

# Partial Protein-Hydrolyzed Infant Formula Decreased Food Sensitization but Not Allergic Diseases in a Prospective Birth Cohort Study

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## Key Words

Partial protein-hydrolyzed infant formula • Cow's milk infant formula • Sensitization • Allergic disease

## Abstract

**Background:** Exposure to cow's milk protein in early infancy could lead to increased rates of allergic diseases later in life. We investigated whether feeding a protein-hydrolyzed formula (HF) in the first 6 months of life decreased allergic diseases up to 36 months later. **Methods:** Newborns who had at least 1 first-degree family member with a history of atopy and could not breast-feed were enrolled. They were fed with HF or cow's milk infant formula (CM) for at least 6 months via an open-label protocol and were monitored prospectively at 6, 18 and 36 months of age to assess allergy sensitization and allergic diseases. **Results:** A total of 1,002 infants were enrolled and 679 infants were consistently fed the same formula for the first 6 months of life (345 HF and 334 CM). The percentage of food sensitization (especially to milk protein) was significantly lower in the HF group than in the CM group at 36 months (12.7 vs. 23.4%,  $p = 0.048$ ). There was no significant difference in the prevalence of aeroallergen sensitization between the groups. Occurrence of allergic diseases during the first 3 years of life was significantly correlated with aeroallergen sensitization, but not to food allergen sensitization, parental atopy or feeding types. **Conclusions:** In-

fant fed with HF during the first 6 months of life had a significantly lower percentage of sensitization to milk protein allergens, but not allergic diseases during the first 3 years of life. Avoidance of cow's milk protein alone in infancy is not enough to decrease rates of allergic diseases.

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## Introduction

The prevalence of atopic disorders has increased globally over the past two decades, especially in children [1, 2]. Currently, strategies for the prevention of atopic disorders tend to focus on recognizing high-risk infants and avoiding exposure to allergens in early life [3–5]. It is thought that avoiding exposure to cow's milk protein in infancy could interrupt the 'allergic march' and reduce the occurrence of allergic diseases later in life. Indeed, a number of clinical studies suggest that early exposure to dietary allergens could be crucial for the development of allergies, particularly food allergies for atopic dermatitis [6–8].

It is recommended that newborns be breast-fed if possible [9, 10]. Protein-hydrolyzed infant formulas (HF) are

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designed to provide a hypoallergenic milk protein to prevent sensitization and intolerance in infants not fed breast milk [10]. Therefore, feeding of HF to infants at risk for atopic diseases is emphasized, not only as it can reduce the incidence of cow's milk protein allergy and allergic diseases, but also because it could induce the development of tolerance [11–13].

In the studies conducted to date, there are major differences in feeding formulations such that the preventive effect of HF in high-risk infants is still inconclusive [12, 14]. Further studies are necessary to assess relevant outcomes of feeding HF compared to regular cow's milk infant formula (CM). Most studies examined the effects of HF on atopic phenotypes in young infants and children. However, atopic features are versatile during the first 3 years of life, and allergic sensitization may not develop until 3 years of age [6, 11, 12, 15, 16]. Few cohort studies have performed long-term tracing of specific allergen sensitization.

Thus, the purpose of this study was to assess whether early avoidance of milk protein exposure by feeding HF was associated with a decreased allergic sensitization and allergic disease in infants at risk for atopy compared to infants fed regular CM.

## Methods

### Study Population

This prospective, observational, uncontrolled, per-protocol birth cohort study was conducted in Chang Gung Memorial Hospital – Kaohsiung Medical Center, Taiwan. Newborns who had at least 1 first-degree family member with a history of atopy and could not breast-feed were enrolled between September 1999 and July 2005. They were fed with HF or CM for at least 6 months according to an open-labeled protocol and monitored prospectively at 6, 18 and 36 months of age to assess allergy sensitization and allergic diseases. Infants fed with mixed infant formulas or both breast milk and infant formula were excluded from further analysis.

A research nurse was trained to explain the purpose of the study to all pregnant mothers during prenatal visits to the obstetrics clinic at Chang Gung Memorial Hospital, Kaohsiung, Taiwan. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. Blood samples were collected after informed consent had been obtained from the parents. A questionnaire was given to collect family atopic and smoking histories. Parents were asked to avoid giving any solid food to infants during the first 6 months, and those infants receiving solid food before 6 months old were excluded from further analysis.

The cohort population was monitored prospectively at 6, 18 and 36 months of age. At each visit, infants underwent physical examination by a pediatrician with a specialty in allergy and clinical immunology, and a questionnaire regarding the duration of

feeding type and atopic symptoms was completed. Only infants fed with HF or CM for 6 months and receiving complete follow-ups with physical examinations and laboratory assessments at 36 months of age were included in the outcome analyses (fig. 1). The HF, provided by Nan HA (hypoallergenic infant formula; Nestle, Geneva, Switzerland), was a partially hydrolyzed whey formula with a molecular weight in the range of 5,000–40,000 Da. The CM was any brand of cow's milk infant formula without hydrolyzed protein.

### Detection of Total IgE and Specific IgE Levels

Serum total IgE levels and specific IgE antibodies in the blood of infants at 6, 18 and 36 months of age were determined using the Pharmacia CAP system (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden), with a detection limit of 0.01 kU/l, as previously described [12, 17, 18]. Parents' blood levels of total IgE and specific IgE were also determined. A low-range total IgE detection system was used to measure cord blood (CB) IgE levels; whereas a full-range total IgE detecting system was used to measure the IgE levels of parents and infants. Six common allergens including 2 common inhaled allergens [*Dermatophagoides pteronyssinus* (Der p) and cockroach] and 4 common food allergens (egg white, milk protein, shrimp and peanut), which have prevalences of sensitization greater than 5% in the study area, as previously determined [17], were included to assess allergen sensitization. The prevalence of other indoor allergen (cat or dog dander) sensitizations are low in the population studied in Taiwan (<5%) and were not included in the analysis [19].

### Definition of Allergic Sensitization and Allergic Diseases

Allergic sensitization was defined by the detection of one or more of 6 common specific IgE antibodies (Der p, cockroach, egg white, milk protein, shrimp and peanut at levels of IgE >0.7 kU/l) in blood [20]. Allergic diseases were defined by a history of atopy and physical examination. Parental history of atopy was determined by questionnaire reports of physician-diagnosed asthma, allergic rhinitis or atopic dermatitis (including typical atopic dermatitis or food allergies). The allergic disease in infants at 6 months of age was defined by eczema (chronic or relapsing dermatitis with erythematous, scaly or itchy rashes distributed on the face, neck, anterior chest wall, extensor areas or the flexural folds of extremities) or gastrointestinal manifestations of food allergy (vomiting, loose stools, excessive crying or abdominal pain) [20]. Asthma and allergic rhinitis were not assessed at 6 months of age, as these conditions are poorly definable at this age. For infants at 18 and 36 months of age, allergic diseases were indicated when they exhibited one or more of the following symptoms: atopic dermatitis (chronic or relapsing dermatitis with erythematous, scaly or itchy rashes on the face, neck, anterior chest wall, extensor areas or the flexural folds of extremities), asthma (recurrent at least 3 episodes of wheezing, coughing or both, requiring bronchodilator treatment, and diagnosed by a physician) and allergic rhinitis (sneezing, running or blocked nose or both, or itchy eyes with seasonal variations in the absence of infection, and diagnosed by a physician).

### Data Analysis and Biostatistics

A per-protocol analysis was carried out on infants evaluated by the examiners at the beginning and end of the study period. Total serum IgE levels were logarithmically ( $\log_{10}$ ) transformed

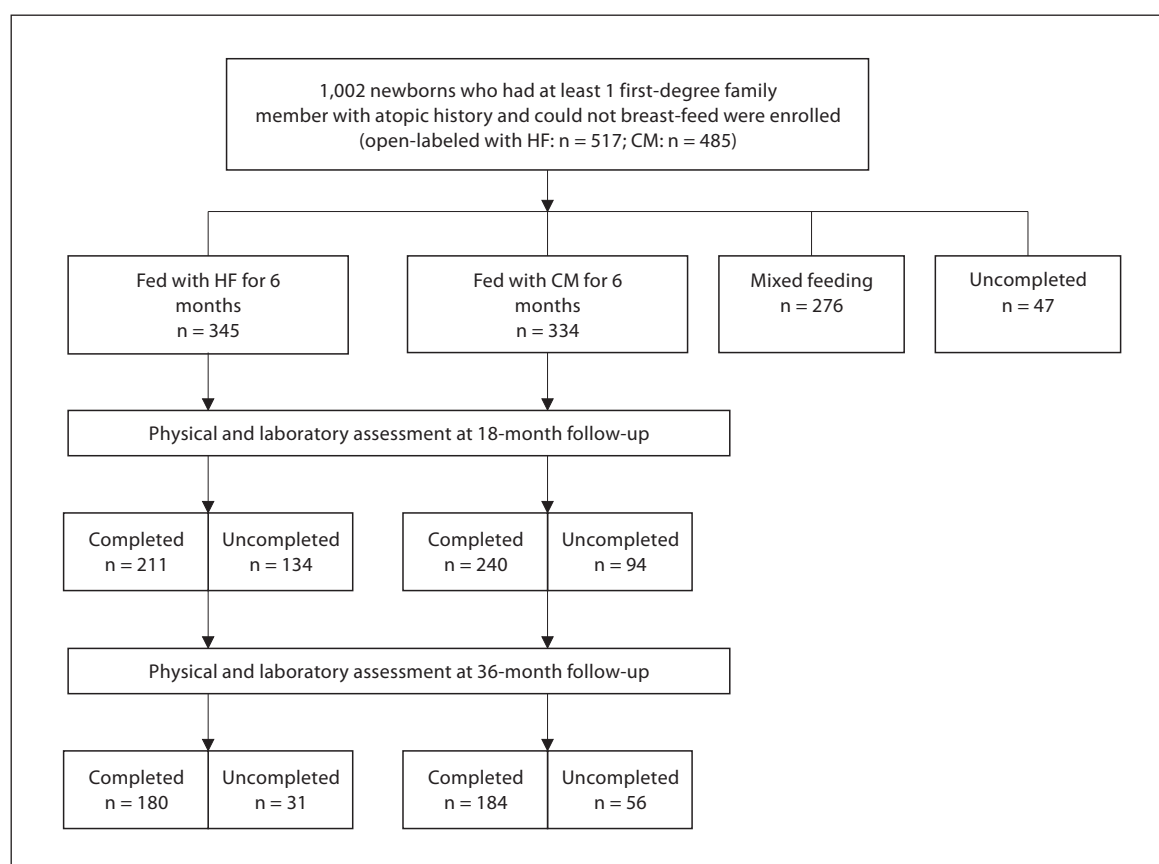


**Fig. 1.** Cohort flow chart: study enrollment and completion from birth to 36 months of age. Completed = Completed all physical and laboratory assessments; uncompleted = did not complete all physical and laboratory assessments.

into normal distribution data and presented as means and standard deviations. Differences in log-transformed mean total IgE values of parents and infants were analyzed using Student's *t* test. Because log-transformed CB IgE values were not normally distributed, we presented the median values of CB IgE levels. The CB IgE cutoff values were 0.5 kU/l, in accordance with previously determined reference cutoff points [17, 21, 22]. For all statistical computations, we used SPSS for Windows XP, version 12.0 (SPSS Inc., Chicago, Ill., USA). Pearson's  $\chi^2$  test and Student's *t* test were used in statistical comparisons, as appropriate. A *p* value of 0.05 or less was regarded as statistically significant.

## Results

### *Comparison of Demographic Data between Infants Completing or Not Completing the Study*

A total of 1,002 infants at high risk for atopy (517 infants initially fed with HF and 485 infants fed with CM) were enrolled in the study (fig. 1). Of these, 679 infants

were consistently fed the same formula for the first 6 months of life (345 fed HF and 334 fed CM). Enrollees who did not complete the study during the first 6 months included those with mixed feeding (276/1,002, 27.5% included the infants who were given solid food) and those whose parents refused to have their child's blood drawn (47/1,002, 4.7%). The demographic data of infants who completed the follow-up at 6 months of age are shown in table 1a. There were no significant differences between infants fed with HF, CM and mixed feeding with respect to gender distribution, gestational age, CB IgE levels, maternal and paternal sensitization, and total IgE levels. At the 18-month follow-up, a total of 451 infants (211 fed HF and 240 fed CM) returned for clinical and laboratory follow-up; of these, 364 infants (180 fed HF and 184 fed CM) completed the follow-up at 36 months of age. Subjects who did not complete the 18-month (134 fed HF and 94 fed CM) or the 36-month follow-ups (31 fed HF and 56

**Table 1.** Demographic data of infants who completed or did not complete the study**a** Follow-up at 6 months of age

|                             | HF (n = 345) | CM (n = 334) | Mixed feeding (n = 276) | p value |
|-----------------------------|--------------|--------------|-------------------------|---------|
| Male gender, %              | 53.4         | 54.6         | 58.3                    | 0.486   |
| Gestational age, weeks      | 38.70 ± 0.07 | 38.61 ± 0.08 | 38.72 ± 0.09            | 0.310   |
| Cord blood IgE, kU/l        | 0.46 ± 0.69  | 0.38 ± 0.55  | 0.43 ± 0.58             | 0.564   |
| Maternal sensitization, %   | 31.3         | 25.7         | 26.5                    | 0.282   |
| Maternal IgE >100 kU/l, %   | 29.3         | 27.4         | 24.4                    | 0.334   |
| Maternal passive smoking, % | 42.4         | 44.6         | 38.2                    | 0.207   |
| Paternal sensitization, %   | 33.7         | 36.2         | 34.5                    | 0.734   |
| Paternal IgE >100 kU/l, %   | 37.3         | 40.9         | 34.6                    | 0.468   |

**b** Infants who completed the study and those who did not complete the 18 months of follow-up

|                             | HF           |              |         | CM           |              |         |
|-----------------------------|--------------|--------------|---------|--------------|--------------|---------|
|                             | C (n = 211)  | NC (n = 134) | p value | C (n = 240)  | NC (n = 94)  | p value |
| Male gender, %              | 54.5         | 53.4         | 0.847   | 55.8         | 52.5         | 0.520   |
| Gestational age, weeks      | 38.74 ± 1.25 | 38.75 ± 1.32 | 0.947   | 38.63 ± 1.66 | 38.60 ± 0.56 | 0.452   |
| Cord blood IgE, kU/l        | 0.46 ± 0.69  | 0.42 ± 0.59  | 0.569   | 0.39 ± 0.63  | 0.36 ± 0.53  | 0.592   |
| Maternal sensitization, %   | 34.4         | 27.4         | 0.213   | 23.4         | 25.7         | 0.450   |
| Maternal IgE >100 kU/l, %   | 31.4         | 26.6         | 0.330   | 27.0         | 27.7         | 0.914   |
| Maternal passive smoking, % | 31.5         | 28.3         | 0.574   | 34.2         | 43.2         | 0.070   |
| Paternal sensitization, %   | 33.6         | 32.2         | 0.806   | 39.5         | 31.5         | 0.170   |
| Paternal IgE >100 kU/l, %   | 39.3         | 34.0         | 0.307   | 42.2         | 35.9         | 0.288   |

**c** Infants who completed the study and those who did not complete the 36 months of follow-up

|                             | HF           |              |         | CM           |              |         |
|-----------------------------|--------------|--------------|---------|--------------|--------------|---------|
|                             | C (n = 180)  | NC (n = 31)  | p value | C (n = 184)  | NC (n = 56)  | p value |
| Male gender, %              | 55.6         | 52.2         | 0.659   | 57.2         | 52.2         | 0.562   |
| Gestational age, weeks      | 38.78 ± 1.37 | 38.66 ± 1.01 | 0.533   | 38.51 ± 1.79 | 38.95 ± 1.24 | 0.080   |
| Cord blood IgE, kU/l        | 0.46 ± 0.60  | 0.47 ± 0.88  | 0.851   | 0.36 ± 0.60  | 0.46 ± 0.68  | 0.312   |
| Maternal sensitization, %   | 33.7         | 31.3         | 0.726   | 24.2         | 25.0         | 0.871   |
| Maternal IgE >100 kU/l, %   | 31.6         | 27.3         | 0.424   | 28.4         | 27.3         | 0.995   |
| Maternal passive smoking, % | 34.2         | 24.5         | 0.229   | 32.7         | 38.3         | 0.434   |
| Paternal sensitization, %   | 38.1         | 32.3         | 0.398   | 37.9         | 32.3         | 0.406   |
| Paternal IgE >100 kU/l, %   | 36.6         | 40.2         | 0.644   | 42.6         | 38.1         | 0.655   |

Data are presented as percentages or means ± SD. Sensitization was defined by the detection of one or more common specific IgE antibodies (IgE >0.7 kU/l) in blood. Maternal smoking was very low at 0.8% in this Chinese cohort population. C = Completion of all physical and laboratory assessments; NC = noncompletion of physical or laboratory assessments.

fed CM) did not return for clinical follow-up or refused to have blood drawn. There were no significant differences regarding demographic data between the HF and CM groups with or without completion of the 18-month (table 1b) or 36-month follow-ups (table 1c).

*Allergic Sensitization in HF-Fed Infants*

Infants fed with HF were postulated to be less sensitive to exogenous proteins, and as a consequence to produce less IgE and exhibit reduced allergen sensitization. However, we found that the serum total IgE level (log-transformed data) did not differ significantly between infants

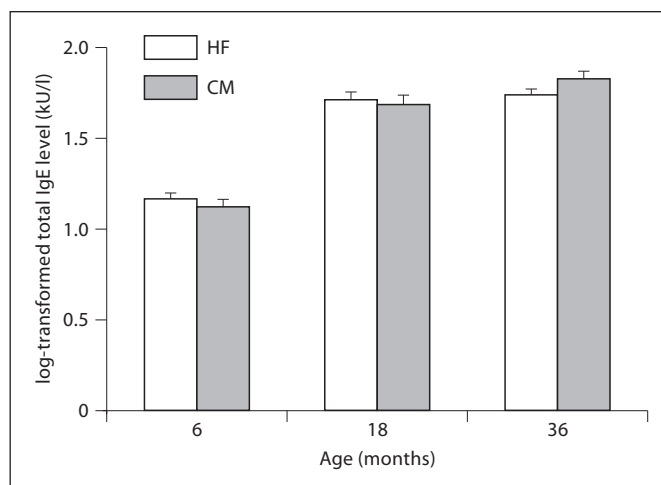
**Table 2.** Allergic sensitization of infants fed with HF and CM

|                                                                  | HF   | CM   | p value |
|------------------------------------------------------------------|------|------|---------|
| <i>6 months old</i>                                              |      |      |         |
| Common allergen sensitization<br>(both aeroallergen and food), % | 8.3  | 8.7  | 0.876   |
| Aeroallergen sensitization, %                                    | 0    | 0    |         |
| Food sensitization, %                                            | 8.3  | 8.7  | 0.876   |
| <i>18 months old</i>                                             |      |      |         |
| Common allergen sensitization<br>(both aeroallergen and food), % | 22.2 | 27.8 | 0.326   |
| Aeroallergen sensitization, %                                    | 7.8  | 8.7  | 0.845   |
| Food sensitization, %                                            | 18.3 | 24.4 | 0.268   |
| <i>36 months old</i>                                             |      |      |         |
| Common allergen sensitization<br>(both aeroallergen and food), % | 36.7 | 43.5 | 0.297   |
| Aeroallergen sensitization, %                                    | 28.3 | 26.1 | 0.675   |
| Food sensitization, %                                            | 15.6 | 26.7 | 0.031*  |

Sensitization was defined by the detection of specific IgE antibodies (IgE >0.7 kU/l) in blood. Aeroallergens are *D. pteronyssinus* and cockroach; food allergens are egg white, milk protein, shrimp and peanut. The asterisk indicates a significant difference between the two study groups as determined using Pearson's  $\chi^2$  test.

fed with HF and CM at the age of 6 months ( $1.16 \pm 0.04$  vs.  $1.12 \pm 0.04$  kU/l,  $p = 0.477$ ), 18 months ( $1.72 \pm 0.04$  vs.  $1.69 \pm 0.05$  kU/l,  $p = 0.669$ ) and 36 months ( $1.74 \pm 0.04$  vs.  $1.83 \pm 0.04$  kU/l,  $p = 0.142$ ; fig. 2).

Analysis of kinetic trends of allergic sensitization found that food allergens were a major part of allergen sensitization detected during young infancy (starting at 6 months of age) and lasted for the first 3 years (table 2). The percentage of infants with food allergen sensitization did not differ significantly between the feeding groups at the ages of 6 and 18 months, but was significantly lower in the HF group than in the CM group at the age of 36 months (15.6 vs. 26.7%,  $p = 0.031$ ). Milk protein sensitization was the most common food allergy detected during the first 3 years of life, and egg white was the second most common allergy. The percentage of milk protein sensitization was significantly lower in HF-fed infants when compared to CM-fed infants at 36 months of age (12.7 vs. 23.4%,  $p = 0.048$ ; fig. 3a). There were no significant differences between groups at any age with regard to egg white sensitization (fig. 3b). The percentages of peanut and shrimp sensitizations were very low in this study (<2.7% at 6, 18 and 36 months of age). Furthermore, milk

**Fig. 2.** log-transformed serum total IgE levels at 6, 18 and 36 months of age in HF- and CM-fed infants. Bars are presented as mean and standard deviation.

protein sensitization from infancy (6 or 18 months of age) and persistent to 3 years of age was significantly higher in the CM compared to the HF group (13.0 vs. 4.4%,  $p = 0.023$ ). The percentage of aeroallergen sensitization in infants at the age of 18 months was 8.2% and increased to 27.2% at 36 months of age (both HF and CM groups combined). Der p antigen was the most commonly detected aeroallergen in this cohort population. There was no difference in Der p and cockroach antigen sensitization between the HF and CM groups during the first 36 months of life (fig. 3c).

#### Allergic Diseases among Infants with HF and CM

The most common allergic disease in 6-month-old infants was eczema (25.6% in the HF group vs. 18.5% in the CM group,  $p = 0.207$ ), followed by gastrointestinal symptoms (5.6% in the HF group vs. 6.5% in the CM group,  $p = 0.793$ ). The prevalence of eczema/atopic dermatitis decreased to 15.6% in the HF group and 15.2% in the CM group at 18 months, and to 16.7% in the HF group and 9.8% in the CM group at 36 months (fig. 4a). In contrast, the prevalence of asthma/allergic rhinitis increased between 18 and 36 months in both groups (from 8.3 to 13.9% in the HF group, from 8.2 to 11.9% in the CM group; fig. 4b). There were no significant differences in the prevalence of allergic rhinitis between the HF and CM groups (6.1 vs. 4.3%, at 18 months,  $p = 0.43$ , and 13.3 vs. 11.4%, at 36 months,  $p = 0.57$ ) or asthma (5.6 vs. 5.9%, at 18 months,  $p = 0.84$ , and 6.7 vs. 6.5%, at 36 months,

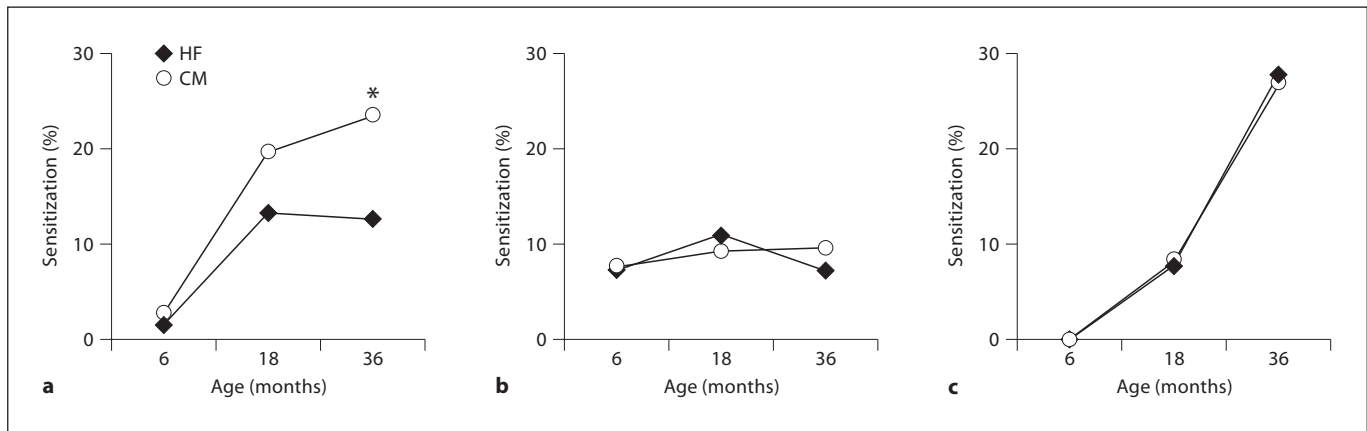


**Fig. 3.** Percentages of infants sensitized to different allergens at 6, 18 and 36 months of age. **a** Milk protein sensitization. The asterisk indicates a significant difference between the two study groups as determined by Pearson's  $\chi^2$  test. **b** Egg white sensitization. **c** *D. pteronyssinus* sensitization.

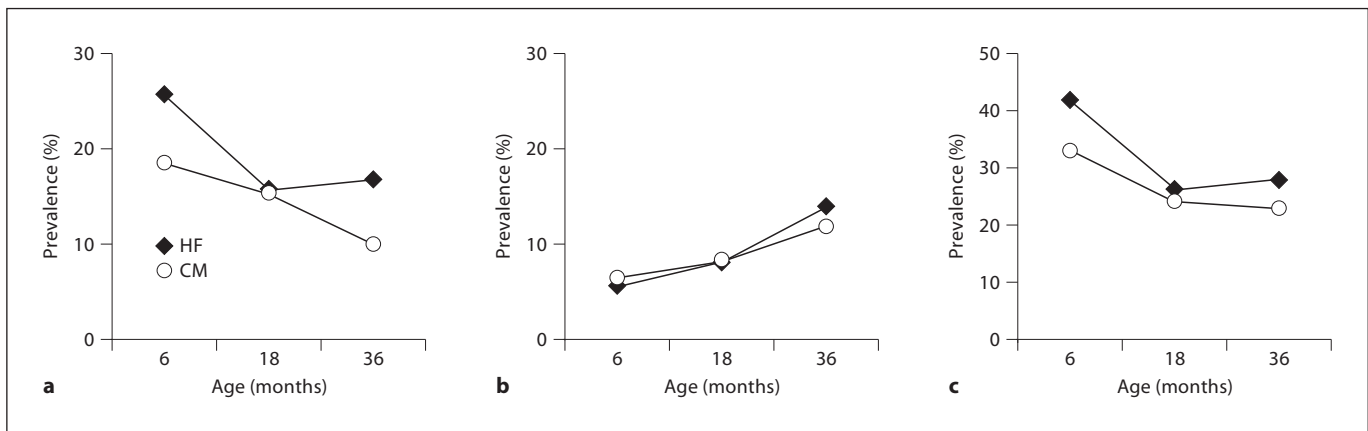


**Fig. 4.** Prevalence of allergic diseases in infants at 6, 18 and 36 months of age. **a** Prevalence of eczema/atopic dermatitis. **b** Prevalence of allergic rhinitis/asthma. **c** Prevalence of any allergic diseases.

$p = 0.85$ ). There were no significant differences in the prevalence of any allergic disease between the HF and CM groups over the study period (fig. 4c).

#### Association of Aeroallergen with Infant Allergic Disease

Food sensitization at 18 months of age was associated with aeroallergen sensitization at 36 months in both groups. Analyses were next performed to determine possible risk factors for allergic diseases by univariate and multivariate logistic regression analyses. The perinatal factors included in the analyses were parental atopy, pa-

rental smoking history, CB IgE levels, gender, infant feeding type, and infant allergen sensitization. Occurrence of allergic disease at 36 months of age was significantly associated with Der p sensitization both in the univariate ( $p < 0.001$ ) and multivariate analyses ( $p = 0.015$ , table 3). The association between milk protein sensitization and allergy disease was not significant in the multivariate analysis ( $p = 0.137$ , table 3). Thus, aeroallergen sensitization, but not food sensitization, was associated with infant allergic disease. These results suggest that HF feeding decreased food allergen sensitization, but not aeroallergen sensitization or allergic disease.

**Table 3.** Perinatal factors and allergic sensitization correlated with atopy at 36 months of age

| Parameters (yes or no)     | p value of UVA | p value of MVA |
|----------------------------|----------------|----------------|
| Gestational age >37 weeks  | 0.637          | 0.863          |
| Male gender                | 0.672          | 0.974          |
| Maternal IgE >100 kU/l     | 0.975          | 0.525          |
| Maternal sensitization     | 0.202          | 0.130          |
| Paternal IgE >100 kU/l     | 0.892          | 0.538          |
| Paternal sensitization     | 0.294          | 0.623          |
| Maternal passive smoking   | 0.408          | 0.497          |
| Cord blood IgE >0.5 kU/l   | 0.806          | 0.453          |
| HF feeding >6 months       | 0.293          | 0.407          |
| Der p sensitization        | <0.001*        | 0.015*         |
| Milk protein sensitization | 0.991          | 0.137          |
| Egg white sensitization    | 0.593          | 0.615          |

UVA = Univariate analysis of  $\chi^2$  test; MVA = multivariate analysis of logistic regression. UVA and MVA were utilized to determine the relationship between infant allergic diseases and each of the parameters. Sensitization was defined by the detection of specific IgE antibodies (IgE >0.7 kU/l) in blood. Parental sensitization was defined by the detection of one or more common specific IgE antibodies (IgE >0.7 kU/l) in blood. Maternal smoking was very low at 0.8% in this Chinese cohort population. The asterisks indicate a significant correlation between the given parameter and infant allergic diseases.

## Discussion

We found that allergy sensitization to food allergens began in early infancy and increased thereafter (up to 3 years of age). We also found that the use of HF in the first 6 months of life resulted in a significant reduction of allergy sensitization, in particular that to food allergen. Although several authors reported that HF feeding decreased the occurrence of some allergic diseases [11, 12], we found that HF feeding decreased milk protein sensitization but not allergic diseases. This suggests that infants from an atopic family who carry allergy-susceptible gene(s) would not change the progression of allergic diseases with avoidance of cow's milk proteins. Avoidance of cow's milk proteins in infancy might not be good enough to decrease the development of allergic diseases. In addition to avoiding cow's milk proteins during infancy, we recommend infants with a high risk for allergy avoid exposure to aeroallergens and not live in a microbe-deprived environment. It is unclear why infants fed with HF exclusively for the first 6 months were sensitized to cow's milk proteins at 6 months of age even though solid food

had not yet been introduced in this period. This may be because HF is a partial protein-hydrolyzed infant formula containing 18% of peptides greater than 6,000 Da, which may also cause sensitization. Another possibility is that allergen sensitization could have occurred in utero [23, 24].

Although the presence of allergen-specific IgE does not necessarily imply atopic disease, it often precedes the disease [25–27]. Our study showed that the presence of food sensitization in early infancy could be used to predict further allergic sensitization later in life. Avoidance of milk protein exposure delayed and decreased milk protein sensitization, but not allergic diseases; this is compatible with our finding that allergy diseases were associated with aeroallergens, but not food allergen sensitization, during the first 3 years of life. Apparently, food sensitization shares certain similar mechanisms to aeroallergen sensitization, which differs in its association with allergic diseases. Indeed, as the prevalence of allergic diseases increased with age, the frequency of food sensitization decreased and that of aeroallergen sensitization increased; and aeroallergen sensitization was the only factor associated with allergic diseases at 3 years of age. This suggests that the natural course of food sensitization is different from that of aeroallergen sensitization. Further studies are needed to clarify whether this is related to oral tolerance with respect to food sensitization, but not aeroallergen sensitization, or related to different genetic controls or antenatal priming of aeroallergen sensitization. The allergic gastrointestinal manifestations of food allergy are difficult to separate from milk protein intolerance. Many of the symptoms shown can also be caused by intolerance. But the incidence of gastrointestinal intolerance symptoms was very low and comparable among all feeding groups in Taiwan. General intolerance, spit-up and flatulence were each reported for less than 6% of infants [28]. The limitation of this study was that it was an uncontrolled trial.

In conclusion, our findings suggest that HF feeding instead of CM feeding during the first 6 months of life reduced the risk of milk protein sensitization only. There were no data suggesting that diet modification changed sensitization of other food allergens or aeroallergens. HF feeding did not decrease allergy diseases during the first 3 years of life, although it decreased food allergen sensitization. Considering food sensitization was not associated with allergic diseases, and avoidance of cow's milk protein in infancy had no effect on reduction of total IgE levels or childhood allergic diseases, prolonged avoidance of CM more than 6 months may not be necessary. Further

study is required to determine whether a combination of dietary control and environmental control with no microbial deprivation or aeroallergen avoidance in infancy (or even in the antenatal stage) could decrease the onset of allergic diseases.

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