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LETTER TO THE EDITOR

Long-term effects of hydrolyzed formulae on atopic diseases in the GINI study

To the Editor,

Prevention of allergic disease in children has been on the agenda for many decades. Extensively hydrolyzed formulae are designed primarily for treatment of cow's milk allergy, and later these and partially hydrolyzed formulae were also recognized for prevention of atopic diseases, but their efficacy has been challenged repeatedly.[1–3] The German Infant Nutritional Intervention (GINI) study allows evaluation of long-term effects of hydrolyzed formulae on allergic diseases in high-risk children.[4,5]

Between 1995 and 1998, 2252 healthy term newborns with high risk of allergy were recruited at birth in Munich and Wesel (Germany) and randomized to one of three hydrolyzed formulae [partially hydrolyzed whey (pHF-W); extensively hydrolyzed whey (eHF-W); extensively hydrolyzed casein (eHF-C)] or a formula based on intact cow's milk (CMF) as reference to be fed during the first four months of life if exclusive breastfeeding was not possible.

At the 20-year follow-up (Appendix S1), intention-to-treat (ITT) and per-protocol (PP) analyses were performed considering

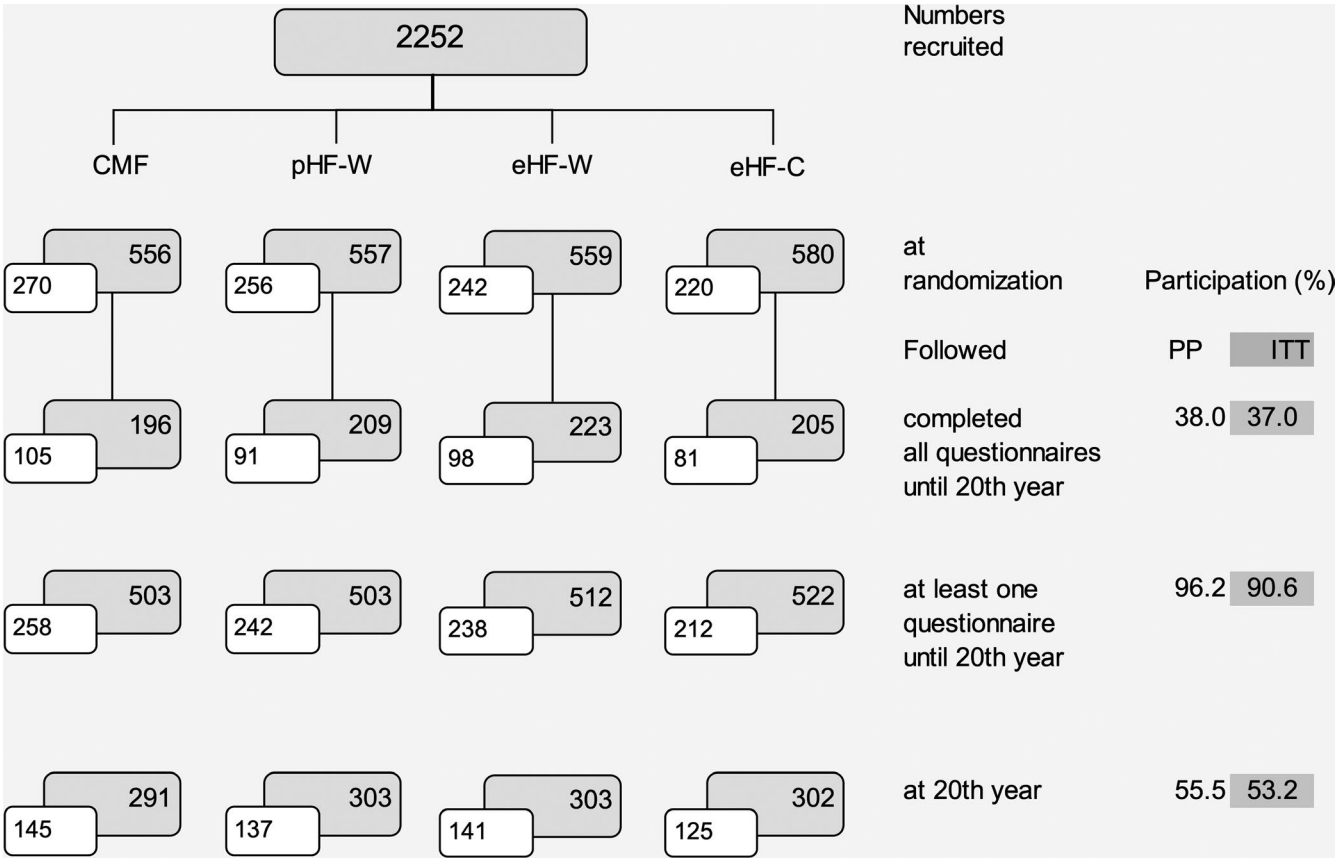

FIGURE 1 Number of subjects and proportion of participation (%) in each study formula group included in the ITT (shaded boxes) and PP (open boxes) analysis at recruitment, with complete information from all follow-ups, at least one follow-up, and at the 20-year follow-up

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TABLE 1 Cumulative incidence from birth to 20 years and period prevalence between 16 and 20 years. Relative risks (RR), adjusted RR (aRR), odds ratios (OR), and adjusted OR for the three different hydrolyzed formula groups, when compared to the cow's milk formula group. Intention-to-treat (ITT) and per-protocol (PP) population

	CMF	pHF-W	eHF-W	eHF-C
ITT, number of followed children (*N* = 2252)	556	557	559	580
Asthma				
Cumulative incidence, 3 to 20 years				
%	16.2	16.1	17.6	14.1
RR (95% CI)	1	1.06 (0.73–1.54)	1.16 (0.81–1.68)	0.90 (0.61–1.31)
Prevalence, 16 to 20 years, *N* = 1184				
%	10.1	5.0	7.1	5.4
OR (95% CI)	1	**0.47 (0.25–0.89)**	0.67 (0.38–1.21)	**0.50 (0.27–0.95)**
aOR[b] (95% CI)	1	**0.44 (0.23–0.85)**	0.64 (0.35–1.16)	**0.46 (0.24–0.87)**
AR				
Cumulative incidence, 4 to 20 years				
%	42.3	39.2	39.9	37.5
RR (95% CI)	1	0.90 (0.71–1.15)	0.92 (0.73–1.17)	0.83 (0.65–1.06)
Prevalence, 16 to 20 years, *N* = 1169				
%	24.0	22.9	22.4	23.8
OR (95% CI)	1	0.94 (0.64–1.38)	0.91 (0.62–1.34)	0.99 (0.67–1.45)
aOR[b] (95% CI)	1	0.94 (0.64–1.39)	0.97 (0.65–1.44)	1.00 (0.68–1.48)
Eczema				
Cumulative incidence, birth to 20 years				
%	44.0	37.5	40.3	32.1
RR (95% CI)	1	**0.73 (0.57–0.94)**	0.86 (0.68–1.10)	**0.61 (0.47–0.78)**
Prevalence, 16 to 20 years, *N* = 1176				
%	9.5	6.4	9.5	5.4
OR (95% CI)	1	0.64 (0.35–1.19)	0.99 (0.57–1.73)	**0.54** (0.28–1.02)
aOR[b] (95% CI)	1	0.60 (0.32–1.13)	0.94 (0.53–1.66)	**0.49 (0.25–0.94)**
PP, number of followed children (*N* = 988)	270	256	242	220
Asthma				
Cumulative incidence, 3 to 20 years				
%	16.9	17.4	15.5	16.3
RR (95% CI)	1	1.10 (0.66–1.84)	0.93 (0.55–1.59)	0.97 (0.57–1.66)
aRR[a] (95% CI)	1	1.05 (0.62–1.79)	0.97 (0.56–1.66)	0.95 (0.55–1.64)
Prevalence, 16 to 20 years, *N* = 539				
%	7.7	3.7	6.5	5.7
OR (95% CI)	1	**0.46** (0.16–1.36)	0.84 (0.34–2.09)	0.73 (0.27–1.95)
aOR[b] (95% CI)	1	**0.45** (0.15–1.36)	0.80 (0.31–2.08)	**0.68** (0.25–1.87)
AR				
Cumulative incidence, 4 to 20 years				
%	40.4	41.1	36.8	40.4
RR (95% CI)	1	1.03 (0.73–1.45)	0.88 (0.62–1.25)	0.95 (0.67–1.34)
aRR[a] (95% CI)	1	1.02 (0.72–1.45)	0.86 (0.61–1.23)	0.97 (0.68–1.37)
Prevalence, 16 to 20 years, *N* = 535				
%	21.4	25.7	20.9	26.7
OR (95% CI)	1	1.27 (0.73–2.22)	0.97 (0.54–1.72)	1.33 (0.75–2.36)
aOR[b] (95% CI)	1	1.27 (0.72–2.26)	0.90 (0.49–1.63)	1.38 (0.76–2.50)

(Continues)

TABLE 1 (Continued)

	CMF	pHF-W	eHF-W	eHF-C
Eczema				
Cumulative incidence, birth to 20 years				
%	42.0	33.2	39.3	27.2
RR (95% CI)	1	**0.63 (0.44–0.91)**	0.83 (0.58–1.18)	**0.49 (0.33–0.72)**
aRR[a] (95% CI)	1	**0.59 (0.41–0.86)**	0.78 (0.54–1.12)	**0.47 (0.31–0.70)**
Prevalence, 16 to 20 years, *N* = 538				
%	6.4	5.2	10.1	5.7
OR (95% CI)	1	0.79 (0.29–2.18)	1.63 (0.68–3.90)	0.88 (0.32–2.43)
aOR[b] (95% CI)	1	0.72 (0.25–2.02)	1.54 (0.63–3.79)	0.77 (0.27–2.18)

Note: CMF standard cow's milk formula (Nutrilon Premium), pHF-W partially hydrolyzed whey (Beba-HA), eHF-W extensively hydrolyzed whey (HIPP-HA, at that time identical with Nutrilon Pepti), eHF-C extensively hydrolyzed casein formula (Nutramigen). Outcomes were defined using yearly questions on doctor diagnoses of eczema, asthma, and allergic rhinitis/hay fever (AR), covering the timeframe since the previous follow-up. Any positive response during lifetime was used to determine cumulative incidence. A positive response and/or disease-specific treatment in the last 12 months was defined as prevalence between 16 and 20 years. Bold values and bold CI represent significant effects; bold values but not bold CI indicate strong effects with loss of significance.

[a]Adjusted for parental history of disease, heredity of family allergy, sex, study region.

[b]Adjusted for parental history of disease, heredity of family allergy, sex, study region, education and cigarette smoking of young adult, actual pets and type of questionnaire.

information obtained by questionnaires from 1199 subjects and 548 subjects, respectively (Figure 1). Asthma prevalence between 16 and 20 years was significantly lower in the eHF-C group [adjusted odds ratio (aOR) = 0.46; 95% confidence interval (CI) = (0.24–0.87)], and in the pHF-W group [aOR = 0.44; 95% CI = (0.23–0.85)], compared to CMF (Table). In the PP analysis, effect sizes were similar but not statistically significant. For allergic rhinitis (AR), no significant differences in incidence or prevalence were observed. In the ITT analysis of eczema, the cumulative incidence was reduced in the eHF-C [relative risk (RR) = 0.61; 95% CI = (0.47–0.78)] and the pHF-W [RR = 0.73; 95% CI = (0.57–0.94)] groups and the prevalence between 16 and 20 years in the eHF-C group [aOR = 0.49; 95% CI = (0.25–0.94)] compared to the CMF group. The effects of eHF-C and pHF-W on the cumulative incidence were even stronger in the PP-analysis, but the effect of eHF-C on prevalence of eczema did not reach statistical significance. The mechanisms through which hydrolyzed formulae might affect allergic disease development are not well understood. As only certain formulae showed a protective effect, it might be speculated that the specific processes of hydrolyzation differ in their effectiveness regarding deterioration of potentially allergy-inducing epitopes.[5] Indirect effects on the immune systems of the formulas cannot be excluded, like different impact on the intestinal microbiome or metabolome or exposure to the skin.

Compared with results obtained up to 15 years of the GINI study,[5] the 20-year follow-up revealed similar effects for eczema incidence. While protective effects for AR observed at 15 years were no longer present, asthma prevalence from 16–20 years was significantly reduced in pHF-W in the ITT analysis, which was not observed previously. Mediation analysis showed that this preventive effect on asthma cannot be explained by the reduction in eczema by certain hydrolyzed formulae in the first 3 years since the percentage of the total association explained by early eczema was 8.1% for eHF-C and 6.6% for pHF-W.

Potential limitations include the lack of objective data such as specific IgE and spirometry, different types of questionnaires over the years (parents versus subjects, paper versus online), higher participation of females and the high drop-out from the original study, which is not uncommon for such long-term birth cohorts. All aspects apply similarly to all study groups and therefore should not have substantially biased the results (Tables S1 and S2). The information on allergic diseases was collected by questionnaires only, using consistent questions since the first year of life, which allows an investigation of their course over the entire follow-up period.

It has been questioned whether hydrolyzed formulae should have a role in primary allergy prevention.[1–3] A recent nationwide observational study from France even found an increase in wheezing in infants who had received partially hydrolyzed formulae in short term.[6] In contrast, our randomized study demonstrates that the preventive effect is different with different hydrolyzed formulae and not entirely dependent on the degree of hydrolyzation. Accordingly, pooling of different types of hydrolyzed formulae is misleading.

CONCLUSION

In the GINI study, both eHF-C and pHF-W reduced prevalence of asthma after puberty in a high-risk population and retained their effect on eczema until adulthood, while eHF-W did not support the idea of preventive effects. Our findings confirm the concept that early nutritional intervention with certain hydrolyzed formulae, if exclusive breastfeeding is not feasible, has a preventive effect until adulthood for both eczema and allergic airway manifestation.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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