# Accidental Allergic Reactions to Immediate-Type Food Allergens in Japanese Children: A Single-Center Study

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## Abstract

**Background:** Accidental allergic reactions (AAR) in children are under-studied, especially with precise pediatrician-based exact diagnoses and follow-ups. This study aimed to assess the prevalence and risk factors for AAR in Japanese children with immediate-type food allergies. **Methods:** This single-center study included children with immediate-type hen's egg (HE), cow's milk (CM), wheat, or peanut allergy who had been followed-up regularly at a national center specialized for allergy in Japan. Low-dose reactivity was defined as allergic reactions to a low dose of [?]250, [?]102, [?]53, or [?]133 mg HE, CM, wheat, or peanut protein, respectively. From January to December 2020, pediatricians followed the AAR experience every 2–4 months. Risk factors for AAR were analyzed using multiple logistic regression. **Results:** Of the 1096 participants, 609, 457, 138, and 90 had HE, CM, wheat, and peanut allergies, respectively. In this cohort, the median age was 5.0 years, 39% had completely eliminated allergenic food, and 24% had low-dose reactivity. The annual AAR rate was 0.130 in all sub-cohorts. Moderate and severe symptoms occurred in 50% and 0.7%, respectively, of children who experienced AAR. Multiple logistic regression revealed that low-dose reactivity was a significant risk factor for AAR in the overall, HE, and CM cohorts, respectively ( $p$ <0.001, $p$ = 0.029 and 0.036). **Conclusion:** In Japanese children with immediate-type food allergies, the annualized rate of AAR was relatively low; however, half of the participants with AAR had moderate to severe symptoms. Children, especially those with low-dose reactivity, would require careful risk management of AAR.

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**Conflict of Interest:**

Motohiro Ebisawa and Sakura Sato have received speaker honoraria from Viatris. All other authors declare that they have no conflicts of interest.

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### Key Message

This single-center study on Japanese children with immediate-type food allergies investigated that the annual rate of accidental allergic reactions was relatively low, while the fact that moderate to severe reactions occurred in half of the cases underscores their clinical significance. Low-dose reactivity emerges as a crucial risk factor, emphasizing the need for careful risk management, especially for children with low-dose reactivity

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**Results:** Of the 1096 participants, 609, 457, 138, and 90 had HE, CM, wheat, and peanut allergies, respectively. In this cohort, the median age was 5.0 years, 39% had completely eliminated allergenic food, and 24% had low-dose reactivity. The annual AAR rate was 0.130 in all sub-cohorts. Moderate and severe symptoms occurred in 50% and 0.7%, respectively, of children who experienced AAR. Multiple logistic regression revealed that low-dose reactivity was a significant risk factor for AAR in the overall, HE, and CM cohorts, respectively ($p$ <0.001, $p$ = 0.029 and 0.036).

**Conclusion:** In Japanese children with immediate-type food allergies, the annualized rate of AAR was relatively low; however, half of the participants with AAR had moderate to severe symptoms. Children, especially those with low-dose reactivity, would require careful risk management of AAR.

**Keywords:** allergic reactions; children; food allergies; prevalence; pediatrics; risk factors

## INTRODUCTION

The prevalence of food allergies in children has increased by 8%–10% over 15 years.[1,2] The main allergy-causing foods are peanuts, tree nuts, hen's egg (HE), and milk in the U.S. and HE, milk, wheat, and peanuts in Japan.[3,4]

Managing food allergies primarily involves dietary avoidance[5,6], but prevention of accidental allergic reactions (AAR) remains challenging,[7,8] causing anxiety among children and their guardians [9,10]. In the U.S., the annualized rate of allergic reactions among preschool children with CM, HE, or peanut allergies is 0.81, with 87% of these reactions being AAR[11]. An online cross-sectional survey conducted in the U.S, UK, Australia, and South Africa found AAR prevalence of 0.53.[12] Similarly, another study reported that 40% of Spanish children with CM allergy experienced AAR.[13]Surveys incorporating oral food challenges (OFCs) and standardized clinical follow-up are scarce, particularly in Japan, despite its unique food culture and allergen labeling.

Prior research has identified young age, history of anaphylaxis, multiple food allergies, and high specific immunoglobulin E (sIgE) levels as risk factors for AAR.[11–15] However, pediatrician-assessed factors, such as reaction thresholds, remain underexplored.

This study aimed to examine AAR prevalence in Japanese children with immediate-type food allergies to HE, CM, wheat, or peanuts, confirmed through pediatrician-led diagnosis and follow-up. Additionally, we evaluated AAR risk factors, including clinical indicators such as sIgE levels and thresholds determined by response to low doses.

## METHODS

### Study design

This study was conducted as a part of prospective cohort study for food allergic children (UMIN000013561). Concurrent with routine medical examinations at Sagamihara National Hospital, data on AAR were collected from outpatients at intervals of 2–4 months between January and December 2020. The study included children aged 0–18 years with a pediatrician-provided diagnosis of an immediate-type food allergy based on the following criteria: developing an allergic reaction in an OFC or having a history of allergic symptoms to HE, CM, wheat, or peanuts within 2 years before study initiation. Children diagnosed with a non-IgE-mediated food allergy or food-dependent exercise-induced anaphylaxis, who had received oral immunotherapy (OIT), whose sIgE levels had not been evaluated, or whose threshold dose had not been obtained within 2 years before the initiation of the study were excluded. Baseline data of the participants were collected at the beginning of the study. The allergic reactions were defined based on Japanese guidelines for food allergies.[4]

During regular follow-up visits over 2–4 months, pediatricians asked outpatients or their parents/guardians whether the patient had experienced AAR between the last visit and the current visit. For children who had experienced AAR, additional questions were asked regarding the dietary form, severity of symptoms, organ symptoms, treatments required, causative food, site, and cause of ingestion.

### Allergic reaction and management of food allergy

Symptoms were categorized according to the organ system, and symptom severity was classified as mild, moderate, or severe.[4]The clinical criteria for anaphylaxis diagnosis were defined by the World Allergy Organization in 2011.[16] For children with an unconfirmed diagnosis of food allergy or undetermined threshold, a low-dose ([?]250, [?]102, [?]53, or [?]133 mg HE, CM, wheat, or peanut protein, respectively) OFC, was performed initially. Patients who passed the low-dose OFC were instructed to consume the low dose 2–3 times per week, which was to include food that was cooked or processed at home. Thereafter, a stepwise OFC was performed.[4,17,18]Acquired tolerance to allergic food was defined as the state in which patients completed a full-dose OFC (6200, 6800, 5300, or 2660 mg for HE, CM, wheat, or peanuts protein, respectively) and were able to consume the same dose at home.

### Immunological parameters

Data of sIgE levels to egg white and ovomucoid for HE allergy, milk and casein for CM allergy, wheat and ω-5 gliadin for wheat allergy, and peanut and Ara h 2 for peanut allergies were measured using the ImmunoCAP assay system (Thermo Fisher Scientific/Phadia AB, Uppsala., Sweden). Thus, data that had been measured at the timepoint closest to the start of the study were used.

### Definition of terms

We defined AAR as symptoms induced by the unintended ingestion of an allergic food. Cases of intentional ingestion of food that was meant to be ingested or cases of symptoms due to ingestion in accordance with a pediatrician's instruction at home after passing the OFC were excluded. Children with low-dose reactivity were defined as those who reacted to low-dose OFCs or experienced allergic symptoms upon ingesting a low dose or less of the allergic food within 2 years preceding the study initiation. Those who passed the low-dose OFC and reacted to a dose higher than the low dose within 2 years preceding the study initiation were defined as those with low-dose tolerance.

### Primary and secondary outcomes

The primary outcome was the annualized rate of the AAR in all cohorts. Secondary outcomes included the rate of anaphylaxis. Additionally, this study examined the abovementioned outcomes in children who completely avoided allergic foods, the symptoms, required treatment, site where the AAR developed, causes of AAR, risk factors for the AAR experienced, and the difference between those with low-dose reactivity and low-dose tolerance in the rate of AAR.

### Statistical analysis

Baseline characteristics were shown in continuous data presented as medians and categorical data were presented as numbers. Comparisons between groups were performed using Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. The annualized rate of reactions was calculated by summing the number of reactions per patient and dividing it by the year. Logistic regression was used to perform univariate and multivariate analyses. The factors significantly associated with AAR were assessed for a crude odds ratio (OR) or an adjusted OR (aOR), with corresponding 95% confidence interval (CI) and associated $p$ -values. Statistical significance was set at $p < .05$. All data were processed and summarized using GraphPad Prism 7 for Mac (La Jolla, CA, USA) and IBM SPSS Statistics for Windows (version 24.0; IBM Corp., Armonk, NY, USA).

Logistic regression analyses were performed to assess risk factors for AAR. In the univariate logistic regression analysis, all patient characteristic variables at baseline were used. In the multiple logistic regression analysis, variables with $p$ <0.1 in the univariate analysis were adjusted.

### Ethical consideration

This study was conducted in accordance with the Declaration of Helsinki and approved by the Sagamihara National Hospital Ethics Committee. We obtained written informed consent for all patients before the initiation of the study at Sagamihara National Hospital. All data were anonymized prior to the analysis.

## RESULTS

### Study population

The patient selection process is illustrated in Figure 1. At baseline, in all cohorts (n = 1,096), the median age was 5.0 years, and there were 674 (61%) males. A history of anaphylaxis to the causative food was observed in 320 (29%) participants. Additionally, 425 (39%) had completely eliminated HE, CM, wheat, or peanuts from their diet, and 277 (25%) had multiple food allergies to HE, CM, wheat, or peanuts. In HE, CM, wheat, and peanut allergies, egg white- and ovomucoid-sIgE levels were 10.5 and 4.8 $kU_A/L$, milk- and casein-sIgE levels were 10.9 and 8.0 $kU_A/L$, wheat- and ω-5 gliadin-sIgE levels were 17.3 and 0.9 $kU_A/L$, and peanut- and Ara h 2-sIgE levels were 12.3 and 6.2 $kU_A/L$, respectively. Furthermore, 261 (24%) had low-dose reactivity, including 72 (12%) in HE, 126 (28%) in CM, 30 (22%) in wheat, and 43 (48%) in peanut allergy (Table 1) subgroups.

### Annualized rate of AAR and anaphylaxis

A total of 143 of 1,096 (13%) participants experienced 148 AAR. The annualized rates of AAR and anaphylaxis were 0.130 and 0.015 in all cohorts, 0.107 and 0.005 for HE, 0.124 and 0.019 for CM, 0.087 and 0.014 for wheat, and 0.111 and 0.011 for peanut allergies (Table 2). Among the patients who completely eliminated allergic foods, the rates of AAR and anaphylaxis were 0.162 and 0.035 in the overall cohort, 0.127 and 0.018 for HE, 0.167 and 0.037 for CM, 0.102 and 0.034 for wheat, and 0.166 and 0.014 for peanut allergies, respectively (Supplementary Table S1).

### Symptom severity, organ symptoms, and treatment required in AAR

Of the 148 AAR, 61 occurred in HE, 57 in CM, 12 in wheat, and 8 in peanut allergies. Mild symptoms were observed in 66 patients (44%), moderate symptoms in 76 (51%), and severe symptoms in 1 (0.7%) in all cohorts. The treatment was required in 101 (68%), and intramuscular adrenaline was administered to 6 (4%) (Table 2). There were 14 cases of anaphylaxis, and 6 received intramuscular adrenaline administered by guardians, teachers, or doctors. Of the 8 cases that were not administered, 5 had been pre-prescribed auto-adrenaline injections but could not use them for AAR. Alternative treatments besides adrenaline administration included the following: 8 cases received 8 antihistamines, 6 steroid administrations, and 2 inhalations of β2-stimulants.

### Consumed foods, sites, and the causes of accidental ingestion

In the overall cohort, 103/148 (70%) AAR developed due to the consumption of processed products. Eighty-eight (59%) AAR developed at home, followed by AAR at restaurants (13%), grandparents' homes (7%), and schools/nursery schools/kinder gardens (7%) (Supplementary Table S2). The most common cause of experiencing AAR was that the guardian or caregiver did not check the labeling (33%), and misunderstood the labeling (16%) (Supplementary Table S3).

**Risk factors for AAR**

The results of the univariate analysis for the overall cohort and HE, CM, wheat, and peanut allergy subcohorts are shown in Supplementary Tables S4A and S4B, respectively. In multiple logistic regression analysis, the significant risk factor for AAR was low-dose reactivity (aOR, 3.293, 95% CI: 2.086–5.200; $p$ <0.001; Table 3A), similar to the risks for moderate and severe AAR (aOR: 3.812, 95%CI: 2.075–7.003, $p$ <0.001, Supplementary Table S6) in the overall cohort. In HE allergy, multiple food allergens were significant risk factors, and low-dose reactivity was significant (aOR: 0.312 and 2.248, 95% CI: 0.146–0.668 and 1.085–4.659, $p = 0.003$ and 0.029, respectively; Table 3B). For CM allergy, a high sIgE level in milk and low-dose reactivity were significant factors, respectively (aOR: 2.113 and 3.707, 95% CI: 1.163–3.842 and 1.665–8.257, $p = 0.014$ and <0.010, respectively; Table 3B).

**Comparison of rate of AAR between patients with low-dose reactivity and tolerance**

The number of patients who experienced AAR was significantly higher in patients with low-dose reactivity than in those with low-dose tolerance in all cohorts (23.0% vs. 9.8%; $p$ <0.001, Figure 2A). Furthermore, the same significant differences were observed for HE, CM, and peanut allergies, respectively (18.1% vs. 9.5%, 25.4% vs. 6.9%, and 16.3% vs. 2.2%; $p = 0.009$, <0.001, and 0.017, respectively; Figure 2B).

## DISCUSSION

This study, led by pediatric allergists, tracked Japanese children with immediate-type food allergies for AAR. While the annualization rate was slightly lower than that reported before, half of the children who had experienced AAR showed moderate to severe allergic reactions. Low-dose reactivity was identified as a risk factor for AAR.

Previous reports in the U.S., UK, and Australia showed an annual rate of 0.5–0.7 for AAR [11,12]. In our study, the annualized rate of AAR was 0.130, which was lower than that in previous studies,[11,12] and this could be attributed to three factors. First, in labeling systems, allergenic ingredients must be shown on packaged foods; however, the form of allergen lists differs in each country.[19] For 15 years, food allergen labeling regulations have been enforced and periodically revised in Japan.[19] Moreover, polymerase chain reaction methods have been implemented to detect allergens in Japanese products.[20] Therefore, the system for allergen labeling in Japan may be relatively strict compared to that in other countries. Second, education for caregivers is important for the prevention of AAR.[11,21,22] Similarly, at Sagamihara National Hospital, most guardians and children were provided instructions about the labeling and prevention of AARs by pediatricians before the study period. Third, the coronavirus disease (COVID-19) pandemic occurred during the study period. A systematic review has reported that restaurants are the most common locations for AARs.[23] In a survey of allergic reactions among school-aged children, 23% of AARs developed in schools and 12% in friends' homes.[24] In our study, 59% of AARs developed at home, 13% at restaurants, and 7% at schools or nursery schools. Therefore, behavioral changes associated with the COVID-19 pandemic may have affected our study results.

In our study, half of the AAR had moderate to severe reactions. Among the eight patients who were not administered intramuscular adrenaline for anaphylaxis in AAR, five were previously prescribed auto-adrenaline injections but could not use them by themselves. Previous research indicates a similar gap in adrenaline use;[11]therefore, regular guidance is required for anaphylaxis caused by AAR.

This study showed that low-dose reactivity in all cohorts, HE or CM allergy, a single food allergy in HE allergy, and high sIgE level in milk in CM allergy were significant risk factors for AAR. Additionally, the number of patients who experienced AAR was significantly higher in the group with low-dose reactivity than

in the group with low-dose tolerance for HE, CM, and peanut allergies. For CM allergies, a high level of sIgE could be a predictor of the development of AAR, similar to the findings of a previous study.[13] In HE allergy, a single allergen was the risk factor, and the finding differed from a previous report.[25] In this study, the median age at inclusion was 4.7 years. In general, it has been suggested that half of the HE allergies at this age may have acquired tolerance.[26] At Sagamihara National Hospital, children with persistent allergies were referred from another hospital and included in this study; a larger cohort in a multicenter study is required. To the best of our knowledge, this is the first study to demonstrate low-dose reactivity as a risk factor in all cohorts. In school children, low-dose reactivity is one of the factors representing persistent HE or peanut allergy.[27,28] Additionally, children with low-dose reactivity may have an extended period during which they are at risk of experiencing AAR compared with those with low-dose tolerance. Therefore, children with low-dose reactivity are likely to experience AAR, and evaluation of low-dose reactivity would be useful for managing food allergies. Regarding the management of children with low-dose reactivity, low-dose OITs prevented the development of AAR in wheat or peanut allergy owing to the elevated threshold to a level that allows the ingestion of low doses.[29, 30]Therefore, low-dose OIT may prevent AAR in the daily lives of patients with low-dose reactivity.

This study has several limitations. First, it was conducted at a single national allergy center, possibly including severe food allergies. Second, food allergy diagnosis and OFC were not performed at the study's outset, potentially affecting diagnostic consistency and treatment. However, only children with thresholds determined within 2 years were included. Third, the study relied on patient/guardian-reported questionnaires, yet data were collected within 2-4 months, minimizing recall bias.

In conclusion, among the immediate types of HE, CM, wheat, and peanut allergies, half of the children who had experienced AAR showed moderate to severe reactions, although the annualized rate of AAR was relatively low. Children with low-dose reactivity would require careful risk management to prevent AAR.

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**Impact statement**

This study focused on accidental allergic reactions (AAR) in Japanese children with immediate-type food allergies. Although the annualized rate of AAR was relatively low, our findings reveal that half of the affected children experienced moderate to severe reactions. Furthermore, identifying low-dose reactivity as a risk factor for AAR could have practical implications for pediatricians and allergists, emphasizing the importance of careful risk management. This research contributes to a better understanding of AAR in children, potentially improving the safety and care of young patients with food allergies.

**Data availability statement**

If a reasonable request is made, the datasets used to support the findings of this trial are available from the corresponding author.

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**TABLES**

TABLE 1. Characteristics of the participants of this study

| | **Overall cohort (n = 1096)** | **HE (n = 609)** | **CM (n = 457)** | **Wheat (n = 138)** | **Peanut (n = 90)** |
|---|---|---|---|---|---|
| Age, years | 5.0 (2.3–8.6) | 4.7 (2.3–8.3) | 5.0 (2.4–8.5) | 4.2 (2.2–6.9) | 8.5 (6.5–10.7) |
| Sex, male | 674 (61%) | 384 (63%) | 274 (60%) | 87 (63%) | 54 (60%) |
| History of anaphylaxis to causative food | 320 (29%) | 116 (19%) | 135 (30%) | 39 (28%) | 28 (31%) |
| Complete elimination of causative food | 425 (39%) | 98 (16%) | 166 (36%) | 50 (36%) | 57 (63%) |
| Complication of allergic disease | | | | | |
| Atopic dermatitis | 747 (68%) | 414 (68%) | 325 (71%) | 99 (72%) | 58 (64%) |
| Bronchial asthma | 287 (26%) | 168 (28%) | 124 (27%) | 47 (34%) | 24 (27%) |
| Allergic rhinitis | 210 (19%) | 120 (20%) | 77 (17%) | 28 (20%) | 32 (36%) |
| Multiple food allergy+ | 277 (25%) | 184 (30%) | 187 (41%) | 83 (60%) | 18 (20%) |
| Total IgE level (IU/L) | 455 (137–1060) | 444 (121–1190) | 487 (150–996) | 515 (162–1055) | 765 (356–1310) |
| Antigen-sIgE level ($kU_A/L$) | N.A. | Egg white 10.5 (3.5–30) | Milk 10.9 (2.9–33.9) | Wheat 17.3 (3.8–45.5) | Peanut 12.3 (4.2–26.7) |

| | **Overall cohort (n = 1096)** | **HE (n = 609)** | **CM (n = 457)** | **Wheat (n = 138)** | **Peanut (n = 90)** |
|---|---|---|---|---|---|
| Component sIgE level ($kU_A/L$) | N.A.- | Ovomucoid 4.8 (1.3–18.9) | Casein (n =446) 8.0 (2.0–29.3) | Omega-5 gliadin 0.9 (0.3–3.5) | Ara h 2 6.2 (2.1–16.5) |
| Low-dose reactivity (low dose: [?]250 mg HE protein, [?]102 mg CM protein, [?]53 mg wheat protein, or [?]133 mg peanut protein) | 261 (24%) | 72 (12%) | 126 (28%) | 30 (22%) | 43 (48%) |

+The study cohort comprised patients with multiple food allergies, including a combination of HE, CM, wheat, or peanut. sIgE levels in all cohorts are not shown because the calculation of different antigen or component sIgE levels would be inapplicable. Asthma was defined according to the Global Initiative for Asthma 2019; atopic dermatitis with persistent eczema was diagnosed using the UK Working Party Criteria, and allergic rhinitis was diagnosed by a physician based on clinical symptoms.

sIgE; specific immunoglobulin E; N.A, not applicable; HE, hens' egg; CM, cow's milk.

TABLE 2. Annualized rate of accidental allergic reaction and anaphylaxis with symptom severity, organ-specific symptom, and treatments

| | Overall cohort (n = 1096) | HE (n = 609) | CM (n = 457) | Wheat (n = 138) | Peanut (n = 90) |
|---|---|---|---|---|---|
| Annualized rate of an accidental allergic reaction (95% CI) | 0.130 (0.109–0.153) | 0.107 (0.082–0.136) | 0.124 (0.094–0.161) | 0.087 (0.044–0.151) | 0.111 (0.053–0.204) |
| Annualized rate of anaphylaxis for accidental allergic reaction (95% CI) | 0.015 (0.009–0.025) | 0.005 (0.001–0.014) | 0.019 (0.009–0.037) | 0.014 (0.002–0.052) | 0.011 (0.0002–0.041) |
| Accidental allergic reactions, n | 148 | 61 | 57 | 12 | 8 |
| Severity of symptoms, n (%) | | | | | |
| Mild | 65 (44%) | 24 (39%) | 27 (47%) | 4 (33%) | 4 (50%) |
| Moderate | 76 (51%) | 32 (52%) | 29 (51%) | 7 (58%) | 4 (50%) |
| Severe | 1 (0.7%) | 0 (%) | 1 (2%) | 0 (0%) | 0 (0%) |
| Unknown | 6 (%) | 5 (8%) | 0 (0%) | 1 (8%) | 0 (0%) |

| | Overall cohort (n = 1096) | HE (n = 609) | CM (n = 457) | Wheat (n = 138) | Peanut (n = 90) |
|---|---|---|---|---|---|
| Symptoms, n (%) | | | | | |
| Skin | 68 (46%) | 25 (41%) | 29 (51%) | 5 (42%) | 4 (50%) |
| Oral mucosal | 31 (21%) | 10 (16%) | 14 (25%) | 1 (8%) | 4 (50%) |
| Respiratory | 32 (22%) | 9 (15%) | 16 (28%) | 4 (33%) | 1 (%) |
| Gastrointestinal | 36 (24%) | 23 (38%) | 6 (11%) | 3 (25%) | 2 (25%) |
| Cardiovascular | 3 (2%) | 1 (2%) | 2 (4%) | 0 (0%) | 0 (0%) |
| Neurological | 3 (2%) | 2 (3%) | 0 (0%) | 0 (0%) | 1 (%) |
| Treatments, n (%) | | | | | |
| Total treatments | 101 (68%) | 41 (67%) | 39 (68%) | 10 (83%) | 6 (75%) |
| Antihistamine | 84 (57%) | 40 (66%) | 31 (54%) | 10 (83%) | 5 (63%) |
| Steroids | 11 (7%) | 3 (5%) | 6 (11%) | 1 (8%) | 1 (13%) |
| β2-agonist inhalation | 5 (3%) | 0 (0%) | 2 (4%) | 2 (17%) | 1 (13%) |
| Intramuscular adrenaline | 6 (4%) | 0 (0%) | 6 (11%) | 0 (0%) | 0 (0%) |

The rates of symptom severity, organ symptoms, and treatments (%) represented accidental allergic reactions in all sub-cohorts: HE, CM, wheat, and peanut.

HE, hens' egg; CM, cow's milk

TABLE 3. Risk factors for accidental allergic reaction in the overall study cohort and among sub-cohorts with HE, or CM on multiple logistic regression

**(A)**

**(B)**

| n = 1069 |
|---|
| Complete elimination of causative food |
| Low-dose reactivity (low dose: [?]250 mg HE protein, [?]102 mg CM protein, [?]53 mg wheat protein, or [?]133 mg peanut p |

| | HE allergy (n = 609) | HE allergy (n = 609) | CM allergy (n = 457) | CM allergy (n = 457) |
|---|---|---|---|---|
| | aOR (95% CI) | *p*-value | aOR (95% CI) | *p*-value |
| Complete elimination of causative food | | | 0.788 (0.354–1.750) | 0.558 |
| Multiple food allergen | 0.312 (0.146–0.668) | 0.003 | | |
| Total-sIgE levels | 0.103 (0.624–1.742) | 0.873 | 0.560 (0.288–1.087) | 0.087 |
| Antigen-sIgE level+ | 1.470 (0.926–2.335) | 0.103 | 2.113 (1.163–3.842) | 0.014 |

| | HE allergy (n = 609) | HE allergy (n = 609) | CM allergy (n = 457) | CM allergy (n = 457) |
|---|---|---|---|---|
| Low-dose reactivity (low dose: [?]250 mg HE protein and [?]102 mg CM protein) | 2.248 (1.085–4.659) | 0.029 | 3.707 (1.665–8.257) | 0.001 |

The study cohort included patients with multiple food allergies, including a combination of HE, CM, wheat, and peanut allergies. Total IgE and antigen-sIgE levels were converted to log 10

values, which were used in the analysis. +Antigen-sIgE levels indicate egg white- or milk-sIgE levels. Multiple logistic regression analysis was performed in A) all cohorts, (B) HE allergy, and (C) CM allergy, respectively. Patients with wheat or peanut allergies were ineligible for inclusion in the multiple logistic regression analysis because of the small sample size. Additionally, for HE or CM allergies, egg white- and ovomucoid-sIgE or milk- and casein-sIgE levels would have been collinear. Therefore, egg white and milk sIgE levels were used as variables in the multiple logistic regression analysis of outcomes as shown in Supplementary Table S5. HE, hen's egg; CM, cow's milk

**Figure Legends**

Figure 1. Flowchart depicting the selection of participants for the study.

Among the 2,028 patients who were diagnosed with an HE, CM, wheat, or peanut allergy and had visited our institute, 24 patients who had been diagnosed with non-IgE-mediated food allergies and 9 with food-dependent exercise-induced anaphylaxis were excluded, as were 629 patients who had received oral immunotherapy (OIT) and 5 whose sIgE levels were not assessed. Furthermore, 265 patients whose threshold in the 2 years preceding the study initiation was not obtained were excluded. Finally, 1,096 participants were included in this study, and comprised 609, 457, 138, and 90 participants with HE, CM, wheat, and peanut allergies, respectively. HE, hen's egg; CM, cow's milk; FDEIAn, food-dependent exercise-induced anaphylaxis; OIT, oral immunotherapy.

Figure 2. Difference in the rate of AAR between children with low-dose reactivity and children with low-dose tolerance**.**

We compared the rates of AAR for patients with low-dose reactivity and those with low-dose tolerance to HE, CM, wheat, and peanut allergies in (A) all cohorts and (B) sub-cohorts. HE, hens' egg; CM, cow's milk.

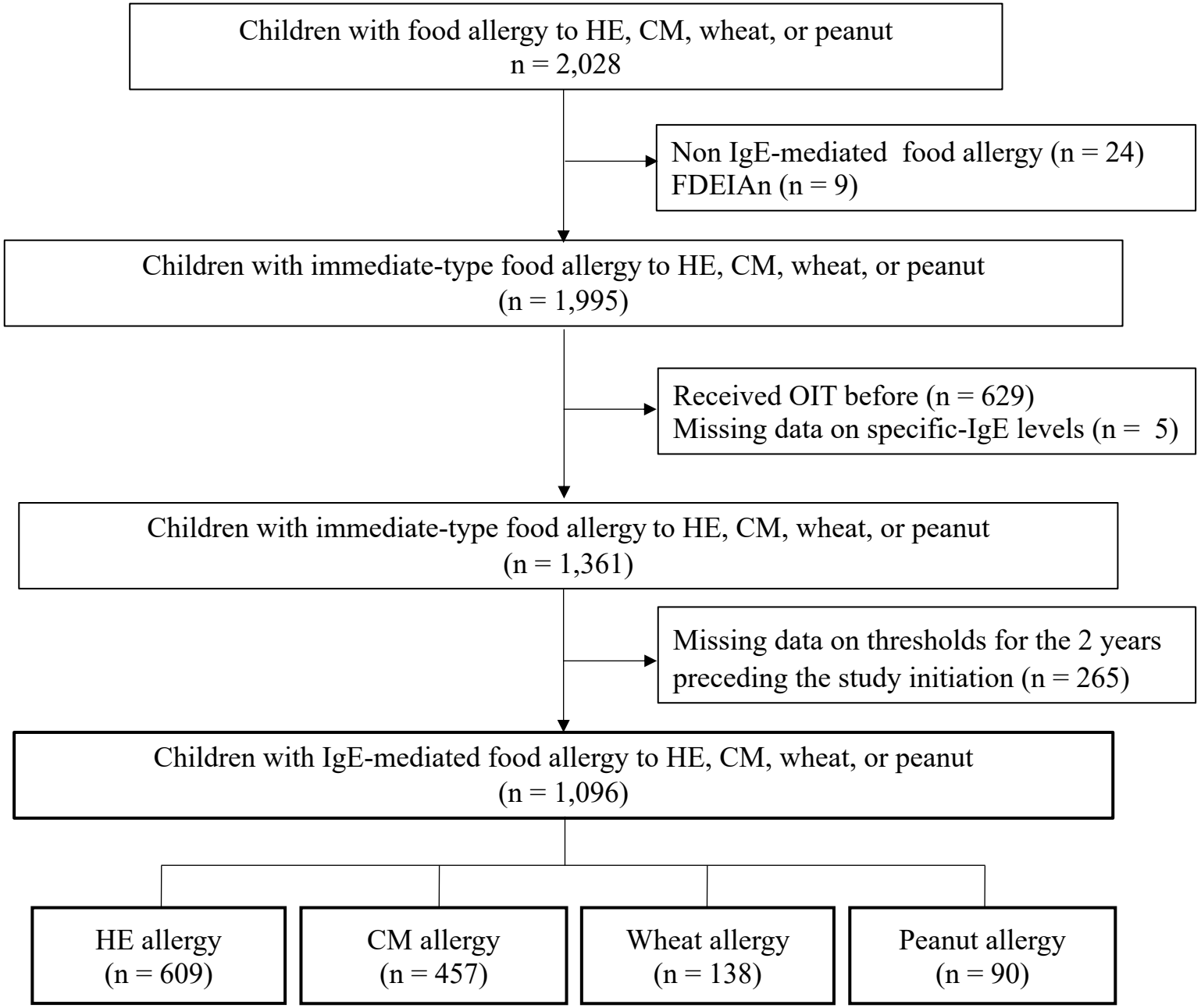
Children with food allergy to HE, CM, wheat, or peanut
n = 2,028
Non IgE-mediated food allergy (n = 24)
FDEIAn (n = 9)
Children with immediate-type food allergy to HE, CM, wheat, or peanut
(n = 1,995)
Received OIT before (n = 629)
Missing data on specific-IgE levels (n = 5)
Children with immediate-type food allergy to HE, CM, wheat, or peanut
(n = 1,361)
Missing data on thresholds for the 2 years preceding the study initiation (n = 265)
Children with IgE-mediated food allergy to HE, CM, wheat, or peanut
(n = 1,096)
HE allergy
(n = 609)
CM allergy
(n = 457)
Wheat allergy
(n = 138)
Peanut allergy
(n = 90)

**Figure 1**

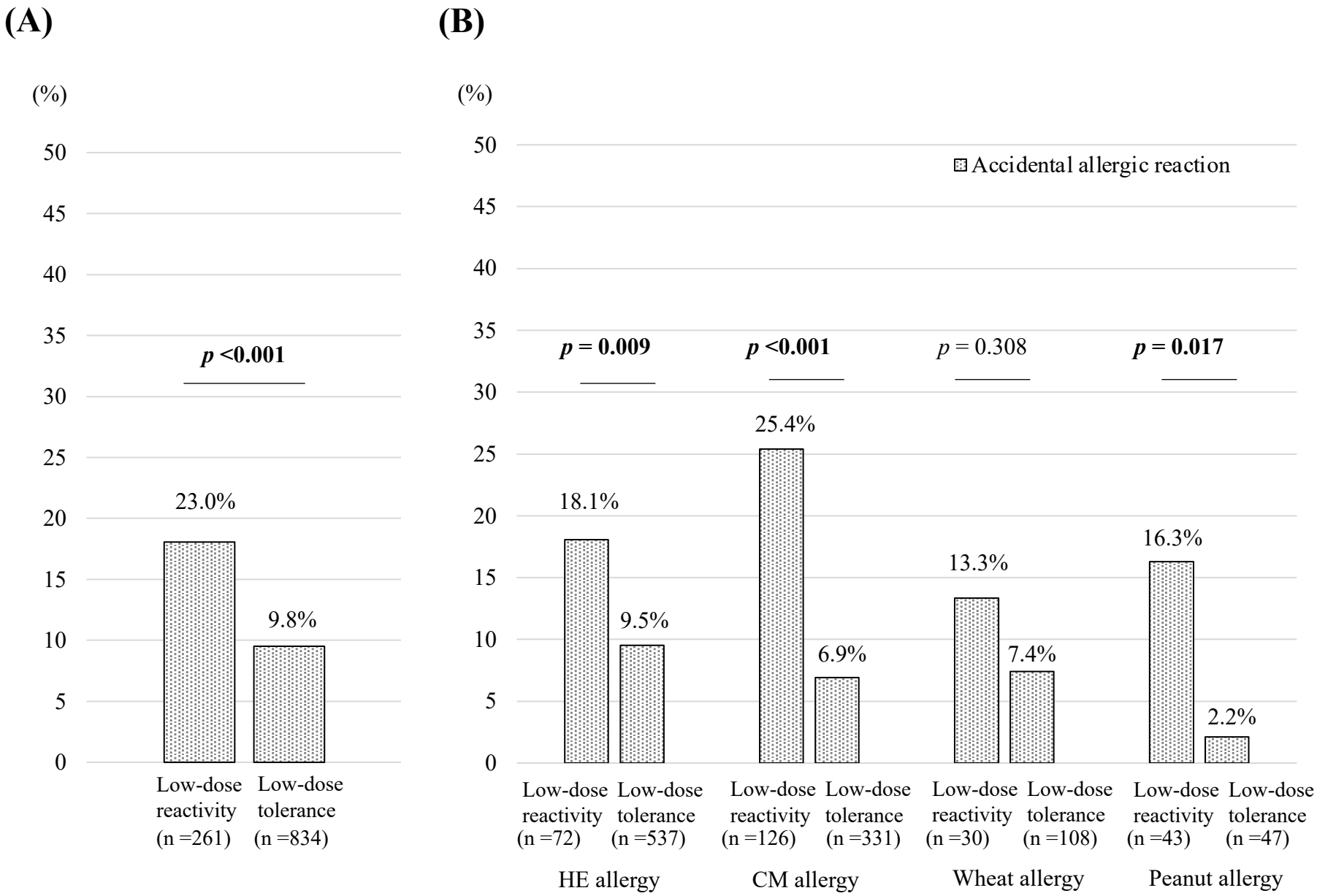
(A)
(%)
50
45
40
35
30
25
20
15
10
5
0
p <0.001
23.0%
9.8%
Low-dose reactivity (n =261)
Low-dose tolerance (n =834)
(B)
(%)
Accidental allergic reaction
p = 0.009
p <0.001
p = 0.308
p = 0.017
18.1%
9.5%
25.4%
6.9%
13.3%
7.4%
16.3%
2.2%
Low-dose reactivity (n =72)
Low-dose tolerance (n =537)
Low-dose reactivity (n =126)
Low-dose tolerance (n =331)
Low-dose reactivity (n =30)
Low-dose tolerance (n =108)
Low-dose reactivity (n =43)
Low-dose tolerance (n =47)
HE allergy
CM allergy
Wheat allergy
Peanut allergy

**Figure 2**