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Original Article

Comprehensive hospital-based regional survey of anaphylaxis in Japanese children: Time trends of triggers and adrenaline use

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AAI Adrenaline auto-injector

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ABSTRACT

Background: Since few studies have analyzed time trends in pediatric anaphylaxis, including triggers and adrenaline usage, this study aimed to reveal these issues in a comprehensive analysis of pediatric anaphylaxis cases.

Methods: The Aichi Medical Association performed a comprehensive survey of pediatric anaphylaxis cases aged under 15 years from 87 secondary and 25 tertiary emergency care hospitals in Aichi Prefecture (population 7.5 million), Japan.

Results: Between April 2016 and March 2020, 3423 cases of anaphylaxis were identified. Food items were the most frequent trigger (73%), followed by exercise after food ingestion (4.3%), and drugs (2.2%). Egg (19%) and milk (17%) specifically were the most frequent among food triggers, while the largest proportional increase was observed in tree nuts from 6.0% in 2017 to 15% in 2019. Overall, 1647 (48%) cases were admitted to the hospital, of which 26 (0.8%) were admitted to the intensive care unit. Drug-induced anaphylaxis was associated with the highest admission rate (71%). Of the 2493 food-induced anaphylaxis cases, 1107 (44%) were treated with adrenaline. Among them, 343 cases included previously prescribed adrenaline auto-injectors (AAI), with 225 (66%) usages prior to hospital arrival. There was no significant difference in the admission rate between the cases in which AAI were used and those with adrenaline administered in the hospital (68% and 72%, respectively).

Conclusions: The proportion of tree nuts in food-induced anaphylaxis increased significantly. Although prehospital AAI use has become widespread, it was not associated with lower admission rate compared to in-hospital adrenaline usage.

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Introduction

Anaphylaxis is a serious, life-threatening systemic hypersensitivity reaction that occurs immediately after exposure to allergenic substances.¹ Food is the most common cause of anaphylaxis in childhood; however, the characteristics of the food items that are frequent triggers vary by country and region.² In Western countries, peanut and cow's milk are the most frequent triggers,^{3,4} whereas in Asia, cow's milk, eggs, and wheat were more common and peanut and tree nuts were relatively rare.^{5–7} However, in a recent report from Hong Kong, peanut has become the most common cause of pediatric food-induced anaphylaxis.⁸ In addition, some reports from the United States indicate that the frequency of anaphylaxis

triggered by tree nuts has increased significantly, approaching that of peanut.^{9,10} Since the causes of pediatric food anaphylaxis not only vary by country or region but also change over time, it is essential to report on the latest trends. While there are many reports from Western countries, there are few from other regions, including Asia. We analyzed the latest trends of causative foods in pediatric anaphylaxis cases in the Japanese population. In addition, we analyzed drug-induced anaphylaxis, which is underreported in childhood anaphylaxis cases.

Despite global recommendations and guidelines to use adrenaline as the first-line treatment for anaphylaxis,^{1,5,11,12} underuse of adrenaline, including the use of adrenaline auto-injectors (AAI), is an issue that has been frequently reported.^{7,13} Unfortunately, there is a limited amount of published data on prehospital use of AAI in studies of pediatric anaphylaxis,^{14,15} and in particular, trends in the rate of AAI use or the association between AAI use and admission rates, are seldom reported. Recent reports from Western countries indicate that the rate of adrenaline administered by health care providers has increased over the last decade,^{10,16} however there are

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conflicting results for the use of AAI in self- or lay-treated anaphylaxis (some show increases¹⁰ while others show no change¹⁶). However, there have been no studies of large pediatric populations, or in Asia, which examine trends in AAI use or the association between having an AAI prescription, prehospital AAI use versus adrenaline administered in the hospital, and admission rates.

To our knowledge, this is one of the first studies to provide a comprehensive analysis of pediatric anaphylaxis cases in Asia. We analyzed contemporary time trends related to specific triggers, prehospital use of AAI and in-hospital adrenaline administration, and admission rates, to better understand and characterize the burden of pediatric anaphylaxis.

Methods

Study design, data source, and participants

Retrospective analysis was performed on the data obtained from the comprehensive surveillance conducted by the Committee of Emergency Medicine of the Aichi Medical Association. All 87 secondary and 25 tertiary emergency care hospitals in Aichi Prefecture, which has a population of 7.5 million (including 1 million children under 15 years of age), were included. We analyzed data from annual questionnaire surveys of anaphylaxis cases in patients under 15 years of age over a period of 4 business years, from April 1, 2016 (beginning of 2016 business year) to March 31, 2020 (end of 2019 business year). The diagnosis criteria for anaphylaxis was based on the World Allergy Organization's guidelines.¹ Food-induced anaphylaxis cases that occurred in hospital during oral food challenges were not included in the survey. This study was approved by the ethics committee of Aichi Children's Health and Medical Center (No. 2020102).

Variables

The following parameters were obtained in the questionnaire: age; sex; method of transportation to the hospital; cause of anaphylaxis; current prescription for and prehospital use of an AAI; adrenaline administered in the hospital; outcome after initial treatment, including admission to an intensive care unit (ICU); and final outcome. Detailed questions regarding specific causative foods and drugs were added to the questionnaire in 2017. The prefecture was divided into six regions based on the secondary medical care areas in Aichi Prefecture. The regions and their pediatric population under 15 years old (as of 2017, published by Aichi Prefecture) are as follows. Nagoya (306,959), Ama and Nishi-Owari (112,285), Owari (166,988), Chita Peninsula (88,474), Nishi-Mikawa (233,876), Higashi-Mikawa (100,484), and the prefecture total (1,009,066).

Statistics

The proportions of each age group, sex, method of transportation, trigger, outcome, and admission were calculated using the number of each outcome as the numerator and the total number of anaphylaxis cases as the denominator. Cases with unspecified causes and cases of undescribed adrenaline and AAI use or outcome were not excluded from the denominator when calculating the proportion. When comparing changes in the number of anaphylaxis cases between years and by region, the denominator was the population of children under 15 years old in Aichi Prefecture and by region. The differences in the proportions were analyzed using the chi-square test or Fisher exact test as appropriate. All significance tests were 2-sided, and $p < 0.05$ was considered statistically significant. All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University,

Saitama, Japan), which is a graphical user interface for R statistical software (The R Foundation for Statistical Computing, Vienna, Austria, version 3.5.1).¹⁷

Results

Demographic characteristics of anaphylaxis cases

Between the 2016 and 2019 business years, 3423 anaphylaxis cases (median patient age, 4 years; interquartile range 2–8 years; 62.5% male) were identified. Approximately 95% of secondary and 100% of tertiary care hospitals responded to the annual questionnaire over the 4-year study period. The number of cases per year was 735, 928, 912, and 848 in 2016, 2017, 2018, and 2019, respectively. The number of anaphylaxis cases in 2016 was significantly lower than in the other years ($p < 0.001$). The demographic and clinical characteristics of the cases are summarized in Table 1.

The distribution by age group and sex remained constant during the 4-year study period. Overall, the 1- to 4-year age group represented the highest percentage (40.3%) of cases, followed by the 5- to 9-year age group (28.9%). The most common method of transportation to the hospital was by car or walk-in accompanied by a family member (58.5%), whereas 32.3% of cases arrived at the hospital by ambulance. The remainder of the cases were transferred from other hospitals or were hospital-onset cases.

Overall, anaphylaxis was caused by food in 2493 (72.8%) of 3423 cases, followed by 148 (4.3%) cases of exercise after food ingestion

Table 1
Demographics and characteristics of anaphylaxis cases.

	2016		2017		2018		2019		All	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total	735		928		912		848		3423	
Age, y										
0	76	10.3	136	14.7	121	13.3	107	12.6	440	12.9
1–4	322	43.8	364	39.2	360	39.5	333	39.3	1379	40.3
5–9	199	27.1	271	29.2	273	29.9	246	29.0	989	28.9
10–14	138	18.8	157	16.9	158	17.3	162	19.1	615	18.0
Male	457	62.2	571	61.5	568	62.3	545	64.3	2141	62.5
Method of transportation to the hospital										
Family member	433	58.9	526	56.7	549	60.2	496	58.5	2004	58.5
Ambulance	221	30.1	304	32.8	289	31.7	293	34.6	1107	32.3
Transfer from other hospital	72	9.8	93	10.0	65	7.1	53	6.3	283	8.3
Hospital-onset	4	0.5	5	0.5	9	1.0	6	0.7	24	0.7
Unspecified	5	0.7	0	0.0	0	0.0	0	0.0	5	0.1
Triggers										
Food	545	74.1	665	71.7	670	73.5	613	72.3	2493	72.8
Food-exercise	41	5.6	30	3.2	42	4.6	35	4.1	148	4.3
Drug	18	2.4	16	1.7	24	2.6	18	2.1	76	2.2
Insect venom	2	0.3	1	0.1	2	0.2	3	0.4	8	0.2
Others [†]	1	0.1	2	0.2	5	0.5	5	0.6	13	0.4
Unspecified	128	17.4	214	23.1	169	18.5	174	20.5	685	20.0
Outcome										
Outpatient treatment only	347	47.2	425	45.8	495	54.3	462	54.5	1729	50.5
Admitted to general ward	380	51.7	457	49.2	413	45.3	371	43.8	1621	47.4
Admitted to ICU	5	0.7	9	1.0	3	0.3	9	1.1	26	0.8
Transferred to other hospital	2	0.3	6	0.6	1	0.1	6	0.7	15	0.4
Unspecified	1	0.1	31	3.3	0	0.0	0	0.0	32	0.9
No. of cases per hospital classification										
Secondary	212	28.8	210	22.6	243	26.6	203	23.9	868	25.4
Tertiary	523	71.2	718	77.4	669	73.4	645	76.1	2555	74.6

ICU, intensive care unit.

[†] Others include canine epithelium, feline epithelium, and mite.

(food-exercise), 76 (2.2%) cases of drug-induced anaphylaxis, and 8 (0.2%) cases of insect venom-induced anaphylaxis. The proportion of food-, food-exercise-, drug-, and insect venom-induced anaphylaxis among the total number of cases did not change significantly over the study period ($p = 0.67, 0.126, 0.58, \text{ and } 0.75$, respectively).

In the comparison of the methods of transportation to secondary and tertiary hospitals, accompaniment by a family member was significantly more common in secondary hospitals whereas arriving by ambulance was significantly more common in tertiary hospitals ($p < 0.001$ for both comparisons) (Supplementary Table 1). Moreover, the number of ICU admissions was significantly higher in tertiary hospitals ($p < 0.001$). However, there were no significant differences in the combined admission rates of the general ward and the ICU, or in the rates of adrenaline use.

Trends in food-induced anaphylaxis

Figure 1 presents the trends in the triggers of food-induced anaphylaxis, which are further detailed in Supplementary Table 2. Overall, egg accounted for the highest rates of food-induced anaphylaxis (19.4%), followed by cow's milk (17.4%). The greatest proportional increase among food triggers was seen with tree nuts, which increased from 6.0% in 2017 to 15.3% in 2019 ($p < 0.001$). There was no significant change in the proportion of other food causes during the study period. Tree nuts and peanut together accounted for the largest proportion of food-induced anaphylaxis in 2018 (18.6%) and 2019 (20.2%). Walnut accounted for the highest incidence among tree nuts (42.6% of tree nuts in 2019, Supplementary Table 3), followed by cashew (19.1% in 2019), pistachio, macadamia, and almond.

The number of food-induced anaphylaxis cases decreased with increasing age, and the number of food-exercise-induced anaphylaxis cases increased in those 10 years of age and older (Fig. 2, Supplementary Table 4). Among the triggers of food-induced anaphylaxis, egg, milk, wheat, tree nuts, and fish roe were more likely to affect younger children (medians, 2, 4, 4.5, 3, and 3 years, respectively), whereas peanut, fruits, and crustacean were more

likely to affect older children (medians, 6, 6.5, and 8.5 years, respectively).

The median age for food-exercise-induced anaphylaxis was 11 years. Of the 25 cases with an identified trigger food, wheat was the most common (11 cases), followed by milk (7 cases), egg (2 cases), and crustacean (2 cases). There were no significant changes in the proportions of each trigger food over the study period (Supplementary Table 5).

Drug-induced anaphylaxis and venom-induced anaphylaxis

Drug-induced anaphylaxis accounted for 2.2% of all causes during the study period (Table 1). The median age for drug-induced anaphylaxis was 6 years and was distributed across all ages, including younger children (Fig. 2, Supplementary Table 4). Of the 58 cases in which a suspected drug was identified, antibiotics and vaccines were the most common (9 cases), followed by contrast agents (5 cases), and antiviral drugs (5 cases) (Supplementary Fig. 1). There were no significant changes in the proportions of each causative drug over the study period (Supplementary Table 5).

Insect venom-induced anaphylaxis was rare and appeared primarily in children older than 10 years of age.

Outcome

Overall, 1729 (50.5%) of the cases were discharged home directly after outpatient treatment, 1621 (47.4%) were admitted to the general ward, and 26 (0.8%) were admitted to the ICU (Table 1). The admission rate for food-induced anaphylaxis was 54.4% and by comparison, was significantly higher for drug-induced anaphylaxis (71.1%, $p = 0.003$, chi-square test, Supplementary Table 6). Of those admitted to the ICU, a trigger for anaphylaxis was identified in 12 cases: 9 were food-induced (milk, wheat, and cashew were identified in two cases each and one case each for macadamia, shrimp, and peach); 2 were contrast-agent-, and one was anesthetic-induced. There were no deaths, and all cases were discharged without sequelae.

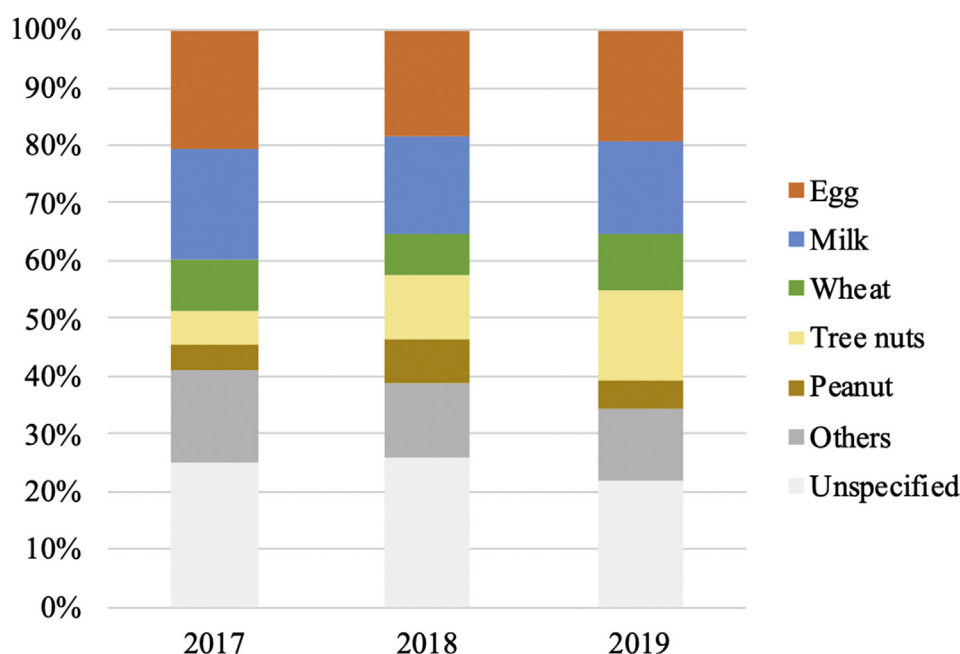


Fig. 1. Trends in proportion of specific triggers in food-induced anaphylaxis by year. Food items other than those specifically mentioned were consolidated into "Others."

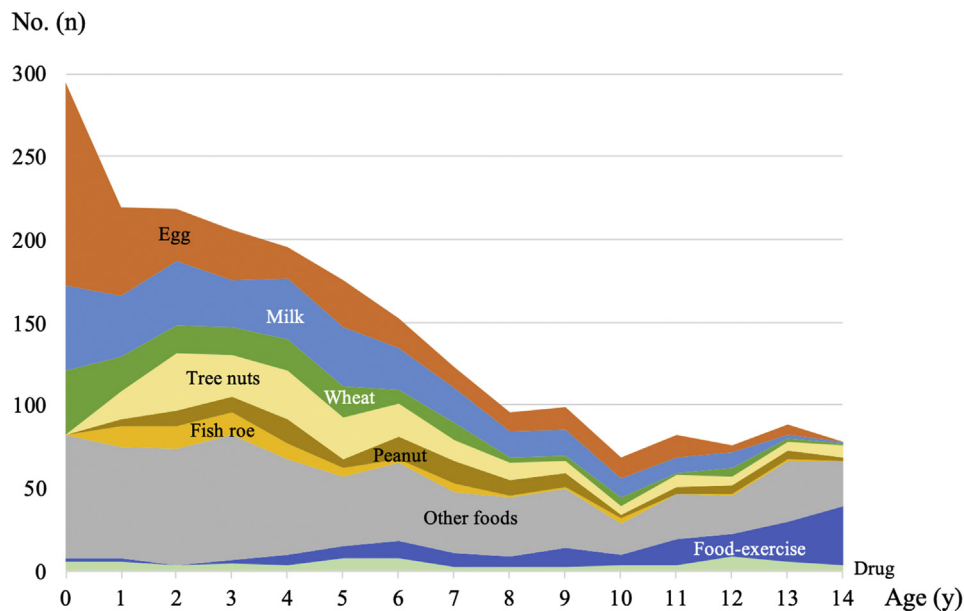


Fig. 2. Triggers of anaphylaxis by age for food, food-exercise, and drug causes. Food items other than those specifically mentioned were consolidated into "Other foods." Food-exercise indicates anaphylaxis caused by exercise after food ingestion.

AAI and in-hospital use of adrenaline

Of the 2493 cases with food-induced anaphylaxis, 1107 were treated with adrenaline, of which 343 had been previously prescribed an AAI; 225 (65.6%) of the 343 used an AAI before arriving at the hospital, while 118 (34.4%) had not used an AAI and received adrenaline in the hospital instead (Table 2). This proportion changed from 53.3% (40 of 75) in 2016 to 65.4% (53 of 81) in 2019, but this difference was not statistically significant ($p = 0.124$, chi-square test). In 37 out of 225 cases, a second dose of adrenaline was used in the hospital. In the analyses not limited to food-induced anaphylaxis, the trends in AAI and adrenaline use in the hospital were similar (Supplementary Table 7).

Of the three cases of drug-induced anaphylaxis in which patients had been previously prescribed an AAI, one of them used it prior to the hospital visit. On the other hand, 28 of the 73 cases who had not received an AAI prescription were given adrenaline in the hospital. For insect venom, 1 case had an AAI prescription and used it before the visit; 2 of 7 cases who had not received an AAI prescription received adrenaline in the hospital. The rates of adrenaline and AAI use in food-exercise-induced anaphylaxis were similar to those of food and did not change significantly over the study period (Supplementary Table 8).

AAI use and admission rates

Of the 276 cases who used an AAI before arriving at the hospital, 185 (67.0%) were admitted (Table 3). On the other hand, 98 of 136 cases (72.1%) who were previously prescribed an AAI but did not use it and instead received adrenaline in the hospital, were admitted ($p = 0.27$, chi-square test). Of the 878 cases who were not prescribed an AAI and received adrenaline after arrival at the hospital, 732 (83.4%) were admitted. Of the 1730 cases who did not receive adrenaline regardless of an existing AAI prescription, 583 (33.7%) were admitted. In the analysis limited to food-induced anaphylaxis, the admission rates with or without an AAI and adrenaline use were similar to those in the analysis of all causes as described above.

Comparison by regions

In the Owari region, the number of anaphylaxis cases per 1000 among the pediatric population was 1.52, which was significantly higher than that of the prefecture as a whole ($p < 0.001$), while the numbers in Ama and Nishi-Owari, and Higashi-Mikawa were significantly lower at 0.62 and 0.38, respectively ($p < 0.001$, for both regions) (Supplementary Fig. 2). The rate of adrenaline use was significantly higher in Nagoya than in the prefecture as a whole ($p < 0.001$), while it was lower in Owari, Chita Peninsula, and Nishi-Mikawa ($p = 0.002$, 0.003, 0.001, respectively). There was no significant difference in the proportion of cases in which AAI was used among those in which an AAI was prescribed and adrenaline administration was required.

Discussion

To our knowledge, this is the first study to report time trends in anaphylaxis triggers in the Japanese pediatric population using a comprehensive database which covers almost all secondary and tertiary care hospitals. Furthermore, trends in prehospital AAI use and in-hospital adrenaline use, and their association with admission rates, were analyzed.

Of the 3423 anaphylaxis cases, the most frequent trigger was food-induced anaphylaxis, followed by food-exercise-induced anaphylaxis. The predominance of food triggers was in line with other data, such as from Europe, the United States, Canada, and Asia.^{3,5,8,18–20} Over the 4-year study period, there was no significant change in the number of anaphylaxis cases. Although we did not obtain the monthly number of cases, it is possible that the COVID-19 pandemic has had an impact on the number of reported cases in the lower quarter of the 2019 business year (ending March 2020).

Among the specific food triggers, egg accounted for the highest rates of food-induced anaphylaxis, followed by milk (overall, 19.4% and 17.4%, respectively). Our results showed the trends of anaphylaxis induced by tree nuts, which increased from 6.0% in 2017 to 15.3% in 2019. Peanut was the fourth or fifth most common cause, alternating with wheat. Since 2018, tree nuts and peanut combined have become the most common cause, surpassing egg.

Table 2

Trends in the use of prehospital AAI and in-hospital adrenaline use (food-induced anaphylaxis).

	2016		2017		2018		2019		All	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total no. of food-induced anaphylaxis	545		665		670		613		2493	
Adrenaline used	255	46.8	291	43.8	298	44.5	263	42.9	1107	44.4
AAI prescribed and used	40		62		70		53		225	
AAI prescribed but NOT used, and adrenaline used in hospital	35		30		25		28		118	
Proportion of cases in which used AAI among those prescribed AAI and required adrenaline administration	53.3%		67.4%		73.7%		65.4%		65.6%	
AAI not prescribed, and adrenaline used in hospital	169		198		203		181		751	
AAI prescription undescribed, and adrenaline used in hospital	11		1		0		1		13	
Adrenaline not used	290	53.2	374	56.2	372	55.5	343	56.0	1379	55.3
Adrenaline use undescribed	0	0.0	0	0.0	0	0.0	7	1.1	7	0.3

Table 3

Outcome and admission rates by prehospital use of an AAI and in-hospital adrenaline use.

	Outpatient	Admission		Transfer	Unspecified	All	Admission rate
		General ward	ICU				
Adrenaline used							
AAI prescribed and used	90	181	4	1	0	276	67.0%
AAI prescribed but NOT used, and adrenaline used in hospital	37	98	0	0	1	136	72.1%
AAI not prescribed, and adrenaline used in hospital	139	720	12	7	0	878	83.4%
AAI prescription undescribed, and adrenaline used in hospital	12	10	2	0	0	24	—
Adrenaline not used	1140	580	3	7	0	1730	33.7%
Adrenaline use undescribed	311	32	5	0	31	379	—
Total no.	1729	1621	26	15	32	3423	48.1%

This is somewhat surprising because tree nuts and peanut allergies were previously considered uncommon in Asia, including Japan. According to previous reports, the most common food allergens in Japan have long been egg, milk, and wheat.⁵ However, our finding was consistent with a 2017 nationwide survey in Japan of immediate-type food allergies, not limited to anaphylaxis, which reported an increase in tree nuts as the cause.²¹ In another report analyzing hospitalized cases of food-induced anaphylaxis in Japan, peanut was found to be an increasing cause in children.²² Peanut and tree nuts are well known as the leading causes for food-induced anaphylaxis in Western countries.^{3,19,20,23} Asia may be experiencing similar trends, even though the rate remains lower than in Western countries. The import of tree nuts in Japan has doubled in the last decade, and more frequent consumption at home may be related to their increased prevalence as a cause of anaphylaxis.^{24,25}

There are few reports of drug-induced anaphylaxis in children in the literature, and it is considered to occur less frequently in children than in adults.^{8,26} In the present study, the proportion of drug-induced anaphylaxis over a 4-year period was 2.2%, a rate that is not uncommon. The ages of the cases were widely distributed, including babies aged 0 years, which is different from previous reports that drug-induced anaphylaxis was less common in younger children and more common in older children and adults.^{23,27} As in previous reports, an antibiotic was the most frequent causative drug,^{3,7} however, there was also a wide range of drugs and dosage forms that were identified, including vaccines, contrast agents, antivirals, antipyretics, allergen immunotherapies, as well as eyedrops and transdermal patches. To our knowledge, no other study has reported as extensively on causative drugs of pediatric drug-induced anaphylaxis as this study. Furthermore, high admission rates for drug-induced anaphylaxis were in some ways consistent with a previous report that drugs were the most common cause of pediatric anaphylaxis cases requiring ICU admission.²⁸

Of the 2493 cases of food-induced anaphylaxis, adrenaline was used in 44.4% (1107 cases), including 9.0% (225 cases) prehospital AAI use and 35.4% (882 cases) in-hospital adrenaline use. The rates of adrenaline use in patients with anaphylaxis was found to vary considerably among reports and among countries and regions, from 14% in the United Kingdom to 23.2% in Europe and 62.4% in Australia.^{14–16} The proportion in this study can be considered comprehensive and presents fairly accurate data on a large number of cases, which is valuable because reporting is scarce in Asia.

The current study also examined the rate of appropriate use among those who were prescribed an AAI. A total of 343 cases that had been prescribed an AAI required adrenaline administration, of which 65.6% (225 cases) used an AAI before arriving at the hospital. The proportion of appropriate use of AAI has changed from 53.3% in 2016 to 65.4% in 2019, but this difference was not statistically significant ($p = 0.124$). Despite universal recommendation by current treatment guidelines, low usage of adrenaline as first-line treatment of anaphylaxis has been noted worldwide.^{7,13} Recent reports from Europe, the United States, and Canada indicated that the use of adrenaline administered by health care providers has increased over the last decade, while changes in the rates of AAI use in self- or lay-treated anaphylaxis have not necessarily increased.^{10,16} Further improving the rate of the appropriate use of adrenaline is an important issue and improved distribution of the guidelines and increased awareness are necessary.

There was no significant difference in the admission rate between the cases who used an AAI before arriving at the hospital, and those who were prescribed an AAI but did not use it and instead received adrenaline in the hospital (67.0% and 72.1%, respectively, $p = 0.27$). Previously in the literature, there have been conflicting data on the association between early treatment with adrenaline and the rate of admission, which may be due to factors such as the high incidence of severe anaphylaxis cases requiring hospitalization in those treated with adrenaline. As far as we could find, there was only one report that examined the association between the timing of adrenaline use and

admission rates in children with food-induced anaphylaxis, and it found that the use of adrenaline before hospital arrival significantly reduced the admission rate when compared with the use of adrenaline in the hospital.²⁹ One of the purposes of AAI when used appropriately is to reduce admissions and healthcare costs, however in this study, AAI use did not contribute to a reduction in admission rates. In Japan, children under 15 years of age are covered by the universal health insurance system, which provides free medical care, including hospital admission in most cases. For anaphylaxis that is relatively severe enough to require the use of an AAI, it is customary to hospitalize the patient overnight as a precaution, which may have influenced our results.

The number of anaphylaxis cases was significantly lower in 2016 compared to the other years; there were no significant differences between 2017, 2018, and 2019. It cannot be ruled out that the number of cases may have increased due to increased awareness of this study after the second year. Therefore, it could not be concluded that there was a constant increase throughout the study period indicating the need to continue the survey in the future.

In the Owari region, where the number of reported cases per 1000 among the pediatric population was significantly higher than in other regions, there are several tertiary care hospitals, and it was assumed that many were overflow cases from neighboring regions. On the other hand, in Awa and Nishi-Owari, a certain number of cases were presumed to have overflowed to the neighboring Nagoya region. The reason for the low number of cases in Higashi-Mikawa is unknown. The differences in anaphylaxis cases by region in this study may reflect the emergency medical care provision system in addition to the actual number of cases. However, since we did not investigate the location of each hospital visit and the location of the patients' residences, we were not able to examine how many cases actually flowed in and out between regions. The rate of adrenaline use also varied by region, however, there was no consistent trend, such as higher rates in urban areas or lower rates in rural areas.

Our study has some limitations. First, the incidence rate could not be calculated because primary medical facilities, including allergist clinics, were not included in the survey. Second, although this study covers one-fifteenth of Japan's population under the age of 15, it is possible that the data does not represent trends for the Japanese population as a whole. Third, two facilities reported only hospitalized cases; therefore, the admission rates are not necessarily accurate. Fourth, the survey did not collect the precise time course or the changes in symptoms after adrenaline use in each event due to the retrospective manner of this project. These issues of time course have been discussed in a different survey we conducted previously, a nationwide surveillance conducted by the Japanese Society of Pediatric Allergy and Clinical Immunology.³⁰ Furthermore, detailed clinical presentations including the prior diagnosis of allergies, the severity of anaphylaxis, or treatments other than adrenaline were not collected. Although the definition of anaphylaxis is clearly stated, it is possible that the application of the criteria may be slightly different in each hospital.

In conclusion, this is a comprehensive report of anaphylaxis in a large population of Japanese children and includes detailed data and trends in food and drug triggers, adrenaline use (including AAI), and admissions for anaphylaxis. Our study demonstrates a significant increase in the proportion of food-induced anaphylaxis cases involving tree nuts. Further nationwide studies of anaphylaxis are needed to better understand the epidemiologic trends and to improve patient care.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.04.009>.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

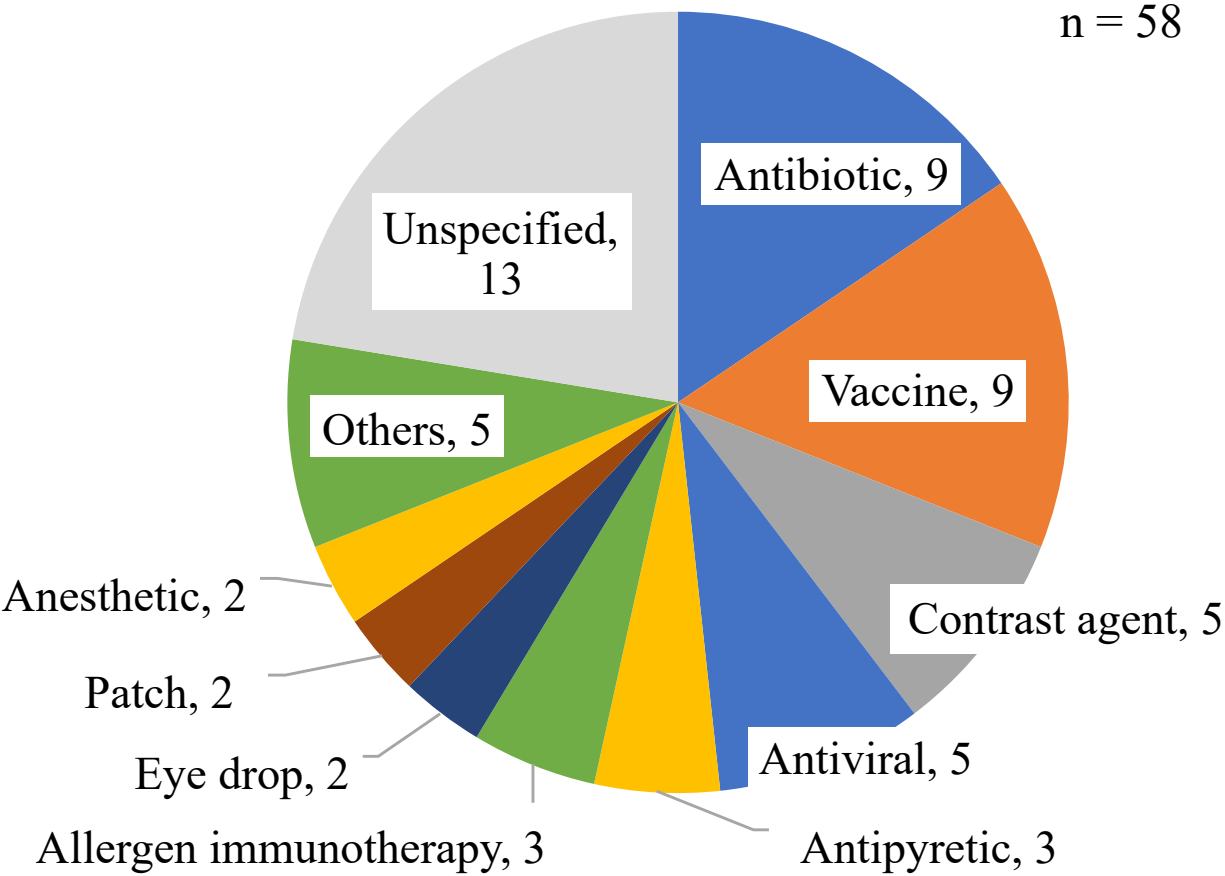
KK, TI, and KI conceived and designed the study. KK analyzed the data and wrote the manuscript. TI was the principal organizer of the survey and KI had the final responsibility of the data analysis. All authors read and approved the final manuscript.

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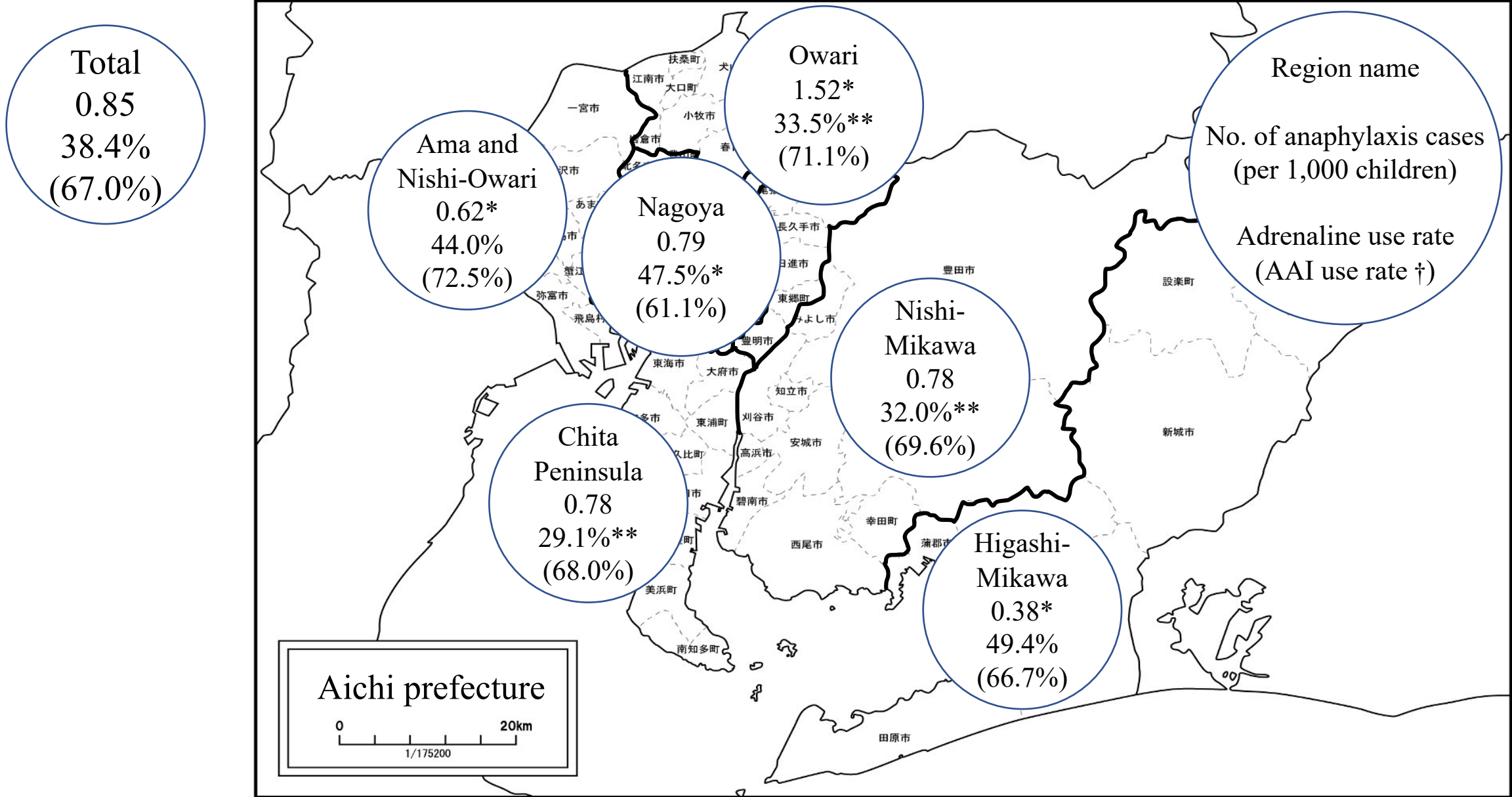
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Supplementary Figure 1. Breakdown of specific causes of drug-induced anaphylaxis (Summary of 2017 to 2019).



Others included cold medicine, monoclonal antibody, fluoride (dental), antiemetic, and probiotic.

Supplementary Figure 2. Number of anaphylaxis and rate of adrenaline use by region.



* $p < 0.001$ compared with total. ** $p < 0.05$ compared with total.

† Proportion of cases in which AAI was used among those AAI was prescribed and adrenaline administration was required.

Supplementary Table 1. Demographics and characteristics of anaphylaxis cases in secondary and tertiary hospitals.

	Secondary		Tertiary	
	No.	%	No.	%
Total	868		2555	
Age, y				
0	131	15.1	318	12.4
1-4	330	38.0	1040	40.7
5-9	251	28.9	738	28.9
10-14	156	18.0	459	18.0
Male	569	65.6	1572	61.5
Method of transportation to the hospital				
Family member	572	66.2	1432	56.1
Ambulance	216	25.0	891	34.9
Transfer from other hospital	69	8.0	214	8.4
Hospital-onset	7	0.8	17	0.7
Unspecified	4	-	1	-
Triggers				
Food	726	90.4	1767	91.3
Food-exercise	44	5.5	104	5.4
Drug	22	2.7	54	2.8
Insect venom	3	0.4	5	0.3
Others†	8	1.0	5	0.3
Unspecified	65	-	620	-
Outcome				
Outpatient treatment only	407	46.9	1322	52.4
Admitted to general ward	446	51.4	1175	46.6
Admitted to ICU	0	0.0	26	1.0
Transferred to other hospital	14	1.6	1	0.0
Unspecified	1	-	31	-
Adrenaline				
Adrenaline used	373	43.0%	935	42.8%
Adrenaline not used	495	57.0%	1250	57.2%
Adrenaline use undescribed	0	-	370	-

ICU, intensive care unit. † Others include canine epithelium, feline epithelium, and mite.

Cases in which method of transportation, trigger, outcome, or adrenaline use were unspecified were excluded when calculating the proportion.

Supplementary Table 2. Trends in the triggers of food-induced anaphylaxis.

	2017		2018		2019		All	
	No.	%	No.	%	No.	%	No.	%
Food	665		670		613		1948	
Egg	137	20.6	123	18.4	118	19.2	378	19.4
Milk	127	19.1	113	16.9	99	16.2	339	17.4
Wheat	60	9.0	50	7.5	61	10.0	171	8.8
Tree nuts	40	6.0	74	11.0	94	15.3	208	10.7
Peanuts	28	4.2	51	7.6	30	4.9	109	5.6
Fish roe	26	3.9	27	4.0	16	2.6	69	3.5
Fruits	15	2.3	17	2.5	16	2.6	48	2.5
Crustacean	13	2.0	5	0.7	14	2.3	32	1.6
Buckwheat	12	1.8	9	1.3	8	1.3	29	1.5
Fish	9	1.4	8	1.2	4	0.7	21	1.1
Soy bean	10	1.5	3	0.4	4	0.7	17	0.9
Others†	23	3.5	17	2.5	15	2.4	55	2.8
Multiple	53	8.0	53	7.9	44	7.2	150	7.7
Unspecified	112	16.8	120	17.9	90	14.7	322	16.5

† Other foods include sesame, barley, squid, shellfish (clam, oyster), coconut, beef, vegetables (yam, snap pea, cucumber, potato, tomato, corn, carrot, paprika, bean sprout, lotus root, and wild plants).

Supplementary Table 3. Proportion of specific tree nuts by year.

	2017		2018		2019	
	No.	%	No.	%	No.	%
Tree nuts	40		74		94	
Walnut	20	50.0	37	50.0	40	42.6
Cashew	6	15.0	9	12.2	18	19.1
Pistachio	0	0.0	0	0.0	5	5.3
Macadamia	3	7.5	2	2.7	4	4.3
Almond	2	5.0	2	2.7	3	3.2
Others†	0	0.0	2	2.7	1	1.1
Unspecified‡	9	22.5	22	29.7	23	24.5

† Others include pecan, hazelnut, and chestnut.

‡ Unspecified includes those described as 'tree nuts' or multiple nuts.

Supplementary Table 4. Number of anaphylaxis cases of specific triggers by age.

Age, y	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total	Median age, y
Triggers, No																	
Food	287	212	214	199	185	160	134	112	87	85	59	63	54	58	39	1948	4
Egg	123	54	31	31	19	28	17	13	12	14	13	13	4	6	0	378	2
Milk	51	37	39	28	36	36	26	21	15	15	12	10	10	2	1	339	4
Wheat	39	21	17	17	19	18	8	10	4	4	5	1	5	2	1	171	4.5
Tree nuts	0	16	34	25	29	25	20	13	10	7	5	7	5	5	7	208	3
Peanut	0	5	10	9	15	6	14	13	10	8	2	4	5	5	3	109	6
Fish roe	0	12	13	14	10	5	2	5	1	1	3	0	1	2	0	69	3
Fruit	7	8	4	0	1	2	2	1	2	5	2	3	2	6	3	48	6.5
Crustacean	2	1	2	2	2	1	3	2	1	5	0	4	1	1	5	32	8.5
Buckwheat	1	1	1	5	5	2	3	0	3	1	0	3	2	1	1	29	5
Fish	1	1	3	1	2	1	2	0	1	0	1	0	0	5	3	21	6
Soy bean	3	4	1	1	1	2	1	0	1	0	0	0	2	0	1	17	3
Others	1	6	4	5	4	2	2	6	5	1	0	4	5	4	6	55	-
Unspecified	59	46	55	61	42	32	34	28	22	24	16	14	12	19	8	472	-
Food-exercise	2	2	0	2	6	7	10	8	6	12	6	15	13	24	35	148	11
Drug	6	6	4	5	4	8	8	3	3	2	4	4	9	6	4	76	6
Venom insect	1	0	0	0	0	2	0	0	0	0	1	1	1	1	1	8	10.5

Supplementary Table 5. Number of food-exercise- and drug-induced anaphylaxis breakdown by year.

	2017	2018	2019
Food-exercise	8	5	12
Wheat	3	4	4
Milk	1	0	6
Egg	1	0	1
Crustacean	0	1	1
Fruit	1	0	0
Multiple	2	0	0
Drug	16	24	18
Antimicrobials	5	4	5
Biologicals	0	8	2
Central nervous system agents	2	3	1
Contrast agents	2	2	1
Others†	4	2	4
Unspecified	3	5	5

† Others included allergen immunotherapy, eye drop, patch, fluoride (dental), antiemetic, and probiotic.

Supplementary Table 6. Outcome and admission rate by triggers.

	Outpatient	Admission		Transfer	Unspecified	All	Admission rate
		General ward	ICU				
Food	1126	1344	12	10	1	2493	54.4%
Food-exercise	67	79	1	1	0	148	54.1%
Drug	21	50	4	1	0	76	71.1%
Insect venom	6	2	0	0	0	8	25.0%
Others†	6	7	0	0	0	13	53.8%
Unspecified	503	139	9	3	31	685	21.6%
Total	1729	1621	26	15	32	3423	48.1%

ICU, intensive care unit.

† Others include canine epithelium, feline epithelium, and mite.

Supplementary Table 7. Trends in the use of prehospital AAI and in-hospital adrenaline use (all causes).

	2016		2017		2018		2019		All	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total no. of anaphylaxis	735		928		912		848		3423	
Adrenaline used	308	41.9	334	36.0	352	38.6	314	37.0	1308	38.2
AAI prescribed and used	50		75		78		67		270	
AAI prescribed but NOT used, and adrenaline used in hospital	40		37		29		30		136	
Proportion of cases in which used AAI among those prescribed AAI and required adrenaline administration	55.6%		67.0%		72.9%		69.1%		66.5%	
AAI not prescribed, and adrenaline used in hospital	196		221		245		216		878	
AAI prescription undescribed, and adrenaline used in hospital	22		1		0		1		24	
Adrenaline not used	427	58.1	446	48.1	449	49.2	423	49.9	1745	51.0
Adrenaline use undescribed	0	0.0	148	15.9	111	12.2	111	13.1	370	10.8

AAI, adrenaline auto injector.

Supplementary Table 8. Trends in the use of prehospital AAI and in-hospital adrenaline use (food-exercise).

	2016		2017		2018		2019		All	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total no. of food-induced anaphylaxis	41		30		42		35		148	
Adrenaline used	19	46.3	13	43.3	23	54.8	16	45.7	71	48.0
AAI prescribed and used	6		5		7		8		26	
AAI prescribed but NOT used, and adrenaline used in hospital	3		3		4		1		11	
Proportion of cases in which used AAI among those prescribed AAI and required adrenaline administration	66.7%		62.5%		63.6%		88.9%		70.3%	
AAI not prescribed, and adrenaline used in hospital	10		5		12		7		34	
AAI prescription undescribed, and adrenaline used in hospital	0		0		0		0		0	
Adrenaline not used	22	53.7	17	56.7	19	45.2	19	54.3	77	52.0
Adrenaline use undescribed	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

AAI, adrenaline auto injector.