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Timing of eczema onset and risk of food allergy at 3 years of age: A hospital-based prospective birth cohort study

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ABSTRACT

Background: Although recent studies suggest that eczema in early childhood is important in the development of food allergy, the importance of the timing of eczema onset has not been fully clarified. **Objective:** This study aim to identify an association between the timing of eczema onset and development of food allergy in a prospective birth cohort study.

Methods: Data were obtained from the Tokyo Children's Health, Illness and Development (T-CHILD) study, which is a hospital-based birth cohort study currently in progress in Japan. A total of 1550 children were born to the recruited women. Outcome data for children were collected from questionnaires completed at 6 months, 1 and 3 years of age. Association between the timing of eczema onset and development of food allergy was estimated by logistic regression analyses. All analysis were performed using SPSS software with a two-sided 5% significance level.

Results: Eczema in the first year of life was a significant risk factor in multivariate analysis (aOR 3.90, 95% CI 2.34–6.52, $p < 0.001$). In each age (by month) stratum, infants with onset of eczema within the first 1–2 months after birth had the highest risk of food allergy at 3 years of age (aOR 6.61, 95% CI 3.27–13.34, $p < 0.001$).

Conclusion: Infants with early eczema onset (especially within the first 1–4 months after birth) were found to have an increased risk of developing food allergy at 3 years of age. Our findings may contribute to a better understanding of the timing of eczema onset as a potentially modifiable risk factor and to defining those who may need to be on guard for food allergy.

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1. Introduction

Food allergy, an abnormal immunologic response to causal foods, most often begins early in life and has potential risks of severe reactions such as anaphylaxis [1,2]. The prevalence of food allergy has been increasing worldwide in recent decades, and the estimated prevalence was reported as 10% in infants and 5% in preschool children [3,4]. The burden of food allergy in young children is a serious health issue, substantially affecting the quality

of life. Although interplay of genetic and environmental factors generally plays an important role in development of food allergy, environmental exposure is likely the primary cause of the rapid increase in food allergy during the last decade.

Eczema is the most prevalent chronic non-communicable skin disease, affecting up to 30% of children [5,6]. The relationship between eczema and food allergy has been enigmatic, with some controversy regarding which came first, eczema or food allergy [7]. Notably, recent studies in this field have been fruitful, resulting in a paradigm shift in our understanding of allergen sensitization, namely, the dual-allergen exposure hypothesis: oral intake of food proteins tends to induce tolerance, whereas epicutaneous exposure to food proteins tends to induce allergic sensitization [8].

Current evidence suggests that epicutaneous exposure to food proteins via eczema in early childhood is a significant risk factor in the development of food allergy. Since studies to date have been based primarily on case-control and cross-sectional study data

Abbreviations: T-CHILD, Tokyo Children's Health, Illness and Development; OR, odds ratio; CI, confidence interval; ISAAC, International Studies of Asthma and Allergies in Childhood.

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[9,10], it is difficult to exclude alternative explanations such as reverse causation and recall bias. Understanding the timing of eczema onset is of particular interest because eczema may be a modifiable risk factor for food allergy, but prospective birth cohort studies investigating this issue are lacking [11]. Therefore, we investigated the association between the timing of eczema onset and the development of food allergy in a prospective birth cohort study, The Tokyo Children's Health, Illness and Development (T-CHILD) study.

2. Materials and methods

2.1. Study design and population

The T-CHILD study, also known as the "Seiiku Cohort Study", was a single-center, prospective birth cohort study, conducted in the National Center for Child Health and Development (NCCHD), Tokyo, Japan [12,13]. Its objective was to investigate the relationship between exposure variables and the development of allergic diseases and the other disorders prospectively. All pregnant women who visited NCCHD before the 16th week of gestation were consecutively invited to join the T-CHILD study between October 2003 and December 2005. Consequently, 1701 women were enrolled in the T-CHILD study during their first trimester. A total of 1550 children were born to the enrolled women from March 2004 to August 2006.

2.2. Questionnaire

After written informed consent was obtained, the pregnant women were followed using mailed questionnaires. Baseline data were collected from questionnaires completed at 16, 23 and 34 weeks' gestation and their medical charts. Outcome data for children were collected from questionnaires completed at 6 months, 1 and 3 years of age.

2.3. Definitions

Food allergy: Children's food allergy was determined at 1 and 3 years of age by having the parents respond to the question: "Has your child experienced any allergic symptom immediately after food intake as follows: urticaria, swelling, wheezing, cough, vomiting, fainting or becoming unconscious?"

Eczema and wheeze: Children's eczema and wheeze were examined using the International Studies of Asthma and Allergies in Childhood (ISAAC) questionnaire [14,15], which was translated into Japanese and validated through the process of back translation in cooperation with the steering committee members. Presence of eczema was determined using a positive answer to the two ISAAC questions: "Has your child had an itchy rash?" and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?" The months of age at eczema onset was determined from questionnaires completed at 6 and 12 months of age and classified into five groups based on the timing of eczema onset: 1) less than 1 month, 2) 1–2 months, 3) 3–4 months, 4) 5–8 months and 5) 9–12 months. Presence or absence of wheeze was also determined using a question from ISAAC: "Has your child ever had wheezing or whistling in the chest at any time in the past?"

2.4. Data analysis

In this analysis, if a pregnancy was multiple, we randomly selected and followed only one child from the multiple births. The following factors, known to be associated with food allergy and/or eczema, were considered as potential confounders: gender, birth

weight, mode of delivery, season of birth, parental history of allergic diseases, breast feeding, timing of solid food introduction, history of wheeze at 1 year, pet ownership, annual household income, and mother's educational level.

2.5. Statistical analysis

We analyzed for association between eczema until 12 months of age and subsequent food allergy in children who had not experienced food allergy symptoms during their first 12 months. The risk of development of food allergy was also calculated by age at eczema onset. We estimated crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for associations between each variable and food allergy. Logistic regression models were constructed, and the potential confounders described above were included in multivariate models to obtain the adjusted ORs. We also conducted logistic regression analysis of the multiply-imputed data. All tests were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA) with a two-sided 5% significance level.

2.6. Ethical approval

This study was approved by the Ethics Committee of the National Center for Child Health and Development (Acceptance Number #52).

3. Results

3.1. Characteristics and causative foods

Fig. 1 shows the flowchart of the study population in the T-CHILD study. We obtained data for 1504 children. The

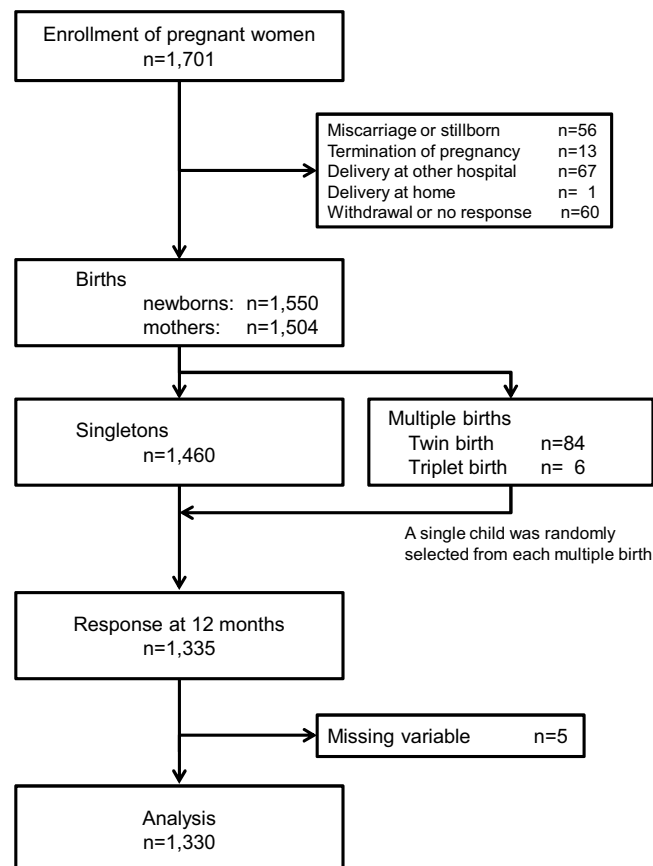


Fig. 1. Flow chart of study population in T-CHILD study.

Table 1
Characteristics of participants.

		Total		No Eczema		Eczema until 1 year of age		p value
		n	%	n	%	n	%	
Gender	male	699	52.6	499	52.0	200	53.9	0.54
	female	631	47.4	460	48.0	171	46.1	
Parental history of allergic diseases	no	289	22.9	228	25.1	61	17.1	<0.01
	yes	975	77.1	680	74.9	295	82.9	
Mother's educational level	college, university or graduate school	1149	90.4	822	89.7	327	92.1	0.20
	middle school or high school	122	9.6	94	10.3%	28	7.9	
Breast feeding	<6 months	217	16.3	156	16.3	61	16.4	0.94
	≥6 months	1113	83.7	803	83.7	310	83.6	
Timing of solid food introduction	<5 months	88	6.6	71	7.4	17	4.6	0.06
	≥5 months	1240	93.4	887	92.6	353	95.4	
Pet ownership	no	1010	78.7	716	77.2	294	82.8	0.03
	yes	273	21.3	212	22.8	61	17.2	
Birth weight	≥2500g	1200	90.4	863	90.1	337	91.3	0.49
	<2500g	127	9.6	95	9.9	32	8.7	
History of wheeze until 1 year	no	1051	79.2	763	79.7	288	77.8	0.45
	yes	276	20.8	194	20.3	82	22.2	
Annual household income	≥400 million yen	1129	93.3	793	92.1	336	96.3	<0.01
	<400 million yen	81	6.7	68	7.9	13	3.7	
Season of birth	spring-summer	660	49.7	467	48.7	193	52.0	0.28
	fall-winter	669	50.3	491	51.3	178	48.0	
Mode of delivery	vaginal delivery	1020	76.9	739	77.2	281	76.2	0.68
	caesarian section	306	23.1	218	22.8	88	23.8	
Food allergy at 1 year	no	1188	91.0	899	94.8	289	80.7	<0.01
	yes	118	9.0	49	5.2	69	19.3	
Food allergy at 3 years	no	1028	92.4	773	95.4	255	84.2	<0.01
	yes	85	7.6	37	4.6	48	15.8	

characteristics of the children in the analysis are shown in Table 1 (The characteristics of children who were excluded are shown in a Supplementary Table in this article's Online Repository). Eczema was reported in 27.9% (371/1330; 5 children were excluded because of missing variables) of children at 12 months of age. Significant differences between children with and without eczema were detected in terms of parental history of allergic diseases, pet ownership and annual household income. Among the followed participants, 9.0% (118/1311) and 7.5% (85/1136), at 1 and 3 years of age, respectively, had experienced food allergy symptoms at some point up to the time of the response. Table 2 shows the details of the causal foods. The most common causative foods at 1 and 3 years of age were eggs and cow's milk.

3.2. Factors associated with development of food allergy at 3 years

Univariate analysis showed that eczema in the first year of life and parental history of allergic diseases increased the risk of food allergy onset at 3 years of age (Table 3). We analyzed only children

with complete data (N=906). Among the confounding factors, eczema remained a significant risk factor in multivariate analysis (aOR 3.90, 95% CI 2.34–6.52, $p < 0.001$) (Table 3). No statistically significant association was found between food allergy and any environmental or socioeconomic factors. When using multiply-imputed data, a similar association was found between eczema in the first year of life and food allergy at 3 years, with an adjusted pooled OR of 4.03, (95%CI 2.54–6.39, $p < 0.001$). In order to investigate the causality, we also analyzed for an association between food allergy and development of eczema at 3 years of age using the data who had shown no eczema symptoms during their first 12 months of life. Eight of 40 children with food allergy (20.0%) and 131 of 765 children without food allergy (17.1%) developed eczema at 3 years. There was no significant association between food allergy at 12 months and eczema at 3 years of age (chi-square test $p = 0.639$), suggesting that there is no reverse causation.

3.3. Timing of eczema onset affects food allergy

The risk of food allergy at each age, estimated for the population of infants, is presented in Table 4. Among 906 cases with complete data analyzed in this model, the numbers of infants who developed eczema at each age were 31 (3.4%), 64 (7.1%), 60 (6.6%), 55 (6.1%) and 38 (4.2%), at less than 1 month, 1–2 months, 3–4 months, 5–8 months and 9–12 months of age, respectively. The risk tended to be different in each age (by month) subgroup. Infants with onset of eczema within the first 1–2 months after birth had the highest risk of food allergy at 3 years of age (aOR 6.61, 95% CI 3.27–13.34, $p < 0.001$) (Table 4).

4. Discussion

This prospective birth cohort study revealed that the timing of eczema onset affects the risk of developing food allergy in childhood. Infants with early eczema onset (especially within the first 1–4 months after birth) were more likely to develop food allergy. This is a birth cohort study, which is the optimal study

Table 2
List of causal foods.

	1 year (N = 118) ^a		3 years (N = 85) ^a	
	n	%	n	%
Egg	68	57.6	43	50.6
Cow's milk	22	18.6	13	15.3
Soy	5	4.2	2	2.4
Wheat	8	6.8	4	4.7
Rice	1	0.8	0	0.0
Fish	7	5.9	6	7.1
Fruits	5	4.2	9	10.6
Chicken	4	3.4	0	0.0
Pork	2	1.7	1	1.2
Meat	2	1.7	1	1.2
Peanuts	0	0.0	9	10.6
Buckwheat	1	0.8	2	2.4
Others	28	23.7	30	35.3

^a Children between 1 year and 3 years were overlapping.

Table 3

Factors associated with the development of food allergy at 3 years of age.

		Crude OR	95% CI	p value	Adjusted OR ^a	95% CI	p value		
Eczema until 1 year	yes vs no	3.79	2.29	6.27	<0.01	3.90	2.34	6.52	<0.01
Gender	female vs male	0.81	0.49	1.33	0.40	0.83	0.49	1.40	0.49
Parental history of allergic diseases	yes vs no	2.08	1.01	4.27	<0.05	1.87	0.90	3.91	0.10
Mother's educational level	low vs high	0.94	0.40	2.25	0.90	1.04	0.42	2.58	0.94
Breast feeding	≥6 months vs <6 months	0.71	0.38	1.35	0.30	0.72	0.37	1.40	0.34
Timing of solid food introduction	≥5 months vs <5 months	0.82	0.32	2.12	0.68	0.69	0.26	1.86	0.46
Pet ownership	yes vs no	1.14	0.64	2.05	0.66	1.21	0.66	2.23	0.53
Birth weight	<2500 g vs ≥2500g	0.73	0.29	1.87	0.51	0.72	0.27	1.92	0.51
History of wheeze until 1 year	yes vs no	1.29	0.73	2.29	0.38	1.21	0.67	2.19	0.53
Annual household income	<400 million yen vs ≥400 million yen	0.71	0.22	2.35	0.58	0.83	0.24	2.87	0.77
Season of birth	fall-winter vs spring-summer	1.39	0.84	2.29	0.20	1.48	0.88	2.48	0.14
Mode of delivery	yes vs no	1.30	0.75	2.25	0.36	1.25	0.70	2.24	0.45

N=906. Missing data were excluded. OR, odds ratio; CI, confidence interval.

^a Adjusted for Parental history of allergic diseases, Mother's educational level, gender, Breast feeding, Timing of solid food introduction, Pet ownership, Birth weight, History of wheeze until 1 year, Annual household income, Season of birth, Mode of delivery.**Table 4**

Timing of eczema onset associated with food allergy at 3 years of age.

	Adjusted OR ^a	Complete data ^b	95% CI	p value	Adjusted OR ^a	Multiple imputation ^c	95% CI	p value
No eczema	1.00				1.00			
Eczema onset								
Less than 1 month	2.92	0.94	9.03	0.063	2.80	1.02	7.69	0.046
1–2 months	6.61	3.27	13.34	<0.001	7.28	3.86	13.74	<0.001
3–4 months	4.69	2.17	10.13	<0.001	4.40	2.19	8.87	<0.001
5–8 months	2.10	0.76	5.80	0.151	2.28	0.96	5.42	0.063
9–12 months	2.13	0.61	7.47	0.238	2.60	0.86	7.85	0.091

OR, odds ratio; CI, confidence interval.

^a Adjusted for Parental history of allergic diseases, Mother's educational level, gender, Breast feeding, Timing of solid food introduction, Pet ownership, Birth weight, History of wheeze until 1 year, Annual household income, Season of birth, Mode of delivery.^b N=906. Missing data were excluded.^c N=1113. Missing data in dependent variable were excluded.

design for elucidating such associations and prospectively tracking longitudinal data, including exposure assessment and outcomes, from birth into childhood. This is especially relevant for eczema, for which onset is usually during the first year of life.

Few studies have examined for an association between the timing of eczema onset and development of food allergy. Martin et al. investigated the clinical risk factors for food allergy among infants with eczema in the HealthNuts study and found that the risk of challenge-proven food allergy in infants with eczema was significantly higher than in those without eczema (aOR 6.2, 95% CI 4.9–7.8) [16]. Our findings by birth cohort study in Japan confirm almost exactly the findings of the HealthNuts study from Australia: preceding eczema, especially in early infancy, was a significant risk factor for later development of food allergy. Conversely, food allergy was not detected as a significant risk factor for eczema. A small discrepancy was probably due, in part, to differences in the questionnaires, genetic and environmental factors, and study designs between the studies.

Recent evidence has begun to highlight the critical role of the skin in the pathogenesis of food allergy [17]. Several clinical and experimental observations strongly indicate that exposure of eczematous skin, but not intact skin, to food proteins is a true risk factor for sensitization to food antigens [18,19]. At present, the underlying mechanism by which eczema skews the immune response towards Th2 remains unclear. Although skin barrier function is usually impaired in eczematous lesions, an animal model with simple barrier dysfunction exhibited Th17-skewed but not Th2-skewed sensitization. Accordingly, promotion of Th2-immune responses in eczematous lesions must involve additional factors, such as skin barrier damage, alarmin/damage-associated molecular patterns, microbe-associated adjuvants and cytokines

produced by tissue structural cells [20,21]. Skin inflammation involving those factors might occur easily in early infancy because functional skin adaptation is a continuous process that takes place in the first year of life [22], and those infants with eczema might recognize environmental food antigens as harmful substances.

We recently reported that daily application of a moisturizer to neonates with a family history of allergic disorders during the first 32 weeks of life can significantly reduce the risk of atopic dermatitis/eczema, but not food sensitization [23]. These observations suggest that the moisturizer protected skin barrier function, but did not block/prevent Th2-immune responses. Thus, careful treatment of eczema is necessary for preventing food allergy, especially in infants with early-onset eczema. Furthermore, recent studies suggested that early introduction of solid food might decrease the incidence of food allergy compared with late introduction or avoidance. For instance, a randomized controlled trial revealed that early introduction of peanuts significantly decreased the frequency of development of peanut allergy (1.9% in the consumption group vs. 13.7% in the avoidance group) [24]. In addition to peanuts, several birth cohort studies and a cross-sectional study suggested that early introduction of eggs [25], cereal grains [26], fish [27] and cow's milk [28] was also associated with lower rates of food allergies, although this remains controversial [29]. Taken together, these observations suggest two possible strategies for the first 6 months of life for prevention of food allergy: one is careful treatment of eczema, and the other is early introduction of solid food—even potentially allergy-inducing foods such as peanuts and eggs—to infants with well-controlled skin. Further research is warranted to clarify whether these strategies for infants with early-onset eczema can actually decrease development of food allergy.

Our study has some potential limitations. Although this study is a prospective birth cohort designed to elucidate any chronological causal relationship between skin barrier dysfunction and onset of food allergy, we used the parents' reported information regarding eczema and food allergy as the outcome. That might lead to overestimation in comparison with a doctor's diagnosis or diagnosis confirmed by oral food challenge. Also, we did not confirm allergen sensitization by using serum IgE or the skin prick test. Some clinical studies assessed food allergy based on positive food-specific IgE or a positive skin prick test. However, those tests might yield false-positive results, especially in children with eczema [30,31].

In conclusion, infants with early eczema onset (especially within the first 1–4 months after birth) were found to have an increased risk of developing food allergy. Our findings may contribute to a better understanding of the timing of eczema onset as a potentially modifiable risk factor and to defining those who may need to be on guard for food allergy.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jdermsci.2016.08.003>.

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