ORIGINAL

Relationship between physique and food avoidance in infants : A study conducted in a community setting in Japan

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Abstract : The relationship between food avoidance during infancy and the growth of Japanese infants in a community health setting has not been well evaluated. In order to assess the growth of infants who avoided either of the three major allergen foods in Japan, eggs, milk or wheat, we employed the results of 4 physical checkups recorded in maternity passbooks and administrated a questionnaire on allergic diseases, height and weight at birth to the guardians of 1,132 infants at the age of 3.5 years. Data was obtained from 890 subjects (78.6%) and 662 subjects (58.5%) who met the inclusion criteria were analyzed. The height, weight and body mass index percentile scores of each subject were calculated. Subjects who avoided either of the three foods at 3.5 years had lower weight percentile scores at 1.5 years, lower height and weight percentile scores at 3.5 years, and lower weight growth rates, compared with the subjects who did not avoid any of the three foods at 3.5 years (*P* =0.02, 0.03, 0.03, 0.01). The results suggested that there was a negative relationship between physique and food avoidance in infants, and that physical and nutritional assessments are important for food avoiders. J. Med. Invest. 62 : 62-67, February, 2015

Keywords **:** *community health, food avoidance, growth, infancy, maternity passbook*

INTRODUCTION

Recently, the prevalence of food allergies has been increasing among Japanese children (1, 2). The estimated prevalence of food allergies in Japan is 5-10% among infants and 1-2% among schoolchildren (3), and the prevalence of food allergies is higher among children than it is in adults (4). It is generally considered that the avoidance of the relevant food allergens is the most important factor in regard to effective management of food allergies.

Atopic dermatitis (AD) is an inflammatory, chronic relapsing dermatitis. In Japan, the average national prevalence of AD was 13.2% in 3-year-old children (5). Although the pathogenesis of AD is still unknown, it is considered a multifactorial disease triggered by the interaction of genetic and environmental factors (food, airborne allergens, and infectious agents) (6). Fiocchi *et al.* (7) reported that diagnostic evaluation of food allergies should be performed in all children with AD, particularly in younger children and those with severe forms of the disease. The results of several previous studies (8-10) have shown that the symptoms of AD improved when specific food allergens were eliminated from the patient's diet. Therapeutic elimination diets have been shown to reduce the symptoms of food allergies and AD (4, 11), but they also could be responsible for nutrient deficiencies and failure to thrive (12), especially when a significant number of foods were avoided. The results of several studies (13-15) suggested that food avoidance in children with food allergy disturbed growth. These previous studies (14, 15) were mainly cross-sectional, and only one longitudinal study (13) was conducted.

In the United States, food allergies usually occur in infancy as an immediate-type allergy to eggs, milk, peanuts or soy (16). Previous studies (13-15) were performed mainly in Europe and the U.S. in clinical settings. In Japan, three major foods (eggs, milk and wheat) have been shown to be frequent allergens for immediate-type allergic reactions in infancy (17). In a school health setting, Mukaida *et al.* (18) reported that food avoiders with allergic disease in infancy had a significantly lower weight at school age, compared with non-food avoiders, in a study adjusted for several confounding factors, such as age, sex, birth order, birth weight, and so on. No research has been conducted on the relationship between food avoidance and physique in Japanese infants in a community health setting.

In the Japanese maternal and child health system, physical checkups for children are conducted at the ages of 4 months, 10 months, 1.5 years and 3.5 years old. At that time, medical staff measure the height and weight of the infant according to a standard technique. The infant's height, weight and measurement date are recorded in maternity passbooks. Thus, the guardians can check their infant's physique on the growth curve in their maternity passbooks by themselves.

In order to perform proper food avoidance, an evaluation of the children's physique during food avoidance is very important. The aim of this study was to assess the rates of Japanese infants who avoided food and the growth of infants who avoided food during infancy (age 4 months to 3.5 years) from maternity passbooks in a community health setting, especially concerning the three major allergen foods, eggs, milk and wheat.

METHODS

Study subjects

Figure 1 shows the outline of our study design. This was a retrospective longitudinal study. From December 2010 through March 2012, the subjects of this study were selected from 1,132 infants (age 3.5 years) who participated in physical checkups at regional

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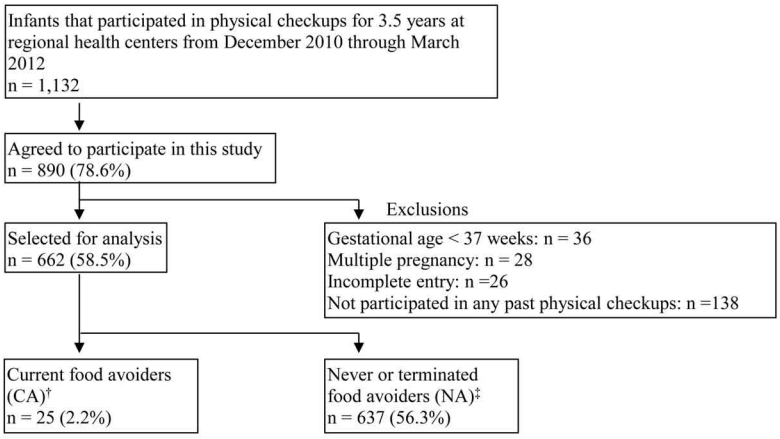

Figure 1. Study design and subjects
† The CA group was defined as those who continued the avoidance of either eggs, milk or wheat at 3.5 years.
‡ The NA group was defined as subjects who had never avoided either eggs, milk or wheat, or who terminated the avoidance of either eggs, milk or wheat at 3.5 years.

health centers in Kyoto, Japan. The participation rate was 90.2%. A questionnaire dealing with allergic diseases and food avoidance (eggs, milk and wheat) were distributed to the guardians. Consent for participation in the study was included as an item agreed upon by turning in the questionnaire, and 890 guardians participated (response rate, 78.6%). We excluded subjects due to the following criteria, gestational age less than 36 weeks, multiple pregnancy, incomplete entries, and non-participation in any past physical checkups. There were 662 infants (58.5% of the total) accepted as final subjects of this study. This study was approved by the Ethics Committee of Kyoto Prefectural University (July 23, 2010. No. 31).

Examination methods

The questionnaire included the infant's birth year and month, sex, items related to the avoidance of eggs, milk and wheat and the related reason, time period and level. On the questionnaire, the guardians were asked to indicate the reason for the food avoidance from the following items : Immediate allergic symptoms, such as skin or respiratory symptoms within 1 to 2 hours after ingesting that food, positive allergic test results but the food was never eaten, positive allergic test results but no problem after eating that food, or other reasons. We included a question about whether or not the subject had ever been diagnosed for allergic diseases, including bronchial asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, food allergy, or no allergic disease. In the questionnaire, the guardians were asked to indicate the height, weight and measurement date of their infant according to the records of maternity passbooks. The participants were asked to indicate their lactation methods during infancy from the following categories : mainly breastfeeding, breastfeeding and formula milk, or mainly formula milk.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Based on the data, age, sex adjusted height, weight and BMI percentiles were calculated according to the Children's Health Management Program, Murata *et al.* Tokyo, Japan (19). It is well known that the distributions of the height or the weight are different by sex. Moreover, the age of each subject at the physical checkups was not exactly the same. Therefore, we used a percentile score for comparing the physical anthropometric data between the infant's statuses. The height and weight growth rates were calculated using the data at 1.5 years, subtracting the data at 4 months, divided by the data at 4 months, and multiplying by 100. In the same way, the height and weight growth rates were calculated using the data at 3.5 years, subtracting the data at 1.5 years, divided by the data at 1.5 months, and multiplying by 100.

Subgroups of the subjects

The CA group was defined as subjects who continued food avoidance of either eggs, milk or wheat at 3.5 years. The NA group was defined as subjects who were not avoiding eggs, milk or wheat at 3.5 years. This group contained both subjects who had never avoided any of the three foods and those who terminated the avoidance.

Statistical Analyses

We summarized the quantitative data into median and quartile values. The medians of continuous variables were compared using the Mann-Whitney U-test (for 2 groups) and the Kruskal-Wallis test (for 4 groups). The Chi-square test was used for proportional comparisons. Missing values were excluded in each analysis. The significance level employed was $P<0.05$. Statistical analyses were performed by using the software package SPSS version 22.0 (U.S., IBM Corporation, 2013).

RESULTS

A total of 662 subjects (315 boys, 347 girls) were selected for analysis. Table 1 shows the characteristics of the children compared by sex. Among the subjects, 25 infants (3.8%, Boys 4.4%, Girls 3.2%) avoided at least one of the three foods at 3.5 years. There was no significant difference shown in the number of food avoiders, when compared by sex. There were 128 subjects who had been diagnosed for an allergic disease, including bronchial asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis and food allergy. The number of those who had been diagnosed with allergic diseases was higher in boys (n=71, 22.5%) than in girls (n=57, 16.4%) ($P=0.05$). The number of those who had been diagnosed with allergic rhinitis was significantly higher in boys than in girls ($P=0.03$). There were no other significant differences shown in the feeding during infancy or at the start of baby food feeding, compared by sex.

Table 2 shows the height, weight and BMI percentile score at 3.5 years, compared by the infant's birth status and allergic diseases. Lower height and weight percentile scores ($P=0.03$, 0.03) were shown in the food avoiders, in the 3.5 years group. Lower

BMI percentile scores (P=0.05) were shown in the food allergy group.

In the CA group, the number of subjects who avoided eggs, milk or wheat at 3.5 years were 22 (88%), 8 (32%) and 3 (12%), respectively. Five infants avoided eggs and milk, and one infant avoided eggs and wheat. One infant avoided eggs, milk and wheat at 3.5 years. The percentages of subjects who responded with the reason for food avoidance at 3.5 years as immediate allergic symptoms for eggs, milk and wheat were 13 (59%), 6 (75%), and 3 (100%), respectively.

Table 3 shows gestational weeks, birth weight and physical percentile scores at the four physical checkups in the CA and NA

Table 1. Characteristics of the study subjects compared by sex

	All n=662		Boys n=315		Girls n=347		P value
Birth weight (median (g), 1st, 3rd quartile)	3056	2820, 3306	3116	2878, 3360	3000	2794, 3260	< 0.001†
< 2500 g (n, %)	29	4.4%	9	2.9%	20	5.8%	
2500～< 4000 g (n, %)	628	94.9%	302	95.9%	326	93.9%	0.07‡
≥ 4000 g (n, %)	5	0.8%	4	1.3%	1	0.3%	
Feeding at infant (n, %)							
breastfeeding	385	58.6%	179	57.4%	206	59.7%	
breastfeeding and formula milk	231	35.2%	116	37.2%	115	33.3%	0.49‡
formula milk	41	6.2%	17	5.4%	24	7.0%	
Start of baby food (n, %)							
4 months before	27	4.2%	16	5.2%	11	3.3%	
5-6 months	516	80.6%	250	80.9%	266	80.4%	0.38‡
after 7 months	97	15.2%	43	13.9%	54	16.3%	
Food avoider at 3.5 years§ (n, %)	25	3.8%	14	4.4%	11	3.2%	0.39‡
Allergic diseases (n, %)	128	19.3%	71	22.5%	57	16.4%	0.05‡
Food allergy	46	6.9%	22	7.0%	24	6.9%	1.00‡
Atopic dermatitis	61	9.2%	31	9.8%	30	8.6%	0.69‡
Allergic rhinitis	28	4.2%	19	6.0%	9	2.6%	0.03‡
Asthma	22	3.3%	15	4.8%	7	2.0%	0.05‡
Allergic conjunctivitis	8	1.2%	5	1.6%	3	0.9%	0.49‡

† Mann-Whitney U test : Anthropometric data compared by sex.
‡ Chi-square test : Basic characteristics compared by sex.
§ Food avoiders was defined as those who continued the avoidance of either eggs, milk or wheat at 3.5 years.
BMI, body mass index
Data are presented as median (1st, 3rd quartile) or n (%).

Table 2. Comparison of height, weight and BMI percentile score at 3.5 years by infants status

			Height percentile score at 3.5 years			Weight percentile score at 3.5 years			BMI percentile score at 3.5 years		
		n	median	1st, 3rd quartile	P value	median	1st, 3rd quartile	P value	median	1st, 3rd quartile	P value
Sex	Boys	315	44.1	19.9, 63.1	0.02†	51.1	29.6, 69.6	0.49†	61.0	39.7, 81.7	0.31†
	Girls	347	50.2	24.4, 75.5		53.0	30.1, 73.1		59.4	37.7, 76.8	
Birth weight	≤ 2820g	168	34.6	11.8, 56.3	< 0.001‡	39.5	21.8, 59.9	< 0.001‡	52.1	32.1, 75.3	< 0.001‡
	2821～3056 g	166	39.2	19.7, 66.0		50.6	26.8, 67.5		57.7	39.5, 74.6	
	3057～3306 g	165	52.0	25.5, 74.7		53.0	36.8, 72.2		61.0	38.9, 80.3	
	≥ 3307 g	163	59.1	36.1, 78.8		65.8	46.5, 84.1		69.6	45.9, 85.1	
Gestational age (week)	≤ 39 weeks	387	42.9	22.2, 67.0	0.02†	51.2	30.5, 71.3	0.64†	62.3	41.5, 81.7	0.04†
	≥ 40 weeks	275	52.0	23.0, 74.7		53.0	29.4, 73.0		56.4	34.4, 77.2	
Food avoider at 3.5 years	Yes (CA)	25	29.9	20.1, 46.1	0.03†	44.8	18.9, 58.3	0.03†	50.2	29.9, 75.0	0.23†
	No (NA)	637	48.0	22.4, 69.8		52.4	30.5,72.6		60.4	39.7, 79.5	
Allergic disease	Yes	128	49.2	23.6, 70.5	0.45†	52.6	31.6, 71.2	0.73†	60.5	36.0, 81.4	0.69†
	No	534	46.1	21.7, 69.3		51.7	29.5, 71.9		60.3	39.9, 79.0	
Asthma	Yes	22	49.7	14.9, 67.9	0.66†	55.6	35.4, 75.7	0.49†	65.4	56.6, 84.1	0.07†
	No	640	47.0	22.6, 69.5		51.5	29.7, 71.8		59.6	37.9, 79.1	
Atopic dermatitis	Yes	61	47.0	21.4, 80.5	0.79†	53.2	27.1, 78.6	0.75†	63.5	33.2, 83.2	0.95†
	No	601	46.9	22.3, 69.2		51.2	30.3, 71.6		60.1	39.9, 79.0	
Allergic rhinitis	Yes	28	49.8	26.0, 63.1	0.75†	43.5	26.2, 72.9	0.45†	58.6	25.9, 76.4	0.14†
	No	634	46.7	22.1, 69.7		52.2	30.5, 71.8		60.5	40.0, 79.6	
Allergic conjunctivitis	Yes	8	55.2	25.0, 81.5	0.42†	55.5	45.8, 78.3	0.48†	61.7	18.6, 86.9	0.91†
	No	654	46.8	22.3, 69.4		51.9	29.8, 71.8		60.3	39.2, 79.1	
Food allergy	Yes	46	37.7	23.3, 64.3	0.39†	45.9	25.9, 61.4	0.08†	47.7	33.3, 70.8	0.05†
	No	616	47.6	22.2, 69.5		53.0	30.2, 72.7		61.0	39.8, 79.8	
Immediate allergic symptoms	Yes	43	38.2	21.4, 72.3	0.53†	47.3	19.2, 65.7	0.15†	45.3	28.0, 75.0	0.08†
	No	619	47.4	22.3, 69.4		52.4	30.5, 71.9		60.7	40.0, 79.6	

† Mann-Whitney U test : Anthropometric data compared by infants status.
‡ Kruskal-Wallis test : Anthropometric data compared by infants status.
BMI, body mass index

Table 3. Comparison of height, weight and BMI percentile scores at the four physical checkups among the CA and the NA groups

	CA n=25		NA n=637		P value†
	Median	1st, 3rd quartile	Median	1st, 3rd quartile	
Gestational age (week)	39	39, 40	39	38, 40	0.81
Birth weight (g)	3064	2942, 3321	3055	2818, 3306	0.57
4 months					
Height percentile score	30.3	21.3, 54.0	40.8	19.8, 67.1	0.20
Weight percentile score	56.9	33.8, 75.6	51.0	26.0, 67.1	0.49
BMI percentile score	60.5	37.9, 84.0	53.5	26.6, 75.5	0.16
10 months					
Height percentile score	32.7	18.9, 54.3	34.2	15.1, 56.7	0.82
Weight percentile score	33.4	24.1, 62.1	43.8	21.8, 70.7	0.42
BMI percentile score	54.4	32.9, 79.4	57.4	33.6, 79.7	0.63
1.5 years					
Height percentile score	23.8	13.8, 46.4	31.6	13.3, 57.4	0.33
Weight percentile score	45.5	18.9, 54.9	53.3	29.2, 76.1	0.02
BMI percentile score	54.6	34.7, 72.9	65.7	42.9, 83.6	0.04
3.5 years					
Height percentile score	29.9	20.1, 46.1	48.0	22.4, 69.8	0.03
Weight percentile score	44.8	18.9, 58.3	52.4	30.5, 72.6	0.03
BMI percentile score	50.2	29.9, 75.0	60.4	39.7, 79.5	0.23
Height growth rate (%)					
1.5 years‡	27.6	24.8, 30.4	27.3	24.8, 30.2	0.75
3.5 years§	19.5	18.1, 20.6	20.3	18.8, 21.9	0.03
Weight growth rate (%)					
1.5 years‡	47.0	40.2, 52.6	54.1	45.3, 65.6	0.01
3.5 years§	37.7	32.1, 44.5	39.2	33.9, 45.0	0.63

† Mann-Whitney U test : Anthropometric data compared by CA and NA groups.
‡ Compared with the height or weight at 4 months.
§ Compared with the height or weight at 1.5 years.
The CA group was defined as those who continued the avoidance of either eggs, milk or wheat at 3.5 years.
The NA group was defined as subjects who had never avoided either eggs, milk or wheat, or who terminated the avoidance of either eggs, milk or wheat at 3.5 years.

groups. There were no significant differences in gestational weeks, birth weight or physical percentile scores at the 4- and 10-months checkups, when comparing the CA and the NA groups. There were significant differences in the weight and BMI percentile score at the 1.5 years checkup (P=0.02, 0.04), showing lower scores for the CA group, compared with those for the NA group. In the CA group, the weight growth rate at 1.5 years and the height growth rate at 3.5 years were significantly lower than that of the NA group (P=0.01, 0.03). No significant differences were shown in the height growth rate at 1.5 years and the weight growth rate at 3.5 years between the two groups.

DISCUSSION

In this study, we focused on the relationship between the avoidance of the three major allergen foods (eggs, milk and wheat) and the growth of Japanese children. Our results revealed that the food (egg, milk and wheat) avoidance rate in the community at 3.5 years was 3.8%. In a study of guardians of elementary school children, Mukaida *et al.* (18) reported that the rates of food avoidance were 1.5% at 3 years, and 0.52% at 6 years. Thus, the rate of food avoidance in our study was higher than that reported in that previous study. For the current food avoidance group at 3.5 years, our results showed that the weight and BMI percentile at 1.5 years were lower, the height and weight percentiles at 3.5 years were lower, the weight growth rate at 1.5 years was lower, and the height growth rate at 3.5 years was lower than that in the never avoided or terminated food avoidance groups. The published studies that reported a relationship between a food elimination diet and physique at infants were as follows. Flammarion *et al.* (14) reported that 4.7 years-old children who avoided three or more foods due to allergies were smaller and lighter in height and weight than those who avoided one or two foods. Christie *et al.* (15) reported that a large number of 3.7 years-old children with two or more food allergies were categorized as less than the 25th percentile height-for-age compared with children with one food allergy. In our study, at 1.5 years-old, the subjects in the CA group were already lighter in weight, compared with the NA group. Food avoidance might effect weight growth earlier than height growth, because the delay of weight growth we observed first appeared at 1.5 year, while the delay of height growth was not observed until 3.5 years. Previous studies were clinical setting, cross-sectional studies, while our study was a community setting, retrospective longitudinal study. Until our study, no survey had been conducted on the physique and food avoidance in a community setting, targeting Japanese infants.

Only a few studies have looked at the effect of a food avoidance on nutrient intake and growth. Flammarion *et al.* (14) reported that children with food allergy had weight and height values significantly lower than controls, and that energy, protein and calcium intakes were similar among the food allergy and control groups. One possible explanation could be the loss of nutrients caused by continuous allergic inflammation and abnormal intestinal permeability despite the eviction diet (14). Christie *et al.* (15) reported that children with two or more food allergies were shorter than those with one food allergy. In addition, children with cow's milk allergy or two or more food allergies consumed dietary calcium less than the recommended amount, compared with children without cow's milk allergy and/or one food allergy. Tiainen *et al.* (20) reported that the height-for-age ratio was lower in children with cow's milk allergy, compared with healthy children, and that the

protein intake shown by the allergic children was lower than that of the healthy children. Thus, the relationship between nutrient intake and food avoidance and infant physique varied. In our study, we didn't carry out a nutritional survey. Therefore, the nutrient intake of the CA group was not clear. The results of our study suggested that the observed growth retardation was due to food avoidance. Therefore, we consider that is important that nutritional and growth assessment be conducted for food avoiders, along with nutritional counseling for guardians of food avoiders. The World Allergy Organization (WAO) (21), the United States National Institute of Allergy and Infectious Disease (NIAID) (22, 23) and the United Kingdom's National Institute for Health and Clinical Excellence have issued guidelines for the diagnosis and management of food allergies ; each independently recommending nutrition therapy or consultation with a dietitian (21-23). In Japan, childhood food allergy disease was added to the list of target diseases for nutrition counseling fees covered by the national health insurance system in 2006.

The guidelines for Food Allergy in Japan (1) recommended that the food allergen should be identified based on a correct diagnosis and the elimination diet should be kept to the minimum required level. Furthermore, the growth and development of children must be assessed by measurement of weight and height conducted over time and by drawing growth graphs in maternity passbooks. The results of our research indicated the importance of physical assessments of infants who avoid food by both parents and doctors. In addition, periodical checkups for tolerance to foods that infants tend to outgrow are necessary (3).

To the best of our knowledge, this is the first study conducted in a community health setting that examined the influence of food avoidance on growth from infancy through childhood in Japanese children. One strength of our study is that it investigated the changes demonstrated over time, based on the growth of 662 children (58.5% of the total subjects), based on data recorded in maternity passbooks. The consultation rate for the physical checkups and the consent rate of the study were high. Food allergies were common in this study. However, there is insufficient data on the rate of infants who conduct food avoidance at the community level. There is only a small number of studies in the literature on the effects of food avoidance on the growth of young children, including the avoidance of eggs and wheat. Previous studies on food avoidance in children were mostly related only to cow's milk (13, 24-26). The subject of food avoidance differs depending on the country. The research performed in this study, on the three major foods avoided by Japanese infants and children, will contribute to the knowledge necessary to prevent growth inhibition in infants who avoid food in Japan.

The main limitations of this study were as followings. We only assessed the physique of the infants, and we could not conduct any nutritional assessments for the subjects. In the future, it will be necessary to conduct adequate nutritional counseling or intervention for food avoiders and assess these efforts through a prospective study. This study was a questionnaire survey carried out in a local region. We did not examine all of the factors that could have affected the physique of the infants studied, such as perinatal diseases, chronic infant diseases, or the physique of the infant's parents. Diseases experienced during pregnancy, such as placenta previa, pregnancy-induced hypertension or diabetes, can affect the timing of birth and birth weight. However, in this study, the effects of these diseases on the infant physique might be less than normally expected, because we only analyzed infants those who were born at full term. According to the registration data for the "pediatric chronic specific disease treatment research project," the registration rates of short stature due to growth hormone deficiency and congenital heart disease was 3.8%, but we considered that this factor would not influence the results of this study in a community setting. Among the CA and the NA groups, there was no significant difference in birth weight, and therefore, the possibility that there was a high difference in the physique of the parents was low. The small sample size was also a limitation. The number of guardians who did not agree to the survey and the number of infants who did not met the analysis criteria were both higher than expected.

Food avoidance is the main therapy for children with food allergies. The results of this study suggested that food avoidance has suppressive effects on the growth of children, and indicated that physical and nutritional assessments are important in order to ensure proper growth for children on food avoidance diets.

CONFLICT OF INTEREST

The authors hereby declare no conflict of interest.

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REFERENCES

1. Mukoyama T, Nishima S, Arita M, Ito S, Urisu A, Ebisawa M, Ogura H, Kohno Y, Kondo N, Shibata R, Hurusho M, Mayumi M, Morikawa A : Guidelines for diagnosis and management of pediatric food allergy in Japan. Allergol Int 56 : 349-361, 2007
2. Kusunoki T, Morimoto T, Nishikomori R, Yasumi T, Heike T, Fujii T, Nakahata T : Changing Prevalence and Severity of Childhood Allergic Diseases in Kyoto, Japan, from 1996 to 2006. Allergol Int 58 : 543-548, 2009
3. Urisu A, Ebisawa M, Mukoyama T, Morikawa A, Kondo N : Japanese guideline for food allergy. Allergol Int 60 : 221-236, 2011
4. Lack G : Clinical practice. Food allergy. N Engl J Med 359 : 1252-1260, 2008
5. Yamamoto S : Prevalence and exacerbation factors of atopic dermatitis. Skin Allergy Frontier 1 : 85-90, 2003
6. Schmid-Grendelmeier P, Simon D, Simon HU, Akdis CA, Wuthrich B : Epidemiology, clinical features, and immunology of the "intrinsic" (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). Allergy 56 : 841-849, 2001
7. Fiocchi A, Bouygue GR, Martelli A, Terracciano L, Sarratud T : Dietary treatment of childhood atopic eczema/dermatitis syndrome (AEDS). Allergy 59 Suppl 78 : 78-85, 2004
8. Agata H, Kondo N, Fukutomi O, Shinoda S, Orii T : Effect of elimination diets on food-specific IgE antibodies and lymphocyte proliferative responses to food antigens in atopic dermatitis patients exhibiting sensitivity to food allergens. J Allergy Clin Immunol 91 : 668-679, 1993
9. Atherton DJ, Sewell M, Soothill JF, Wells RS, Chilvers CE : A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. Lancet 1 : 401-403, 1978
10. Lever R, MacDonald C, Waugh P, Aitchison T : Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. Pediatr

Allergy Immunol 9 : 13-19, 1998
11. Ewan PW, Clark AT : Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy : proposal for good practice. Clin Exp Allergy 35 : 751-756, 2005
12. David TJ, Waddington E, Stanton RH : Nutritional hazards of elimination diets in children with atopic eczema. Arch Dis Child 59 : 323-325, 1984
13. Isolauri E, Sutas Y, Salo MK, Isosomppi R, Kaila M : Elimination diet in cow's milk allergy : risk for impaired growth in young children. J Pediatr 132 : 1004-1009, 1998
14. Flammarion S, Santos C, Guimber D, Jouannic L, Thumerelle C, Gottrand F, Deschildre A : Diet and nutritional status of children with food allergies. Pediatr Allergy Immunol 22 : 161-165, 2011
15. Christie L, Hine RJ, Parker JG, Burks W : Food allergies in children affect nutrient intake and growth. J Am Diet Assoc 102 : 1648-1651, 2002
16. Sicherer SH, Sampson HA : Food hypersensitivity and atopic dermatitis : pathophysiology, epidemiology, diagnosis, and management. J Allergy Clin Immunol 104 : S114-122, 1999
17. Imai T, Iikura Y : The national survey of immediate type of food allergy. Arerugi 52 : 1006-1013, 2003
18. Mukaida K, Kusunoki T, Morimoto T, Yasumi T, Nishikomori R, Heike T, Fujii T, Nakahata T : The effect of past food avoidance due to allergic symptoms on the growth of children at school age. Allergol Int 59 : 369-374, 2010
19. Murata M, Kato N : The Children's Health Management Program. Shobi printing co.,ltd, Tokyo, 2009
20. Tiainen JM, Nuutinen OM, Kalavainen MP : Diet and nutritional status in children with cow's milk allergy. Eur J Clin Nutr 49 : 605-612, 1995
21. Fiocchi A, Brozek J, Schunemann H, Bahna SL, von Berg A, Beyer K, Bozzola M, Bradsher J, Compalati E, Ebisawa M, Guzman MA, Li H, Heine RG, Keith P, Lack G, Landi M, Martelli A, Rance F, Sampson H, Stein A, Terracciano L, Vieths S : World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. World Allergy Organ J 3 : 57-161, 2010
22. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, Plaut M, Cooper SF, Fenton MJ, Arshad SH, Bahna SL, Beck LA, Byrd-Bredbenner C, Camargo CA, Jr., Eichenfield L, Furuta GT, Hanifin JM, Jones C, Kraft M, Levy BD, Lieberman P, Luccioli S, McCall KM, Schneider LC, Simon RA, Simons FE, Teach SJ, Yawn BP, Schwaninger JM : Guidelines for the Diagnosis and Management of Food Allergy in the United States : Summary of the NIAID-Sponsored Expert Panel Report. J Allergy Clin Immunol 126 : 1105-1118, 2010
23. Groetch M, Nowak-Wegrzyn A : Practical approach to nutrition and dietary intervention in pediatric food allergy. Pediatr Allergy Immunol 24 : 212-221, 2013
24. Black RE, Williams SM, Jones IE, Goulding A : Children who avoid drinking cow milk have low dietary calcium intakes and poor bone health. Am J Clin Nutr 76 : 675-680, 2002
25. Paganus A, Juntunen-Backman K, Savilahti E : Follow-up of nutritional status and dietary survey in children with cow's milk allergy. Acta Paediatr 81 : 518-521, 1992
26. Henriksen C, Eggesbo M, Halvorsen R, Botten G : Nutrient intake among two-year-old children on cows' milk-restricted diets. Acta Paediatr 89 : 272-278, 2000