1369	66.6	1	605	68.5	1
Low	82	42.1	0.41 (0.31-0.56)	60	57.1	0.69 (0.45-1.05)

aOR, Adjusted odds ratio.

*Models included all variables listed in the table.

TABLE E2. Participation (in percentages) at 10 years in the study groups stratified by diagnosis of AD and AM in the first 2 years

	All (%)	CMF (%)	pHF-W (%)	eHF-W (%)	eHF-C (%)
ITT population (n = 1906)*					
(A) AD in the first 2 y					
No (n = 1504)*	70.4	69.2	72.9	69.0	70.6
Yes (n = 368)*	73.6	68.8	69.9	79.8	76.8
(B) AM‡ in the first 2 y					
No (n = 1337)*	71.2	68.4	74.2	69.7	72.5
Yes (n = 524)*	70.8	69.8	67.8	75.9	69.3
PP population (n = 892)†					
(C) AD in the first 2 y					
No (n = 705)†	69.6	69.7	70.5	68.0	70.5
Yes (n = 173)†	69.9	65.6	58.3	83.3	72.0
(D) AM‡ in the first 2 y					
No (n = 630)†	70.0	69.3	71.6	67.1	72.2
Yes (n = 243)†	69.1	67.0	60.7	81.7	66.7

Interactions between study formulas (4 levels) and early manifestation of AM or AD were modeled by using logistic regression. *P* values for the different strata are .203 (A), .246 (B), .079 (C), and .070 (D).

*Participants in the first 2 years (n = 1906); not listed are the strata with missing information on diagnosis of AD (n = 34) and AM (n = 45).

†Participants in the first 2 years (n = 892); not listed are the strata with missing information on diagnosis of AD (n = 14) and AM (n = 19).

‡Defined as any of the following: physician-diagnosed AD, urticaria, and food allergy/intolerance.

TABLE E3. Outcomes at 10 years of follow-up (comparison with ISAAC) for the ITT population

	CMF	pHF-W	eHF-W	eHF-C
Eczema and symptoms				
0-10 Cumulative incidence of parent-reported physician's diagnosis (n = 2252)				
	40.5%	35.3%	34.8%	29.3%
RR	1	0.82 (0.68-1.00)	0.91 (0.76-1.10)	0.72 (0.58-0.88)
0-10 y; Has your child ever had atopic eczema (n = 1444)				
	24.9%	23.8%	24.4%	15.8%
RR	1	0.96 (0.74-1.24)	0.98 (0.76-1.27)	0.63 (0.47-0.85)
0-10 y; Flexural rash ever for at least 6 months (n = 1429)				
	9.7%	10.5%	12.4%	8.1%
RR	1	1.08 (0.70-1.68)	1.28 (0.83-1.96)	0.83 (0.52-1.33)
7-10 y; Parent-reported physician's diagnosis in 7th to 10th years (n = 1389)				
	11.2%	13.2%	9.6%	8.2%
RR	1	1.18 (0.79-1.77)	0.86 (0.55-1.34)	0.74 (0.47-1.16)
7-10 y; Parental reported atopic eczema (n = 1411)				
	11.6%	13.5%	11.1%	7.9%
RR	1	1.16 (0.78-1.73)	0.95 (0.63-1.45)	0.68 (0.43-1.07)
10th year; Flexural rash for at least 6 months in the last 12 months (n = 1428)				
	2.9%	3.9%	5.1%	2.7%
RR	1	1.31 (0.59-2.91)	1.72 (0.81-3.67)	0.91 (0.38-2.16)
Asthma and wheezing				
3-10 Cumulative incidence of parent-reported physician's diagnosis (n = 2252)				
	8.1%	11.4%	11.4%	8.9%
RR	1	1.56 (0.97-2.49)	1.58 (0.99-2.25)	1.08 (0.66-1.79)
0-10 y; Has your child ever had asthma (n = 1443)				
	9.3%	10.4%	13.3%	7.7%
RR	1	1.12 (0.72-1.75)	1.43 (0.93-2.17)	0.83 (0.51-1.34)
0-10 y; Has your child ever had wheezing or whistling in the chest (n = 1441)				
	22.7%	24.7%	25.3%	23.1%
RR	1	1.09 (0.84-1.42)	1.45 (0.86-1.45)	1.02 (0.78-1.33)
7-10 y; Parent-reported physician's diagnosis in 7th to 10th years (n = 1407)				
	7.4%	9.3%	11.3%	6.3%
RR	1	1.26 (0.76-2.07)	1.53 (0.95-2.48)	0.85 (0.49-1.47)
7-10 y; Parental reported asthma (n = 1404)				
	6.8%	7.6%	9.6%	5.4%
RR	1	1.12 (0.66-1.92)	1.41 (0.85-2.36)	0.80 (0.45-1.44)
10th year; Wheezing or whistling in the chest in the last 12 months (n = 1436)				
	9.9%	11.9%	10.6%	10.5%
RR	1	1.19 (0.78-1.83)	1.07 (0.69-1.66)	1.05 (0.68-1.63)
Rhinitis and hay fever				
4-10 Cumulative incidence of parent-reported physician's diagnosis (n = 2252)				
	20.4%	18.9%	21.0%	18.7%
RR	1	0.95 (0.69-1.30)	0.93 (0.69-1.26)	0.92 (0.67-1.25)
0-10 y; Has your child ever had hay fever (n = 1422)				
	18.5%	15.4%	20.6%	14.9%
RR	1	0.83 (0.60-1.15)	1.11 (0.82-1.51)	0.80 (0.58-1.12)
7-10 y; Parent-reported physician's diagnosis (n = 1393)				
	17.2%	14.7%	19.4%	14.0%
RR	1	0.85 (0.60-1.21)	1.13 (0.82-1.55)	0.82 (0.58-1.15)
10th year; Sneezing, runny, or blocked nose in the last 12 months without cold or flu, accompanied by itchy-watery eyes (n = 1422)				
	16.2%	17.6%	19.0%	19.4%
RR	1	1.09 (0.78-1.51)	1.17 (0.85-1.62)	1.20 (0.87-1.65)

TABLE E4. Outcomes at 10 years of follow-up (comparison with ISAAC) for the PP population

	CMF	pHF-W	eHF-W	eHF-C
Eczema and symptoms				
0-10 Cumulative incidence of parent-reported physician's diagnosis (n = 988)				
	40.2%	30.9%	31.9%	25.0%
aRR*	1	0.67 (0.51-0.88)	0.77 (059-1.02)	0.58 (0.42-0.80)
0-10 y; Has your child ever had atopic eczema (n = 663)				
	25.7%	18.5%	22.7%	13.1%
aRR*	1	0.68 (0.46-1.02)	0.80 (0.55-1.16)	0.49 (0.31-0.79)
0-10 y; Flexural rash ever for at least 6 months (n = 660)				
	9.2%	10.2%	12.6%	6.5%
aRR*	1	1.06 (0.56-2.02)	1.33 (0.72-2.44)	0.70 (0.33-1.49)
7-10 y; Parent-reported physician's diagnosis in 7th to 10th years (n = 632)				
	11.5%	8.9%	8.8%	5.3%
aRR*	1	0.70 (0.37-1.33)	0.65 (0.34-1.23)	0.42 (0.19-0.92)
7-10 y; Parental reported atopic eczema (n = 652)				
	13.0%	9.6%	12.1%	6.0%
aRR*	1	0.66 (0.36-1.19)	0.76 (0.44-1.33)	0.41 (0.20-0.84)
10th y; Flexural rash for at least 6 months in the last 12 months (n = 660)				
	3.4%	3.6%	5.4%	1.9%
aRR*	1	1.00 (0.33-3.03)	1.49 (0.54-4.07)	0.56 (0.14-2.19)
Asthma and wheezing				
3-10 Cumulative incidence of parent-reported physician's diagnosis (n = 988)				
	9.4%	13.2%	9.6%	11.0%
aRR†	1	1.43 (0.77-2.64)	1.00 (0.52-1.96)	0.94 (0.50-1.79)
0-10 y; Has your child ever had asthma? (n = 660)				
	9.8%	10.8%	12.0%	9.2%
aRR†	1	1.08 (0.52-2.24)	1.35 (0.66-2.74)	0.88 (0.41-1.90)
0-10 y; Has your child ever had wheezing or whistling in the chest (n = 661)				
	19.5%	23.4%	22.9%	25.3%
aRR†	1	1.28 (0.75-2.19)	1.27 (0.74-2.18)	1.44 (0.84-2.49)
7-10 y; Parent-reported physician's diagnosis (n = 638)				
	7.7%	10.6%	10.2%	7.3%
aRR†	1	1.42 (0.65-3.09)	1.40 (0.63-3.08)	0.85 (0.36-2.00)
7-10 y; Parental reported asthma (n = 637)				
	7.1%	9.4%	8.9%	6.6%
aRR†	1	1.33 (0.59-2.99)	1.30 (0.57-2.96)	0.84 (0.35-2.05)
10th year; Wheezing or whistling in the chest in the last 12 months (n = 660)				
	9.2%	12.0%	9.6%	9.7%
aRR†	1	1.32 (0.64-2.72)	1.11 (0.52-2.38)	1.05 (0.48-2.27)
Rhinitis and hay fever				
4-10 Cumulative incidence of parent-reported physician's diagnosis (n = 988)				
	18.9%	19.7%	19.7%	17.4%
aRR‡	1	1.08 (0.70-1.66)	0.87 (0.56-1.35)	0.93 (0.58-1.48)
0-10 y; Has your child ever had hay fever (n = 651)				
	17.5%	15.8%	17.8%	12.4%
aRR‡	1	0.89 (0.56-1.42)	1.01 (0.64-1.58)	0.74 (0.44-1.25)
7-10 y; Parent-reported physician's diagnosis (n = 632)				
	16.0%	15.3%	17.0%	12.9%
aRR‡	1	0.98 (0.60-1.60)	1.07 (0.66-1.72)	0.87 (0.51-1.49)
10th year; Sneezing, runny, or blocked nose in the last 12 months without cold or flu, accompanied by itchy-watery eyes (n = 651)				
	14.1%	19.5%	18.8%	19.1%
aRR‡	1	1.36 (0.84-2.20)	1.31 (0.80-2.12)	1.42 (0.87-2.31)

*Adjusted for family history of AD, heredity of family allergy, sex, and study region.
†Adjusted for family history of asthma, heredity of family allergy, sex, and study region.
‡Adjusted for family history of hay fever, heredity of family allergy, sex, and study region.