

Infant feeding practices and physician diagnosed atopic dermatitis: a prospective cohort study in Taiwan

Chuang CH, Hsieh WS, Chen YC, Chang PJ, Hurng BS, Lin SJ, Chen PC. Infant feeding practices and physician diagnosed atopic dermatitis: a prospective cohort study in Taiwan.

Pediatr Allergy Immunol 2010.

© 2010 John Wiley & Sons A/S

It is common to recommend breastfeeding and a delayed introduction of solids to prevent atopic dermatitis (AD). However, the scientific evidence for this is inconclusive. The aim of this study was to explore the effect of breastfeeding and solids on AD, when taking account of reverse causality. This on-going birth cohort study was designed to sample 24,200 representative post-partum women and their babies from the Taiwan National Birth Registration database. Using two home interviews at 6 and 18 months after birth, with structured questionnaires about diet and physician's diagnosis of AD by parental reports, a total of 20,172 pairs (83.4%) were reviewed completely. Considering reverse causality, we excluded 2399 children with AD in the first 6 months of life and 18,733 were finally recruited. All study participants provided informed consent as approved by the Ethics Review Board of the National Taiwan College of Public Health. After adjustment for potential confounders, the overall results showed that the increased duration of breastfeeding seemed to increase the risk of AD at 18 months in children. However, no significant effect was found for the delayed introduction of solids on the risk of AD. There is no evidence of a protective effect of prolonged breastfeeding and a delayed introduction of solids against AD among children at age 18 months, and may even be a risk factor of AD.

**Chao-Hua Chuang¹, Wu-Shiun Hsieh²,
Yi-Chun Chen³, Pei-Jen Chang⁴,
Baai-Shyun Hurng⁵, Shio-Jean Lin⁶
and Pau-Chung Chen⁷**

¹Department of Nursing, Chang Jung Christian University, Tainan County, Taiwan, ²Department of Pediatrics, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan, ³School of Nutrition and Health Sciences, Taipei Medical University, Taipei, Taiwan, ⁴Department of Nursing, National Taipei College of Nursing, Taipei, Taiwan, ⁵Population and Health Research Center, Bureau of Health Promotion, Department of Health, Taichung, Taiwan, ⁶Department of Pediatrics, National Cheng-Kung University Hospital and National Cheng-Kung University College of Medicine, Tainan, Taiwan, ⁷Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan

Key words: breastfeeding; solid food; atopic dermatitis; cohort study; reverse causality

Dr Chao-Hua Chuang, Department of Nursing, Chang Jung Christian University, 396, Sec.1, Chang Jung Road, Kway Jen, Tainan 71101, Taiwan
Tel.: +886-6-278-5123
Fax: +886-6-278-5581
E-mail: chchuang@mail.cjcu.edu.tw

Accepted 29 January 2010

Atopic dermatitis (AD) is associated with gene and sensitization against both food and environmental allergens (1–3). Decreasing the risk of food sensitization has been proposed to reduce the prevalence of AD. The protective effect of exclusive breastfeeding against AD has received widespread support (4–7), and therefore current prophylactic feeding guidelines for the prevention of atopic diseases recommend a delayed introduction of solid foods (8). Nevertheless, studies have shown inconclusive evidence of breastfeeding's effect on the development of

allergic diseases (9–16), and inconsistent evidence of the influence of a delayed solid food introduction on atopic diseases, eczema, or asthma (17–21).

Bias may occur because of disease-related modification of exposure, such as the outcome influencing the exposure, also known as reverse causation (10, 17). As it is widely believed that prolonged breastfeeding and the delayed introduction of solids have benefits with regard to AD, it is thus possible that mothers extend their breastfeeding (22) and delay introducing solid

food if their children have suspected symptoms of allergy diseases, resulting in reverse causation (17).

As the role of infant feeding practices, in particular duration of breastfeeding and timing of solid foods introduced, in the prevention of AD is unclear (23–25), the aim of this study was to explore the effect of breastfeeding and solids on AD, when taking account of reverse causality.

Methods

Study population and sampling strategy

The Taiwan Birth Cohort Study (TBCS), the first such national in Taiwan, is a prospective longitudinal study. In the current study, multistage stratified systematic sampling was designed to obtain representative samples from the Taiwan National Birth Registration database for 2005. A total of 369 towns in Taiwan were divided into 12 strata according to the administrative division (four strata), and the total fertility rate (three strata) was ranked, and 90 towns of the total were sampled. Using the principle of proportion probability to size, newborns and their mothers were sampled randomly from these 90 towns, for a total of 24,200 pairs.

Data collection

The process of data collection is shown in Fig. 1. The first and secondary home interviews with the 24,200 post-partum women were conducted at 6 and 18 months after their deliveries by using a structured questionnaire in the period from June 2005 to December 2007. There were a total of 4028 (2952 and 1076, respectively) cases of loss to follow-up in the two interviews because of refusal to participate, moving home, incorrect addresses, infant deaths, and other miscellaneous reasons. A total of 21,248 and 20,172 women were interviewed, and the completed interview rate was thus 87.8% and 83.4%, respectively, in the two interviews. Considering reverse causality, we excluded 2399 children with physician diagnosed AD in the first 6 months of life and 18,733 were finally recruited. All study participants provided informed consent as approved by the Ethics Review Board of the National Taiwan College of Public Health.

Definition of exposures

Data were obtained from the Taiwan National Birth Registration database and the interview questionnaire. Variables related to infant nutrition were collected, including breastfeeding and

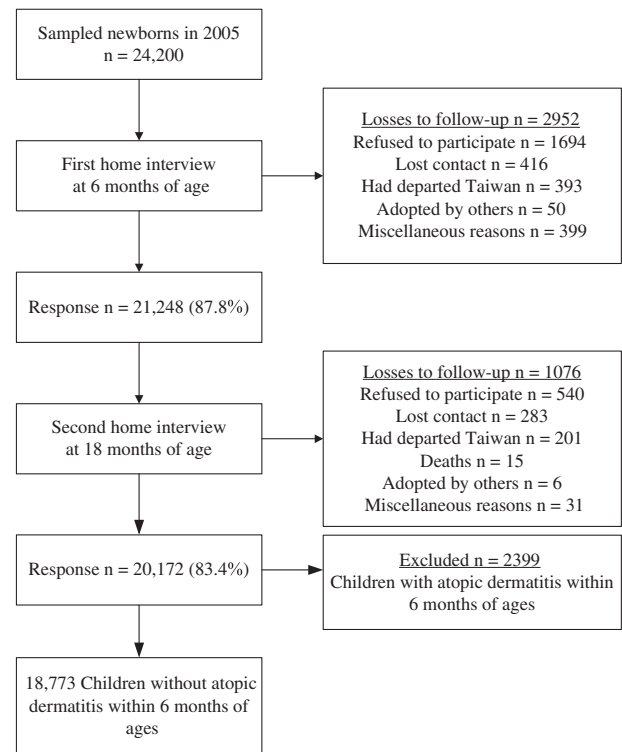


Fig. 1. Process of data collection.

solid food. The initiation and duration of breastfeeding were measured. Solids feeding was defined as the infant receiving any solid food (e.g. fruit mash, porridge, or dairy products), and data on the start and kinds of feeding were collected.

Outcome measurements

Information about AD was obtained in the 6-month and 18-month questionnaires. The main outcome measure was a physician's diagnosis of AD within 6 and 18 months according to the parent reports. Considering reverse causality, we excluded children with AD in the first 6 months of life, thus finally analyzed those without AD.

Definitions of confounders

The population of mothers and fathers were grouped by age: 19 yr old and below, 20–34, and 35 or above. Their educational levels were stratified into three groups: university and college or above, senior high school, junior high school or below. The allergic history of the parents and maternal smoking during pregnancy were also measured. Variables related to the infants included gender, birth order (grouped into one, two, and three or more), birth weight, and

gestational age. Environmental risk factors included place of residence (categorized as urban, main street of a rural area, and rural area), maternal smoking during pregnancy, passive smoking by the pregnant women, and mold spots, a carpet, or a pet in the home.

Statistical analysis

A chi-square test was performed to assess the difference in basic characteristics and potential risk factors of AD in groups with or without AD between 6 and 18 months of life. Multiple logistic regressions were performed to estimate odds ratios (ORs) and their 95% confidence intervals (CIs) of AD after adjusting for the potential confounding effects of parents' age, education, and allergic history; gender, birth order, birth weight, gestational age of the infant; place of residence, maternal smoking during pregnancy, exposure to passive smoking by the pregnant women, and mold spots, a carpet, or a pet in home. The statistical analysis was performed using SPSS for Windows, Release 11.0 (SPSS Inc: Chicago, USA).

Results

The characteristics of the children we interviewed without AD in the first 6 months of life and the risk factors are summarized in Tables 1 and 2. Most of the parents were in the category of 20–34 yr old, and those with a university education or above predominated. About half of the mothers were primiparous (50.2%), and 51.9% of the infants were boys. The prevalence of low birth weight and preterm delivery was 6.9% and 8.4%, respectively. A history of allergic disease was found in 30.1% of parents. Most of children were breastfed within 1 month (26.9%), and 85.5% were introduced to solid food between 4 and 6 months old. Most of the families resided in urban areas (46.7%). The families that had mold spots, a carpet, or a pet in the home was 35.5%, 6.0%, and 74.6%, respectively. The percentage of women who smoked during pregnancy was 3.5 and 60.9% pregnant women were exposed to passive smoking.

After adjustment for potential confounders (parental age, education, allergic history, maternal smoking during pregnancy, residence, birth order, gender of infants, birth weight, gestational age, passive smoking by pregnant women, mold spots, carpets, or pets in the home), a solid result showed that the increased duration of breastfeeding seemed to increase the risk of children with AD at 18 months [with none as the refer-

Table 1. Characteristics of the study subjects

Characteristics	N (%)	Physician diagnosed AD between 6 and 18 months of life		
		Yes	No	p-Value
Total	18,773 (100.0)	1050 (5.6)	17,723 (94.4)	
Maternal				
Age (yr)				
≤ 19	391 (2.1)	11 (1.0)	380 (2.1)	0.020
20–34	16,054 (85.5)	893 (85.0)	15,161 (85.5)	
≥35	2328 (12.4)	146 (13.9)	2182 (12.3)	
Education				
Junior high school–	2827 (15.1)	76 (7.2)	2751 (15.5)	<0.001
Senior high school	7609 (40.5)	337 (35.9)	7232 (40.8)	
University+	8337 (44.4)	597 (56.9)	7740 (43.7)	
Paternal				
Age (yr)				
≤ 19	34 (0.2)	1 (0.1)	33 (0.2)	0.226
20–34	12,619 (67.2)	683 (65.0)	11,936 (67.3)	
≥35	6120 (32.6)	366 (34.9)	5754 (32.5)	
Education				
Junior high school–	2621 (14.0)	75 (7.1)	2546 (14.4)	<0.001
Senior high school	7700 (41.0)	378 (36.0)	7322 (41.3)	
University+	8452 (45.0)	597 (56.9)	7855 (44.3)	
Infant				
Male	9735 (51.9)	587 (55.9)	9148 (51.6)	0.007
Birth order				
1	9420 (50.2)	543 (51.7)	8877 (50.1)	0.031
2	7239 (38.6)	415 (39.5)	6824 (38.5)	
3+	2114 (11.3)	92 (8.8)	2022 (11.4)	
Low birth weight	1294 (6.9)	69 (6.6)	1225 (6.9)	0.672
Preterm delivery	1573 (8.4)	87 (8.3)	1486 (8.4)	0.911

Values in parentheses are percentages. AD, atopic dermatitis.

ence, adjusted odds ratios (adj ORs) with 95% confidence intervals (CIs): 1.25 (1.00–1.56), 1.37 (1.08–1.74), 1.47 (1.17–1.8), 1.44 (1.11–1.87), and 1.49 (1.15–1.93) for breastfeeding duration within 1, 2, 6, 12, and more than 12 months, respectively]. However, no significant effect was found for the different timings of solid food introduction on the risk of AD [<4 months as the reference, adj ORs with 95% CIs: 1.11 (0.80–1.53), and 1.08 (0.74–1.57) for solid food introduction at age 4–6, and beyond 6 months, respectively] (Table 3).

Considering the effect of maternal education on breastfeeding practice and AD reported, we analyzed odds ratio of AD beyond 6 months by maternal educational level in Table 4. After adjustment for potential confounders, prolonging breastfeeding did not show the protective effect on AD among 18 months children, even significantly increased the risk of AD in children whose mothers had high educational level.

Discussion

This population-based, prospective birth cohort study showed longer duration of breastfeeding

Table 2. Risk factors of atopic dermatitis (AD)

Risk factors	N (%)	Physician diagnosed AD between 6 and 18 months of life		p-Value
		Yes	No	
Total	18,773 (100.0)	1050 (5.6)	17,723 (94.4)	
Duration of breastfeeding				
None	3127 (16.7)	123 (11.7)	3004 (16.9)	<0.001
≤ 1 month	5059 (26.9)	266 (25.3)	4793 (27.0)	
≤ 2 months	3004 (16.0)	175 (16.7)	2829 (16.0)	
≤ 6 months	3660 (19.5)	232 (22.1)	3428 (19.3)	
≤ 12 months	1960 (10.4)	124 (11.8)	1836 (10.4)	
>12 months	1963 (10.5)	130 (12.4)	1833 (10.3)	
Time of solids introduction				
<4 months	847 (4.5)	41 (3.9)	806 (4.5)	0.593
4–6 months	16,045 (85.5)	906 (86.3)	15,139 (85.4)	
>6 months	1881 (10.0)	103 (9.8)	1778 (10.0)	
Allergic history of parents	5646 (30.1)	460 (43.8)	5186 (29.3)	<0.001
Place of residence				
Urban area	8771 (46.7)	572 (54.5)	8199 (46.3)	<0.001
Main street of rural area	5215 (27.8)	273 (26.0)	4942 (27.9)	
Rural area	4787 (25.5)	205 (19.5)	4582 (25.9)	
Maternal smoking during pregnancy	652 (3.5)	34 (3.2)	618 (3.5)	0.669
Passive smoking by the pregnant women in the home (days per wk)				
No	7322 (39.1)	434 (41.3)	6888 (38.9)	0.132
<3	6412 (34.2)	366 (34.9)	6046 (34.2)	
3–5	1259 (6.7)	58 (5.5)	1201 (6.8)	
6–7	3751 (20.0)	192 (18.3)	3559 (20.1)	
Mold spots in the home	6672 (35.5)	435 (41.4)	6237 (35.2)	<0.001
Carpet in the home	1131 (6.0)	76 (7.2)	1055 (6.0)	0.089
Pet in the home	14,011 (74.6)	804 (76.6)	13,207 (74.5)	0.138

Values in parentheses are percentages.

and a delayed introduction of solids did not prevent the AD by age 18 months when reverse causality was considered.

Some studies on infant diet and AD diseases showed possible distortion because of reverse causality (10, 17, 26). We thus finally recruited the children without AD in the first 6 months to prevent the effect of the reverse causality (Table 3). The results showed that the long duration of breastfeeding seemed to be the risk factor for children with AD at 18 months. Furthermore, the results showed that a delayed introduction of solids did not protect children against AD at 18 months of age. Besides, it is known that parental compliance to guidelines of infant feeding practices is better with an increased educational level. Thus, we analyzed the odds ratio of AD by maternal educational level (Table 4). The result about the trend of prolonged breastfeeding on AD is similar to the former results in the overall children (Table 3). It showed that longer duration of breastfeeding and a delayed introduction of solids did not prevent AD by age 18 months, and even increase the risk of AD in the subgroup of mothers with high educational level.

One potential limitation was worthy of consideration. The outcome of our study was limited by the use of questionnaire for ascertaining AD, physician diagnosed AD reported by parents, which might not be as specific as the standard diagnostic criteria by a dermatologist. Nevertheless, one study showed that maternal report of doctor diagnosed AD was highly concordant with clinical examination (27), and thus a formal clinical examination does not seem to be absolutely necessary. Furthermore, we determined the prevalence rate of parent-reported, physician-diagnosed AD during the first 18 months to be 2449 cases (12.1%) among 20,172 children (data not shown), in close agreement with other studies

Table 3. Odds ratio of atopic dermatitis (AD) from 6 to 18 months

Factors	N (%)	Prevalence of AD from 6 to 18 months	Crude odds ratio (95% CIs)	p-Value	Adjusted odds ratio* (95% CIs)	p-Value
Total	18,773 (100.0)	1050 (5.6)				
Duration of breastfeeding		p < 0.001		<0.001		0.012
None	3127 (16.7)	123 (3.9)	1.00 (Reference)		1.00 (Reference)	
≤ 1 month	5059 (26.9)	266 (5.3)	1.36 (1.09, 1.69)	0.006	1.25 (1.00, 1.56)	0.049
≤ 2 months	3004 (16.0)	175 (5.8)	1.51 (1.19, 1.91)	0.001	1.37 (1.08, 1.74)	0.009
≤ 6 months	3660 (19.5)	232 (6.3)	1.65 (1.32, 2.07)	<0.001	1.47 (1.17, 1.84)	0.001
≤ 12 months	1960 (10.4)	124 (6.3)	1.65 (1.28, 2.13)	<0.001	1.44 (1.11, 1.87)	0.006
>12 months	1963 (10.5)	130 (6.6)	1.73 (1.35, 2.23)	<0.001	1.49 (1.15, 1.93)	0.003
Time of solids introduction		p = 0.593		0.594		0.810
<4 months	847 (4.5)	41 (4.8)	1.00 (Reference)		1.00 (Reference)	
4–6 months	16,045 (85.5)	906 (5.6)	1.18 (0.85, 1.62)	0.321	1.11 (0.80, 1.53)	0.539
>6 months	1881 (10.0)	103 (5.5)	1.14 (0.79, 1.65)	0.493	1.08 (0.74, 1.57)	0.698

CI, confidence interval.

*Adjusted for gender, birth order, birth weight, and gestational age of infants; parents' age, parents' education, parents' allergic history, place of residence, maternal smoking during pregnancy, passive smoking by the pregnant women in the home, and mold spots, carpet, and pet in the home.

Table 4. Odds ratio of atopic dermatitis (AD) from 6 to 18 months by maternal educational level

Factors	N (%)	Prevalence of AD from 6 to 18 months	Crude odds ratio (95% CIs)	p-Value	Adjusted odds ratio* (95% CIs)	p-Value
Maternal education: senior high school-						
Total	10,436 (100.0)	453 (4.3)				
Duration of breastfeeding		p = 0.643		0.644		0.786
None	2355 (22.6)	88 (3.7)	1.00 (Reference)		1.00 (Reference)	
≤ 1 month	3090 (29.6)	143 (4.6)	1.25 (0.95, 1.64)	0.107	1.13 (0.86, 1.49)	0.375
≤ 2 months	1542 (14.8)	66 (4.3)	1.15 (0.83, 1.60)	0.395	1.06 (0.76, 1.47)	0.746
≤ 6 months	1710 (16.4)	74 (4.3)	1.17 (0.85, 1.60)	0.342	1.08 (0.78, 1.48)	0.660
≤ 12 months	854 (8.2)	39 (4.6)	1.23 (0.84, 1.81)	0.287	1.18 (0.80, 1.74)	0.407
>12 months	885 (8.5)	43 (4.9)	1.32 (0.91, 1.91)	0.150	1.28 (0.88, 1.87)	0.198
Time of solids introduction		p = 0.019		0.020		0.056
<4 months	538 (5.2)	21 (3.9)	1.00 (Reference)		1.00 (Reference)	
4–6 months	8917 (85.4)	406 (4.6)	1.17 (0.75, 1.84)	0.481	1.19 (0.76, 1.87)	0.448
>6 months	981 (9.4)	26 (2.7)	0.67 (0.37, 1.20)	0.180	0.73 (0.40, 1.31)	0.292
Maternal education: University+						
Total	8337 (100.0)	597 (7.2)				
Duration of breastfeeding		p = 0.010		0.011		0.107
None	772 (9.3)	35 (4.5)	1.00 (Reference)		1.00 (Reference)	
≤ 1 month	1969 (23.6)	123 (6.2)	1.40 (0.96, 2.06)	0.085	1.29 (0.87, 1.89)	0.206
≤ 2 months	1462 (17.5)	109 (7.5)	1.70 (1.15, 2.51)	0.008	1.54 (1.04, 2.29)	0.032
≤ 6 months	1950 (23.4)	158 (8.1)	1.86 (1.28, 2.70)	0.001	1.65 (1.13, 2.41)	0.010
≤ 12 months	1106 (13.3)	85 (7.7)	1.75 (1.17, 2.63)	0.007	1.53 (1.02, 2.31)	0.042
>12 months	1078 (12.9)	87 (8.1)	1.85 (1.24, 2.77)	0.003	1.51 (1.00, 2.28)	0.049
Time of solids introduction		p = 0.214		0.215		0.378
<4 months	309 (3.7)	20 (6.5)	1.00 (Reference)		1.00 (Reference)	
4–6 months	7128 (85.5)	500 (7.0)	1.09 (0.69, 1.73)	0.715	0.93 (0.58, 1.49)	0.770
>6 months	900 (10.8)	77 (8.6)	1.35 (0.81, 2.25)	0.246	1.12 (0.66, 1.88)	0.673

CI, confidence interval.

*Adjusted for gender, birth order, birth weight, and gestational age of infants; parents' age, paternal education, parents' allergic history, place of residence, maternal smoking during pregnancy, passive smoking by the pregnant women in the home, and mold spots, carpet, and pet in the home.

in Japan (28) and Germany (29), which showed 12.4% and 13.4% of children, respectively, developed AD in the first year of life.

Another limitation of this study is that we did not have detailed information on the frequency or quantity of water and specific solids fed to infants, which are difficult to measure in a large survey that covers a considerable period of time. However, further examining when solids are first fed and what foods are used will provide more information of interest to test our hypothesis.

In the present study, prolonged breastfeeding did not seem to prevent the child's AD at 18 months, but instead, to raise the risk. This result contradicted some results on the benefits of breastfeeding (5–7), but supported some studies showing the risks (9, 16). Most of the existing studies focus on the effect of exclusive breastfeeding on the child's allergy diseases (6, 13, 14), but this study included mixed and exclusive breastfeeding. The practice of breastfeeding in Taiwan is rarely follows the WHO definition of exclusive breastfeeding, which refers to the practice of feeding only breast milk, without other liquids or any solids. Consequently, we could not adequately measure the effect of the

exclusive breastfeeding on AD, so we cannot totally dismiss the supposed benefits of exclusive breastfeeding with regard to AD.

Atopic dermatitis is a chronic, inflammatory, genetic-related skin disease, and most cases present in the first year of life with skin abnormalities. The real cause is unknown, but the hygienic theory and the development of oral tolerance (30) are promising candidates. The results of our study showed that children fed solids beyond 6 months of age did not have the protection against AD of children fed solids at a younger age. The probable biologic explanation is that the introduction of solid foods exposes the child to novel food antigens and affects the gut flora, helping children with developing oral tolerance to reduce allergic reaction.

Our results are consistent with studies which showed that postponing the introduction of solids beyond the sixth month was not protective in relation to AD at 2 and 6 yr of age (15, 17), or asthma (12) and eczema at preschool age (21). In this study, the majority of solids provided before 6 months were rice powder (64.5%), rice porridge (43.9%), cereal porridge (30.0%), and fruit mash (47.2%) (data not shown). This result

showed that current feeding guidelines, which recommend delaying the introduction of solids until 6 months for the prevention of allergies, need to be reconsidered to take account of not only the time of introduction, but also the kinds of solid food.

Other studies showed that family history of AD, environmental factors, or characteristics of infants were the risk factors for developing AD (1–3). In the present study, living in urban areas (adj ORs 1.43; 95% CIs 1.69–1.20), having mold spots in the home (adj ORs 1.32; 95% CIs 1.16–1.50), and being girl (adj ORs 1.22; 95% CIs 1.07–1.38), were the significant risk factors (data not shown). Parental history of atopy, a carpet, or a pet in the home, and other potential confounders that were measured were not significantly related to the likelihood of infantile AD at 18 months of life.

This prospective population-based birth cohort study was funded and conducted by the Bureau of Health Promotion, Department of Health, Taiwan National Birth Registration data and home interview data were collected, as such multiresource data offer increased accuracy and more complete information on factors of interest. Despite incomplete data among 17% subjects and significant differences with regard to low birth weight and preterm deliveries, the basic characteristics between the respondents and the non-respondents were similar, although there were some statistically significant differences because of the effect of the large sample sizes (data not shown). The reason for no response appeared to be unrelated to our measurement outcomes. To reduce the recall bias, we only recruited subjects with a completed interview within 6 and 18 months after their deliveries. We measured whether or not they ever breastfed and the duration until they were interviewed. In addition, the home interviews using a structured questionnaire and conducted by well-trained interviewers were effective in minimizing the recall bias. Furthermore, most of the study was focused on one nutritional or environmental effect separately, and we measured and controlled for potential environmental factors.

In conclusion, our study showed there is no evidence of a protective effect of prolonged breastfeeding and a delayed introduction of solids against AD among children at age 18 months and may even be a risk factor of AD.

Acknowledgments

This study was based on the data from the Taiwan Birth Cohort Study Database and supported by grants BHP-PHRC-92-4, DOH93-HP-1702, DOH94-HP-1802, DOH95-

HP-1802, and DOH96-HP-1702 from the Bureau of Health Promotion, Department of Health, Taiwan. The views expressed herein are the authors' own. We thank the enduring support and assistance from Professor Tung-Liang Chiang, Institute of Health Policy and Management, National Taiwan University College of Public Health, Taipei, Taiwan; Professor Yueliang Leon Guo, Department of Environmental and Occupational Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine; Professor Meng-Chin Lee, Institute of Medicine, Professor Hui-Sheng Lin, School of Public Health, Chung Shan Medical University, Taichung, Taiwan; and Professor Bih-Ching Shu, Institute of Allied Health Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

References

1. KARINO S, OKUDA T, UEHARA Y, TOYO-OKA T. Breastfeeding and prevalence of allergic diseases in Japanese university students. *Ann Allergy Asthma Immunol* 2008; 101: 153–9.
2. ZEIGER RS, HELLER S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995; 95: 1179–90.
3. ILLI S, VON MUTIUS E, LAU S, et al. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001; 108: 709–14.
4. SNIJDERS BEP, THIJIS C, KUMMELING I, PENDERS J, VAN DEN BRANDT PA. Breastfeeding and infant eczema in the first 2 year of life in the KOALA birth cohort study: a risk period-specific analysis. *Pediatrics* 2007; 119: 137–41.
5. SNIJDERS BEP, THIJIS C, DAGNELIE PC, et al. Breastfeeding duration and infant atopic manifestations, by maternal allergic status, in the first 2 year of life (KOALA study). *J Pediatr* 2007; 151: 347–51.
6. SCHOETAZU A, FILIPIAN-PITTOFF B, KOLETZKO S, et al. Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age. *Pediatr Allergy Immunol* 2002; 13: 234–42.
7. SAARINEN UM, KAJOSAARI M, BACKMAN A, SIIMES MA. Prolonged breastfeeding as prophylaxis for atopic diseases. *Lancet* 1979; 2: 163–6.
8. WHO. Fifty-Fourth World Health Assembly. WHA54.2. Agenda Item 13.1. Infant and Young Child Nutrition. Geneva, Switzerland: World Health Organization, 2004.
9. SEARS MR, GREENE JM, WILLAN AR, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002; 360: 901–7.
10. CHULADA PC, ARBES SJ, DUNSON D, ZELDIN DC. Breast-feeding and the prevalence of asthma and wheeze in children: analyses from the third national health and nutrition examination survey, 1988–1994. *J Allergy Clin Immunol* 2003; 111: 328–36.
11. LAUBEREAU B, BROCKOW I, ZIRNGIBL A, et al. Effect of breastfeeding on the development of atopic dermatitis during the first 3 years of life: results from the GINI-birth cohort study. *J Pediatr* 2004; 144: 602–7.
12. LUDVIGSSON JF, MOSTROM M, LUDVIGSSON J, DUCHEN K. Exclusive breastfeeding and risk of atopic dermatitis

- in some 8,300 infants. *Pediatr Allergy Immunol* 2005; 16: 208–10.
13. PESONEN M, KALLO MJT, RANKI A, SIIMES MA. Prolonged exclusive breastfeeding is associated with increased atopic dermatitis: a prospective follow-up study of unselected healthy newborns from birth to age 20 years. *Clin Exp Allergy* 2006; 36: 1011–8.
14. KRAMER MS, MATUSH L, VANILOVICH I, et al. Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial. *BMJ* 2007; 335: 815–20.
15. SARIACHVILI M, DROSTE J, DOM S, et al. Is breast feeding a risk factors for eczema during the first year of life? *Pediatr Allergy Immunol* 2007; 18: 410–7.
16. MIYAKE Y, TANAKA K, SASAKI S, et al. Breastfeeding and atopic eczema in Japanese infants: the Osaka maternal and child health study. *Pediatr Allergy Immunol* 2009; 20: 234–41.
17. ZUTAVERN A, BROCKOW I, SCHAAF B, et al. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. *Pediatrics* 2008; 121: e44–52.
18. FILIPIAK B, ZUTAVERN A, KOLETZKO S, et al. Solid food introduction in relation to eczema: results from a four-year prospective birth cohort study. *J Pediatr* 2007; 151: 352–8.
19. ANDREASYAN K, PONSONBY A-L, DWYER T, DEAR K, COCHRANE J. Infant feeding and childhood atopy: does early introduction of non-milk fluids matter? *Pediatr Allergy Immunol* 2007; 18: 250–7.
20. ZUTAVERN A, BROCKOW I, SCHAAF B, et al. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. *Pediatrics* 2006; 117: 401–11.
21. ZUTAVERN A, VON MUTIUS E, HARRIS J, et al. The introduction of solids in relation to asthma and eczema. *Arch Dis Child* 2004; 89: 303–8.
22. BERGMANN RL, DIEPGEN TL, KUSS O, et al. Breast-feeding duration is a risk factor for atopic eczema. *Clin Exp Allergy* 2002; 32: 205–9.
23. YANG YW, TSAI CL, LU CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. *Br J Dermatol* 2009; 161: 373–83.
24. MIHRSHAH S, AMPON R, WEBB K, et al. The association between infant feeding practices and subsequent atopy among children with a family history of asthma. *Clin Exp Allergy* 2007; 37: 671–9.
25. FREDRIKSSON P, JAAKKOLA N, JAAKKOLA JJ. Breast-feeding and childhood asthma: a six-year population-based cohort study. *BMC Pediatr* 2007; 7: 39.
26. KHAKOO GA, LACK G. Introduction of solids to the infant diet. *Arch Dis Child* 2004; 89: 295.
27. LAUGHTER D, ISTVAN JA, TOFTE SJ, HANIFIN JM. The prevalence of atopic dermatitis in Oregon school children. *J Am Acad Dermatol* 2000; 43: 649–55.
28. SUGIYAMA M, ARAKAWA H, OZAWA K, et al. Early-life risk factors for occurrence of atopic dermatitis during the first year. *Pediatrics* 2007; 119: 716–23.
29. ILLI S, VON MUTIUS E, LAU S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004; 113: 925–31.
30. CALDER PC, KRAUSS-ETSCHMANN S, DE JONG EC, et al. Early nutrition and immunity- progress and perspectives. *Br J Nutr* 2006; 96: 774–90.