Eur J Nutr 39:89–102 (2000)
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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 I: study design and 6-month nutritional behaviour

Summary *Background:* The best nutritional option for newborn infants is mother's milk. However, some newborn babies may not be exclusively breastfed during the first months of life, potentially leading to reduced overall health status and the early onset of allergic diseases in some infants. Considerable research has been devoted to the development and assessment of infant nutrition programmes, particularly to the prevention of allergies in high-risk infants. However, equal numbers of infants with and without an elevated familial risk of allergies will eventually develop allergic diseases. Therefore, optimizing nutritional programmes for the early infant population as a whole is an important – but as yet insufficiently studied – area of investigation. Moreover, although safe and effective nutrition must primarily support healthy development of the infant, few studies have evaluated the overall health benefits of nutritional interventions, but have focussed on specific allergic manifestations. In animal models, an allergen-reduced moderate whey hydrolysate formula (pHF, Nestlé Beba HA) induces the development of oral tolerance towards cow's milk proteins, without inducing sensitization. In infants with a high risk for allergies, pHF formulae reduce the early onset of allergic disease during the first 5 years of life by approximately 50 % compared with a dietary regimen of unaltered proteins. At present, very little is known about the overall health benefits of such a dietary intervention on the unselected infant population as a whole.

Aim of the study: The aim of our prospective, controlled study was to investigate the overall health benefits of an allergen-reduced nutritional programme in a newborn infant population unselected for atopic risk factors. The population in our study was as comparable as possible to the general population of healthy newborn infants. Our study included exclusive breastfeeding, use of a moderate whey hydrolysate formula (pHF, Nestlé Beba HA) if infant formula was needed, and delayed introduction of low-allergenic weaning foods. The study included assessments of compliance with the dietary programme, and evaluated nutritional habits, growth, and overall health status for 24 months. The health evaluation included allergic manifestations but did – by porpose – not define or evaluate them specifically. Part I of this paper gives results for nutritional habits during the first 6 months of life, Part II gives results for growth and general health status for the same time period, Part III will present feeding habits during the second half of the first year of life, and Part IV will present results to 24 months of age. The complete study report is published as a supplement to this journal.

Methods: Nutritional assignment was to demographically comparable intervention (Z) or control (FF) cohorts according to the infant's place of birth. In the intervention cohort (*Z, n*=564), the recommended dietary regimen was breastfeeding and/or the pHF formula, with no weaning food before 4 months of age. In the control cohort (*FF, n*=566), there was no intervention. Longitudinal diet groups, defined for 4 months, excluding dropouts and noncompliants, were exclusive breastfeeding (eBF, *Z, n*=201, *FF, n*=162), partial breastfeeding (pBF, *Z, n*=222, *FF, n*=311), or non-breastfeeding (nBF, *Z, n*=43, *FF, n*=62). Imbalances between groups and cohorts in confounding factors that could influence health-related symptoms were integrated as

Received: 14 December 1999
Accepted: 2 May 2000

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European Journal of Nutrition, Vol. 39, Number 3 (2000)
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covariates into the main analyses using logistic regression. Nutritional surveillance was carried out using continuous prospective monitoring.

Results: The overall rate of breastfeeding, irrespective of partial or exclusive breastfeeding or the additional use of weaning foods, was similar in both cohorts at 4 and 6 months. However, from ages 3 to 6 months, significantly more Z than FF infants were exclusively breastfed ($p < 0.05$), and weaning foods were introduced at a significantly later age in Z than FF (22 versus 18 weeks; $p < 0.0001$). Infants in the Z cohort received fewer different kinds of weaning foods compared with FF (2 versus 10; $p < 0.0001$). Six-month rates of dropout were very low in both groups (Z=4.3 %, FF=1.8 %) and compliance with the programme was excellent over the strict intervention period of 4 months (Z=86.9 %) until the sixth month.

Conclusions: A dietary recommendation that promotes breastfeeding, includes a moderate whey hydrolysate formula (Nestlé Beba HA), and delays the introduction of highly allergenic weaning foods (an allergen-reduced dietary regimen) significantly increases breastfeeding and delays weaning in a normal infant population without any compliance problem to the moderate hydroysate formula that is quite often seen in eHF. The regimen was followed closely, with a high degree of compliance and a low dropout rate compared with previous allergy-prevention studies. Compliance with the dietary regimen was excellent over the 4 months of intervention and throughout the following 2 months.

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

List of abbreviations:

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
OR	odds ratio
pBF	partially breastfed
pHF	partially/moderately hydrolysed infant formula (Nestlé Beba HA)
Z	intervention cohort in Zug

Introduction

Mother's milk is the normal and natural diet during the first months of an infant's life, and is the food that best supports the primary objective of any nutritional programme – namely the healthy development of the newborn infant. However, for various reasons, infants may not be exclusively breastfed in early life, with breast milk being supplemented or replaced by cow's milk-based infant formula [1]. Many studies have addressed the topic of breastfeeding's potential protection against allergic diseases. It is generally accepted that the incidence of cow's milk protein allergy (CMPA) is considerably lower in breastfed infants than in formula-fed infants (0.5 to 1.5 % compared with 3 to 6 %) [2–11]. Some years ago, Kramer's assessment of the protective effects of breast milk on overall allergies led to somewhat ambiguous conclusions [12]. More recent reviews and studies on the protective effect of breast milk conclude that a short duration of breastfeeding with early introduction of weaning foods has no protective effect. In contrast, exclusive breastfeeding for the first 4 to 6 months of life, with delayed introduction of weaning foods up to the fifth month or later, reduces the incidence of allergic diseases (including atopic eczema, gastrointestinal reactions, allergic rhino-conjunctivitis, and asthma) [6, 13–19]. An extensive review of the literature additionally shows that exclusively breastfed infants exhibit improved overall health status [20–22]. These findings are attributed to the low allergenic load, active immunologic factors, and possible bifidogenic effects of breast milk that may help to induce oral tolerance to food proteins.

Because cow's milk-based formulae (IF) contain intact cow's milk proteins (CMP), food allergens may be introduced to infants in high amounts at a very early age. Indeed, in Western Europe, CMPs are the most common food allergens in early infancy [2–4]. Recent studies show that residual minute amounts of food allergens in human milk, originating from the mother's diet, are more likely to induce oral tolerance than allergic reactions in breastfed infants [4, 23]. In contrast, the content of CMP allergens in cow's milk may be 100,000 to 1,000,000 times greater than the natural allergen content of human milk [5, 24]. Because early food allergy or sensitization is highly predictive of later allergic diseases, CMPA (along with other factors) may be a contributory factor in the large increase of atopic diseases in children in industrialized societies. The incidence of those atopic diseases has approximately doubled during the last few decades [6, 13, 25–30, 71], with around 30–40 % of children under the age of 15 years now likely to be affected [1, 6, 7, 27]. Atopic disease meanwhile plays a major role in the morbidity of people in developed industrialized countries [13].

For these reasons, much research has been devoted to establishing practical and feasible prevention programmes for early food sensitization and allergy [1, 3, 13–16, 31, 32]. One important preventive feature is the avoidance of food

Animal model:	Guinea pig indirect anaphylactic model	Antibody suppression mastocyte modulation
Immunologic reaction:	Sensitization/allergization	Oral tolerance
Intact CMP formula	☑	☑
pHF	—	☑
eHF	—	—

Fig. 1 The effect of infant formulae on various animal models of oral sensitization and tolerance. Intact cow's milk protein (CMP) formulae induce oral tolerance but can also induce sensitization. Extensively hydrolysed formulae (eHF) neither induce sensitization nor tolerance. In contrast, pHF formulae induce oral tolerance due to their residual allergenicity, but do not induce sensitization, fulfilling the requirements of alimentary allergy prevention.

sensitization and the induction of oral tolerance to food protein allergens during the first few months of life [33–37]. In response to this need, a new category of infant formula was made available in the mid-1980s, whose allergenicity is – in contrast to the extensively hydrolysed therapeutic formulae (eHF) – only moderately hydrolysed. These infant formulae were designated pHF (partially/moderately hydrolysed formulae) by the European Society of Paediatric Allergology and Clinical Immunology (ESPACI) [38], and are also referred to as partial whey hydrolysate, and as *H. A. hypoallergenic formulae* in Europe [39, 40]. In animal models, pHF formulae are shown to induce tolerance without sensitization, whereas formulae containing intact CMP normally induce tolerance but may lead to sensitization in predisposed individuals (Fig. 1) [41–44]. In contrast, extensively hydrolysed formulae (eHF) are "inert" and therefore induce neither sensitization nor tolerance because the level of residual allergens approximates zero. These findings are supported in a recent clinical study in which infants with elevated allergic risk developed fewer food and respiratory sensitizations with the Nestlé pHF formula compared with two other eHF formulae [45, 46].

In selected high-risk animals and infants, exclusive breastfeeding, and/or the use of a pHF infant formula with or without breastfeeding is shown to lower the onset of first allergic symptoms without inducing sensitization to CMP [3, 17, 18, 31, 43, 47–49]. Indeed, studies with the original pHF formula (Nestlé Beba HA) demonstrate that a hypoallergenic (H. A.) diet can reduce the onset of allergies in high-risk children by up to 50 % in the first 3 to 5 years of life [3, 17, 18, 49, 50]. Newborn infants should not be exposed to high cow's milk allergen loads through supplementary bottle feeding in the hospital (the so-called *hidden bottle*), as such practices double the incidence of CMP allergy regardless of allergic risk [8, 51, 52]. The pHF formulae are now recommended by most nutritional committees in Europe for non-breastfed (nBF) or partially breastfed (pBF) infants with an elevated risk of allergies due to family risk or high umbilical cord-blood immunoglobulin E (IgE) readings [31, 40, 53, 54].

Most studies on food sensitization and the use of hypoallergenic infant formulae have focussed on infants with a high risk of allergy, despite selection criteria for such infants being insufficiently specific or sensitive [55–57]. Additionally, the numbers of infants who eventually develop allergic disease are similar in those *without* known familial risk factors (70 % of all newborn infants, still with ca 15 % residual allergic risk = 11/100 newborn infants) compared with those considered to be at high risk due to unifamilial (25 % of all newborn infants, ca 20–40 % risk of later allergies = 8/100 newborn infants) or bifamilial (5 % of all newborn infants, ca 50–50 % risk of later allergies = 3/100 newborn infants) [2, 27, 56, 57].

The equally high incidence of allergies in infants with and without an elevated risk of allergies, and the better overall health status of exclusively breastfed infants, suggest that nutritional programmes in the infant population as a whole are of great importance. However, little information is currently available on the effects of allergen-reduced diets in the early life of an unselected infant population that reflects the healthy infant population as a whole [58]. Moreover, it has not been established whether allergen-reduced nutrition recommendations are safe and beneficial for all, and should therefore be recommended in all infants. Mother's milk is shown to have beneficial effects on overall health status, but the effects of various nutritional interventions on general health have rarely been evaluated.

We report on the ZUFF study (*Zug-Frauenfeld-study*), the first large-scale study to evaluate a pHF-based nutritional programme in the broader unselected infant population. Our study is new in that it focuses on the overall health benefits of an allergen-reduced diet (notably nutritional status, infant growth, and overall health status including allergic symptoms) without identifying or assessing specific allergic symptoms.

European Journal of Nutrition, Vol. 39, Number 3 (2000)
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Methods

Study design and patients

The objective of the ZUFF study was to determine whether an intervention programme that supports breastfeeding and reduces food allergen exposure in early infant nutrition by including a pHF feeding regimen has any positive or negative effects on overall feeding behaviour, growth, and health-related parameters in the overall infant population. Our study is a prospective, controlled, epidemiological trial conducted in two unselected cohorts of neonates in the Swiss cities of Zug (Z) and Frauenfeld (FF) and their immediate surroundings. We designed the study to enable a controlled but pragmatic evaluation of an altered dietary recommendation without the obvious difficulties of randomization and without attempting to blind a dietary recommendation, while minimizing social interactions between the two cohorts of parents. To ensure minimum changes in the normal medical-dietary setting, study evaluations were carried out by local health care providers in Z or FF after an intensive training programme, and not by specially appointed study physicians.

The two cities of Zug and Frauenfeld are located approximately 50 km apart, a sufficient distance to avoid most – if not all – interactions between the two communities, while ensuring demographically comparable populations. Indeed, independent socio-demographic, socio-economic, and geographical evaluations conducted before the start of the study supported the comparability of the two regions in terms of population and climate [72]. Z had a slightly more urban population and character. For the purposes of training, quality control, and monitoring, we established a study centre between the two cities.

Our reporting of the study includes results for dietary behaviour from birth to 6 months of age in the current paper (Part I), and results for infant growth and health-related parameters over the same period in an accompanying paper (Part II). The dietary pattern from 6 months to 1 year of age will be reported in a third paper (Part III), and results at 2 years will be presented in a fourth paper (Part IV). The complete study report is published as a supplement to this journal.

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.

Our study included infants born between January 1991 and June 1993. The potential study population was 7,350 infants. We invited all families from the regions of Z and FF who were expecting a baby during the study timeframe to participate. Invitation to participate was by several modes of communication:

- Press release and information via the media,
- Provision of oral and written information during pregnancy information courses,
- Collaboration with obstetricians, midwives, and maternity wards by means of leaflets, posters, and oral presentations.

All maternity wards within the study regions were actively involved in the recruitment procedure. During their stay in the maternity ward, mothers received their first oral information on the study from the hospital staff. Any mother who was interested in participating in the study received a further oral explanation of the study purpose and requirements from the study nutritionists. This personal interview took about 1 hour. If parents remained interested, they subsequently received all written study materials, which included the so-called "baby's diary" that gave the study explanation, dietary recommendations, questionnaires, and other general information on the well-being of a newborn baby. They were to retain all these materials, and later received copies of the study questionnaires. Parents were required to return their informed consent within 2 weeks. Parents who chose not to participate in the study did not have to give their reasons. After receiving informed consent, we informed the family paediatrician of the family's participation, and provided him or her with the study questionnaires for the participant. Each participant received a unique study number that was attached to all study materials.

Study questionnaires were collected during scheduled visits with the health professionals (medical doctors), who returned the completed materials to us together with growth and health evaluations. Each parent could contact the study centre in case of questions, but were advised firstly to contact their personal mother's consultant. All mother's consultants within the two regions collaborated with our study. Parents were to contact their medical doctor if any questions remained unanswered, and finally the study centre for any issues that remained unresolved. This sequence of contacts was intended to guarantee that the study environment was as normal as possible. Two retired mother consultants worked exclusively for the study and were responsible for compliance. They reassured parents, helped them with issues on the questionnaires, maintained regular contact during specific events, organised Zug and Frauenfeld study festivals, and notified parents of special events. This procedure produced a higher compliance than normally achieved in similar large-scale intervention studies with unselected populations.

The study included full-term (gestation of at least 37 weeks) newborn babies weighing more than 2 kg and able to feed normally. Selection of participants in the ZUFF study did not include risk factors for atopic disease or any other selection criteria, and both cohorts were comparable with respect to all selection criteria. After enrolment in the study, one variable – the type of infant feeding – differed between cohorts. The strict dietary intervention period was from birth to 4 months. From 4 to 6 months, we made dietary recommendations that were not a part of the strict compliance regimen. The total period of evaluation was up to 2 years of age.

We allocated subjects to dietary regimens according to place of birth, with Z being the intervention cohort and FF the control cohort. In neither case did we provide specific recommendations regarding maternal diet. The subjects' normal health care providers (general practitioners, paediatricians, and mother's consultants) were available for general consulting on maternal diet and other aspects of medical care within the context of general health care provision.

Dietary recommendations

Intervention cohort (Z): For the intervention cohort, we have recommended exclusive breastfeeding for at least 4 months, and for up to 6 months if possible. Where the parents chose not to breastfeed, supplementary pHF formula was to be used (Nestlé Beba HA), and if breastfeeding was discontinued during the 4-month intervention period, this formula was to be used exclusively. Weaning foods were not permitted during the first 4 months, although gradual introduction of a restricted range of weaning foods with a low allergenicity was suggested thereafter, with the recommendation to start after 6 months of age. We recommended a free choice of infant diet after the age of 12 months, in line with the results of studies evaluating various prevention strategies [18, 50, 59]. The pHF formula recommended in the intervention cohort (Nestlé, Beba HA) [17, 18, 43, 60] was in accordance with the EU directive on starter formulae [39, 40].

Control cohort (FF): For the control cohort, we asked parents to follow the feeding regimen issued by the Nutrition Committee of the Swiss Paediatric Society in 1989, which included exclusive breastfeeding for the first 3 months, a nonhydrolysed CMP-based starter formula as required, and the introduction of weaning foods after the third month of life [61].

Both feeding recommendations were presented to parents orally and as a brochure with explanations. Recommendations were presented in a similar manner for both cohorts in order to minimize information or compliance bias. All study partners (hospitals, nurses, midwives, mother's consultants, and doctors) followed the study guidelines.

Outcome variables

For the purpose of assessment, we categorized infants into one of three longitudinal diet groups according to their actual feeding regimens (Table 1), reported prospectively and continuously, and categorized as follows: (1) exclusively breastfed (eBF) (received no other food during the first 4 months of life but breast milk; use of glucose or dextromaltose during the first days of life was permitted); (2) nonbreastfed (nBF) (some breastfeeding during the first 4 weeks of life at most, thereafter only hypoallergenic pHF and no weaning food in Z, and a free choice of infant formula and weaning food in FF); or (3) partial breastfed (pBF) (those not conforming to the first two groups and who were not dropouts or noncompliants). Typically, the pBF group included a very small subgroup of infants who received pHF during the first few days of life in Z or regular infant formula in FF. Within each group, as appropriate, the type of infant formula (high or reduced degree of allergenicity), and the timing, variability, and type of weaning or supplementary food were reported prospectively and continuously. We classified subjects according to their complete feeding regimen, and recorded all qualitative – but not quantitative – components of the diet, no matter how small.

Table 1 Longitudinal diet groups: definitions and numbers of infants

Population	**Intervention group (Z)**		**Control group (FF)**	
		n (%)		*n (%)*
Effective study population		**564 (100)**		**566 (100)**
Included in diet groups[a]		**466 (82.6)**		**535 (94.5)**
Exclusive breastfeeding (eBF)[a]	MM only weeks 1–16	201 (35.6)	MM only weeks 1–16	162 (28.6)
Partial breastfeeding (pBF)[a]	MM only < week 16 Supplementary formula pHF only	222 (39.4)	MM only < week 16 Conventional infant formula (no pHF) Weaning foods allowed	311 (54.9)
Non-breastfeeding (nBF)[a]	MM only ≤week 4 Supplementary formula pHF only	43 (7.6)	MM only ≤week 4 Conventional infant formula (no pHF) Weaning foods allowed	62 (11.0)

[a] Excludes dropouts (Z=4.3 %; FF=1.8 %) and noncompliants (Z=13.1 %; FF=3.7 %) (see Table 2).
MM: Mother's milk.

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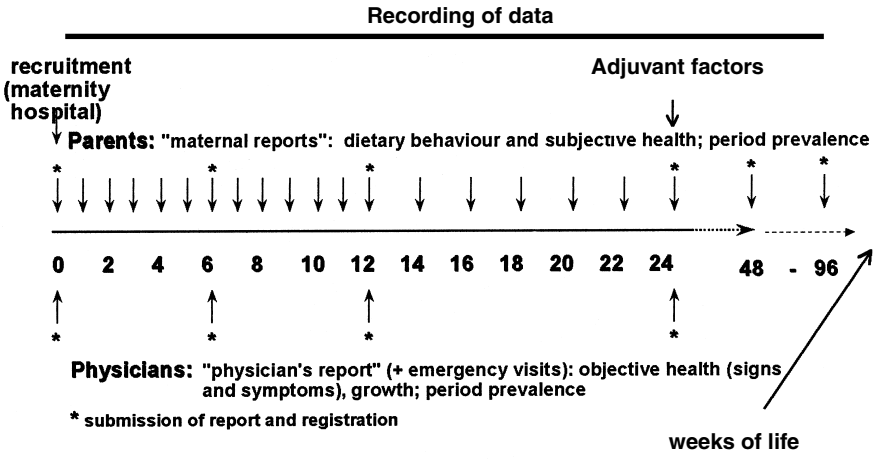

Fig. 2 Schedule of study evaluations from birth (week 0) to the end of study (24 months). Recruitment occurred at birth. The times of parent and physician reporting on the study assessments, and the recording of adjuvant factors, are shown for the first 24 weeks of the study.

Detailed nutritional surveillance during the first few days of life was carried out by trained study nurses or maternity consultants. This was to ensure that no regular infant formula was taken in Z, and to evaluate whether additional feeding would negatively influence the subsequent rate of breastfeeding.

Thereafter, we provided dietary and well-being journals for parents to complete weekly during the first 12 weeks of life, and every 2 weeks up to 12 months (Fig. 2). Monitoring of compliance took place during regular follow-up interviews with the participating physician and maternity consultants. Study journals were returned to the study centre by the physician after each check-up, together with the evaluations. Copies were sent to the parents.

We clearly defined and precisely documented dropouts and noncompliants. Infants were defined as dropouts if the physician's report or the parents' journal was unavailable on two consecutive dates, if the final 6-month report was unavailable, or if discontinuation occurred on account of serious nonstudy-related diseases or a change in address. Noncompliants in Z were infants who received any food during the first 4 months of life that was not included in the dietary recommendation (even on one occasion and accidentally). We specifically identified infants in FF who were exclusively fed pHF during the first 4 months of life because use of pHF was not a part of the feeding regimen in the control group. Hereafter, the term noncompliant is used for these two sets of subjects.

Physicians' evaluations of nutritional, growth, and health parameters were recorded at birth, and at the ages of 6, 12, and 24 weeks (Fig. 2) (Part I and II of this study presentation). Thereafter, check-ups were at 12 and 24 months (Part IV). Parental assessments of health-related events were recorded in the weekly journals. Study parameters included nutritional pattern, infant growth parameters, and infant health status including objective assessments of gastroenterological signs, respiratory signs, and skin findings (evaluated by the physician, with subjective assessments carried out by the parents). Growth and general health status evaluations were carried out according to standard international methods. Details are given in Part II of this report. Adjuvant factors, which included familial information and data on the home environment, were recorded at the end of the intervention period because earlier assessments could have interfered with the dietary intervention. The questionnaires corresponded to international standards concerning family history of allergies, level of education, and smoking habits (details are reported in Part II).

Statistical methods

Descriptive statistics (longitudinally for the dietary groups and cross-sectionally for the overall cohorts) were used to compare Z and FF in nutritional behaviour as period prevalences over all time points. For the per-protocol analyses, we used two-sided tests at a level of significance α=0.05. In the confirmatory main analysis, which compared data as period prevalences at weeks 12 and 24, we used an intention-to-treat data set that included noncompliants. In addition, dropouts were included in a worst-case type of analysis. Our primary confirmatory analyses ("main analysis") were to be the following comparisons between Z and FF: extent of breastfeeding at 16 weeks irrespective of weaning foods; time of introduction of weaning foods; infant weight and length at 12 and 24 weeks; general health status from 12 to 24 weeks; and cumulative incidence of physician-assessed gastrointestinal, respiratory, and skin findings at 24 weeks. The main statistical methods included odds ratios, 95% confidence intervals, analyses of variance and covariance, linear and logistic regressions. All other statistical analyses were descriptive. Standard statistical methods were used in all calculations [62].

Further comparisons were carried out between cohorts using logistic regression to evaluate the possible role of confounding factors for general health, such as parity, ed-

ucational level of both parents, family history of allergies, place of residence (urban or rural, although it is difficult to clearly differentiate between rural and urban environments in Switzerland), pets in the household, and smoking in the infant's environment.

Results

Study population

The total number of births in the regions was 3,188 (Z) and 3,153 (FF) during the recruitment period from 1 January 1991 to 30 June 1993. A total of 21 % of all births in Z and in FF were to non-German speaking families, and were not qualified for entry into the study. Of the qualifying births, we recruited 564 neonates in the Z cohort and 566 in the FF cohort, which constituted 22.5 % (Z) and 22.7 % (FF) of all qualifying births. We were therefore able to include one in five qualifying newborn babies in both regions. The study infants were 50 % boys and 50 % girls in Z, and 48 % boys and 52 % girls in FF (not significant).

The 6-month dropout rates were 24 (4.3 %) in Z and 10 (1.8 %) in FF. Of those, only 9 infants in Z dropped out of the study because the mothers were dissatisfied with the feeding recommendations. Other reasons for dropout were change in residence (Z=2, FF=2), time involved in completing the diet journal (Z=8, FF=3), mother returned to work (Z=3, FF=1), noncompliance of participating physicians (Z=0, FF=4), divorce (Z=1, FF=0), and illness of the mother (Z=1, FF=0).

Reasons for deviations from the dietary regimen are given in Table 2. There were 74 (13.1 %) noncompliants in Z, the most common reason for noncompliance being regular use of weaning foods (62 %) and regular feeding with non-pHF infant formulae (39 %); some infants received both. A total of 21 (3.7 %) infants in FF were exclusively pHF-fed: 52 % of these including weaning foods and 48 % without weaning foods (for the latter group, the diet regimen corresponds to the recommended intervention in Z).

We evaluated noncompliants in Z and FF to determine whether they differed from their cohorts as a whole with respect to atopic risk factors, and therefore whether knowledge of an elevated risk of allergies might have influenced compliance. In the Z cohort, the percent of subjects with an elevated risk of allergies was comparable between noncompliants (52 %) and the diet groups as a whole (56 %). In contrast, in the FF cohort, the percent of subjects with an elevated risk of allergies was considerably greater in noncompliants (89 %) than in all diet groups (49 %). This suggests that some parents in the FF control cohort were already aware that an allergen-reduced diet reduces the incidence of allergies in those at high risk, and that (21) somefew parents of high-risk infants elected to follow the recommended dietary regimen of the intervention cohort. These findings were not expected to affect the results of the study, principally because noncompliants are included in the intention-to-treat data set. Furthermore, inclusion of FF noncompliants, who closely followed the dietary recommendations of the Z cohort, provides a worst-case scenario for the comparison between Z and FF.

Table 2 Study population: dropouts and reasons for noncompliance

	n (%)
Z (intervention group)	**564 (100)**
Dropouts	*24 (4.3)*
Noncompliants	*74 (13.1)*
Noncompliants	*(100 %)*
Regular use of non-pHF infant formula	30 (38.5)
Regular use of weaning foods	48 (61.5)
≤ 5 bottles of cow's milk formula altogether	4 (5.1)
Short-term use of one weaning food	11 (14.1)
More than one of above categories	15 (20.3)
FF (control group)	**566 (100)**
Dropouts	*10 (1.8)*
Noncompliants (exclusively pHF-fed)	*21 (3.7)*
Exclusively pHF-fed	*(100 %)*
Used pHF with weaning foods	11 (52.4)
Used pHF without weaning foods	10 (47.6)

Table 3 summarizes characteristics of the study population. Logistic regression was used to compare the two study cohorts, and statistically significant differences were shown for the following variables: parents' education individually, pets in the home, place of residence urban versus rural), smoking in the home, and parity (number of older siblings). The study cohorts including the noncompliants did not differ in family history of allergy, use of day care facilities, birth weight, or period of gestation. The results suggested a more urban study population in Z than FF with a higher degree of education in Z and a lower incidence of pets in the home. Altogether, we considered the Z cohort to be somewhat more likely than FF to develop health-related symptoms, including initial signs of allergic manifestations. We integrated all relevant confounding factors into the main confirmatory analyses using logistic regression. Other factors, which included nationality, mother's age, gestational age at birth, infant weight and length at birth, Apgar score, sex, and day care arrangements, were not included in the logistic regression because they did not reveal any statistical differences between study cohorts.

Nutritional pattern

The numbers of infants in each dietary group are shown in Table 1. The pBF group included a small subgroup of infants who received pHF during the first few days of life

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Table 3 Description of the study population and confounding variables

	Intervention group (Z) n/N (%)		Nonintervention group (FF) n/N (%)	
Parents/environment (*)				
Residence: predominantly urban[a]	158/517	(30.6)	112/540	(20.7)
Educational level mother/father:				
University entry qualification; University or tertiary education				
Mother[a]	68/517	(13.1)	43/540	(8.0)
Father[a]	154/517	(29.8)	96/540	(17.8)
Family history of allergy:				
None	228/517	(44.1)	266/540	(49.3)
1 parent	202/517	(39.1)	189/540	(35.0)
Both parents	87/517	(16.8)	85/540	(15.7)
Household pets ≥1[a]	141/517	(27.2)	258/540	(47.8)
Smoking in the home[a]	95/564	(16.8)	134/566	(23.7)
Infants				
Sex: male (ns)	282/564	(50.0)	293/566	(52.0)
Parity[a]:				
1 (no older siblings)	320/564	(56.7)	252/566	(44.5)
2 (1 older sibling)	196/564	(34.8)	208/566	(36.7)
≥3 (≥2 older siblings)	48/564	(8.5)	106/566	(18.8)
Attends day care (ns)	88/564	(15.6)	104/566	(18.4)
Mean gestation (weeks) (ns)	39.6		39.8	
Mean birth weight (g) (ns)				
Male	3440		3420	
Female	3300		3270	

[a] Statistically significant difference between cohorts: p≤0.05. (*) not all participants returned the questionnaire of adjuvant factors (93.5 % response). ns=not significant

in Z (n=26) and regular infant formula in FF (n=7). The data show a significantly higher level of exclusive breastfeeding up to week 16 in Z (n=201, 35.6 %) than in FF (n=162, 28.6 %) (p< 0.001 in the confirmative main analysis), although the overall numbers of infants who were breastfed (eBF + pBF) were similar between treatments. This was true at 4 months (OR=1.08; CI: 0.82–1.43) and 6 months (OR=0.96; CI: 0.96–1.62). Therefore, the intervention did affect the overall breastfeeding rate, but increased the exclusive breastfeeding significantly. Only a small number of infants were categorized as being truly non-breastfed: 43 (7.6 %) in Z and 62 (11 %) in FF.

The time course of dietary behaviour is shown in Fig. 3. The majority of infants were exclusively breastfed during the first few days of life, with more FF than Z infants receiving mother's milk during the first days of life only (FF=498, 88 %; Z=395, 70 %; p < 0.01). The difference was not due to non-breastfeeding (FF=11, 1.9 %; Z=7, 1.3 %) but due to the more frequent feeding of additional formula (pHF) in Z (pBF: FF=57, 10.1 %; Z=162, 28.7 %). At the time of discharge from hospital, exclusive breastfeeding (eBF) had further increased in both cohorts but remained significantly different between cohorts (FF=521, 92 %; Z=468, 83 %; p < 0.01). Fewer infants were partially breastfed (pBF) in both cohorts, but the difference was significant (Z=60, 10.6 %; FF=16, 2.9 %; p < 0.01). Comparable numbers of infants were non-breastfed (Z=22, 3.9 %; FF=21, 3.7 %; ns). A total of 7 infants in Z (1.3 %) and 4 infants in FF (0.7 %) were born at home and were therefore excluded from the data on nutritional pattern at discharge from the hospital.

Differences between cohorts in feeding patterns due to the higher frequency of additional formula feeding in otherwise breastfed infants in the Z cohort were considered to be a reflection of feeding practices at the various hospitals and had no effect on the subsequent feeding pattern. All Z infants who received such supplementary feedings in the hospital were fed with pHF formula as required by the dietary recommendation; only 5 of the 37 supplementary fed FF infants received pHF formula, and all others received a nonhydrolysed regular IF.

At 6 weeks, similar numbers of subjects (Z=66 %,

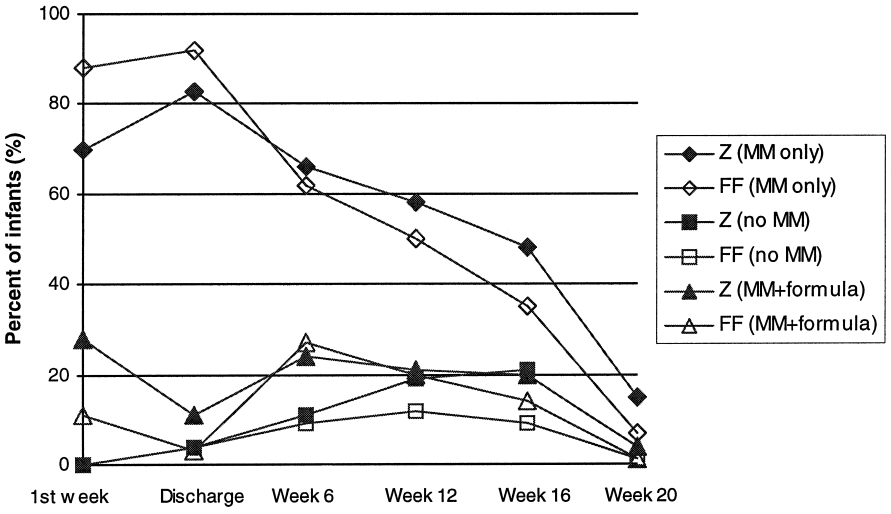

Fig. 3 Time course of nutritional behaviour without weaning foods. Infants who received MM only (eBF), MM + formula (pBF), or no MM (nBF), in each cohort from birth to 6 months (24 weeks). *(MM=mother's milk; formula=pHF in Z and unhydrolysed infant formula=IF in FF)*

Cross-sectional analysis (no longitudinal defined feeding groups)

FF=62 %) had received mother's milk only, but thereafter more Z than FF infants were exclusively breastfed. At 3 months, a significantly greater number of subjects in the Z cohort (58 %) than in the FF cohort (50 %) were exclusively breastfed ($p < 0.05$), and these differences persisted up to 6 months. At 6 months, 83 infants remained exclusively breastfed in the Z cohort (15.4 %), whereas only 38 (6.8 %) of FF infants remained exclusively breastfed (without weaning foods) ($p < 0.01$). In the main analysis, the 4-month rate of exclusive breastfeeding (corresponding to the main intervention period of the study) was significantly greater for Z than FF (odds ratio=1.42, CI=1.08–1.86, $p < 0.01$). This was confirmed in the worst-case analysis, without any significant confounder effects.

At the ages of 4 and 6 months, there were no differences between the intervention and control cohorts in the numbers of infants who received any breastfeeding at all irrespective of weaning foods: at 4 months Z=74 % and FF=71 % (odds ratio=1.08, CI=0.82–1.43) and at 6 months Z=62 % and FF=57 % (odds ratio=1.25, CI=0.96–1.62). Comparability of study cohorts was confirmed by intention-to-treat analysis with a worst-case assessment. Non-smoking parents and a higher level of paternal education were shown to be significant factors positive for the rate of overall breastfeeding. Together, these results suggest that the intervention procedure and dietary recommendation in the Z cohort had no negative effect on the overall breastfeeding rate.

Weaning foods were introduced at a significantly later age in Z infants than in FF ($p < 0.0001$), with the median age at initial introduction of weaning food being 22 weeks in Z and 18 weeks in FF. Smoking was the only negative confounding factor in the main analysis. At 6 months, the median number of weaning food types was 2 in Z and 10 in FF (odds ratio=0.13, CI=0.10–0.17, $p < 0.0001$), with more FF infants having received ≥4 types of weaning foods than Z infants by this age (odds ratio=0.12, CI=0.09–0.16, $p < 0.0001$). There were no confounding factors according to the intention-to-treat and worst-case analyses. Throughout the first 6 months of study, considerably more control (FF) than intervention subjects (Z) received weaning foods. At the end of the 4-month strict intervention period, 11 % of Z and 43 % of FF infants had already received weaning foods. By 5 months, 44 % of Z and 78 % of FF infants had received weaning foods, and by 6 months, 75 % of Z and 92 % of FF infants had received weaning foods. The number of infants who had not received any weaning foods at 6 months was significantly greater in Z than in FF ($p < 0.01$). The result of these trends was a considerably greater allergenic load in FF than Z, which continued through month 6, 2 months after the end of the strict intervention period. This was due to the later introduction of weaning foods, less variety in protein sources, and the use of protein sources with low allergenicity. This trend of reduced allergenic load in the Z-cohort was followed on even later (see Part III).

Dietary patterns irrespective of weaning (Fig. 4) and the feeding of weaning food (Fig. 5) for the fifth and sixth months after birth are shown by milk feeding regimen. This interval begins after the strict 4-month intervention period. The overall number of breastfed infants (regardless of weaning foods) was comparable in Z and FF, but the number of exclusively breastfed infants was significantly higher in Z than in FF. Considerably more FF infants received conventional infant's formula during the fifth and sixth month. Most exclusively breastfed infants in FF started on non-pHF infant formula and weaning foods immediately after the recommended 4 months of exclusive breastfeeding. Few FF infants received pHF. At the end of 6 months, 15.4 % of Z and only 6.8 % of FF infants had been exclusively breastfed throughout the study ($p < 0.01$), and 25.1 % of Z and only 8.3 % of FF infants had received

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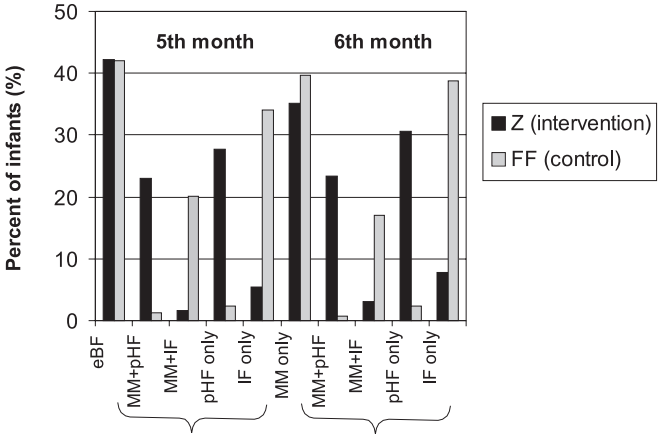

Fig. 4 Infant diet after the end of the intervention period, regardless of weaning foods (with or without): 5th month (weeks 17 to 20) and 6th month (weeks 21 to 24). Diet was categorized as eBF (MM only), MM+pHF (Nestlé Beba HA) formula, MM+IF, pHF only, or IF (could include some proportion of pHF). (*MM=mother's milk; IF=nonallergenic infant formula.)*

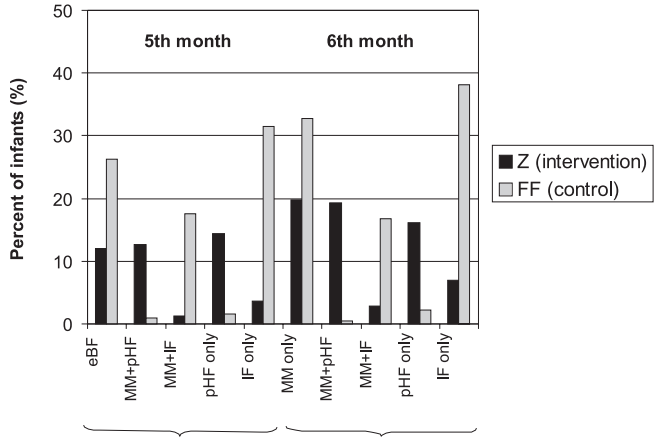

Fig. 5 Weaning foods only during the 5th and 6th months within the various milk feeding groups (MM only), breastfeeding with pHF (Z), breastfeeding with IF (FF), non-breastfeeding with pHF (Z), non-breastfeeding with IF (FF)

no weaning foods at all ($p < 0.01$). Overall, these results show that many subjects in Z followed the dietary regimen for up to 2 months after the end of the strict intervention programme.

Discussion

The ZUFF study was designed to determine whether an intervention programme that reduces food allergen exposure in early infant nutrition by breastfeeding, use of an allergen-reduced infant formula (pHF) when not breastfeeding, and late introduction of weaning foods with a low degree of allergenicity, has any overall health benefits (or negative effects) in a population-based infant study. The focus of our study was on the overall health benefits of such an allergen-reduced nutritional intervention and not on specific atopic health symptoms. Almost all previous studies have included only those infants with a high risk of allergy, and have therefore not demonstrated whether primary dietary prevention measures are safe and potentially beneficial in the infant population as a whole. Moreover, results of studies in selected high-risk infant populations must be interpreted with caution due to nonspecific or inexact definitions of a high risk of atopic disorders, which are shown to be somewhat unreliable [55–57]. The effectiveness and safety of pHF-based (Nestlé Beba HA) allergen-reduced diets in reducing first atopic manifestations in high-risk infants have been adequately demonstrated in numerous clinical trials [1, 3, 6, 17, 18, 45, 46, 49, 50, 60], whereas the overall health benefits of such a nutritional programme in the infant population as a whole have never been evaluated in a study with large numbers of subjects.

Some important aspects of our study design require emphasis. The ZUFF study focussed specifically on the use of a dietary intervention that included breastfeeding, the use of a pHF infant formula, and delay of weaning, particularly highly complex and allergenic weaning foods. We integrated appropriate confounding factors for overall health development into the statistical analysis of results, thereby eliminating bias due to environmental and familial factors. Family-related risk of allergy was integrated as a covariate in the confirmatory statistical analyses and was not used as a selection criterion in the study.

Our study was conducted prospectively, thereby eliminating any problems with the later recall of feeding regimens, a problem occurring often in retrospective studies. Furthermore, the precise reporting even of small amounts of ingested foods was important in our study, which therefore had rigorous criteria for noncompliance. Our study was nonrandomized and unblinded, even though randomized double-blinded trials are most likely to be free of bias. In general, blinding and double-blind methods are difficult to apply to interventional feeding regimens for a number of reasons [49, 63], principally because the mother cannot be blinded to breastfeeding or to the introduction or type of weaning foods, and because she can often distinguish between different feeding formulae by their taste, and by the appearance of her infant's stools.

We did not randomize the dietary intervention because of a high likelihood of non-compliance [1, 6]. Normal social interactions between randomized cohorts in open dietary intervention studies are likely to modify dietary pattern, thereby corrupting the randomization. In addition, we wanted to conduct a study in the natural surrounding and setting of an unselected infant population. Our study setting excluded artificial blinding and intervention. Instead, we elected to assign intervention and control cohorts in

separate geographic regions approximately 50 km apart, thereby ensuring few interactions between study cohorts and limiting the likelihood of one cohort modifying the other's dietary patterns. The two regions were closely matched in most socio-demographic, socio-economic, and geographical factors [72]. Overall, the Zug region was slightly more urban and industrialized, with a slightly higher level of education and purchasing power (150 % purchasing power in Z compared to the Switzerland's average (=1=100 %) compared with 133 % in Frauenfeld). This was reflected in the two study cohorts (Table 3). These differences at best would favour FF and could be regarded almost as a worst-case scenario.

In each region, we enrolled one in three newborn infants who qualified for study. The number of infants included was remarkably similar in each cohort: n (Z)=564; n (FF)=566. Enrolment in the study was open to all qualifying newborn infants in each region, and was not based on limiting recruitment to a predefined maximum number of subjects. The potential enrolment population, recruitment time, and recruitment practices were identical in both regions. In each region, regular paediatricians, obstetricians and other physicians, midwives, nurses, mother's consultants, and other professionals normally involved in the healthcare of newborn babies, participated in the study. This ensured comparable and high levels of recruitment. We consider that recruiting one in three qualifying newborn infants in such a large population-based study requires a high degree of involvement from the participants over a considerable period of time (2 years); our result in this respect is an unusually high achievement. We deliberately designed our study to exclude blinded observers and allergologists. Our study was designed to demonstrate whether an overall allergen-reduced nutritional intervention impacts growth and general health development, assessed within the subjects' usual health care surrounding. Our study did not focus on allergies.

A comparison of the characteristics of the final study cohorts with the total available population showed that our cohorts were representative of the total infant population in each of the regions with one exception: both cohorts in our study had a somewhat higher risk of allergies (56 % in Z, 51 % in FF) (Table 3) than a newborn population as a whole (typically 30 to 40 %) [1, 2, 7, 27]. In a later evaluation of subgroups of our study cohorts without an elevated risk of allergies, we demonstrated that results were comparable with the total cohorts (Part II publication). Comparing noncompliants with the total study cohorts showed that noncompliants in FF had a higher allergic risk (89 %) compared with compliants in FF (49 %). This suggests that some parents of noncompliants were aware of the preventive potential of an allergen-reduced diet, and therefore chose to feed their infants with allergen-reduced infant formula (Table 2).

The nature of the ZUFF study as an epidemiological cohort trial included large numbers of subjects in each study cohort, ensuring sufficient statistical power for conclusive analyses. Howie determined that 500 subjects per cohort, as used in the ZUFF study, was sufficient to investigate the effects of nutritional interventions on general health status [21]. The size of the cohorts was calculated before the beginning of the ZUFF study.

In addition, this study design was ideally suited to assess whether a recommendation to follow certain dietary restrictions is feasible in a normal environment. The normal health care and nutritional counselling setting was altered by the study as little as possible, and included only those health care providers who were previously involved in nutritional counselling and medical care of the individual probands in the two study regions.

Few previous data are available to demonstrate compliance with the dietary recommendations of various committees on nutrition. In our study, compliance with the feeding regimen of the Swiss Paediatric Society [61] in the FF cohort was relatively high. Fewer than 20 % of infants received weaning foods that were not recommended within the first 3 months of life, whereas half of FF infants were exclusively breastfed and a further 26 % were partially breastfed, at 3 months. Overall, comparable numbers of subjects in the Z and FF groups were breastfed, with or without supplementary feeding, at 3, 4, and 6 months.

After 3 and 6 months, breastfeeding rates in both cohorts of the ZUFF study were greater than those in other relevant studies (Fig. 6), which include a retrospective Swiss study [64], the German MAS study [58], the European Growth study [65], and a retrospective breastfeeding study conducted in Geneva [66]. These comparisons do not account for the introduction of weaning foods. A comparison of the median age at which weaning foods were introduced in the ZUFF study and the Glasgow longitudinal infant growth study [67], the most appropriate large-scale study for comparison, also suggests a significant delay in the introduction of weaning foods in both cohorts of the ZUFF study.

Few previous data are available to demonstrate whether a specific allergen-reduced dietary recommendation will be followed in unselected population-based infant studies. Our study demonstrates that the dietary recommendation in the intervention group (Z) ensures a high compliance with the reduced allergen diet (n=74/563, 13.1 % noncompliants) (Tables 1 and 2). In addition, in our study, infants in the intervention cohort (Z) were exclusively breastfed from 6 weeks and throughout the intervention period of 4 to 6 months at a significantly higher rate than in the control cohort (FF): exclusive breastfeeding without weaning foods at 4 months was 35.6 % (Z) versus 28.6 % (FF); at 6 months, 15.4 % (Z) versus 6.8 % (FF) ($p < 0.01$). This occurred despite the fact that the intervention cohort received more supplementary feedings (with pHF formula) than the control cohort (with normal infant formula) during the first few days of life. These findings suggest that supplementary bottle feedings early in life are not predictive of a lower rate

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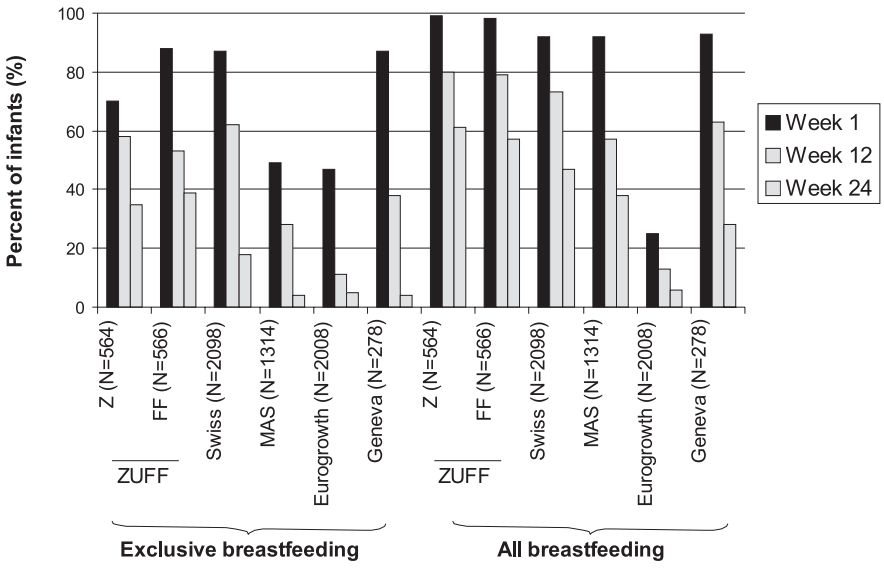

Fig. 6 Comparison of breastfeeding activity in ZUFF and other published dietary studies up to 24 weeks (6 months): percent of all breastfed and exclusively breastfed infants. Numbers of infants at start of each study are shown (*N*). Dates of studies: ZUFF 1991–1992, Swiss 1994, MAS 1990, Eurogrowth 1991–1993, Geneva 1993. In MAS and Eurogrowth studies, cumulative assessments were made at weeks 4 (for comparative purposes, these data are presented under week 1 in the figure), 12, and 24. After 12 and 24 weeks, breastfeeding rates in the ZUFF study are greater than those in most other studies.

of breastfeeding in subsequent weeks and months [68, 69], and may simply reflect normal practice at the region's clinics. The value of the intervention in the ZUFF study was also demonstrated by the significantly later age at which infants in our intervention cohort received weaning foods than those in the control cohort: median (Z)=22 weeks, (FF)=18 weeks; and the significantly fewer types of weaning foods received up to the age of 6 months: (Z)=2, (FF)=10 types of weaning foods. Notably, 11 % of Z and 43 % of FF infants received weaning foods by the end of the 4-month strict intervention period, and only 75 % of Z but 92 % of FF infants had received weaning foods at 6 months.

Considering the dietary pattern after the strict 4-month intervention period, the ZUFF study shows that dietary recommendations in the intervention cohort continued to be followed during the fifth and sixth months of life. Indeed, these infants in the intervention cohort received a considerably lower allergenic load than those in the control cohort throughout the intervention period and up to 2 months thereafter (Figs. 4 and 5).

The 6-month dropout rate in the ZUFF study was extremely low in both cohorts (Z=4.3 %, FF=1.8 %), particularly when compared with other intervention studies, even those that included exclusively high-risk populations with a high incentive for compliance [32, 70]. In Zeiger's study, the dropout rate was 38 % in the intervention cohort and 13 % in the control cohort [32, 70]. We interpret the low dropout rate in our study as a willingness of parents to follow our dietary recommendation, (and the realistic easily to following feeding recommendations including a good tasting formular CpHF) supported by the excellent motivation provided by members of the study centre and the healthcare providers. An analysis of reasons for dropout revealed only 9 infants in the intervention cohort who were withdrawn because their mothers were dissatisfied with the overall feeding recommendations. Furthermore, only 13 % of subjects in the intervention cohort failed to comply with the 4-month programme, despite rigorous criteria for non-compliance. Those high rates of compliance in the ZUFF study demonstrate a willingness and easiness to follow this allergen-reduced dietary intervention regimen, even in an infant population at no known risk of atopic disease.

Overall, our study demonstrates that an allergen-reduced dietary recommendation in an unselected infant population has no negative effect on the overall breastfeeding rate and actually produces a significantly higher rate of exclusive breastfeeding compared with a control population. Notably, the recommended dietary regimen in the control cohort of this study included exclusive breastfeeding for 3 months, thereby validating the comparison between cohorts with respect to breastfeeding. Our recommended dietary regimen was not only highly accepted by the intervention cohort, but was followed for at least 2 months after the end of the 4-month intervention period. We conclude that a dietary recommendation that includes an allergen-reduced diet based on breastfeeding, a moderately hydrolysed infant formula (pHF), and a delay in introducing simple weaning foods during the first 4 to 6 months of life, is a realistic and feasible recommendation in the healthy infant population as a whole.

Acknowledgements Financial support for this work was provided by Nestlé Suisse SA, Vevey, Switzerland.
The authors want to thank paediatricians Dr. V. Meier, Dr. F. Schmid, Dr. J. Waltenspühl, and Dr. F. Saur for their extensive involvement in the study. They were the responsible paediatricians for maternity wards in both regions and oversaw some study infants at a later date in their outpatient practices. Without their immense and unceasing

efforts to set up this study, it would not have been possible to undertake such a vast endeavour. Furthermore, we want to thank H. Tacier-Eugster, a paediatric allergologist who helped us with valuable advice concerning all questions of allergy. In addition, we owe a deep debt of gratitude to Elsbeth Frey (†) and Gisèle Domenjoz, the two mother's consultants responsible for the compliance of study participants. Only because of their efforts were we able to reduce dropout and noncompliant rates in this study compared with other studies.

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