

4. Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy*. 2018;73(4):799-815.
5. Unal D, Coskun R, Demir S, Gelincik A, Colakoglu B, Buyukozturk S. Successful beef desensitization in 2 adult patients with a delayed-type reaction to red meat. *J Allergy Clin Immunol Pract*. 2017;5(2):502-503.
6. Barbi E, Longo G, Berti I, et al. Adverse effects during specific oral tolerance induction: in-hospital "rush" phase. *Eur Ann Allergy Clin Immunol*. 2012;44(1):18-25.
7. Chung CH, Mirakhor B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med*. 2008;358(11):1109-1117.
8. Mabelane T, Basera W, Botha M, Thomas HF, Ramjith J, Levin ME. Predictive values of alpha-gal IgE levels and alpha-gal IgE: total IgE ratio and oral food challenge-proven meat allergy in a population with a high prevalence of reported red meat allergy. *Pediatr Allergy Immunol*. 2018;29(8):841-849.
9. Bircher AJ, Hofmeier KS, Link S, Heijnen I. Food allergy to the carbohydrate galactose-alpha-1,3-galactose (alpha-gal): four case reports and a review. *Eur J Dermatol*. 2017;27(1):3-9.
10. Hamsten C, Starkhammar M, Tran TA, et al. Identification of galactose-alpha-1,3-galactose in the gastrointestinal tract of the tick *Ixodes ricinus*; possible relationship with red meat allergy. *Allergy*. 2013;68(4):549-552.
11. Uzunoglu E, Polat E, Oguz ID, et al. Tick bite cases among hazelnut farm workers in Giresun. *Cumhuriyet Med J*. 2017;39(2):473-478.

DOI: 10.1111/pai.13095



Accidental ingestion of food allergens: A nationwide survey of Japanese nursery schools

To the Editor,

The accidental ingestion of food allergens is an important problem in preschool-aged children with food allergy (FA).¹ However, reports regarding accidental ingestion in nursery school children are limited. This nationwide questionnaire-based survey determined the incidence of accidental ingestion in this population and identified the associated risk factors.

Data were gathered using a nationwide questionnaire survey² dispatched by post to all childcare facilities in Japan (Table S1).

Accidental ingestion was defined as unintended accidental allergen exposure leading to allergy symptoms. Data were expressed as n (%) or means (standard deviation). This study was approved by the ethics committee of Jikei University. The detailed methods of the survey administered to nursery schools, and the regulations in Japan are described in Appendix S1.

Questionnaire responses were received from 15 722 (48.8%) of 32 210 institutions. A total of 1 390 481 children were enrolled in the survey (Figure S1). Among 51 531 children with FA, 408 and 5317 were excluded owing to missing data and nursery center information, respectively. Finally, 45 806 children with FA met the inclusion criteria; their characteristics are shown in Table 1. The mean age of the children was 2.3 ± 1.6 years (median: 2.0 years). Egg allergy was the most common FA (74.8%). A person accountable for FA was identified in 65.6% of nursery schools. Adrenaline auto-injectors (AAIs) were prescribed to 5123 (11.2%) children, 1154

(2.5%) of whom brought them to their nursery school. Of 4853 children with a history of anaphylaxis, 1450 (29.9%) had been prescribed AAIs, 784 (16.2%) of whom brought them to their nursery school. Overall, 3497 (7.6%) children had experienced accidental ingestion with symptoms in the current fiscal year, 44 (0.1%) of whom required hospitalization. Only, 11 children (0.02%) had used an AAI in their nursery school. Data on symptom severity were obtained from 2113 children, but were unknown in 2155 children. Severe (requiring hospitalization), moderate (requiring doctor treatment), and mild symptoms (not requiring treatment) were observed in 44, 303 and 1766 children, respectively. There were no cases of mortality.

Significant associations with accidental ingestion were observed for sex, age, history of anaphylaxis to causative food, milk allergy, wheat allergy, fish allergy, number of eliminated foods, number of children in the nursery center, and the absence of a person accountable for FA (Table 1). The incidence of accidental ingestion was highest in children younger than one year of age (9.7%) and gradually decreased with age (*P*-value for trend: <0.001; Figure S2). Larger facilities with more children had a lower incidence of accidental ingestion, while the incidence increased in smaller nursery schools (*P*-value for trend: <0.001; Figure S3).

The factors significantly associated with accidental ingestion were assessed for crude odds ratios (ORs) and adjusted ORs (aORs; Table 2). These factors were categorized as related to either children or nursery centers. The significant risk factors in children were male sex (male; aOR: 1.115), younger age (per one-year increase; aOR:

[The copyright line was changed on 24 December 2019 after original online publication.]

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2019 The Authors. *Pediatric Allergy and Immunology* published by John Wiley & Sons Ltd

TABLE 1 Characteristics of the children with food allergy and the nursery centers

	Total (N = 45 806)	Accidental ingestion (n = 3497)	No exposure or no symp- toms due to accidental ingestion (n = 42 309)	P-value
Children characteristics				
Sex (male) (n, %)	28 090 (61.3)	2243 (64.1)	25 847 (61.1)	<0.001
Age (y) (mean, SD)	2.3 (1.6)	2.1 (1.6)	2.3 (1.6)	<0.001
History of anaphylaxis to causative food (n, %)	4853 (10.6)	687 (19.6)	4166 (9.8)	<0.001
Egg allergy, current (n, %)	34 285 (74.8)	2607 (74.5)	31 678 (74.9)	0.671
Milk allergy, current (n, %)	12 857 (28.1)	1207 (34.5)	11 650 (27.5)	<0.001
Wheat allergy, current (n, %)	3661 (8.0)	424 (12.1)	3237 (7.7)	<0.001
Peanut allergy, current (n, %)	3236 (7.1)	247 (7.1)	2989 (7.1)	0.997
Fish allergy, current (n, %)	2527 (5.5)	331 (9.5)	2196 (5.2)	<0.001
Number of eliminated foods (mean, SD)	1.7 (1.3)	2.0 (1.5)	1.7 (1.3)	<0.001
Nursery center characteristics				
Number of children in the nursery center (mean, SD)	122.5 (59.7)	116.8 (56.9)	123.0 (60.0)	<0.001
Lunch box eliminating causative foods by nursery center (n, %)	44 738 (98.5)	3430 (98.7)	41 308 (98.5)	0.551
Absence of a person responsible for managing food allergies (n, %)	15 780 (34.4)	1292 (36.9)	14 488 (34.2)	0.001

Note: Accidental ingestion was defined as unintended accidental allergen exposure leading to allergic symptoms. At least 83.3% of the children submitted documents with details about their food allergies and the related instructions, written by their doctors, to their nursery school.

Abbreviation: SD, standard deviation.

0.893), history of anaphylaxis to causative foods (aOR: 2.199), current milk allergy (aOR: 1.239), current wheat allergy (aOR: 1.266), and current fish allergy (aOR: 1.191). The number of eliminated foods was significant only in univariate analysis (crude OR: 1.126). The significant factors associated with accidental ingestion in nursery centers were fewer children (per 10-fold increase; aOR: 0.703)

and the absence of a person accountable for FA (aOR: 1.128). The risk factors for severe reactions were similar (Table S2).

Our study covered two-thirds of preschool children who attend nursery school in Japan (Appendix S1). While few children were prescribed AAIs, only one-fifth of these children brought them to nursery school. Our results indicated that younger children had a

TABLE 2 Risk factors for accidental ingestion among children with symptoms in the current fiscal year

	Accidental ingestion with food allergy symptoms			
	Crude OR (95% CI)	P-value	Adjusted OR ^a (95% CI)	P-value
Patient characteristics				
Sex (male)	1.139 (1.060-1.224)	<0.001	1.115 (1.037-1.199)	0.003
Age (y)	0.909 (0.889-0.930)	<0.001	0.893 (0.873-0.914)	<0.001
History of anaphylaxis to causative food	2.238 (2.047-2.448)	<0.001	2.199 (2.005-2.411)	<0.001
Current milk allergy	1.387 (1.290-1.492)	<0.001	1.239 (1.142-1.346)	<0.001
Current wheat allergy	1.665 (1.495-1.855)	<0.001	1.266 (1.115-1.438)	<0.001
Current fish allergy	1.910 (1.692-2.156)	<0.001	1.919 (1.681-2.191)	<0.001
Number of eliminated foods (continuous)	1.126 (1.102-1.151)	<0.001	1.013 (0.983-1.044)	0.399
Information about the nursery center				
Log (total number of nursery school children) (continuous)	0.638 (0.550-0.740)	<0.001	0.703 (0.604-0.818)	<0.001
Absence of an accountable person for food allergy	1.125 (1.047-1.209)	0.001	1.128 (1.049-1.213)	0.001

Note: Odds ratio of "age"; per one-year increase. Odds ratio of "number of eliminated foods"; per one-item increase. Odds ratio of "total number of nursery school children"; per 10-fold increase.

Abbreviations: CI, confidence interval; OR, odds ratio.

^aOR was adjusted using the significant variables in Table 1: sex, age, history of anaphylaxis to causative food, milk allergy, wheat allergy, peanut allergy, fish allergy, number of eliminated foods, total number of children in nursery centers, and the absence of a person responsible for managing food allergies.

greater risk of accidental ingestion. Younger children are more likely to share another child's meal, as indicated in our previous report in which 16.9% of nursery school children shared meals with other children.² Male sex was also a risk factor, which may be due to gender differences in infant behavior,³ although further study is required to determine the cause of this finding.

A history of anaphylaxis to causative food was also a risk factor for accidental ingestion. This finding is supported by those of another study.⁴

Our results indicated that milk, wheat, and fish allergies were major risk factors for accidental ingestion. These are the second, third, and ninth most common allergens in Japan.⁵ Other studies have indicated that cow's milk, but not wheat, is a common cause of anaphylaxis in preschool children in Europe.⁶ Wheat allergy is a primary cause of anaphylaxis in Japan.⁵ Wheat allergy may be more common in Asian countries than in European countries and in the United States.⁷ The prevalent allergens differ between countries partly due to differences in the foods commonly consumed.⁸ Fish products are used in traditional Japanese seasoning in many meals and are difficult to eliminate from all foods in Japan. For example, "dashi" stock is commonly used to flavor food both at home and in schools. This may lead to a higher incidence of an accidental ingestion of fish. Similarly, the number of eliminated foods was a risk factor for accidental ingestion only in the univariate analysis in our study; it may be more difficult to prevent accidental ingestion in schools because the staff would need to eliminate more causative foods.

School staff should be trained to respond appropriately to accidental ingestion.⁹ Among factors related to nursery schools, the absence of a person accountable for FA was an independent risk factor in the present study. Since it is not possible to eliminate other risk factors such as age, history of anaphylaxis to causative food, and allergy to causative food, an effective management strategy for FA in nursery schools must be developed. A team or person accountable for FA would play an important role in improving the management of FA in nursery schools and, consequently, may help to prevent accidental ingestions. These results indicate the critical need for individuals to monitor FA in all nursery schools.

Our study had several limitations. Although most children were diagnosed with food allergy by a medical doctor, this questionnaire-based survey study has the potential for study bias. The response rate was around 50%, which may indicate a selection bias. Finally, complications such as atopic dermatitis and bronchial asthma, which affect the severity of allergic reactions, were not considered in this survey.

In conclusion, accidental ingestion in nursery schools is common. The risk factors included male sex, younger age, history of anaphylaxis, milk allergy, wheat allergy, fish allergy, fewer children in the nursery school, and the absence of a person accountable for FA. Furthermore, children who were prescribed AAIs rarely brought them to nursery school. Thus, while nursery schools must appoint a school official accountable for FA management, both schools and parents should collaborate to ensure child safety.

ACKNOWLEDGEMENTS




We thank H. Saito for the useful discussions and suggestions. We are particularly grateful to the staff who participated in the survey and data collection. Editorial support, in the form of medical rewriting and the creation of high-resolution images based on the authors' detailed directions, collating author comments, copyediting, and fact-checking, was provided by Editage, Cactus Communications.

CONFLICTS OF INTEREST

M. Ebisawa serves on the DBV Technologies Scientific Advisory Board. All other authors have no conflicts of interest to declare.

FUNDING INFORMATION

This study was supported by funds from the Ministry of Health, Labour and Welfare of Japan.

Noriyuki Yanagida^{1,2} 
 Motohiro Ebisawa² 
 Toshio Katsunuma³ 
 Jyoji Yoshizawa⁴

¹Department of Pediatrics, NHO Sagami National Hospital, Kanagawa, Japan

²Japan Clinical Research Center for Allergy and Rheumatology, NHO Sagami National Hospital, Sagami, Japan

³Department of Pediatrics, Daisan Hospital, The Jikei University School of Medicine, Tokyo, Japan

⁴Division of Pediatric Surgery, Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan
 Email: sagami@foodallergy.jp

ORCID

Noriyuki Yanagida  <https://orcid.org/0000-0001-9643-744X>

Motohiro Ebisawa  <https://orcid.org/0000-0003-4117-558X>

Toshio Katsunuma  <https://orcid.org/0000-0003-2646-3006>

REFERENCES

1. Fleischer DM, Perry TT, Atkins D, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. *Pediatrics*. 2012;130:e25-e32.
2. Yanagida N, Ebisawa M, Katsunuma T, Yoshizawa J. Ministry of health 2015 national treasury subsidy consultation for research projects to promote re-search on child and child care support, ministry of health, Labour and Welfare Japan. *Arerugi*. 2018;67:202-210.
3. Chaplin TM, Aldao A. Gender differences in emotion expression in children: a meta-analytic review. *Psychol Bull*. 2013;139:735-765.
4. Pettersson ME, Koppelman GH, Flokstra-de Blok B, Kollen BJ, Dubois A. Prediction of the severity of allergic reactions to foods. *Allergy*. 2018;73:1532-1540.

5. Ebisawa M, Ito K, Fujisawa T, Committee for Japanese Pediatric Guideline for Food Allergy TJSOPA, Clinical Immunology TJSOA. Japanese guidelines for food allergy 2017. *Allergology International*. 2017;66(2):248-264.
6. Grabenhenrich LB, Dölle S, Moneret-Vautrin A, et al. Anaphylaxis in children and adolescents: the European anaphylaxis registry. *J Allergy Clin Immunol*. 2016;137(1128-1137):e1.
7. Loh W, Tang M. The epidemiology of food allergy in the global context. *Int J Environ Res Public Health*. 2018;15(9):2043.
8. Lee AJ, Thalayasingam M, Lee BW. Food allergy in Asia: how does it compare? *Asia Pac Allergy*. 2013;3:3-14.
9. Wang J, Bingemann T, Russell AF, Young MC, Sicherer SH. The allergist's role in anaphylaxis and food allergy management in the school and childcare setting. *J Allergy Clin Immunol Pract*. 2018;6:427-435.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.