Short- and long-term effects of feeding hydrolyzed protein infant formulas on growth at ≤6 y of age: results from the German Infant Nutritional Intervention Study[1–3]

Peter Rzehak, Stefanie Sausenthaler, Sibylle Koletzko, Dietrich Reinhardt, Andrea von Berg, Ursula Krämer, Dietrich Berdel, Christina Bollrath, Armin Grübl, Carl Peter Bauer, H-Erich Wichmann, and Joachim Heinrich for the German Infant Nutritional Intervention Study Group

ABSTRACT

Background: The short- and long-term effects of feeding with hydrolyzed formulas on growth are uncertain.

Objective: Our aim was to investigate the potential differences in body mass index (BMI) over the first 6 y of life between infants fed with partially hydrolyzed whey (pHF-W), extensively hydrolyzed whey (eHF-W), extensively hydrolyzed casein (eHF-C), or cow-milk formula (CMF) and infants exclusively breastfed for the first 16 wk of life.

Design: We established a prospective, randomized, double-blind trial of full-term neonates with atopic heredity in the German birth cohort followed by the German Infant Nutritional Intervention Study through the first 6 y of life. Intention-to-treat and per-protocol analyses of absolute and World Health Organization–standardized BMI trajectories for 1840 infants (pHF-W: $n = 253$; eHF-W: $n = 265$; eHF-C: $n = 250$, CMF: $n = 276$; breastfed: $n = 796$) were performed.

Results: No significant differences in absolute or World Health Organization–standardized BMI trajectories were found among the pHF-W, eHF-W, CMF, and breastfed groups during the 6-y follow-up. However, in the eHF-C group, both intention-to-treat and per-protocol analyses showed a significantly slower sex-adjusted BMI gain through the 8th to 48th week of life (−0.1 to −0.2 lower BMI *z* score) but not beyond. Analyses of weight and length revealed that this difference is due to a slightly diminished weight gain in the first year of life because growth in length did not differ among study groups for the entire follow-up.

Conclusions: To our knowledge, this is the first randomized trial investigating both short- and long-term effects of partially and extensively hydrolyzed formula (pHF-W, eHF-W, eHF-C), CMF, and breastfeeding on growth in one trial. Feeding with eHF-C led to a transient lower weight gain in the first year of life. No long-term consequences of different formulas on BMI were observed. *Am J Clin Nutr* 2009;89:1846–56.

INTRODUCTION

Randomized controlled trials (RCTs) investigating the long-term effects of infant feeding with hydrolyzed formulas on the development of growth in infancy and childhood are rare (1). Shorter trials have included follow-up periods of the first few weeks (2–4), 6 mo (5, 6), and the first year of life (7, 8). Of the 3 previous prospective RCTs with a longer study period (≥1 y), none fully assessed both the long-term and the short-term effects (<6 mo) on growth in detail (1, 7, 8). Moreover, we do not know of any RCT that has studied in one trial the short- *and* long-term effects of infant feeding on growth for infants fed with partially hydrolyzed whey (pHF-W), extensively hydrolyzed whey (eHF-W), extensively hydrolyzed casein (eHF-C), or cow-milk formula (CMF). To our knowledge only one trial—which reported growth variables at birth and at 6 mo—has been published for these 4 formula groups (6).

Thus, the aim of this study was to use data from a prospective, randomized, double-blind trial of full-term neonates with atopic family history—the German birth cohort of the German Infant Nutritional Intervention Study—to assess potential differences in period-specific body mass index (BMI; in kg/m^2) change from birth up to the age of 6 y for the 4 formula-feeding groups (pHF-W, eHF-W, pHF-C, CMF) and a group of infants exclusively breastfed for 16 wk. The research questions were as follows: Are

[1] From the Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Neuherberg, Germany (PR, SS, H-EW, and JH); Ludwig Maximilians University Munich, the Institute of Medical Data Management, Biometrics, and Epidemiology, Munich, Germany (PR and H-EW); Ludwig Maximilians University of Munich, Dr von Hauner Children's Hospital, Munich, Germany (SK and DR); the Department of Pediatrics, Marien Hospital Wesel, Wesel, Germany (AvB, DB, and CB); the Institut für Umweltmedizinische Forschung, University of Düsseldorf, Düsseldorf, Germany (UK); and Department of Pediatrics, Technical University of Munich, Munich, Germany (AvB and CPB).

[2] Supported for 3 y by grants from the Federal Ministry for Education, Science, Research, and Technology (grant no. 01 EE 9401-4). The 6-y follow-up of the German Infant Nutritional Intervention-plus Study was partly funded by the Federal Ministry of Environment (Institut für Umweltmedizinische Forschung, grant no. FKZ 20462296). The analysis presented here has been partly conducted with financial support from the Nutricia Research Foundation (project no. 2007-12). Personal and financial support by the Munich Center of Health Sciences, which contributed to this research, is gratefully acknowledged.

[3] Address correspondence to P Rzehak, Helmholtz Zentrum München, German Research Center for Environmental Health. Institute of Epidemiology, Ingolstädter Landstrasse 1, D-85764 Neuherberg, Germany. E-mail: peter.rzehak@helmholtz-muenchen.de.

Received December 16, 2008. Accepted for publication March 7, 2009.

First published online April 15, 2009; doi: 10.3945/ajcn.2008.27373.

there any short and/or long-term differences in growth? Are all formulas safe for natural growth and development?

SUBJECTS AND METHODS

Study design and population

The German Infant Nutritional Intervention Study is an ongoing birth cohort study with an embedded prospective randomized double-blind trial of 2252 full-term neonates with atopic heredity born between September 1995 and July 1998 in either Munich or Wesel, Germany, and followed for 6 y. The main objective of the trial was to investigate whether feeding 4 different formulas would prospectively influence the manifestation of atopic diseases in these high-risk children. Details of design, recruitment, and follow-up of this intervention study have been published previously (9–11). At birth, children were randomly assigned to 1 of 3 hydrolyzed infant formulas or to a regular cow-milk formula [pHF-W: Beba-HA (Nestlé, Vevey, Switzerland); eHF-W: HIPP_HA (HIPP, Pfaffenhofen, Germany)—at that time identical with Nutrilon Peptil (Nutrica/Numico, Zoetermeer, Netherlands); eHF-C: Nutramigen (Mead Johnson, Dietzenbach, Germany); or standard CMF: Nutrilon Premium (Nutrica/Numico)]. The main components of the study formulas are listed in **Table 1**. Exclusive breastfeeding for the first 4 mo with the introduction of solid foods postponed to after the end of the fourth month was recommended. An overview of the duration and exposure to breastfeeding, the formula used, and the first introduction of solids or juice for the formula-feeding groups within the intervention period is shown in **Table 2**.

At the end of the intervention period (ie, after the first 16 wk of life), the 1172 infants who were fed study formulas (interventional arm) and the 889 infants who were exclusively breastfed (observational arm) were followed in yearly intervals up to 3 y and again at 6 y by both physical examination (skin) and detailed questionnaire. At the age of 4 y, follow-up was conducted by questionnaire. The remaining 191 infants left the trial for various reasons, mainly problems with the study formula (41%) and time problems (34%). The progress of the study population from randomization to the end of the intervention period and the number of infants included in the analysis population for the 5 study groups are shown in **Figure 1**. The actual analyzed study population with known anthropometric data included 1840 infants in the intention-to-treat analyses (pHF-W: $n = 253$; eHF-W: $n = 265$; eHF-C: $n = 250$, CMF: $n = 276$; breastfed: $n = 796$) and 1654 infants in the per-protocol analyses (pHF-W: $n = 214$; eHF-W: $n = 219$; eHF-C: $n = 189$, CMF: $n = 236$; breastfed: $n = 796$).

TABLE 1
Composition of study formulas per 100 mL[1]

	pHF-W	eHF-W	eHF-C	CMF
Protein (g)	1.6	1.6	1.9	1.4
Casein-whey ratio	0:100	0:100	100:0	40:60
Fat (g)	3.4	3.6	3.4	3.6
Carbohydrates (g)	7.4	6.9	7.4	7.1
Lactose	5.1	2.6	0	7.1
Others	2.3	4.3	7.4	0
Energy (kcal)	67	67	68	66

[1] pHF-W, partially hydrolyzed whey; eHF-W, extensively hydrolyzed whey; eHF-C, extensively hydrolyzed casein; CMF, cow-milk formula.

In addition, anthropometric measurements of weight and length were collected by pediatricians from physical examinations of each child at birth, at days 3–10, at weeks 4–6, and at months 3–4, 6–7, 10–12, 21–24, 43–48, and 60–64 of life (designated time schedule) to monitor physical growth and indications of adverse health outcomes. These data are available through the recorded preventive medical check-ups in the well-baby check-up books.

The study protocol was approved by the local ethics committees (Bavarian General Medical Council, Medical Council of North Rhine Westphalia), and written consent was obtained from all participating families.

Outcome definition

BMI in absolute terms is defined as weight in kilograms divided by squared length in meters. Because of the variation in actual age at the time the weight and length measurements (up to 9 measurements/infant over the entire follow-up) were taken, data are available for almost every month during the first 2 y of life. Because there were only 2 measurement occasions after the seventh examination at ≈2 y, data gaps in anthropometric measurements exist between the ages of 2 and 3 y and between the ages of 4 and 5 y. BMI was transformed to SD scores (z scores) according to the new sex- and age-specific World Health Organization (WHO) Child Growth Standards for 0–5-y-old (≤1856 d) children and according to the WHO Growth Standards for School-Aged Children and Adolescents for children aged >1856 d (12, 13). Using z scores in the analysis allows a numerical comparison of our cohorts with the current growth standard and reference and with future growth studies. Using these new WHO Child Growth Standards in other populations may result in lower z scores in early life and in higher z scores in later infancy than previous growth standards such as those of the Centers for Disease Control and Prevention, the National Center for Health Statistics, or the EURO Growth Study charts (14).

Statistical analysis

Piecewise, linear, random-coefficient models were applied to assess subject-specific (individual) and population-averaged (mean) growth trajectories and period-specific change between 0–8, >8–16, >16–52, >52–104, and >104 wk of life. The choice of the time segments is based on previous literature (15) and on the intention to study both short- and long-term effects on change in weight, length, BMI, and BMI z scores over time for the 4 formula-feeding groups and the breastfeeding group. Such longitudinal models are described in detail in Singer et al and Fitzmaurice et al (16, 17). The model used here is a special longitudinal regression model with a random intercept term and a random slope of the variable age to account for individual variation around the baseline mean of the outcome and for subject-specific variation around the population-averaged trajectory within each time period. This model accounts for the correlated data structure due to the repeated measurements and uses the exact ages at the time when measurements were taken and all available data for each infant even if a measurement is intermittently missing. By incorporating piecewise linear

TABLE 2
Duration and exposure to breast- and formula feeding and first introduction of any solids or juice in the first 16 wk of life in the 4 formula-feeding groups

	Formula-feeding group[1]							
	pHF-W (n = 253)		eHF-W (n = 265)		eHF-C (n = 250)		CMF (n = 276)	
	n	Mean ± SD	n	Mean ± SD[2]	n	Mean ± SD	n	Mean ± SD
Duration	246[2]		254[2]		241[2]		269[2]	
Exclusive breastfeeding (wk)		6.3 ± 5.9		5.4 ± 5.6		5.7 ± 5.7		5.7 ± 5.5
Exclusive formula feeding (wk)		5.1 ± 6.2		5.4 ±6.3		5.2 ± 6.4		5.9 ± 6.4
Exposure to formula (wk)		9.1 ± 6.0		9.8 ± 5.8		9.0 ± 6.1		9.8 ± 5.8
First exposure to formula (wk)	238[2]	4.6 ± 4.7	245[2]	3.7 ± 3.9	222[2]	3.6 ± 4.0	262[2]	4.3 ± 4.4
First introduction of any solids/juice (wk)	26[3]	11.7 ± 4.2	31[3]	13.7 ± 3.0	33[3]	12.6 ± 3.2	41[3]	12.9 ± 3.6

[1] Formula-feeding group assignment was according to intention-to-treat randomization at birth. pHF-W, partially hydrolyzed whey; eHF-W, extensively hydrolyzed whey; eHF-C, extensively hydrolyzed casein; CMF, cow-milk formula.
[2] Number of infants among the respective formula-feeding groups with valid information in the analysis population.
[3] Number of infants among the respective formula-feeding groups exposed to any solids or juice within the intervention period (first 16 wk of life).

functions (B-splines) that structure the time-process axes for age into 5 time segments, regression coefficients for each time segment can be estimated, and thus potentially complex non-linear age effects on the outcome (eg, BMI) can be approximated by simple, connected linear regression lines, which allows an interpretation of period-specific change. By including interactions between the period-specific age variables and 4 of the 5 indicator-coded variables for the study groups (reference breastfed group), the period- and study group–specific, population-averaged growth trajectories can be estimated for each of the study groups over time. Formally, the basic piecewise, linear, random intercept slope model used here can be expressed as follows:

$$
\begin{aligned}
E(Y_{ij}) = {} & \beta_{0_i} + \beta_1 \,\mathrm{Boy}_i + \beta_{2i}\,\mathrm{Age}_{ij} + \beta_3(\mathrm{Age}_{ij} - 8)_+ \\
& + \beta_4(\mathrm{Age}_{ij} - 16)_+ + \beta_5(\mathrm{Age}_{ij} - 52)_+ + \beta_6(\mathrm{Age}_{ij} \\
& - 104)_+ + \beta_7\,\mathrm{Age}_{ij} \times \mathrm{pHF-W} + \beta_{8_i}\,\mathrm{Age}_{ij} \\
& \times \mathrm{eHF-W} + \beta_{9_i}\mathrm{Age}_{ij} + \mathrm{eHF-C} + \beta_{10_i}\mathrm{Age}_{ij} \times \mathrm{CMF} \\
& + \cdots \\
& + \beta_{27}(\mathrm{Age}_{ij} - 104)_+ \times \mathrm{pHF-W} + \beta_{28}(\mathrm{Age}_{ij} - 104)_+ \\
& \times \mathrm{eHF-W} + \beta_{29}(\mathrm{Age}_{ij} - 104)_+ \times \mathrm{eHF-C} \\
& + \beta_{30}(\mathrm{Age}_{ij} - 104)_+ \times \mathrm{CMF} \qquad (1)
\end{aligned}
$$

where $\beta_{0_i} = \beta_0 + u_{0_i}$ (ie, intercept plus the individual deviation from this estimated baseline mean) and $\beta_{2_i} = \beta_2 + u_{2_i}$ [ie, slope (here age) plus the individual deviation from this estimated average slope]. Age_{ij} is the chronological age in weeks of an infant (i, at measurement, j, since birth): $(\mathrm{Age}_{ij} - c)_+ = 0$ before $\mathrm{Age}_{ij} = c$ wk and $(\mathrm{Age}_{ij} - c)_+ > 0$ if $\mathrm{Age}_{ij} > c$ (ie, time passed since the infant reached the age of c wk); c defines the beginning of the time segment [$c \in (8, 16, 52, 104)$] in weeks.

The statistical significance of differences between trajectories of the study groups was assessed by 95% prediction bands. If an average trajectory of a study group did not run within the prediction band of another group, there was a significant difference between these trajectories with a 5% probability error. Because weight and length are known to be higher for boys, sex was included as a main effect and was adjusted for.

In addition to the main analyses, several sensitivity analyses that adjusted the described longitudinal model for potential confounders were performed. The confounders included any solids or juice within the intervention period and the number of weeks that a subject was breastfed or was exclusively exposed to study formula or a repeated analysis with restricted study populations (ie, the exclusion of the 159 infants who developed urticaria or eczema and the restriction of the 147 infants who were exposed to study formula from the first week onward).

To test potential differences among the 5 study groups (formulas and breastfeeding) at birth that might confound the longitudinal results despite randomization for the 4 formula groups, we conducted two-way analyses of variance for the outcomes of weight, length BMI, BMI z score, mother's age at birth, and logistic regression modeling for the categorical outcomes. For the percentage of maternal smoking during pregnancy and the percentage of low parental education, we modeled each outcome for the main effects of sex, study group, and their interaction. The statistical significance of each main and interaction effect was assessed by type III F tests, 2-factor analyses of variance, or chi-square tests (logistic regression) (*see* **Table 3**).

Descriptive analyses, analyses of variance, and logistic regressions were conducted using the statistical software SAS, version 9.1.3 (18). Longitudinal, piecewise, linear, random-coefficient analyses were performed with the software for multilevel modeling MLwiN, version 2.02 (19).

RESULTS

Characteristics of the study population at birth for each randomized formula group and for the group exclusively breastfed within the first 16 wk are depicted in Table 3. Except for the mother's age at birth, the percentage of maternal smoking during pregnancy, and the percentage of low parental education, there were no substantial differences among the 5 study groups, and no significant interaction effects between sex and study group were detected by 2-factor analyses of variance F tests or by logistic regression chi-square tests for continuous and categorical outcomes, respectively. These significant differences were mainly because of the older age of the mothers and the substantially lower percentages of maternal smoking and the higher

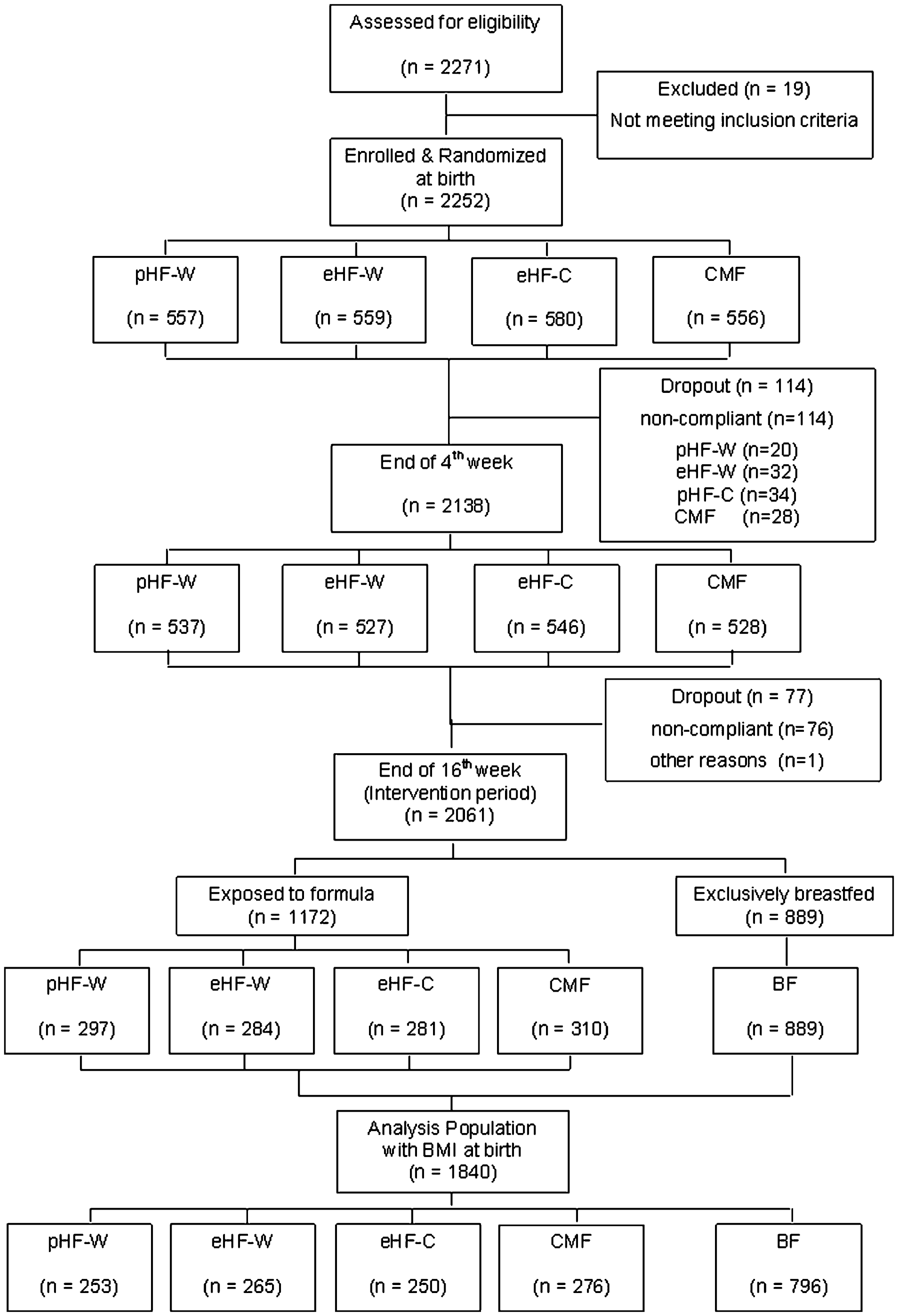

FIGURE 1. Flow chart of the study population during the intervention period (birth to week 16). Specific reasons for the 191 dropouts up to the end of week 16 were mainly problems with the study formula [total: 41%; pHF-W (partially hydrolyzed whey): 47%; eHF-W (extensively hydrolyzed whey): 36%; eHF-C (extensively hydrolyzed casein): 57%; CMF (cow-milk formula): 26%] and lack of time (total: 34%; pHF-W: 26%; eHF-W: 40%; eHF-C: 29%; CMF: 39%). BF, breastfed group.

parental education in the breastfed group. Restricting the comparative analyses to the 4 formula groups did not show any significant differences among the 4 formula groups. The observed anthropometric data for boys and girls for whom measurements were performed within the designated 9 time periods of physical examination are shown in **Table 4** and **Table 5**, respectively.

Results of the sex-adjusted longitudinal analyses of BMI development over the different time windows (0–8, >8–16, >16–52, >52–104, and >104–312 wk) using data for all children at their exact ages—independent of compliance to the designated time schedule of anthropometric measurements—are displayed in **Figure 2** and in **Figure 3**. Figure 3 is the same as Figure 2 but restricted in display to the first 56 wk to allow a more detailed graph of the BMI gain in the first year of life.

There were no significant differences in absolute or WHO-standardized BMI trajectories among the pHF-W, eHF-W, and CMF groups over the 6-y follow-up. This was true for the intention-to-treat-based analyses and the analyses based on the per-protocol study population (data for the latter not shown) depicted in Figures 2 and 3.

The American Journal of Clinical Nutrition

TABLE 3
Characteristics of the study population at birth

	Formula-feeding group[1]										
	pHF-W		eHF-W		eHF-C		CMF		Breastfed group[2]		
	n	Value	*n*	Value	*n*	Value	*n*	Value	*n*	Value	*P* value
Weight at birth (kg)											0.27[3]
Boys	133	3.50 ± 0.4[4]	145	3.54 ± 0.5	130	3.53 ± 0.4	155	3.55 ± 0.5	394	3.57 ± 0.4	<0.0001[5]
Girls	120	3.35 ± 0.5	120	3.44 ± 0.5	120	3.37 ± 0.4	121	3.39 ± 0.5	402	3.43 ± 0.4	0.92[6]
Length at birth (cm)											0.35[3]
Boys	133	52.4 ± 2.4	145	52.4 ± 2.5	130	52.6 ± 2.1	155	52.7 ± 2.6	394	52.7 ± 2.3	<0.0001[5]
Girls	120	51.7 ± 2.6	120	51.9 ± 2.3	120	51.5 ± 2.4	121	52.0 ± 2.6	402	52.0 ± 2.2	0.69[6]
BMI at birth (kg/m^2)											0.17[3]
Boys	133	12.7 ± 1.2	145	12.9 ± 1.3	130	12.7 ± 1.1	155	12.7 ± 1.2	394	12.8 ± 1.2	0.01[5]
Girls	120	12.5 ± 1.2	120	12.8 ± 1.3	120	12.7 ± 1.2	121	12.5 ± 1.1	402	12.7 ± 1.1	0.76[6]
BMI at birth (*z* score)[7]											0.17[3]
Boys	133	−0.60 ± 1.0	145	−0.50 ± 1.1	130	−0.60 ± 0.9	155	−0.62 ± 1.0	394	−0.51 ± 1.0	0.13[5]
Girls	120	−0.76 ± 1.0	120	−0.53 ± 1.1	120	−0.61 ± 1.1	121	−0.75 ± 1.0	402	−0.58 ± 1.0	0.88[6]
Mother's age at birth (y)											<0.0001[3]
Boys	133	30.1 ± 4.1	145	30.6 ± 4.0	130	30.1 ± 4.4	154	30.3 ± 4.6	394	31.7 ± 3.8	0.16[5]
Girls	120	31.1 ± 4.1	120	30.7 ± 4.1	120	30.6 ± 4.3	121 ±	30.0 ± 4.1	402	31.8 ± 3.4	0.44[6]
Maternal smoking during pregnancy (%)											<0.0001[8]
Boys	23/133	17.3 (17.2, 17.4)[9]	34/145	23.4 (23.4, 23.5)	21/130	16.2 (16.1, 16.2)	38/155	24.5 (24.4, 24.6)	38/394	9.6 (9.5, 9.7)	0.48[10]
Girls	29/120	24.2 (24.1, 24.3)	25/120	20.8 (20.7, 20.9)	24/119	20.2 (20.1, 20.3)	23/121	19.0 (18.9, 19.1)	33/402	8.2 (8.1, 8.3)	0.36[11]
Parental (both) education <10 y (%)											<0.001[8]
Boys	11/133	8.3 (8.2, 8.3)	14/145	9.7 (9.6, 9.7)	10/130	7.7 (7.6, 7.8)	21/155	13.5 (13.5, 13.6)	9/394	2.3 (2.2, 2.4)	0.84[10]
Girls	7/120	5.8 (5.8, 5.9)	13/120	10.8 (10.8, 10.9)	13/119	10.9 (10.8, 11.0)	13/121	10.7 (10.7, 10.8)	10/402	2.5 (2.4, 2.6)	0.74[11]

[1] Formula-feeding group assignment was made according to intention-to-treat randomization at birth. pHF-W, partially hydrolyzed whey; eHF-W, extensively hydrolyzed whey; eHF-C, extensively hydrolyzed casein; CMF, cow-milk formula.

[2] Exclusively breastfed for ≥16 wk from birth.

[3] *P* value from an *F* test of a main effect difference between the 5 study groups (group) in a 2-factor ANOVA (weight, length, BMI, BMI *z* score, or mother's age = group + sex + group × sex). No significant differences were observed for any of the outcomes when the sample was restricted to the 4 formula groups.

[4] Mean ± SD (all such values).

[5] *P* value from an *F* test of a main effect difference between boys and girls in a 2-factor ANOVA (same model as in footnote 3).

[6] *P* value from an *F* test of an interaction effect between the 5 study groups and sex in a 2-factor ANOVA (same model as in footnote 3).

[7] According to World Health Organization child growth standards (12, 13).

[8] *P* value from a chi-square test of a main effect difference between the 5 study groups (group) in a logistic regression model (model: %smoking or %low education = group + sex + group × sex). No significant differences were observed for any of the outcomes when the sample was restricted to the 4 formula groups.

[9] 95% CI in parentheses (all such values).

[10] *P* value from a chi-square test of a main effect difference between boys and girls in a logistic regression model (same model as in footnote 8).

[11] *P* value from a chi-square test of an interaction effect between the 5 study groups and sex in a logistic regression model (same model as in footnote 8).

TABLE 4

Average anthropometric measurements in boys by formula-feeding group at designated times of well-baby check-up examinations

	Formula-feeding group[1]									
	pHF-W		eHF-W		eHF-C		CMF		Breastfed group[2]	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Weight (kg)										
Birth[3]	133	3.5 ± 0.4	145	3.5 ± 0.5	130	3.5 ± 0.4	155	3.5 ± 0.5	394	3.6 ± 0.4
3rd–10th d	120	3.4 ± 0.5	129	3.4 ± 0.5	114	3.4 ± 0.4	139	3.4 ± 0.5	357	3.4 ± 0.4
4th–6th wk	97	4.6 ± 0.6	119	4.5 ± 0.6	108	4.5 ± 0.5	119	4.6 ± 0.6	327	4.8 ± 0.6
3rd–4th mo	109	6.7 ± 0.8	118	6.6 ± 0.8	110	6.4 ± 0.8	115	6.6 ± 0.7	321	6.7 ± 0.7
6th–7th mo	105	8.3 ± 0.9	120	8.4 ± 1.0	101	8.0 ± 0.9	107	8.3 ± 0.9	311	8.2 ± 0.9
10th–12th mo	75	9.8 ± 1.0	87	10.1 ± 1.1	60	9.8 ± 1.1	83	9.9 ± 1.2	242	9.7 ± 1.0
21st–24th mo	64	12.9 ± 1.5	82	12.8 ± 1.5	71	12.4 ± 1.3	73	12.6 ± 1.4	209	12.6 ± 1.4
43rd–48th mo	41	16.9 ± 2.4	34	17.1 ± 2.0	35	17.1 ± 1.6	51	17.2 ± 2.2	145	17.0 ± 2.0
60th–64th mo	83	20.2 ± 2.8	80	20.2 ± 3.0	74	19.5 ± 2.2	94	19.9 ± 2.3	260	19.6 ± 2.5
Length (cm)										
Birth	133	52.4 ± 2.4	145	52.4 ± 2.5	130	52.6 ± 2.1	155	52.7 ± 2.6	394	52.7 ± 2.3
3rd–10th d	120	52.5 ± 2.4	129	52.4 ± 2.5	114	52.6 ± 2.1	139	52.7 ± 2.6	357	52.7 ± 2.2
4th–6th wk	97	55.8 ± 2.2	119	55.5 ± 2.5	108	55.6 ± 2.0	119	56.0 ± 2.4	327	56.5 ± 2.1
3rd–4th mo	109	63.8 ± 2.4	118	63.7 ± 2.6	110	63.0 ± 2.8	115	63.5 ± 2.7	321	63.9 ± 2.4
6th–7th mo	105	69.6 ± 2.6	120	70.1 ± 2.5	101	69.3 ± 2.5	107	69.9 ± 2.6	311	69.5 ± 2.6
10th–12th mo	75	76.0 ± 3.0	87	76.7 ± 3.0	60	76.6 ± 3.0	83	76.4 ± 3.0	242	75.9 ± 3.0
21st–24th mo	64	88.4 ± 3.5	82	88.3 ± 3.0	71	88.3 ± 3.0	73	88.0 ± 2.9	209	88.1 ± 3.7
43rd–48th mo	41	104.5 ± 4.8	34	104.4 ± 3.9	35	104.4 ± 3.4	51	105.1 ± 4.3	145	105.1 ± 4.0
60th–64th mo	83	114.5 ± 5.4	80	113.2 ± 4.1	74	112.3 ± 4.3	94	113.7 ± 4.0	260	113.3 ± 4.7
BMI (kg/m^2)										
Birth	133	12.7 ± 1.2	145	12.9 ± 1.3	130	12.7 ± 1.1	155	12.7 ± 1.2	394	12.8 ± 1.2
3rd–10th d	120	12.2 ± 1.2	129	12.3 ± 1.3	114	12.3 ± 1.1	139	12.1 ± 1.1	357	12.4 ± 1.2
4th–6th wk	97	14.8 ± 1.3	119	14.5 ± 1.3	108	14.6 ± 1.4	119	14.7 ± 1.3	327	15.0 ± 1.3
3rd–4th mo	109	16.5 ± 1.6	118	16.3 ± 1.4	110	16.2 ± 1.5	115	16.5 ± 1.5	321	16.4 ± 1.5
6th–7th mo	105	17.2 ± 1.6	120	17.0 ± 1.5	101	16.7 ± 1.6	107	17.0 ± 1.5	311	16.9 ± 1.5
10th–12th mo	75	17.0 ± 1.5	87	17.1 ± 1.5	60	16.7 ± 1.3	83	17.0 ± 1.3	242	16.8 ± 1.3
21st–24th mo	64	16.5 ± 1.5	82	16.4 ± 1.4	71	16.0 ± 1.3	73	16.3 ± 1.3	209	16.2 ± 1.3
43rd–48th mo	41	15.5 ± 1.4	34	15.7 ± 1.3	35	15.7 ± 0.8	51	15.5 ± 1.2	145	15.4 ± 1.1
60th–64th mo	83	15.4 ± 1.5	80	15.7 ± 1.7	74	15.5 ± 1.3	94	15.3 ± 1.2	260	15.2 ± 1.2
BMI z score[4]										
Birth	133	−0.60 ± 1.0	145	−0.50 ± 1.1	130	−0.60 ± 0.9	155	−0.62 ± 1.0	394	−0.51 ± 1.0
3rd–10th d	120	−0.98 ± 1.0	129	−0.88 ± 1.0	114	−0.92 ± 0.9	139	−1.03 ± 0.9	357	−0.85 ± 1.0
4th–6th wk	97	−0.32 ± 0.9	119	−0.51 ± 1.0	108	−0.52 ± 1.0	119	−0.45 ± 1.0	327	−0.17 ± 0.9
3rd–4th mo	109	−0.39 ± 1.2	118	−0.57 ± 1.0	110	−0.66 ± 1.1	115	−0.45 ± 1.0	321	−0.49 ± 1.1
6th–7th mo	105	−0.17 ± 1.1	120	−0.28 ± 1.1	101	−0.54 ± 1.2	107	−0.30 ± 1.1	311	−0.41 ± 1.1
10th–12th mo	75	0.03 ± 1.1	87	0.14 ± 1.1	60	−0.17 ± 1.0	83	0.02 ± 1.0	242	−0.14 ± 0.0
21st–24th mo	64	0.48 ± 1.1	82	0.44 ± 1.1	71	0.09 ± 1.1	73	0.34 ± 1.1	209	0.26 ± 1.0
43rd–48th mo	41	0.03 ± 1.1	34	0.21 ± 1.0	35	0.22 ± 0.6	51	0.07 ± 0.9	145	−0.02 ± 1.0
60th–64th mo	83	0.00 ± 1.1	80	0.25 ± 1.1	74	0.10 ± 0.9	94	0.02 ± 0.9	260	−0.07 ± 0.9

[1] Formula-feeding group assignment was made according to intention-to-treat randomization at birth. pHF-W, partially hydrolyzed whey; eHF-W, extensively hydrolyzed whey; eHF-C, extensively hydrolyzed casein; CMF, cow-milk formula.

[2] Exclusively breastfed for ≥16 wk from birth.

[3] Mean (SD) ages at the measurement occasions for boys were as follows: 0 (0) d, 4.5 (1.5) d, 5.0 (0.7) wk, 3.4 (0.4) mo, 6.4 (0.4) mo, 11.4 (0.6) mo, 23.3 (0.7) mo, 47.1 (1.0) mo, and 61.8 (1.2) mo.

[4] z Score was calculated according to the World Health Organization Child Growth Standards (12, 13).

However, for the eHF-C group, both intention-to-treat- and per-protocol-based analyses showed a significantly slower BMI change between the 8th and the 48th week of life (−0.1 to −0.2 lower BMI SD scores) in comparison with all other formula groups. The difference in the eHF-C group from the breastfed group over time is smaller and significant between the 8th and the 28th week only. The statistical significance of these differences is indicated by the 95% prediction band around the eHF-C group, which does not include the trajectories of all other groups in the mentioned periods. However, after the first year of life, this prediction band clearly includes the trajectories of all 5 study groups, which indicates that the effect on the eHF-C formula-fed infants is no longer significantly different for the further study period up to the age of 6 y.

Additional longitudinal analyses of weight and length revealed that, although weight gain for the eHF-C group is reduced in weeks 0–8, 8–16, and 16–52 (but not beyond), growth in length does not significantly differ among study groups for the entire 6-y follow-up (data not shown). Thus, the retarded gain in BMI of the eHF-C group within the first year of life is because

TABLE 5
Average anthropometric measurements in girls by formula-feeding group at designated times of well-baby check-up examinations

	Formula-feeding group[1]									
	pHF-W		eHF-W		eHF-C		CMF		Breastfed group[2]	
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
Weight (kg)										
Birth[3]	120	3.3 ± 0.5	120	3.4 ± 0.5	120	3.4 ± 0.4	121	3.4 ± 0.5	402	3.4 ± 0.4
3rd–10th d	107	3.2 ± 0.5	112	3.3 ± 0.5	114	3.2 ± 0.4	111	3.2 ± 0.5	348	3.3 ± 0.4
4th–6th wk	107	4.3 ± 0.5	93	4.4 ± 0.6	89	4.2 ± 0.5	99	4.2 ± 0.6	318	4.4 ± 0.5
3rd–4th mo	100	6.1 ± 0.7	100	6.1 ± 0.7	94	6.0 ± 0.8	95	6.0 ± 0.7	324	6.1 ± 0.7
6th–7th mo	92	7.7 ± 0.9	92	7.9 ± 0.8	85	7.6 ± 0.8	101	7.6 ± 0.8	295	7.5 ± 0.8
10th–12th mo	69	9.4 ± 1.1	69	9.4 ± 1.0	73	9.3 ± 0.9	75	9.2 ± 1.1	232	9.0 ± 0.9
21st–24th mo	59	12.0 ± 1.4	67	12.2 ± 1.5	61	12.1 ± 1.2	61	11.9 ± 1.2	213	11.9 ± 1.3
43rd–48th mo	34	16.4 ± 2.1	37	16.5 ± 2.0	33	16.1 ± 1.8	38	16.9 ± 3.3	132	16.7 ± 2.1
60th–64th mo	78	19.5 ± 2.8	65	19.2 ± 2.7	64	19.7 ± 2.7	70	19.6 ± 3.2	263	19.5 ± 2.5
Length (cm)										
Birth	120	51.7 ± 2.6	120	51.9 ± 2.3	120	51.5 ± 2.4	121	52.0 ± 2.6	402	52.0 ± 2.2
3rd–10th d	107	51.5 ± 2.5	112	51.8 ± 2.3	114	51.4 ± 2.4	111	52.0 ± 2.6	348	52.0 ± 2.1
4th–6th wk	107	54.8 ± 2.5	93	55.0 ± 2.3	89	55.0 ± 2.3	99	54.8 ± 2.2	318	55.1 ± 2.1
3rd–4th mo	100	62.0 ± 2.4	100	62.1 ± 2.5	94	61.8 ± 2.7	95	61.7 ± 2.6	324	61.9 ± 2.6
6th–7th mo	92	68.1 ± 2.6	92	68.6 ± 2.8	85	68.0 ± 2.7	101	68.0 ± 2.7	295	67.5 ± 2.6
10th–12th mo	69	74.7 ± 2.7	69	75.0 ± 3.1	73	74.7 ± 2.7	75	75.0 ± 2.9	232	74.1 ± 2.6
21st–24th mo	59	87.2 ± 3.5	67	86.9 ± 3.7	61	86.7 ± 2.7	61	86.7 ± 3.5	213	86.3 ± 3.2
43rd–48th mo	34	102.7 ± 3.2	37	103.3 ± 3.7	33	103.2 ± 3.9	38	104.1 ± 5.1	132	103.4 ± 4.7
60th–64th mo	78	112.0 ± 5.0	65	111.4 ± 4.9	64	112.7 ± 5.0	70	112.5 ± 5.7	263	112.4 ± 4.5
BMI (kg/m^2)										
Birth	120	12.5 ± 1.2	120	12.8 ± 1.3	120	12.7 ± 1.2	121	12.5 ± 1.1	402	12.7 ± 1.1
3rd–10th d	107	12.0 ± 1.1	112	12.4 ± 1.4	114	12.1 ± 1.3	111	11.8 ± 1.1	348	12.1 ± 1.1
4th–6th wk	107	14.2 ± 1.3	93	14.4 ± 1.4	89	13.9 ± 1.4	99	14.1 ± 1.5	318	14.4 ± 1.3
3rd–4th mo	100	15.9 ± 1.5	100	15.9 ± 1.4	94	15.6 ± 1.5	95	15.8 ± 1.6	324	15.8 ± 1.5
6–7th mo	92	16.7 ± 1.6	92	16.7 ± 1.5	85	16.4 ± 1.7	101	16.5 ± 1.5	295	16.5 ± 1.5
10th–12th mo	69	16.8 ± 1.6	69	16.6 ± 1.2	73	16.6 ± 1.5	75	16.3 ± 1.5	232	16.5 ± 1.4
21st–24th mo	59	15.7 ± 1.2	67	16.2 ± 1.6	61	16.1 ± 1.3	61	15.8 ± 1.3	213	16.0 ± 1.3
43rd–48th mo	34	15.5 ± 1.6	37	15.4 ± 1.3	33	15.1 ± 1.1	38	15.5 ± 1.7	132	15.5 ± 1.3
60th–64th mo	78	15.5 ± 1.5	65	15.4 ± 1.4	64	15.4 ± 1.4	70	15.4 ± 1.4	263	15.4 ± 1.3
BMI *z* score[4]										
Birth	120	−0.76 ± 1.0	120	−0.53 ± 1.1	120	−0.61 ± 1.1	121	−0.75 ± 1.00	402	−0.58 ± 1.0
3rd–10th d	107	−1.08 ± 0.9	112	−0.76 ± 1.1	114	−0.95 ± 1.0	111	−1.18 ± 0.96	348	−0.93 ± 1.0
4th–6th wk	107	−0.40 ± 0.9	93	−0.30 ± 0.9	89	−0.69 ± 1.0	99	−0.57 ± 1.10	318	−0.26 ± 0.9
3rd–4th mo	100	−0.47 ± 1.0	100	−0.44 ± 1.0	94	−0.67 ± 1.0	95	−0.52 ± 1.12	324	−0.51 ± 1.0
6th–7th mo	92	−0.19 ± 1.1	92	−0.17 ± 1.0	85	−0.43 ± 1.2	101	−0.36 ± 1.05	295	−0.29 ± 1.0
10th–12th mo	69	0.20 ± 1.0	69	0.07 ± 0.8	73	0.08 ± 1.0	75	−0.13 ± 1.03	232	−0.03 ± 1.0
21st–24th mo	59	0.16 ± 0.9	67	0.47 ± 1.1	61	0.46 ± 0.9	61	0.20 ± 0.95	213	0.35 ± 0.9
43rd–48th mo	34	0.09 ± 1.3	37	0.05 ± 0.9	33	−0.15 ± 0.8	38	0.08 ± 1.15	132	0.14 ± 0.9
60th–64th mo	78	0.07 ± 0.9	65	0.04 ± 0.9	64	0.05 ± 0.9	70	0.01 ± 0.92	263	0.03 ± 0.9

[1] Formula-feeding group assignment was according to intention-to-treat randomization at birth. pHF-W, partially hydrolyzed whey; eHF-W, extensively hydrolyzed whey; eHF-C, extensively hydrolyzed-casein; CMF, cow-milk formula.
[2] Exclusively breastfed for ≥16 wk from birth.
[3] Mean (SD) ages at the measurement occasions for girls were as follows: 0 (0) d, 4.4 (1.4) d, 5.0 (0.7) wk, 3.4 (0.4) mo, 6.4 (0.4) mo, 11.4 (0.5) mo, 23.3 (0.7) mo, 47.0 (1.2) mo, and 61.8 (1.3) mo.
[4] *z* Score was calculated according to the World Health Organization Child Growth Standards (12, 13).

of lower weight gain and not because of overall impaired development.

Moreover, we performed sensitivity analyses (20) (excluding the 159 infants of our analysis population who developed eczema or urticaria within the first year of life) and found no substantial differences. The eHF-C group still had a lower BMI gain during the first year of life but not beyond, although the difference in weight and BMI between the eHF-C group and the other formula groups was no longer significant after week 35. Adjusting for any solid food or juice introduced within the first 16 wk or for the number of weeks breastfed did not substantially change the results for analyses with or without inclusion of the exclusively breastfed group. Nor did the results change substantially when adjusting for the number of weeks exclusively exposed to formula. Because we lacked precise information about the amount of formula intake, we adjusted the analyses regarding the 4 formula groups by the duration of breastfeeding. Again, no substantial differences in BMI-change trajectories

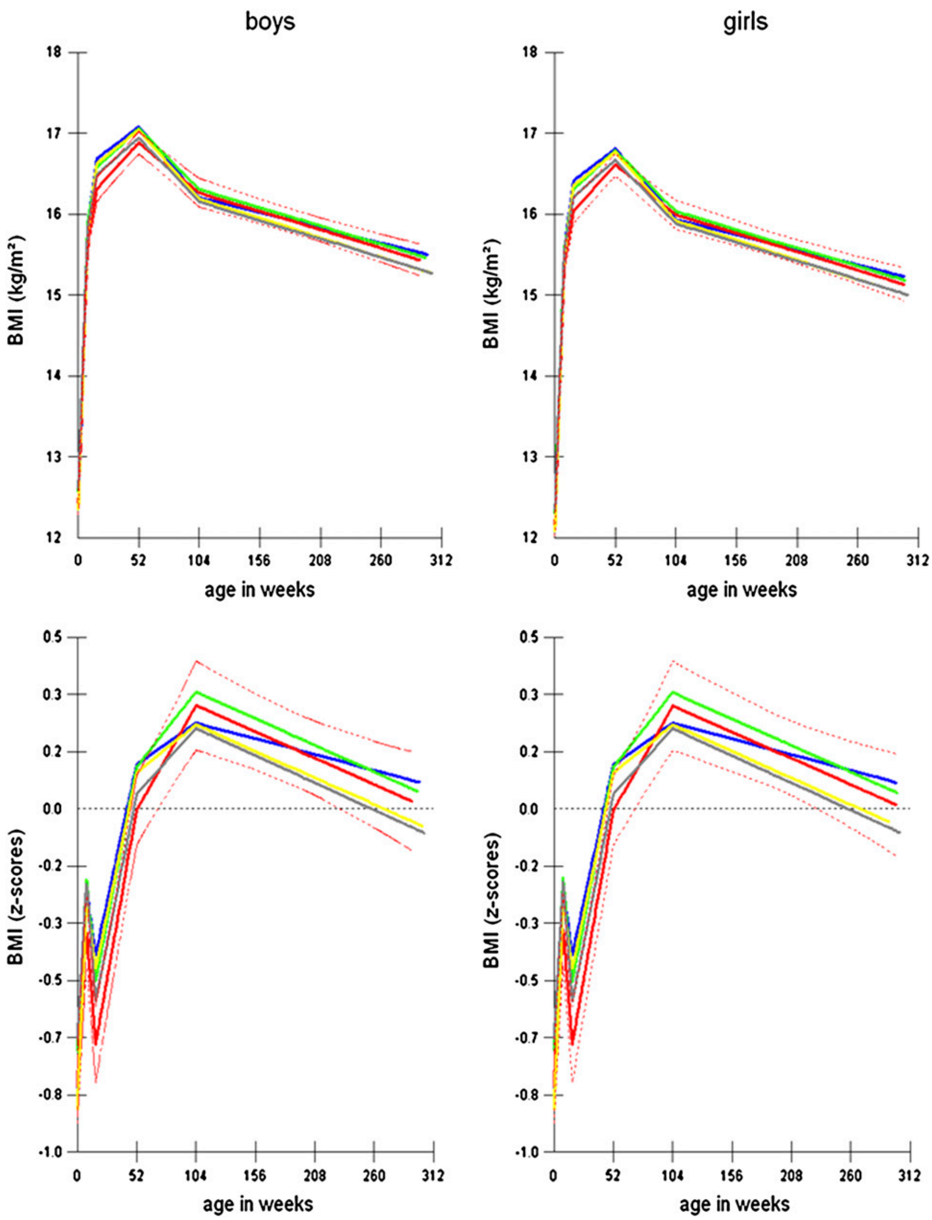

FIGURE 2. Period-specific development of absolute and World Health Organization–standardized BMI for boys and girls in intention-to-treat analyses between birth and 6 y of life. The study groups are indicated by the following: solid blue line, pHF-W (partially hydrolyzed whey; $n = 253$); solid green line, eHF-W (extensively hydrolyzed whey; $n = 265$); solid red line, eHF-C (extensively hydrolyzed casein; $n = 250$); solid yellow line, CMF (cow-milk formula; $n = 276$); gray line, BF (exclusively breastfed for 16 wk; $n = 796$); dashed red line, 95% prediction band around the trajectory of the eHF-C study group.

were seen. In addition, we conducted a sensitivity analysis on the 147 infants who were exposed exclusively to the study formulas from the first week of life. Again, we had the same result: the eHF-C had a significantly lower BMI gain within the first life year, but this difference did not persist into later childhood (data not shown).

DISCUSSION

To our knowledge, this is the first randomized trial investigating both short- and long-term effects of partially and extensively hydrolyzed formula feedings (pHF-W, eHF-W, eHF-C) and CMF and infants exclusively breastfed for at least 16 wk in one trial and, in enough detail, from birth up to 6 y of age. Infants fed with eHF-C formula show a significantly lower gain in weight and BMI than the other formula groups in the first year of life and up to the first half year of life for breastfed infants. No significant differences in weight and absolute or WHO-standardized BMI trajectories were found among the other formula groups (pHF-W, eHF-W, and CMF) or the breastfed group over the entire 6-y follow-up. Because growth in length is equal for all 4 formula groups, the reduced BMI gain for the eHF-C group within the first year of life is because of slower weight-change velocities compared with the other formula groups (in particular for the first 16 wk) and not because of an overall impaired growth. Despite double-blind randomization to formula-feeding groups at birth, all mothers received the nutritional recommendation to breastfeed their infants within the first 16 wk and to formula feed only

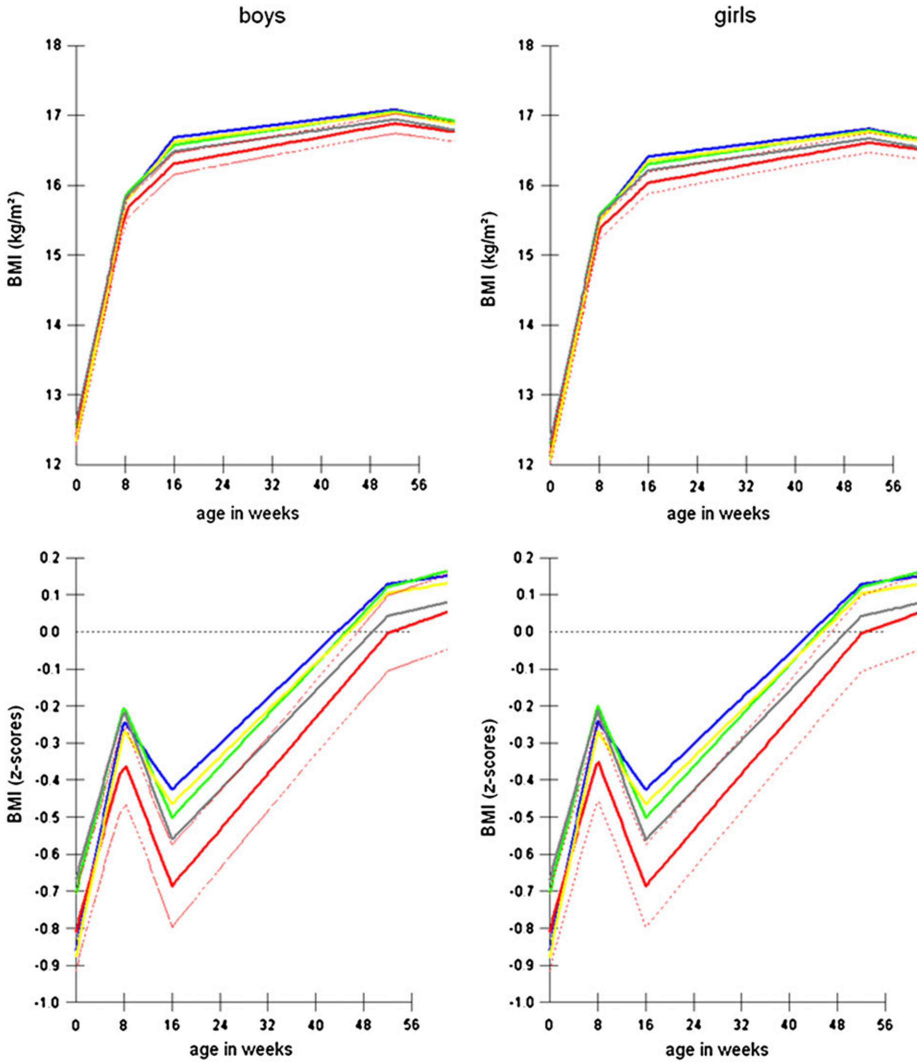

FIGURE 3. Period-specific development of absolute and World Health Organization–standardized BMI for boys and girls in intention-to-treat analyses in the first year of life. The study groups are indicated by the following: solid blue line, pHF-W (partially hydrolyzed whey; $n = 253$); solid green line, eHF-W (extensively hydrolyzed whey; $n = 265$); solid red line, eHF-C (extensively hydrolyzed casein; $n = 250$); solid yellow line, CMF (cow-milk formula; $n = 276$); gray line, BF (exclusively breastfed for 16 wk; $n = 796$); dashed red line, 95% prediction band around the trajectory of the eHF-C study group.

when breast milk did not suffice or when the mothers wanted to wean. Consequently, some selection bias between all study groups (formula and breastfeeding groups) cannot be ruled out.

Only 1 (6) of the 8 (1–8) previous RCTs analyzed the 4 formulas included in this study. However, this previous study analyzed the effect of the 4 formulas on weight and length at only 2 time points, birth and 6 mo. Moreover, only 3 of these RCTs followed growth through the first year of life (1, 7, 8) and only 1 had a follow-up time of 4 y (1). Furthermore, only 3 short-term trials, which investigated growth up to the first 6 mo, had several measurements within this period (2, 4, 5). Most studies used weight-for-age or weight-for-length *z* scores with various reference standards, which are comparable but not the same as the age- and sex-specific BMI *z* scores standardized to the new WHO Children's Growth Standards used in the present study (12, 13). Thus, a direct comparison of these previous results to the ones presented here is limited.

The finding of a reduced growth in weight and BMI in the first life year for the eHF-C group is supported by a previous trial. However, this previous study analyzed growth only up to 6 mo (5).

Moreover, a 1-y RCT comparing breast milk with soy protein, rice-hydrolyzed, and casein-hydrolyzed formulas did not show a significant difference in weight-for-age and weight-for-length *z* scores (standardized to the Centers for Disease Control and Prevention reference charts) (7). Two other RCTs comparing eHF-C formula to eHF-W formula also did not show an adverse effect on weight change for the eHF-C formula (4, 8). However, in contrast to our study, these previous studies may have lacked the power to detect these differences because of their small group size. The only study that analyzed the 4 groups considered here did not find any substantial differences among any formula groups (6).

Unfortunately, the only long-term trial with larger group sizes did not study the effect of eHF-C but studied eHF-W in comparison with soy-based formula (1). Nevertheless, this study supports our results insofar as it was shown that an eHF-W formula does not impair growth in both weight and length regarding the long-term effects of formula feeding. Moreover, all cited RCTs analyzing 1 or 2 formulas studied in this trial are in line with our result of no substantial difference in the growth of length for pHF-W (4), eHF-W (1, 8), eHF-C (4, 7, 8), and CMF (2).

What might explain the decreased weight gain of the eHF-C group in the first year of life? It is possible that formula composition (21, 22) could explain these findings. Regarding energy density and the macronutrients of protein, fat, and carbohydrates, Table 1 revealed that the higher protein fraction of eHF-C is the most striking difference among the 4 formulas (1.9 g/100 ml compared with 1.4–1.6 g/100 ml). Our results of a lower weight gain are in agreement with the findings of Giovannini et al (5) The authors compared the anthropometric indexes of infants who were fed 1 of 3 extensively hydrolyzed formulas (based on hydrolyzed whey, casein, or a mixture of soy plus collagen), a whole-protein soy formula, or human milk. Infants who received the hydrolyzed casein formula showed a lower BMI at 3 mo of age despite a comparable or even higher caloric and protein intake and higher blood nitrogen concentrations. This indicates that hydrolysates from pure casein may have a lower biologic value with a lower nitrogen utilization compared with whey protein, most likely because of amino acid imbalances. In an RCT in 21 preterm infants who were provided with the same caloric and nitrogen intake, Maggio et al (23) reported a significantly lower weight gain and a higher urinary amino acid concentration in infants receiving a hydrolyzed than those receiving a full-protein formula. Differences in the nutritional value, weight gain, and amino acid imbalances were also noted by Rigo et al (3) who compared 5 different hydrolyzed formulas with human milk.

It was also shown that infants with a cow-milk allergy have lower absorption rates of macronutrients and show a significantly depressed growth in both weight and length (24). However, because infants were randomly assigned at birth to the study formulas, we think it is unlikely that all children developing a cow-milk allergy were assigned to the eHF-C group.

Moreover, we performed sensitivity analyses (20) and excluded the 159 infants of our analysis population who developed eczema or urticaria within the first year of life and found no substantial differences. The eHF-C group still had lower BMI values during the first year of life but not beyond, although the difference in weight and BMI between the eHF-C group and the other formula groups was no longer significant after week 35 (data not shown). Thus, malabsorption due to allergic manifestation may explain only a small part of the lower weight gain of the eHF-C group within the first year of life. Further sensitivity analyses reported in Results confirmed the results of the main analyses as well. However, we did not adjust analyses for multiple testing. Hence, it cannot be ruled out totally that the significant lower BMI gain of the eHF-C group could be because of confounding by a known difference (percentage of maternal smoking during pregnancy, maternal age at birth, and percentage of low parental education; *see* Table 3) and by unknown differences among the groups. However, we consider it unlikely that these differences at the start of follow-up confounded the reported longitudinal results because these differences were mainly because of the breastfed group. Furthermore, all analyzed infants had a familial history of atopic diseases. In a previous publication on this trial, the eHF-C group showed the lowest risk of actual allergic manifestation over time. In addition, both the eHF-C and the pHF-W group showed a significantly lower risk of developing eczema in comparison with the CMF group (9–11). Because of this preventive effect of the eHF-C formula for atopy and eczema, parents whose infants are at higher risk of atopy or have a cow-milk allergy should not abstain from feeding their infants eHF-C formula despite the decreased weight gain in the first year of life. On the other hand, we lack information on intake amounts and therefore cannot rule out the possibility that the known lower palatability of the eHF-C formula resulted in lower intake and consequently in a retarded weight gain in the first year of life. The particular lower weight gain of the eHF-C group in the first 16 wk may point somewhat in this direction. It is also unlikely that the degree of hydrolyzation itself is responsible for a large weight-depression effect because the eHF-W formula group does not show this adverse weight-retarding effect and has only a slightly, but not significantly, lower trajectory in the first life year than the pHF-W formula group. Moreover, the BF group, similar to the eHF-C group, also had a lower (but nonsignificant) BMI trajectory within the first year of life compared with the other formula groups (pHF-W, eHF-W, CMF). In comparison with the eHF-C group, the trajectory of the BF group is significantly higher only between the 8th and the 28th week. However, as already mentioned above, some bias, particularly for the breastfeeding group, cannot be ruled out.

In any case, further investigations into the potential reasons for the adverse effect found with eHF-C formula are needed. Nevertheless, because there is no difference in growth in length and because the weight retardation of the eHF-C group is already compensated in comparison with the breastfed group after the first half year and because this weight retardation does not persist to later childhood, all 4 study formulas can be regarded as safe with respect to growth development up to 6 y.

In conclusion, to our knowledge, this is the first randomized trial investigating both short- and long-term effects of partially and extensively hydrolyzed formula feedings (pHF-W, eHF-W, eHF-C), CMF, and breastfeeding in one trial and in detail from birth to 6 y of age. Infants fed with eHF-C formula show a lower BMI gain in the first year of life than those fed with hydrolyzed-whey and cow-milk formula. However, no adverse long-term effect on BMI up to age 6 was found for the eHF-C or for any other formula group whether comparisons were made between formula groups or with respect to breastfed children. Because growth in length was not impaired in any studied formula group, all 4 formulas may be considered safe from a developmental point of view. However, nutritional adequacy of the eHF-C formula and potential reasons for this weight-gain retardation should be investigated in more detail.

Members of the German Infant Nutritional Intervention-plus Study Group are as follows: Institute of Epidemiology, Helmholtz Zentrum Muenchen-German Research Center for Environmental Health, Neuherberg (HE Wichmann, J Heinrich, A Schoetzau, M Popescu, M Mosetter, J Schindler, K Franke, B Laubereau, S Sausenthaler, A Thaqi, A Zirngibl, A Zutavern, B Filipiak, U Gehring); Department of Pediatrics, Marien-Hospital, Wesel (D Berdel, A von Berg, B Albrecht, A Baumgart, C Bollrath, S Büttner, S Diekamp, I Gros, T Jakob, K Klemke, S Kurpiun, M Möllemann, J Neusüss, A Varhelyi, C Zorn C); Ludwig Maximilians University of Munich, Dr von Hauner Children's Hospital (S Koletzko, D Reinhard, H Weigand, I Antonie, B Bäumler-Merl, C Tasch, R Göhlert, C Sönnichsen); Clinic and Polyclinic for Child and Adolescent Medicine, University Hospital rechts der Isar of the Technical University Munich (CP Bauer, A Grübl, P Bartels, I Brockow, U Hoffmann, F Lötzbeyer, R Mayrl, K Negele, E-M Schill, B Wolf); Institut für Umweltmedizinische Forschung-Environmental Health Research Institute, Düsseldorf (U Krämer, E Link, D Sugiri, U Ranft).

We thank the families for participation in the studies, the obstetric units for allowing recruitment, the German Infant Nutritional Intervention Study teams for excellent work, and the several funding agencies listed on the opening page. In addition, we gratefully acknowledge the editorial work of Elaina MacIntyre.

The authors' responsibilities were as follows—PR: data analysis, interpretation of data, and manuscript preparation; SS, SK, and JH: assisted in the interpretation of results and the critical revision of the manuscript; DR, AvB, DB, CB, CPB, AG, UK, H-EW, and JH: data collection; and PR and JH: developed the design and analysis plan of this study. None of the authors had a conflict of interest.

REFERENCES

1. Seppo L, Korpela R, Lonnerdal B, et al. A follow-up study of nutrient intake, nutritional status, and growth in infants with cow milk allergy fed either a soy formula or an extensively hydrolyzed whey formula. Am J Clin Nutr 2005;82:140–5.
2. Lasekan JB, Koo WW, Walters J, Neylan M, Luebbers S. Growth, tolerance and biochemical measures in healthy infants fed a partially hydrolyzed rice protein-based formula: a randomized, blinded, prospective trial. J Am Coll Nutr 2006;25:12–9.
3. Rigo J, Salle BL, Putet G, Senterre J. Nutritional evaluation of various protein hydrolysate formulae in term infants during the first month of life. Acta Paediatr Suppl 1994;402:100–4.
4. Schmelzle H, Wirth S, Skopnik H, et al. Randomized double-blind study of the nutritional efficacy and bifidogenicity of a new infant formula containing partially hydrolyzed protein, a high beta-palmitic acid level, and nondigestible oligosaccharides. J Pediatr Gastroenterol Nutr 2003;36:343–51.
5. Giovannini M, Agostoni C, Fiocchi A, Bellu R, Trojan S, Riva E. Antigen-reduced infant formulas versus human milk: growth and metabolic parameters in the first 6 months of life. J Am Coll Nutr 1994;13:357–63.
6. Hernell O, Lonnerdal B. Nutritional evaluation of protein hydrolysate formulas in healthy term infants: plasma amino acids, hematology, and trace elements. Am J Clin Nutr 2003;78:296–301.
7. Agostoni C, Fiocchi A, Riva E, et al. Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period. Pediatr Allergy Immunol 2007;18:599–606.
8. Estrada-Reyes E, Garcia-Hernandez G, Martinez-Gimeno A, Nava-Ocampo AA. Effect of extensively hydrolyzed milk formula on growth and resistance to bronchitis and atopic dermatitis in infants and toddlers. J Investig Allergol Clin Immunol 2006;16:183–7.
9. von Berg A, Koletzko S, Grubl A, et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. J Allergy Clin Immunol 2003;111:533–40.
10. von Berg A, Koletzko S, Filipiak-Pittroff B, et al. Certain hydrolyzed formulas reduce the incidence of atopic dermatitis but not that of asthma: three-year results of the German Infant Nutritional Intervention Study. J Allergy Clin Immunol 2007;119:718–25.
11. von Berg A, Filipiak-Pittroff B, Kramer U, et al. Preventive effect of hydrolyzed infant formulas persists until age 6: long-term results from the German Infant Nutritional Intervention Study (GINI). J Allergy Clin Immunol. 2008;121:1442–7.
12. de Onis M, Garza C, Onyango AW, Borghi E. Comparison of the WHO child growth standards and the CDC 2000 growth charts. J Nutr 2007;137:144–8.
13. Butte NF, Garza C, de Onis M. Evaluation of the feasibility of international growth standards for school-aged children and adolescents. J Nutr 2007;137:153–7.
14. Ziegler EE, Nelson SE. The new WHO growth standards. Ann Nestlé (Engl) 2007;65:109–15.
15. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life: a systematic review. Obes Rev 2005;6:143–54.
16. Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. Hoboken, NJ: John Wiley & Sons, 2004.
17. Singer JD, Willett JB. Applied longitudinal data analysis: modeling change and event occurrence. Oxford, United Kingdom: Oxford University Press, 2003.
18. SAS Institute Inc. SAS/STAT 9.1 user's guide. Cary, NC: SAS Institute Inc, 2004.
19. Rasbash J, Steele F, Browne W, Prosser BA. Users's guide to MLwiN. Version 2.0. London, United Kingdom: Center for Multilevel Modelling, Institute of Education, University of London, 2004.
20. Lash TL, Fink AK. Semi-automated sensitivity analysis to assess systematic errors in observational data. Epidemiology 2003;14:451–8.
21. Koletzko B, Baker S, Cleghorn G, et al. Global standard for the composition of infant formula: recommendations of an ESPGHAN coordinated international expert group. J Pediatr Gastroenterol Nutr 2005;41:584–99.
22. Koletzko B, Shamir R. Standards for infant formula milk. BMJ 2006;332:621–2.
23. Maggio L, Zuppa AA, Sawatzki G, Valsasina R, Schubert W, Tortorolo G. Higher urinary excretion of essential amino acids in preterm infants fed protein hydrolysates. Acta Paediatr 2005;94:75–84.
24. Isolauri E, Sutas Y, Salo MK, Isosomppi R, Kaila M. Elimination diet in cow's milk allergy: risk for impaired growth in young children. J Pediatr 1998;132:1004–9.