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ORIGINAL CONTRIBUTION

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Improved general health status in an unselected infant population following an allergen-reduced dietary intervention programme: the ZUFF-STUDY-PROGRAMME

Part II: infant growth and health status to age 6 months

Summary *Aim of the study.* An allergen-reduced dietary intervention programme with strict dietary requirements was implemented over the first four months of life in an unselected population-based infant cohort and compared to a non-intervention cohort (the ZUFF study). Recommendations for the dietary programme in the intervention cohort were extended, but not strictly implemented, until the end of month six. The intervention was based on breastfeeding, a moderate whey hydrolysate formula (pHF), and delayed introduction of weaning foods with a high allergenicity. This study was a prospective, controlled, and unblinded study, the first to assess the effects of an allergen-reduced, pHF-based early nutritional programme in a broad unselected infant population. Because overall healthy development of the infant is a major objective of any nutritional programme, the study evaluated the effects of the dietary intervention on infant growth and general health status rather than specific allergic manifestations. Part I of this paper gave results for nutritional behaviour only, and Part II gives results for growth and general health status during the intervention period through the sixth month of life.

Methods. Assignment of study infants was to demographically comparable intervention (Z) or control (FF) cohorts according to place of birth. In the intervention cohort (*Z*=564), the recommended dietary regimen was breastfeeding and – if exclusive breastfeeding was not possible – supplementation with a moderately hydrolysed, allergen-reduced infant formula (pHF). Weaning foods were delayed until four months of age or later in case of weaning foods with high allergenicity. In the control cohort (*FF*=566), there was no specific intervention. Imbalances between cohorts in confounding (adjuvant) factors that could influence health-related outcomes were integrated as covariates into the logistic regression of the main analyses. Growth parameters included weight, length, head circumference, BMI, and Z scores (SDS). General health status was assessed by clinically significant findings in gastrointestinal, respiratory, or skin symptoms.

Results. Growth at 6 weeks and at 3 and 6 months was similar for Z and FF. Significantly fewer Z than FF infants had clinically noteworthy health findings at 3 months (*Z*=27 % versus *FF*=37 %, odds ratio=0.63, CI=0.48–0.82) and 6 months (*Z*=33 % versus *FF*=49 %, odds ratio=0.51, CI= 0.40–0.66). This corresponds to a 30 % reduction in overall health concerns at 6 months for the intervention cohort. At 3 and 6 months, differences between cohorts in most measures of general health status were strongly influenced by a lower incidence of skin symptoms in the Z cohort. Within FF, there were fewer exclusively breastfed (eBF) infants with health problems at 3 months compared with those who were partially (pBF) or non-breastfed (nBF) (*eBF*=31 %, *pBF*=40 %, *nBF*=39 %, $p < 0.05$). In contrast, in the Z intervention cohort, the number of infants with health concerns was similar for exclusively breastfed infants and for those in whom mother's milk was supplemented or replaced by pHF (*eBF*=29 %, *pBF*=25 %, *nBF*=26 %, ns). In a subanalysis of overall health findings in infants without a family risk of allergies, there were again significantly fewer Z than FF infants with any health or any skin problem.

Conclusion. An allergen-reduced dietary recommendation that includes a moderate whey hydrolysate infant formula (pHF) has no negative effects on growth parameters up to

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6 months of life in an infant population unselected for atopic risk. The dietary intervention produced improvements in general health status when compared with a control cohort that received infant formula with unhydrolysed proteins (IF), and high allergenic weaning foods at an earlier age. The difference between cohorts was principally due to fewer adverse skin findings. In infants following our allergen-reduced feeding recommendation, 3-month general health status was comparable between those who were exclusively breastfed and those in whom breastfeeding was supplemented or replaced by pHF. Our results demonstrate that a pHF feeding recommendation during the first 4 to 6 months of life – when exclusive breastfeeding is not possible – is a safe and feasible regimen not only in high-allergic risk populations but in a general unselected infant population. The general use of pHF formula in non- or partly breastfed infants could therefore be considered an important contribution to optimised infant nutrition.

Key words infant nutrition – breastfeeding – partial whey hydrolysate – prevention programme – growth – general health

List of abbreviations:

BMI	body mass index
CI	confidence interval
CMP	cow's milk protein
CMPA/I	cow's milk protein allergy/intolerance
eBF	exclusively breastfed
eHF	extensively hydrolysed infant formula
FF	control cohort in Frauenfeld
IF	unaltered conventional infant formula
IgE	immunoglobulin E
nBF	non-breastfed
ns	not significant
OR	odds ratio
pBF	partially breastfed
pHF	partially (=moderately) hydrolysed infant formula (Nestlé Beba HA)
Z	intervention cohort in Zug

Introduction

For all newborn infants, mother's milk will always be the ideal nutrition. Of all available foods, mother's milk best ensures the healthy short- and long-term development of newborns. Mother's milk enhances immune functions, is hypoallergenic, and its overall composition aids in establishing bifidogenic gut flora (1–3). However, some infants may not be exclusively breastfed in early life, and the food industry (beginning with the work of Henri Nestlé in 1867) has devoted considerable research into providing the best possible nutritional alternatives to breast milk. Nowadays, the result is infant formulae that are designed to meet the needs of safe nutrition, adequate growth, and the healthy development of infants in the first months of life. Meanwhile, research continues into further improvements on infant formulae. Currently, most nutritional committees in Europe recommend for infants at a high risk of allergies that – if necessary – breastfeeding should be supplemented with a hypoallergenic, moderately hydrolysed infant (pHF) formula (4–6). A consensus paper recently published by the European Society of Paediatric Allergology and Clinical Immunology (ESPACI) and the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommends the exclusive use of hypoallergenic formulae whose effectiveness has been demonstrated in clinical studies conducted in infants with high familial atopic risk (7).

Numerous studies have demonstrated that a hypoallergenic diet incorporating the Nestlé pHF formula can reduce the onset of early allergic manifestations in children at high risk of atopic disease. The reporting on these studies includes a meta-analysis of 15 studies conducted over at most the first 5 years of a child's life (8–14). The purpose of these studies was the prevention of first manifestations of allergic diseases in general that have their onset in over 90 % during the first 3 years of life. A preventive effect was shown principally for atopic eczema (14) and only a few studies for respiratory allergies (10, 12). Two studies evaluated cow's milk protein allergy (CMPA) individually, and demonstrated a drastic reduction in CMPA by means of controlled elimination and provocation methods (10, 14).

Almost all studies to date have focussed on infants with an elevated familial risk of allergies. Meanwhile, it is well accepted that selection criteria in common usage for high-risk infants (≥1 first-degree family member with allergy and/or elevated cord blood IgE > 0.5 kU/l) are not sufficiently specific or sensitive (15–18). Moreover, a simple calculation demonstrates that similar numbers of so-called no-risk (no known allergies in the family) infants eventually develop symptoms of allergic disease compared with medium risk (one first-degree family member with a known allergy) plus high-risk (≥1 first-degree family member with a known allergy) infants. Of those infants termed no risk (approximately 70 % of all newborns), there is a statistical 15 % residual allergic risk, and 11/100 infants will eventually develop an allergy at a later age; of medium-risk infants (approximately 25 % of all newborns), there is a 20 to 40 % risk of developing allergies, and 8/100 infants will develop an allergy at a later age; and of the high-risk infants (approximately 5 % of all newborns), there is a 50 to 80 % risk of developing allergies, and 3/100 infants will develop an allergy at a later age. Calculations based on these data show identical absolute numbers of infants with (11/100) and without (11/100) allergic risk who are likely to eventually develop allergies (Fig. 1) (18). For this reason, it

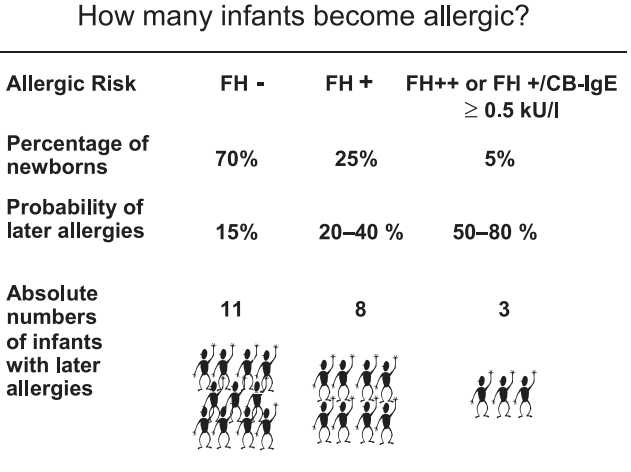
could be argued that allergy prevention programmes should be directed towards the newborn population as a whole, and not only towards those infants with a known elevated allergic risk.

It can be shown that exclusively breastfed infants are somewhat healthier than non-breastfed or partially breastfed infants during the first year of life, particularly with respect to fewer gastrointestinal or respiratory tract infections and fewer skin findings (19–21). Until now, no large-scale studies have demonstrated whether an allergen-reduced infant diet that mimics primary prevention measures is safe and beneficial for an unselected infant population, and could therefore be recommended for all infants who are non- or partly breastfed.

As discussed in Part I of this paper, pHF formulae can induce oral tolerance but not sensitisation in animal models, in contrast to eHF formulae that do not induce sensitisation nor tolerance (22–24). It has not been proven whether this observation is applicable to human infants. A study in infants with a high allergic risk demonstrated that pHF formulae induce lower sensitisation (specifically IgE) against cow's milk protein (CMP), other food allergens, and respiratory allergens when compared with eHF-fed infants (25, 26). In this respect, pHF formulae imitate the effect of mother's milk by inducing oral tolerance consistent with alimentary allergy prevention. For this reason, maximal reduction of allergens in the early diet of infants might not be an ideal goal of infant nutrition, and a diet that includes sufficient allergens to induce oral tolerance while avoiding sensitisation may be preferable. Such a feeding regimen may improve healthy development in a broad newborn infant population, and not only those at a high risk of developing allergic manifestations.

In the current study, we evaluate the effects of a nutritional intervention programme on growth and general health status in an infant population unselected for atopic risk factors. The recommended allergen-reduced dietary regimen included a moderately hydrolysed infant formula (pHF, Nestlé Beba HA) shown in previous studies to reduce the onset of allergies in at-risk populations (8–14). Our study focuses on the overall benefits of an allergen-reduced diet (nutritional status, infant growth, and overall health status including but not specifying allergic symptoms) rather than effects on specific atopic health symptoms, which have been well documented in numerous previous studies in high-risk infants. Results for dietary patterns during the strict intervention period from birth to 4 months of age and less strict until 6 months of age in the current study were presented in Part I. In the current paper, we present results for infant growth and health-related parameters during the same time period.

Fig. 1 Number of newborns who will eventually develop an allergic reaction according to their familial risk of allergies (adapted from (17)). *FH +* unifamilial elevated allergic risk; *FH ++* bifamilial elevated allergic risk; *CB-IgE* Cord-blood-IgE



Methods

Study design and patients

The objective of the ZUFF (*ZU*g-*F*rauen*F*eld) study was to determine whether an intervention programme that reduces food allergen exposure in early infant nutrition has any negative effects on overall feeding behaviour, growth, and health-related symptoms compared to a non-intervention cohort. We designed the study to enable a controlled but pragmatic evaluation of an altered dietary recommendation without the obvious difficulties of randomisation or blinding. The questions of non-blinding and non-randomisation in this study are discussed in Part I. We assured that social interactions between parents in the two cohorts were minimised. Study evaluations were carried out through objective observations by the usual healthcare providers in the two regions Zug (Z) and Frauenfeld (FF) and through subjective observations by parents, thereby ensuring minimal changes in the normal medical-dietary setting but guaranteeing (through various quality measures) reliable results. The study design is described and discussed in Part I of this paper in detail.

The study was approved by the ethical committee of the Children's Hospital, University of Zurich, in 1991. One or both parents of each infant participating in the study were duly informed and signed a declaration of informed consent before the start of the study.

Outcome variables

As stated in Part I, we categorised each infant within Z and FF into one of three longitudinal diet groups according to their actual feeding regimens, reported prospectively and continuously, and categorised as follows: 1) exclusively breastfeeding (eBF), 2) non-breastfeeding (nBF), or 3) partial breastfeeding (pBF) (Part I, Table 1). Dropouts and

noncompliants were clearly defined and precisely documented (Part I, Table 2).

Study parameters included nutritional behaviour, infant growth parameters, and infant health status, recorded at birth and at the ages of 6, 12, and 24 weeks, and 12 and 24 months (Part I Fig. 2). Adjuvant factors that could be regarded as possible confounders and which included familial information and data on the home environment were recorded at the end of the intervention period (Part I, Table 3).

Growth measurements

Growth data, measured by the physicians at scheduled visits, included measurements of infant weight, length, and head circumference, and the calculation of body mass index (BMI) and Z scores (SDS). Growth parameters were measured according to the methods of the European Growth Study (27), Falkner and Tanner (28), and the anthropometric standardisation reference manual by Lohman, Roche, and Matorell (29). Reference values for growth parameters, BMI, and Z scores were taken from WHO standards (30, 31) and the Zurich growth study of Prader and coworkers (32). In terms of quality control we ensured that all physicians received detailed training sessions and written instructions on the methods to be used.

General health status

The primary purpose of our general health evaluations was to demonstrate the effects of our dietary recommendation in an unselected infant population, and to compare our recommendation with exclusive breastfeeding. Health status was determined from two main assessments: parental monitoring (subjective measures), and physician's reports (objective measures) evaluating health findings. In each case, we asked the assessors to evaluate gastrointestinal, respiratory, and skin signs and symptoms. Parents recorded ongoing subjective assessments of the infant's well-being in weekly study diaries. In these evaluations, parents recorded their subjective descriptions of the infant's well-being, counting each significant finding from 0 to 6 within a given period prevalence. For quality control they were instructed in written form exactly on the definitions of the various health related findings that were of interest.

The physician's report of objective general health status was recorded by study physicians at scheduled visits and at any emergency visit. Records included the physician's assessment of any significant health-related finding since the previous consultation. Observations made by the study physicians were combined into specific symptoms for the purpose of analysis. These symptoms were clearly defined according to objective criteria rather than subjective diagnoses. Again, in terms of quality assurance and control we ensured that all physicians received detailed training sessions and written instructions on the definitions of symptoms that were to be reported. Each symptom was determined using international definitions from the literature up to 1991 (beginning of recruitment) as follows: gastrointestinal findings (vomiting (33), diarrhoea (34), constipation (35, 36), and infantile colic (37)), conjunctivitis, upper and lower respiratory tract findings (rhinitis (38, 39), tonsillitis, pharyngitis (39), otitis media (40), syringitis, coughing (39, 41), wheezing (42), chronic coughing (43), obstructive bronchitis or bronchial asthma (44, 45), and pseudocroup or laryngo-tracheitis (39)), and skin findings (seborrhoeic dermatitis (46), atopic dermatitis (47, 48), urticaria (49), nappy rash (46), cradle cap (48), and non-attributable exanthemas). We use the term *any health-related finding* instead of *health problems* because none of the infants were seriously ill yet exhibited symptoms suggesting they were visibly unwell. The term *any health-related finding* refers to one or more health finding in the gastrointestinal, respiratory tract, or skin system. Only significant health findings were reported, which were clearly defined, as described in the complete ZUFF study report which will be published as a supplement to the European Journal of Nutrition (in press 2000).

Statistical methods

The main statistical methods included odds ratios (95 % confidence intervals), analyses of variance and covariance, and linear and logistic regressions. Standard statistical methods were used in all calculations (see Part I). Descriptive statistics (for comparing longitudinal diet groups and for cross-sectional comparison of the overall cohorts) were used to compare Z and FF in growth and health parameters as period prevalences and cumulative incidences, as appropriate. For the per protocol analyses, we used two-sided tests at the α=0.05 level of significance. In the confirmatory main analysis, we compared general health status in Z and FF as period prevalences between the 12^{th} and 24^{th} weeks. Physician's findings were also analysed as cumulative incidences from birth to 24 weeks. An additional confirmatory intention-to-treat analysis that included noncompliants and dropouts was analysed using a worst-case type of analysis.

As described in Part I (Table 3), there was a slight imbalance between study cohorts in the following variables: parents' education, pets in the home, place of residence (urban versus rural), smoking in the home, and parity (number of older siblings), indicating a somewhat more rural population in FF and a more urban population in Z. In the light of the recent study results concerning adjuvant factors, we considered that this imbalance provided a worst-case type of scenario for Zug, with a slightly greater risk factor for health problems (57). In addition, there was a trend towards a greater family history of allergies in Z, but

with no statistically significant difference between cohorts. We integrated all adjuvant factors as confounding factors into the confirmatory main analyses using logistic regression.

Our primary analyses were the following comparisons between Z and FF: infant weight and length at weeks 12 and 24, general health status as period prevalences for weeks 12 to 24, and cumulative incidence of physician-assessed gastrointestinal, respiratory, and skin findings from birth to 24 weeks. For growth assessments, we calculated percentiles and Z scores based on study data. We accounted for deviations between planned and actual observation days by using cubic splines to adapt the data to the planned assessment time, using linear interpolation. The results were compared with the Zürich growth (32) and WHO data charts (30, 31). The following growth parameters were calculated: mean differences in Z minus FF, 95 % CIs using analysis of covariance, and 95 % CIs for the ratios of residual standard deviations using the F distribution. For general health status, comparisons between cohorts in physician assessments were carried out using logistic regression. Comparisons between cohorts in parent assessments were carried out using analysis of variance. The Bonferroni correction with a correction factor of 2 was applied to reduce the risk of a type-I error.

Results

Study population

A total of 1130 infants were enrolled in the study (564 in Z and 566 in FF). All infants included in the dietary groups (Z=466 and FF=535) were available for assessments of growth and general health status at 6, 12, and 24 weeks. Details of the study population, including numbers of dropouts and non-compliants, were given in Part I.

Growth

Growth parameters are summarised in Table 1 as descriptive data and in Table 2 as Z scores. The results were comparable between Z and FF, with no notable or statistically significant differences between cohorts. Likewise, we found no differences between Z and FF within the eBF, pBF, or nBF dietary groups (data not shown). Our results were comparable with the WHO standards (30, 31) and data from the Zurich Growth Study (32).

In both cohorts, we found a significant adjuvant effect of smoking for infant weight between 12 and 24 weeks of age, with the mean weight of those infants whose mothers smoked being approximately 120 g (12 weeks) and 160 g (24 weeks) lower than those whose mothers did not smoke. No other confounding effects were noted.

Table 1 Anthropometric data: median values (longitudinal dietary groups; excluding dropouts and non-compliants, n(Z)=466; n(FF)=535)

	Male		Female	
	Z	FF	Z	FF
Number of subjects at birth	282	293	282	273
Weight (g)				
Birth	3440	3420	3300	3270
6 weeks	4740	4700	4409	4408
12 weeks	5847	5933	5395	5397
24 weeks	7368	7464	6966	6952
Length (cm)				
Birth	50.0	50.0	50.0	49.0
6 weeks	55.8	55.7	54.0	54.4
12 weeks	60.0	60.0	58.7	58.6
24 weeks	66.1	66.3	64.5	64.6
Head circumference (cm)				
6 weeks	38.6	38.4	37.6	37.5
12 weeks	40.6	40.6	39.5	39.5
24 weeks	43.5	43.4	42.2	42.2
BMI (kg/cm^2)				
Birth	13.4	13.6	13.3	13.5
6 weeks	15.3	15.3	15.1	14.6
12 weeks	16.2	16.3	15.7	15.8
24 weeks	16.8	16.8	16.4	16.4

Table 2 Infant weight and length: Z scores and results of main analysis

	Z score (SDS)					
	Male		Female		Z versus FF	
	Z	FF	Z	FF	Mean diff.[a]	95 % CI
Weight (g)						
Birth	0.12	0.08	0.00	–0.07	–	–
6 weeks	0.84	0.76	0.71	0.71	–	–
12 weeks	0.61	0.75	0.43	0.43	0.01	–0.10–0.13
24 weeks	–0.06	0.06	–0.04	–0.06	–0.03	–0.15–0.10
Length (cm)						
Birth	–0.30	–0.30	0.04	–0.48	–	–
6 weeks	0.10	0.05	–0.32	–0.12	–	–
12 weeks	0.03	0.05	–0.06	–0.12	–0.04	–0.14–0.06
24 weeks	–0.30	–0.21	–0.34	–0.30	–0.07	–0.18–0.04

[a] Mean difference score: mean FF Z-score minus mean Z Z-score for both sexes combined.

Overall health status

Physician's reports on health status

Overall health status from the physician's report is summarised in Table 3. There were similar numbers of infants

Table 3 Overall health status from physician's report: numbers of infants with one or more health-related finding (longitudinal diet groups excluding dropouts and noncompliants)

	Number (percent) of infants				Odds ratio	95 % CI
	Z *n (%)*		FF *n (%)*			
Total number of infants	466	(100)	535	(100)		
Gastrointestinal symptom						
6 weeks	55	(11.8)	63	(11.8)	1.00	0.68–1.47
3 months	18	(3.9)	33	(6.2)	0.61	0.34–1.10
6 months	20	(4.3)	43	(8.0)	0.51	**0.30–0.89**
Respiratory tract symptom						
6 weeks	56	(12.0)	79	(14.8)	0.79	0.55–1.14
3 months	66	(14.2)	95	(17.8)	0.76	0.54–1.08
6 months	111	(23.8)	149	(27.9)	0.81	0.61–1.08
Skin symptom						
6 weeks	123	(26.4)	165	(30.8)	0.80	0.61–1.06
3 months	65	(13.9)	121	(22.6)	0.56	**0.40–0.77**
6 months	54	(11.6)	152	(28.4)	0.33	**0.24–0.46**
Any health symptom[a]						
6 weeks	189	(40.6)	240	(44.9)	0.84	0.65–1.08
3 months	125	(26.8)	197	(36.8)	0.63	**0.48–0.82**
6 months	153	(32.8)	261	(48.8)	0.51	**0.40–0.66**

[a] One or more symptom in either the gastrointestinal, respiratory tract, or skin body system.

in the Z and FF cohort with health findings in gastrointestinal, respiratory, or skin signs and symptoms at 6 weeks, but fewer Z than FF subjects in all categories at 3 and 6 months. Approximately one third of the between-cohorts differences for the various measures were statistically significant (skin at 3 and 6 months and gastrointestinal symptoms at 6 months). Results for gastrointestinal symptoms at 3 months and respiratory symptoms at 3 and 6 months were comparable between cohorts. The results suggest a 30 % reduction in overall health findings in our intervention cohort at 6 months. Differences between cohorts were most marked in skin findings at 6 months (Z=12 % versus FF=28 %). We were able to show that most individual skin manifestations occurred in a greater number of FF than Z infants (Table 4), suggesting that the higher incidence of skin findings in FF was not due to one specific symptom.

The total of all health findings was confirmed in the confirmatory main analyses for the 12- to 24-week period prevalence including dropouts and noncompliants, using an intention-to-treat analysis including a worst-case-calculation (Table 5). The results showed significantly fewer Z (33 %) compared with FF (50 %) infants with any health finding. Multiparity (≥2 older siblings) was the only positive adjuvant factor for the incidence of significant health-related findings. No other confounding factors were noted.

The numbers of infants with one or more health finding by dietary group within the Z and FF cohorts are shown in Table 6. Analysis at 3 months shows a significant effect of dietary group within the FF cohort: there were significantly fewer infants with one or more health finding who were exclusively breastfed (eBF) (31 %) compared with those who received formula or weaning foods together with breast milk (pBF) (40 %) or no breast milk at all (nBF) (39 %) ($p< 0.05$). In contrast, results for the Z intervention cohort showed no significant differences between infants who were exclusively breastfed (eBF) (29 %) and those who had received pHF as a proportion of their diet (pBF) (25 %) or as their complete 3-month diet (nBF) (26 %).

Table 4 Incidence of individual skin-related findings at 24 weeks

	Number (percent) of infants[a]			
	Z *n (%)*		FF *n (%)*	
Total number of infants	541	(100)	556	(100)
Any skin finding	65	(12.0)	154	(27.7)
Seborrhoeic dermatitis	14	(2.6)	37	(6.7)
Atopic dermatitis	38	(7.0)	66	(11.9)
Nappy rash	7	(1.3)	21	(3.8)
Cradle cap	3	(0.6)	17	(3.1)
Other eczema	17	(3.1)	68	(12.2)

[a] Each infant may have more than one skin finding.

Table 5 Overall health status from physician's report: confirmatory main analyses (including dropouts and noncompliants)

Infants with any health finding: period prevalence weeks 12 to 24 (months 4 to 6)							
Z *n (%)*		FF *n (%)*		Odds ratio	95 % CI	p value	Analysis
540	(100)	556	(100)	–	–	–	
180	(33.3)	276	(49.6)	0.51	0.40–0.65	< 0.0001	Excludes adjuvant factors
				0.58	0.44–0.75	< 0.0001	Includes adjuvant factors[a]
				0.60	0.46–0.77	< 0.0001	Worst-case analysis[a]

[a] By logistic regression.

Table 6 Overall health status from the physician's report by dietary group: number of infants with one or more health-related symptom

	Number (percent) of infants with any health-related symptom												
	Z n (%)						P value[a]	FF n (%)					P value[a]
	eBF N=201		pBF N=222		nBF N=43			eBF N=162		pBF N=311		nBF N=62	
6 weeks	80	39.8	95	42.8	14	32.6	NC	70	43.2	144	46.3	26	41.9	NC
3 months	**58**	**28.9**	**56**	**25.2**	**11**	**25.6**	**NS**	**50**	**30.9**	**123**	**39.5**	**24**	**38.7**	**< 0.05**
6 months	66	32.8	75	33.8	12	27.9	NC	82	50.6	144	46.3	35	56.5	NC

[a] P value for comparison between dietary groups within Z or FF.

NC not calculated; *NS* not significant.

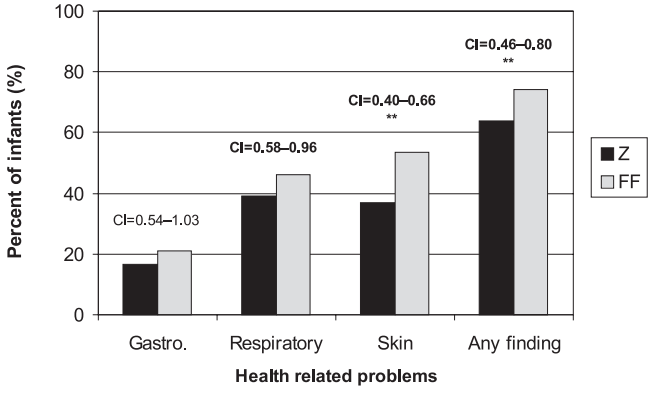
Feeding groups were defined for 4 months only, thereafter, any feeding regimen was permitted in FF, and an allergen-reduced feeding regimen in Z.

At 6 weeks and 3 months, there were similar numbers of exclusively breastfed infants in Z and FF with any health finding (Table 6). The longitudinal feeding groups were defined for 4 months. At 6 months, considerably fewer Z than FF infants in this eBF dietary group had any health finding (Z=33 % versus FF=51 %, odds ratio=0.48, CI=0.31–0.73). This was also shown for skin findings (Z=11 % versus FF=27 %, odds ratio=0.34, CI=0.19–0.60). We interpret this rapid change in general health status as due to deviations in dietary behaviours at the end of the strict intervention period at 4 months (see Part I). For partially breastfed (pBF) infants, there were still fewer Z than FF infants with any health symptoms at 3 and 6 months: 3 months Z=25 % versus FF=40 % (odds ratio=0.52, CI=0.35–0.75), 6 months Z=34 % versus FF=46 % (odds ratio=0.59, CI=0.41–0.85) (Table 6). The differences between cohorts were again due to skin findings: 3 months Z=15 % versus FF=24 % (odds ratio=0.54, CI=0.34–0.85), 6 months Z=13 % versus FF=28 % (odds ratio=0.37, CI=0.23–0.58). In the small nonbreastfed (nBF) study group, there were also fewer Z than FF infants with health-related findings at 6 months (Z=28 % versus FF=57 %, odds ratio=0.3, CI=0.13–0.69), again largely due to significant differences in skin findings (Z=9 % versus FF=34 %, odds ratio=0.20, CI=0.06–0.64) However, the numbers of infants in the eBF group was somewhat small (Table 6).

The cumulative incidence of health findings from birth to 6 months is shown in Fig. 2. There were significantly more FF than Z infants with any health finding (Z=64 % versus FF=74 %, odds ratio=0.61, CI=0.46–0.80) or with skin findings (Z=37 % versus FF=54 %, odds ratio=0.51, CI=0.40–0.66). Differences in respiratory findings approached significance (Z=39 % versus FF=46 %, odds ratio=0.75, CI=0.58–0.96), but differences in gastroenterological findings between cohorts were not significant. Differences between Z and FF in skin findings were significant in all three dietary groups (data not shown). In the confirmatory main analysis of the cumulative incidence, there were significantly more FF than Z infants with any health symptom: odds ratio=0.64, CI=0.48–0.84, p< 0.005 (logistic regression with confounders), odds ratio=0.67, CI=0.51–0.87, p< 0.005 (+ worst-case analysis).

We evaluated the *frequency of health findings* in each infant. For infants between the ages of 3 and 6 months, the mean number of health findings per symptomatic infant was 1.5 in both the Z and FF cohorts. In all dietary groups, the frequency of respiratory findings was identical for Z and FF, whereas the number of gastroenterological and skin findings was somewhat greater in FF than Z. At 3 and 6 months, slightly more FF than Z infants exhibited 2 or more significant health findings: 3 months Z=6 % versus FF=7 %; 6 months Z=12 % versus FF=16 %.

Fig. 2 Main analysis of cumulative incidence of health-related findings from 0 to 6 months: number of infants with 1 or more symptom during the reference period. Differences between Z and FF (by logistic regression) were significant for skin symptoms (odds ratio=0.51, CI=0.40–0.66) and for any health symptom (odds ratio=0.61, CI=0.46–0.80). Differences between Z and FF were not significant for gastrointestinal and respiratory symptoms. Dropouts were excluded.



Parents' subjective report on health status. We analysed parents' subjective findings. Overall, we did not find a statistically significant difference between cohorts because of the high level of subjective reporting of gastrointestinal symptoms in both cohorts during the period 13 to 24 weeks (3.3 times in Z and 3.1 times in FF). These findings were not confirmed by the physicians' reports, which did not report minor unspecified health issues. However, for the parent's reports on skin findings, we again observed significant differences between cohorts in favour of Z, including confounders and the intention-to-treat analysis with worst-case calculations (Table 7).

Analysis by subpopulation: infants without a family risk of allergies. In our study, the percent of infants with an elevated risk for allergies was somewhat greater than in the normal infant population (approximately 50 % in ZUFF versus 40 % in the normal population) (58). We therefore conducted a subanalysis of overall health findings for those infants without a known family risk of allergies. The total number of infants in this category was 494, consisting of 228 infants in Z (44 % of the total Z cohort) and 266 in FF (49 % of the total FF cohort). The main analysis of this subpopulation, conducted using logistic regression, is shown in Table 8. The results show still significantly fewer Z than FF infants with any health or any skin finding.

Effect of infant formula on general health status. An evaluation of the type of formula feeding on general health status from 4 to 6 months was planned to demonstrate whether the character of the formula itself (hydrolysed or non-hydrolysed) made a significant contribution to the positive overall health effect of our dietary recommendations. In the analysis, we combined the Z and FF cohorts, and included only those infants who had received formula during the intervention period. Therefore, eBF infants were excluded from analysis. The 736 infants who received formula were categorised as 1) pHF only, 2) cow's milk formula (IF) only, or 3) infants who were switched from pHF to IF during the intervention period. We excluded the 34 infants who had switched from IF to pHF, because they did

Table 7 Incidence of individual skin-related findings from the mother's journal during the fourth to sixth month

Mean number of subperiods with a skin-related finding during weeks 13 to 24 (months 4 to 6) (total subperiods in interval=6)					
Mean subperiods					
Z	FF	Mean difference	95 % CI	p value	Analysis
1.50	1.93				Excludes adjuvant factors
		–0.48	–0.73 – –0.23	< 0.0001	Includes adjuvant factors[a]
		–0.45	–0.71 – –0.20	< 0.0001	Worst-case analysis[a]

[a] By logistic regression.

Table 8 Overall health status from physician's report: main analyses of infants without a familial risk of allergies

Infants with no known family risk of allergies Health related symptoms at period prevalence weeks 12 to 24 (months 4 to 6)							
Z		FF					
n	(%)	n	(%)	Odds ratio	95 % CI	p value	Analysis
228	44.1	266	49.3	0.51	0.35–0.76	< 0.001	Any health symptom
				0.26	0.15–0.45	< 0.0001	Any skin symptom

[a] Comparison between Z and FF by logistic regression.

Table 9 General health status as a function of infant formula from month 4 to 6

All infants (Z+FF)			
	pHF	IF	PHF to IF
Number of infants who received formula	338	354	44
Infants with any health symptom (%)	34.6	50.0	38.6
pHF versus IF:	Odds ratio=0.53 P value < 0.05		–
Infants with skin symptoms (%)	13.9	29.7	15.9
pHF versus IF:	Odds ratio=0.35 P value < 0.001		–

not fit into the study protocol. The results are shown in Table 9. Comparable numbers of infants received pHF (338) and IF (354), and 44 switched from pHF to IF during the evaluation period. A statistically smaller number of pHF than IF infants experienced one or more health symptoms (pHF=35 % versus IF=50 %) or skin symptoms (pHF=14 % versus IF=30 %). These results showed that type of infant formula itself during the first 6 months of life has a significant influence on overall health-related and skin findings. An allergen-reduced infant formula (pHF) led to fewer health problems during the fourth to sixth month compared with infants who received IF, and demonstrated that the better health status in Z infants was not only due to a higher degree of exclusive breastfeeding and the later introduction of weaning foods with a lower degree of allergenicity and less variants, but was also due to the type of infant formula. Within this evaluation, overall health findings were again influenced by parity ≥2 and parental smoking only.

Discussion

The ZUFF study is the first prospective, large-scale study to evaluate an allergen-reduced dietary intervention regimen in a large unselected infant population. Our study was designed to determine whether an intervention programme that reduces food allergen exposure in early infant nutrition has undesirable effects or demonstrates an advantage for the infant population as a whole. Most previous preventive food intervention studies have included only those infants with a known high risk of allergy. These infants were assumed to be at greatest risk of developing allergies when breastfeeding is not an option. However, definitions of infants at high risk of atopic disorders are not sufficiently specific or sensitive (15–18), and the predictive likelihood for later allergies is comparable for infants with (11/100 infants) and without familial risk factors (11/100 infants) (Fig. 1) (18). These data suggest that the whole newborn population should be considered for such prevention programmes. However, it has not been demonstrated whether such primary dietary prevention measures are safe or beneficial in the infant population as a whole. Additionally, most previous studies have focused on evaluating specific manifestations of atopic disease only, whereas the primary objective of any nutritional intervention should be the overall healthy development of the infant given that exclusively breastfed infants appear to have a lower incidence of infections during the first year of life than formula-fed infants (19–21). For this reason, the ZUFF study evaluated the overall health benefits of an allergen-reduced dietary intervention in an unselected infant population reflecting to the extent possible the infant population as a whole.

As previously stated, the moderate whey hydrolysate formula used in the current study (Nestlé Beba HA) has shown beneficial effects in previous studies. This formula was shown to reduce CMPA and other first manifestations of atopic disease (especially atopic eczema) in high-risk infants; in some studies, reductions in respiratory allergies are documented up to 5 years (8–14). The long-term benefit of this pHF formulae when fed from birth as part of a dietary prevention programme suggests a true prevention of atopy and not just a delay in the development of allergic symptoms (10, 11, 14, 50). Indeed, allergen-reduced (hydrolysed) infant formulae are so effective that increasingly more researchers state that the inclusion of cow's milk formulae in feeding regimens for high-risk infants is no longer ethically or practically feasible (14, 50, 51). Our study demonstrates that primary dietary prevention measures are safe and beneficial in the wider infant population.

Some small-scale and uncontrolled studies from 1987 and 1988 demonstrated normal growth in unselected infants who were fed the pHF formula used in this study (52, 53). Until now, growth has not been studied in a large population-based controlled study. In our study, we showed that infant growth up to 6 months was identical in intervention and control cohorts. Moreover, growth in both cohorts of the ZUFF study was comparable with WHO standards (30, 31) and data from the Zurich Growth Study (32). This demonstrates that an allergen-reduced diet that includes the Nestlé moderate whey hydrolysate formula (Nestlé Beba HA) and restricts weaning foods does not restrict infant growth, as has been shown for some other hydrolysed infant formulae (19, 54, 55).

The assessments of general health status consistently showed fewer negative findings in the intervention cohort, mainly due to a lower incidence of skin findings. Gastrointestinal and respiratory findings were in most cases similar between cohorts. Results for all skin findings demonstrated that such symptoms are reduced by the allergen-reduced dietary programme. Our dietary programme reduced the incidence of a wide variety of skin symptoms, not only those normally associated with early allergies (Table 4). This suggests that our programme helps to reduce skin problems that are common in early life.

In the ZUFF study, the 6-month cumulative incidence of any significant health-related finding was 64 % in the intervention cohort and 74 % in the control cohort. This difference was statistically significant, and was strongly influenced by a lower incidence of skin findings in the intervention cohort. At 6 weeks, general health status was comparable between intervention and control cohorts in most assessments. However, at 3 and 6 months, the total incidence of significant health findings was consistently lower in those infants who received the low-allergen dietary regimen than in those who did not follow any dietary intervention. This was particularly noteworthy in the assessment of infants who were exclusively breastfed during the 4-month dietary intervention period: during the first 4 months of life, general health status was – as expected – identical in both cohorts. However, at 6 months, infants who had been exclusively breastfed for 4 months and who had thereafter continued to follow the recommended allergen-reduced regimen showed a significantly lower incidence of overall health symptoms than control infants. We interpret these results as a rapid deviation in overall health status between intervention and control cohorts over the 4- to 6-month period due to the rapid inclusion of weaning foods and IF-containing infant formulae in the control cohort (see Part I). Infants who continued to be breastfed, in whom weaning foods were delayed, and for whom breastfeeding was partly or wholly supplemented with pHF between months 4 and 6 (as in many intervention infants) had fewer health problems.

The only adjuvant factors found in this study were smoking and parity ≥2. From previous allergy prevention studies, it is well known that smoking in the home increases the risk of allergies. However parity has previously been shown to reduce the risk of first allergic disease (50, 51, 56). The current study does not evaluate allergic symptoms separately or individually. Therefore, siblings may have increased the likelihood of general infections and may act as confounding factors for increased health problems.

By means of logistic regression, we were able to evaluate individual components of the dietary recommendation. We achieved this by integrating dietary components as covariates in the analysis and reserving the adjuvant factors as possible confounders. By this means, we were able to demonstrate that the better general health status of the intervention cohort was not only a consequence of a higher rate of breastfeeding and the later introduction of fewer and lower allergenic weaning foods, but was also directly correlated with the use of the allergen-reduced infant formula.

As previously stated, our study population had a slightly higher risk of allergies compared with the infant population as a whole (58). Therefore, we conducted a separate analysis of infants without a known allergic risk. We were able to demonstrate a significantly improved overall health status with respect to skin findings in this subgroup of infants. These results enable an extrapolation of the general health benefits of our study to the infant population as a whole.

A notable finding in the intervention cohort of our study was the comparability in overall health status between infants who were exclusively breastfed and those who had received supplemental pHF or exclusive pHF during the first 3 months of life. These results suggest that the moderate whey hydrolysate has a better effect on general health than regular nonhydrolysed IF. As expected, infants in the control cohort in whom breastfeeding was supplemented or replaced by CMP-containing formulae or weaning foods at an early age fared significantly worse compared with those who were exclusively breastfed or pHF-fed.

The ZUFF study was not designed to evaluate definitive and individual atopic symptoms because they are not the parameters of primary interest in assessing the healthy development of the newborn infant. Nonetheless, the evaluation of overall health status did include allergic manifestations as components of our clearly defined health assessments. Nevertheless, our results are in agreement with those from allergy prevention studies conducted in high-risk infants, which demonstrate a high degree of protection against skin-related symptoms (8–14).

We conducted a check on the reliability of our results by comparing general health status of eBF infants at 3 months in Z and FF. Because the eBF dietary group includes only those infants exclusively breastfed up to 4 months, we expected no differences between Z and FF in nutrition or health outcomes at the specified timeline. The results demonstrated the comparability of cohorts in the number of infants with any health finding (Table 6): Z=29 % versus FF=31 % (odds ratio=0.91, CI=0.58–1.43), confirmed in the main analysis (odds ratio=1.12, CI=0.74–1.70), and for skin findings only (odds ratio=0.90, CI=0.54–1.50). These results demonstrate that we did not introduce study bias in our selection of subjects or physicians in Z and FF.

As described in Part I of this paper, the ZUFF study was notable in its low subject dropout rate and in the high rate of compliance with our feeding recommendation. These are distinctive features of our study when compared with other programmes described in the literature, and suggest a willingness for parents to follow the dietary recommendation.

The cost of the pHF formula used in this study is somewhat higher than regular infant formula: although variations occur between countries, the price of pHF is on average about 25 % greater than regular infant IF. However, the

costs of prevention and management of allergies, as estimated by Chandra in allergy prevention studies, suggest that pHF formula is very cost effective (10). In the infant population as a whole, cost benefit estimates may be different. However, taking into account the allergy preventive result for one-third of infants with an elevated allergic risk and an overall reduction of about 30 % in health problems, a pHF formula is still cost effective.

We conclude that our study demonstrates that an allergen-reduced dietary recommendation in an unselected infant population has no negative effects on infant growth, and leads to improved general health status, mainly due to improvements in skin findings compared with a control cohort. There was a high acceptance of our recommended dietary regimen over a 6-month period, demonstrating the practicality of the programme. These results suggest that the following recommendation might be discussed for the infant population as a whole if exclusive breastfeeding is not possible: a low-allergenic diet that includes a moderately hydrolysed infant formula (pHF) and delays the introduction of highly complex weaning foods, with simple low-allergenic weaning foods when introduced. Such a dietary programme could become the standard for all infants during the first 4 to 6 months of life. Optimisation of such a nutritional programme should form the basis for future interventional studies.

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