



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Letter to the Editor

Fall birth is associated with prolonged elimination in Japanese children with hen's egg allergy: A population-based study

Dear Editor,

Hen's egg allergy (HEA) usually occurs in infancy, and is likely to resolve by 6 years of age.¹ However, the remaining 30% of children have to continue elimination. The risk factors that predict the need for continuation of the elimination have not yet been clearly elucidated.^{1,2} Moreover, most studies included only children who visited medical institutions. Also, it is not known whether risk factors for food allergy (FA) also affect its later elimination status. Therefore, in children with HEA recruited from the general Japanese population, we sought to identify potential background factors that can predict the elimination status at 6 years of age.

In September 2019, the questionnaire was distributed to the parents of all of the 6853 public school students (6–14 years old) in Omihachiman City, Shiga, Japan. The questionnaire contained an explanation of the objective and scope of the study and indicated that participation was voluntary. Therefore, participants were considered to have provided their consent if they returned the questionnaire to the school. The study was approved by the Ethics Committee of Shiga Medical Center for Children (R1-4).

Those who answered "yes" to the following questions were regarded as having either immediate-type FA or a past history of immediate-type FA: (1) "Does your child ever have the allergic symptoms shown in [Supplementary Table 1](#) within 1–2 h after ingesting a particular food?"; (2) "Does your child avoid particular foods due to these symptoms?"; and (3) "Was the avoidance instructed by a physician?". For those who had FA, the duration of the avoidance of each food was also asked. Those who answered "hen's egg" as one of the particular foods that they avoided starting before the age of 6 years were considered to have HEA. The potential background factors to be examined were those that could be determined by about 2 years of age; sex, season of birth (fall birth vs. others),³ birth order (firstborn vs. second-born or later),⁴ presence of a family history of allergy, daycare attendance under 1 year of age, cesarean birth,⁵ onset of eczema under 2 years of age, and onset of a FA other than HEA by 2 years of age. Fall birth was defined as birth in September, October, or November. Onset of eczema under 2 years of age was defined on the basis of the International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire.⁶

The chi-squared test or Mann–Whitney U test was used to compare the background characteristics between the groups with and without HEA. Univariate and multivariate logistic regression models were constructed to compare the prolonged elimination status at 6 years of age between those with and without potential background factors.

IBM SPSS Statistics (Version 27.0. Armonk, NY, USA) was used, and two-tailed P values < 0.05 were considered to be statistically significant.

Questionnaires were returned for 4991 of the 6853 schoolchildren (response rate: 72.8%). In total, 288 children (5.8% of the total) who had either a present HEA or a past history of HEA before the age of 6 years were included ([Fig. 1](#)). Comparisons of the background characteristics between the groups with and without HEA are shown in [Supplementary Table 2](#). At 6 years of age, 79 children (1.6% of the total) had prolonged hen's egg elimination (elimination rate: 27.4%; [Fig. 1](#)). In the univariate logistic regression analysis ([Table 1](#)), the rate of elimination at 6 years of age was significantly higher among those who had a fall birth (35.7% vs. 24.1%; odds ratio (OR), 1.75; 95% confidence interval (95%CI), 1.01–3.03), were the second-born or later (22.0% vs. 34.8%; OR, 1.90; 95%CI, 1.12–3.22), had the onset of eczema under 2 years of age (50.6% vs. 18.7%; OR, 4.47; 95%CI, 2.55–7.84), and had the onset of a FA other than HEA by 2 years of age (41.5% vs. 17.6%; OR, 3.31; 95%CI, 1.94–5.68). In the multivariate logistic regression analysis ([Table 1](#)), the significance still remained for fall birth (OR, 2.08; 95%CI, 1.11–3.90), onset of eczema under 2 years of age (OR, 4.14; 95%CI, 2.20–7.78), and onset of a FA other than HEA by 2 years of age (OR, 2.89; 95%CI, 1.57–5.32). The elimination rate at 6 years of age was, although not statistically significant, the highest in those with fall birth and the lowest in those with spring birth ([Supplementary Fig. 1](#)).

FA in childhood has been shown to be more prevalent among those born in the fall or winter,³ and the prevalence of FA is particularly high among those born in the fall.⁷ A relative deficiency of vitamin D during infancy among those born in the fall or winter as a result of decreased sunlight exposure during those seasons has been speculated to promote IgE sensitization by affecting the immune system.⁸ Also, in this study, there tended to be more individuals born in the fall in the group with HEA, although there was no statistical significance. Moreover, among children with HEA, the elimination rate at 6 years of age was significantly higher among those born in the fall, suggesting that a fall birth may affect not only the development, but also the prolongation of HEA.

A strength of this study is the high response rate obtained from the general population for schoolchildren without selection bias. The limitations of this study also need to be highlighted. Firstly, the diagnosis of FA was made based solely on the reports from parents. However, the prevalence of FA in our study was consistent with the reported prevalence in other studies,^{9,10} lending credibility to the definition of FA used in this study. Secondly, we did not strictly evaluate the adequacy of continued elimination at 6 years of age. However, the fact that they had to continue elimination suggests that their allergic status was not mild enough to stop elimination by 6 years of age. Lastly, unknown

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2021.06.002>

1323–8930/Copyright © 2021, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

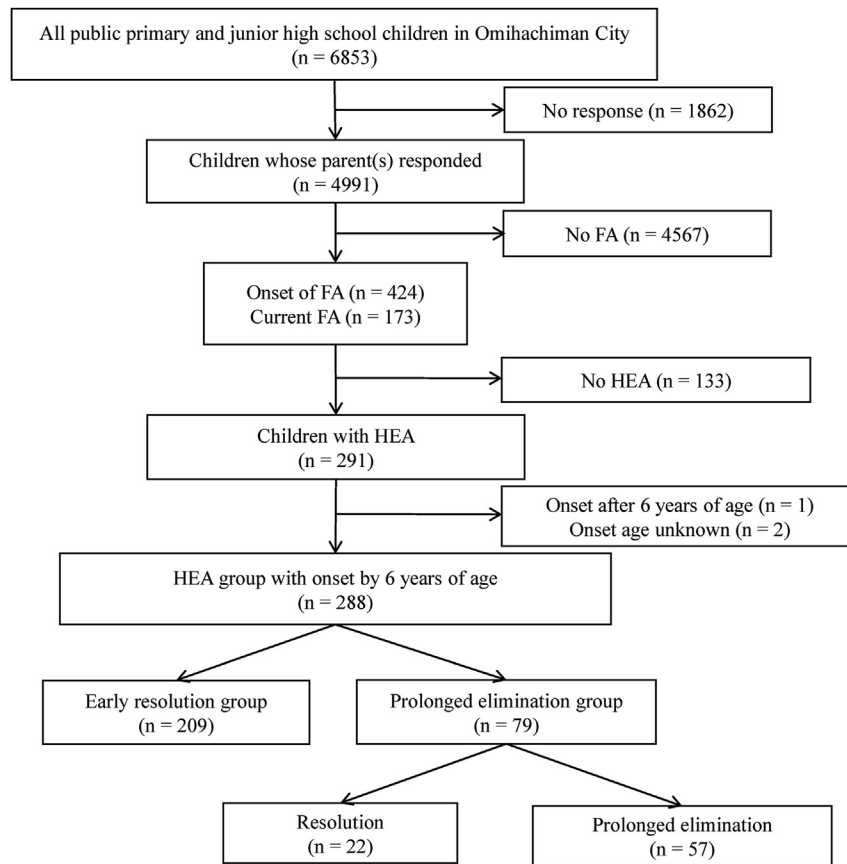


Figure 1. Study flow chart. FA, food allergy; HEA, hen's egg allergy.

Table 1
Comparison of the elimination rates according to several background factors.

Background factors	Elimination rate (%)	Univariate		Multivariate	
		OR (95%CI)	P value	OR (95%CI)	P value
Sex					
Female	37/131 (28.2)				
Male	42/157 (26.8)	0.93 (0.55–1.56)	0.78	0.73 (0.40–1.33)	0.31
Season of birth					
Non-fall birth	49/203 (24.1)				
Fall birth	30/84 (35.7)	1.75 (1.01–3.03)	.047	2.08 (1.11–3.90)	.02
Birth order					
Firstborn	38/173 (22.0)				
Second-born or later	39/112 (34.8)	1.90 (1.12–3.22)	.02	1.36 (0.74–2.49)	0.32
Family history of allergy					
No	26/111 (23.4)				
Yes	53/177 (29.9)	1.40 (0.81–2.41)	0.23	1.26 (0.68–2.36)	0.46
Daycare attendance under 1 year of age					
No	69/253 (27.3)				
Yes	8/29 (27.6)	1.02 (0.43–2.40)	0.97	1.07 (0.41–2.85)	0.89
Cesarean birth					
No	65/228 (28.5)				
Yes	14/56 (25.0)	0.84 (0.43–1.63)	0.60	0.76 (0.35–1.66)	0.50
Onset of eczema under 2 years of age					
No	39/209 (18.7)				
Yes	40/79 (50.6)	4.47 (2.55–7.84)	< .001	4.14 (2.20–7.78)	< .001
Onset of a FA other than HEA by 2 years of age					
No	30/170 (17.6)				
Yes	49/118 (41.5)	3.31 (1.94–5.68)	< .001	2.89 (1.57–5.32)	.001

FA, food allergy; HEA, hen's egg allergy; OR, odds ratio; CI, confidence interval.

The results with P values < 0.05 were considered to be statistically significant, and were shown in [bold].

confounding factors may influence the results, although factors that have been considered to be associated with the onset of FA were set as confounding factors based on the Japanese Pediatric Guideline for Food Allergy 2016 and other published references.

In conclusion, among children with HEA recruited from the general Japanese population, fall birth was associated with prolonged elimination at 6 years of age, in addition to early onset of eczema and early onset of a FA other than HEA. These factors might be useful as early

predictive markers for the elimination status at 6 years of age. Further verification of the utility of these predictors is necessary. It is also important to see whether they are applicable to FAs other than HEA.

Acknowledgments

We thank the participating parents and the members of the Omihachiman City Board of Education for their contributions to this study. This study was funded by a Grant-in-Aid for Scientific Research (KAKENHI, Grant/Award Number: 20K10470), and by the Shiga Prefecture Pediatric Allergic Disease Control Promotion Project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.06.002>.

Conflict of interest

The authors have no conflict of interest to declare.

Yuie Motoyama^a, Takeshi Morimoto^b, Jiro Takeuchi^b, Takashi Kusunoki^{a,c,*}

^a Laboratory of Child Health and Nutrition, Department of Food Science and Human Nutrition, Faculty of Agriculture, Ryukoku University, Shiga, Japan

^b Department of Clinical Epidemiology, Hyogo College of Medicine, Hyogo, Japan

^c Department of Pediatrics, Shiga Medical Center for Children, Shiga, Japan

* Corresponding author. Laboratory of Child Health and Nutrition, Department of Food Science and Human Nutrition Faculty of Agriculture, Ryukoku University, 1-5 Yokotani, Seta, Oe-cho, Otsu, Shiga, 520-2194, Japan.

E-mail address: tkusunoki@agr.ryukoku.ac.jp (T. Kusunoki).

References

- Ohtani K, Sato S, Syukuya A, Asaumi T, Ogura K, Koike Y, et al. Natural history of immediate-type hen's egg allergy in Japanese children. *Allergol Int* 2016;**65**: 153–7.
- Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: a population-based assessment. *J Allergy Clin Immunol* 2015;**135**: 1257–66. e1–2.
- Kusunoki T, Morimoto T, Sakuma M, Mukaida K, Yasumi T, Nishikomori R, et al. Effect of eczema on the association between season of birth and food allergy in Japanese children. *Pediatr Int* 2013;**55**: 7–10.
- Kusunoki T, Mukaida K, Morimoto T, Sakuma M, Yasumi T, Nishikomori R, et al. Birth order effect on childhood food allergy. *Pediatr Allergy Immunol* 2012;**23**: 250–4.
- Mitselou N, Hallberg J, Stephansson O, Almqvist C, Melén E, Ludvigsson JF. Cesarean delivery, preterm birth, and risk of food allergy: nationwide Swedish cohort study of more than 1 million children. *J Allergy Clin Immunol* 2018;**142**: 1510–4.e2.
- Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**: 733–43.
- Keet CA, Matsui EC, Savage JH, Neuman-Sunshine DL, Skripak J, Peng RD, et al. Potential mechanisms for the association between fall birth and food allergy. *Allergy* 2012;**67**: 775–82.
- Matsui T, Tanaka K, Yamashita H, Saneyasu KI, Tanaka H, Takasato Y, et al. Food allergy is linked to season of birth, sun exposure, and vitamin D deficiency. *Allergol Int* 2019;**68**: 172–7.
- Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis MM, et al. The public health impact of parent-reported childhood food allergies in the United States. *Pediatrics* 2018;**142**: e20181235.
- Grabenhenrich L, Trendelenburg V, Bellach J, Yürek S, Reich A, Fiandor A, et al. Frequency of food allergy in school-aged children in eight European countries—the EuroPrevall-iFAAM birth cohort. *Allergy* 2020;**75**: 2294–308.

Received 15 April 2021

Received in revised form 25 May 2021

Accepted 1 June 2021

Available online xxx

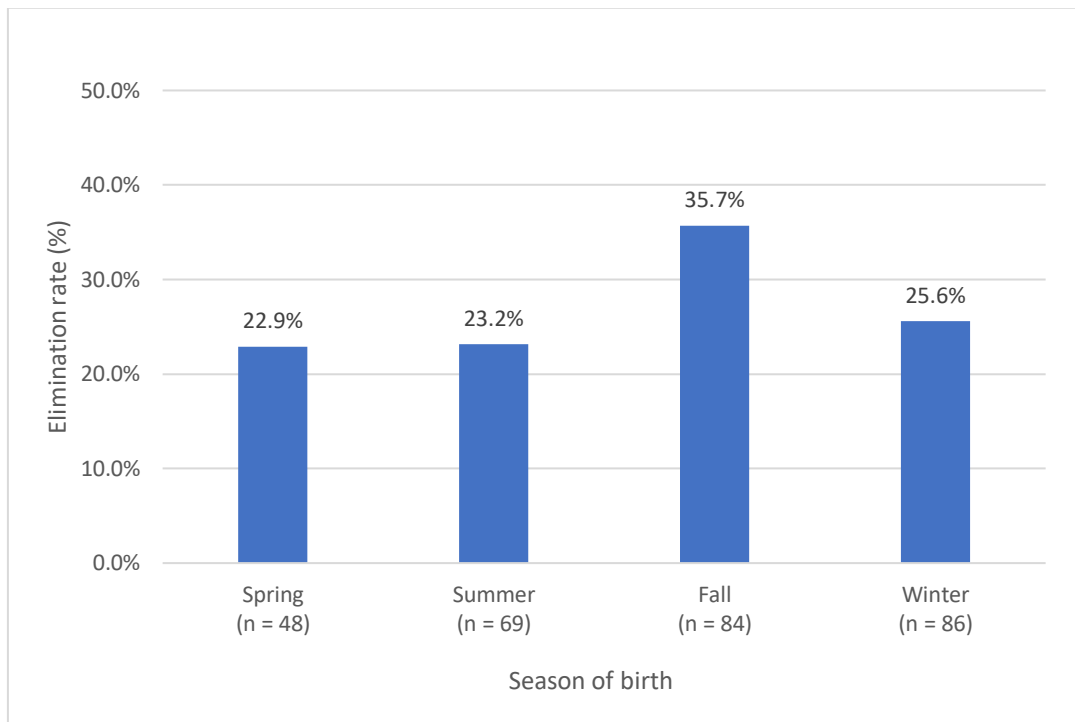
Supplementary Table 1. Symptoms of food allergies

Organ	Symptoms
Skin	Erythema, urticaria, pruritus
Mucous membrane	Conjunctival hyperemia and edema, blepharedema Rhinorrhea, nasal congestion, sneezing Discomfort/swelling of the oral cavity/pharynx/lips/tongue
Respiratory organs	Tightness in the pharyngolarynx, dysphagia, wheezing, feeling of chest tightness, dyspnea
Digestive organs	Nausea, vomiting, abdominal pain, diarrhea
Nerves	Headache, lowered vigor, impaired consciousness
Circulatory organs	Decreased blood pressure, tachycardia, pallor

Supplementary Table 2. Background characteristics of the participants

Background characteristics	Group with HEA (n = 288)	Group without HEA (n = 4703)	P value
Age, median years (IQR)	9 (7 - 11)	10 (8 - 12)	.02
Male, n (%)	157/288 (54.5)	2338/4702 (49.7)	.11
Fall birth, n (%)	84/287 (29.3)	1159/4682 (24.8)	.09
Firstborn, n (%)	173/285 (60.7)	2225/4616 (48.2)	< .001
Family history of allergy, n (%)	177/288 (61.5)	2052/4703 (43.6)	< .001
Daycare attendance under 1 year of age, n (%)	29/282 (10.3)	478/4579 (10.4)	.93
Cesarean birth, n (%)	56/284 (19.7)	926/4598 (20.1)	.86
Onset of eczema under 2 years of age, n (%)	79/288 (27.4)	292/4695 (6.2)	< .001
Onset of a FA other than HEA by 2 years of age, n (%)	118/288 (41.0)	61/4703 (1.3)	< .001

IQR, interquartile range; FA, food allergy; HEA, hen's egg allergy.



Supplementary Figure 1. Elimination rate according to each season of birth.

The continued hen's egg elimination rate is the highest in fall and the lowest in spring, although there was no statistical significance by the Mantel-Haenszel test for trends ($P = .48$).