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Original Article

Evaluation of adrenaline auto-injector prescription profiles: A population-based, retrospective cohort study within the National Insurance Claims Database of Japan

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ABSTRACT

Background: Adrenaline is the first-line medication for managing anaphylaxis. A better understanding of prescription trends for adrenaline auto-injectors (AAIs) is important to improving patient care as well as information on health education interventions and medical guidelines. However, it has been difficult to gather comprehensive data in a sustainable manner. Thus, we aimed to investigate trends in AAI prescriptions in Japan.

Methods: We searched the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), a unique and comprehensive database of health insurance claims, and investigated prescriptions for AAIs for all ages (April 2017 to March 2018). We assessed the annual number of prescriptions per person as well as prescription rates per 100,000 population per year by age, sex, and geographic region.

Results: A total of 88,039 subjects (56,109 males, 31,930 female) and 116,758 devices (1.33 AAIs per patient per year) were prescribed AAIs at least once a year for all ages. The prescription rate for AAIs was

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Abbreviations:

AAI	adrenaline auto-injector
ICD-10	International Classification of Diseases-10
JMDC	Japan Medical Data Center
MHLW	Ministry of Health, Labour and Welfare, Japan
NDB	The National Database of Health Insurance Claims and Specific Health Checkups of Japan

69.5 per 100,000 population-years. Patients aged 0–9 years were prescribed AAIs at the rate of 278.9 per 100,000 population-years. Patients aged 0–19 years were 6.4 times more likely to be prescribed AAIs than those over 20 years of age. Males were more frequently prescribed AAIs than females in all age groups, except for those aged 20–24 years. We also evaluated differences in prescription rates by geographic region.

Conclusions: This comprehensive evaluation revealed trends in AAI prescriptions, thus helping develop preventive strategies with respect to anaphylaxis in Japan.

Introduction

Anaphylaxis is the most severe and life-threatening allergic reaction and is most commonly triggered by food, drugs, and insect stings.[1,2] The estimated lifetime prevalence of anaphylaxis is 0.3–5.1%, though this varies widely according to geographic region, populations, and study methodology.[3–5] The occurrence of anaphylaxis has increased in recent years, with devastating health and economic costs.[5] In Japan, the Ministry of Health, Labour and Welfare (MHLW) has played an essential role in tackling this major societal problem. For example, the Basic Law on Measures Against Allergic Diseases came into force in June 2014,[6] and the Strategic Outlook Toward 2030 (Japan's applied research and health policy program on allergy and immunology, also termed Strategy 2030) was formulated in 2018.[7]

Intramuscular adrenaline is recommended as the first-line drug for the treatment of anaphylaxis.[8] Rapid administration of adrenaline is universally recommended in the current guidelines for anaphylaxis,[2] and the early treatment of food-induced anaphylaxis with an adrenaline injection is associated with a statistically significantly lower risk of hospitalization.[9] Adrenaline auto-injectors (AAIs) are recommended as the primary treatment for anaphylaxis patients in self-treatment conditions, and all patients who experienced anaphylaxis should be prescribed an AAI at the time of discharge from a health care setting according to universally accepted medical guidelines.[2] However, previous studies have shown that AAI prescription rates are frequently low,[10,11] and that some patients are never prescribed AAIs even after experiencing anaphylaxis.[12]

AAIs are registered in the National Health Insurance System in Japan. Specifically, a 0.3 mg dose AAI (EpiPen^R 0.3 mg; Pfizer, New York, NY, USA, Mylan EPD, Canonsburg, PA, USA) as well as a 0.15 mg dose AAI (EpiPen^R 0.15 mg) became available for patients with bee sting-induced anaphylaxis reactions in 2003, and these treatments likewise became available for patients with food-induced anaphylaxis in 2005. A better understanding of prescription trends for AAIs is important to improving patient care, health education, and medical guidelines, as well as for evaluating medical equalization.[2] However, real-world evidence regarding AAI prescriptions has not been sufficiently and sustainably accumulated at the population level.

Recent studies have utilized the National Database of Health Insurance Claims and Specific Health Check-ups of Japan (NDB) to investigate the incidence of common diseases or variations in fracture risk by season and weather.[13–16] The NDB is a comprehensive database of health insurance claims covered by the Japanese National Health Insurance System and is considered representative of almost all health claims databases containing medical care datasets generated from insured inpatient and outpatient visits. Since NDB data are registered every year, this database has the advantage of continuous follow-up.[13–16]

Herein, we investigated AAI prescription patterns via the NDB to improve our understanding of the epidemiology of anaphylaxis and to develop preventive strategies/This study was conducted with the goal of improving and informing medical care and public health interventions.

Methods

Data and study design

We conducted a population-based retrospective cohort study using an NDB dataset. The study cohort consisted of individuals enrolled in the NDB. Japan has a universal health coverage system, and the NDB thus includes all patients with any type of private insurance program. However, local governments provide payment for the <2% of the population who are on welfare, and hence data for approximately two million citizens are not contained in the NDB. In addition, foreigners who stay in Japan for <3 months are not included in this database, as (1) they comprise a heterogenic group that might confound the results of the present longitudinal study, and (2) they are not covered by medical insurance.

The NDB database provides information on each patient's personal identifier (ID variable), dates of prescriptions and medical visits, age group, sex, a region where the procedures were carried out, and a description of these procedures, World Health Organization International Classification of Diseases (ICD-10) diagnosis codes, and information on medical care received (including specific medical examinations); however, this dataset does not contain the results of clinical evaluations or laboratory testing. The NDB contains information on prescribed drugs, including prescription amount, brand names, generic names, dosages, and the number of days a given drug was prescribed; this information is independent of physician or patient reports.

This study was approved by the ethics committee of Nara Medical University (project approval number 1123–2) and was conducted in accordance with the tenets of the Declaration of Helsinki and its later amendments. Informed consent was waived due to the retrospective nature of this study. All patient data were anonymized prior to analysis.

Data extraction

We were granted permission to access the NDB as members of a research group funded by the Health Science and Labour Research Grant from the MHLW. We extracted from the original NDB database for all patients who were prescribed AAIs (EpiPen^{R}0.15 mg or 0.3 mg) based on data collected between April 2017 and March 2018. Data were extracted using procedure codes for the following AAIs: EpiPen^R 0.15 mg (No. 628704702) and EpiPen^R 0.15 mg (No. 628704802).

Statistical analysis

We investigated the number of subjects prescribed an AAI at least once as well as the total number of prescribed AAIs per year and summarized the descriptive data by age and sex. We evaluated the data according to 10-year age groups. Patients prescribed AAIs were expressed as counts per 100,000 population as well as by 10-year age group and region.

We used comparative summary data from the Vital Statistics of Japan in the same year, available on the MHLW website (https://www.mhlw.go.jp/english/database/db-hw/populate/index.html), to estimate prescription counts per population. We then calculated the average number of prescriptions per person per year and evaluated the data according to sex and age group. We likewise evaluated correlations between prescription rates per population and the number of available allergists. Linear trend models and 95% confidence curves were generated using Tableau Desktop software (Tableau Software, Seattle, WA, USA).

We obtained the counts as well as the causes of fatal anaphylaxis in Japan from Statistics of Japan (e-Stat, a portal site for Japanese Government Statistics; https://www.e-stat.go.jp/en) (Supplementary Table 1) and obtained the counts of available allergists from the Japanese Society of Allergology website (https://www.jsaweb.jp/modules/ninteilist_general/).

Results

AAI prescriptions

A total of 88,039 patients (56,109 males, 31,930 females) were prescribed AAIs during one representative year of the study period (Table 1). The total number of prescriptions was 116,758 devices (EpiPen^{R} 0.15 mg, 43,618 [37.4%]; EpiPen^{R} 0.3 mg, 73,140 [62.6%]). The prescription rate of AAIs was 69.5 per 100,000 population-years.

Age difference

The database enrolled 50,039 patients under 19 years of age, accounting for 56.8% of the total number of AAI prescriptions (Table 1). There were 28,338 enrolled patients aged 0–9 years (representing 32.2% of the study population), and 21,701 patients aged 10–19 years old (representing 24.6% of the study population). When evaluating children under nine years of age, we found that AAIs were rarely prescribed for patients aged ≤1 year. However, we found that prescriptions increased in patients aged two years (as compared to those aged ≤1 year), peaked at six years of age, and subsequently decreased (Supplementary Fig. 1).

The prescription rates for AAIs according to age group are shown in Figure 1A. Patients aged 0–9 years had the highest prescription rates (278.9 per 100,000 population-year), followed by patients aged 10–19 years (189.9 per 100,000 population-year), whereas we observed a prescription rate of 36.1 per 100,000 population years for those over age 20 years. Patients aged <19 years were 6.4 times more likely to be prescribed AAIs as compared with those over 20 years of age.

Sex differences

The male-female ratio of the total number of prescriptions was 1.76:1 for all age groups. When evaluating children aged 0–9 years, we found that the number of prescriptions for males was twice that of prescriptions for females (ratio, 1.92:1) (Supplementary Fig. 2). There was an increasing trend in females aged 10–29 years, and the proportion of females was highest at ages 20–29 (ratio, 1.04:1). In addition, there was a slight increase in prescription trends among males aged 30–69 years.

When evaluating those under 20 years of age, we found that males had a higher prescription rate than females (Fig. 2). When evaluating patients aged 0–9 years, we found a prescription rate of 363.3 per 100,000 population-years for males and a much lower prescription rate (190.3 per 100,000 population-years) for females (ratio, 1.91:1). However, no statistically significant differences in prescription rates were observed in comparative evaluations of males and females between the ages of 20 and 50 years. The study demonstrated a slight increase in prescription rates for males over 50 years of age.

Geographic region differences

The counts for patients prescribed AAIs according to the geographic region are shown in Table 2. Among patients of all ages, Tokyo (14.6%) had the most overall cases, followed by Kanagawa (6.9%), Aichi (6.3%), Osaka (6.1%), Chiba (4.8%), Hokkaido (4.5%), Saitama (4.1%), Hyogo (4.0%), Nagano (2.8%), Fukuoka (2.7%), and Shizuoka prefectures (2.7%). The prescription frequencies for those aged 0–19 years were as follows: Tokyo (18.5%), Osaka (8.0%), and Aichi (7.8%). For those over 20 years of age, prescription frequencies were as follows: Tokyo (9.5%), Hokkaido (6.6%), and Kanagawa (6.0%).

The number of patients prescribed AAIs per 100,000 population-years varied by geographic region (Fig. 2A). The highest AAI prescription rate was found in Shimane (138.4 per 100,000 population-year), followed by Nagano (120.8), Tottori (100.0), Gifu (96.5), Tokyo (93.6), Yamanashi (93.3), Iwate (92.6), Tochigi (87.0), Tokushima (84.4), and Toyama (81.9) (Fig. 2A, Supplementary Table 2). Among patients aged 0–19 years, Tokyo had the highest prescription rate (253.1 per 100,000 population-years), followed by Shiga (195.6), Aichi (179.0), Gifu (163.0), Kagawa (162.3), Osaka (156.2), Toyama (147.4), Chiba (145.3), and Kanagawa (136.7) (Fig. 2B, Supplementary Table 2). In patients over 20 years of age, the highest prescription rates were found in Shimane (138.7 per 100,000 population-years), followed by Nagano (92.7), Iwate (77.3), Tottori (73.7), Fukushima (66.8), Tokushima (62.6), Yamanashi (62.2), Miyazaki (62.1), and Yamagata (57.9) (Fig. 2C, Supplementary Table 2). Among the 47 regions, 44 regions had higher AAI prescription rates in patients aged 0–19 years as compared with those aged over 20 years. Shimane, Aomori, and Miyazaki demonstrated higher prescription rates for adults than for children.

Table 1
Demographical and characteristics of patients.

Number of patients prescribed AAI	
Total	88,039
Male	56,109 (63.7%)
Age category, years	
0–9	28,338 (32.2%)
10–19	21,701 (24.6%)
20–29	4820 (5.5%)
30–39	5231 (5.9%)
40–49	6544 (7.4%)
50–59	6748 (7.7%)
60–69	8512 (9.7%)
≥70	6145 (7.0%)
Number of AAI prescriptions	
Total	116,758
0.15 mg	43,618 (37.4%)
0.3 mg	73,140 (62.6%)

Data are expressed as n (%) provided in parentheses. AAI, adrenaline auto-injector.

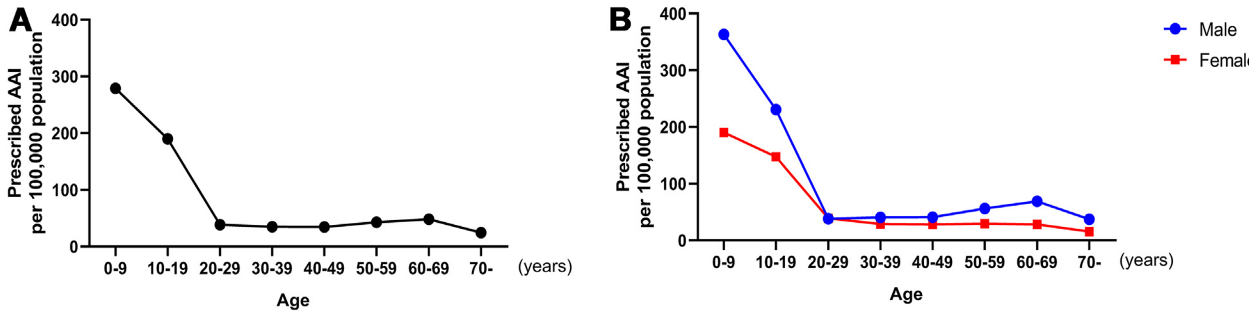

Fig. 1. The number of cases prescribed adrenaline auto-injector per 100,000 population-year by age group **(A)** and by gender **(B)** within the National Insurance Claims Database of Japan. Comparative population statistics were obtained from Vital Statistics (Japan), available on the Ministry of Health, Labour, and Welfare (MHLW) website (https://www.mhlw.go.jp/english/database/db-hw/populate/index.html). AAI, adrenaline auto-injector.

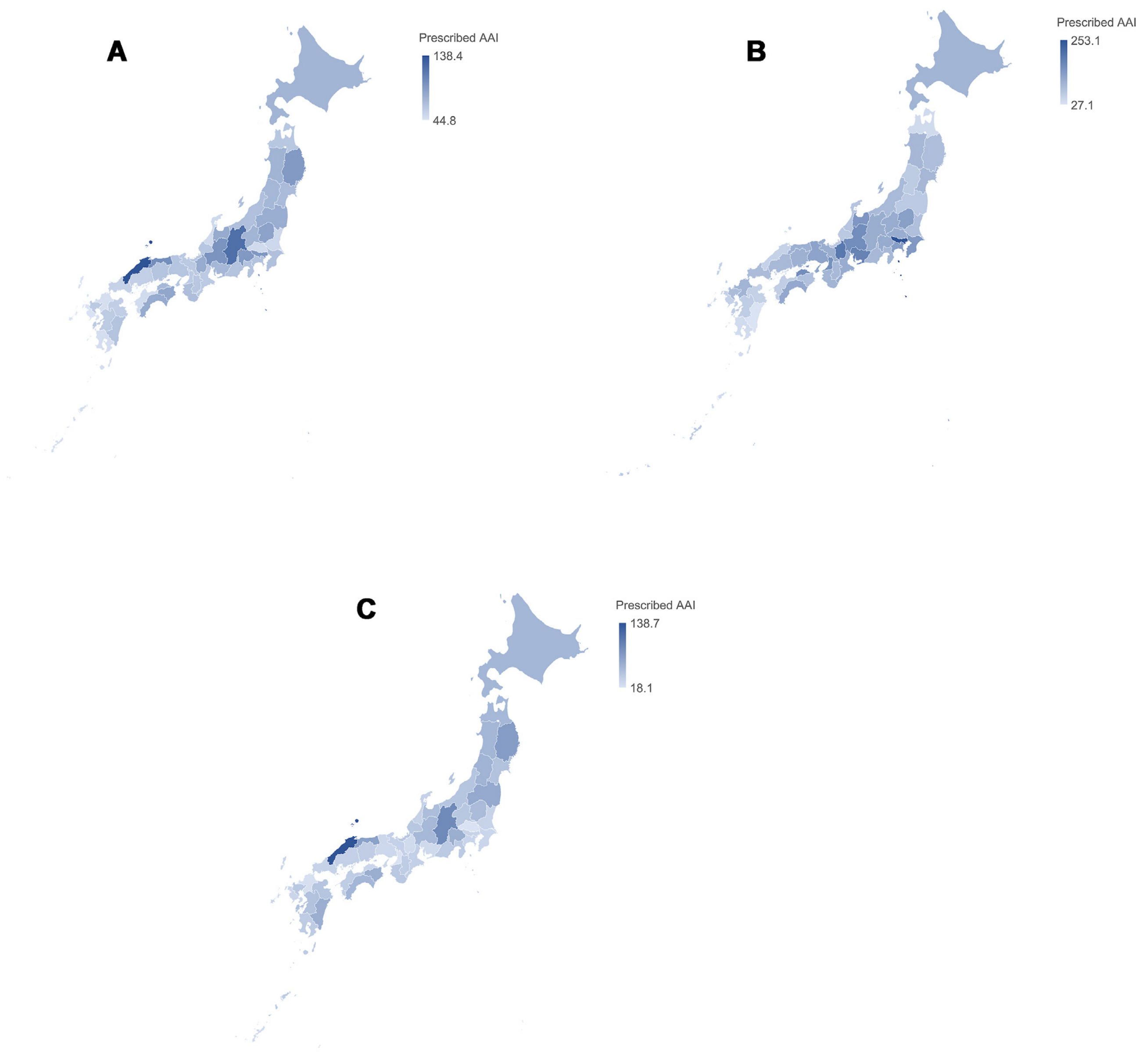

Fig. 2. The number of adrenaline auto-injector prescriptions per 100,000 population by geographic region in all cases **(A)**, in cases aged 0–19 years **(B)**, and in cases aged over 20 years of age **(C)** within the National Insurance Claims Database of Japan. Comparative population statistics were obtained from Vital Statistics (Japan), available on the Ministry of Health, Labour, and Welfare (MHLW) website (https://www.mhlw.go.jp/english/database/db-hw/populate/index.html).

Table 2
Number of patients prescribed adrenaline auto-injector by geographic region.

Geographic region	All age (n = 88,039)	0–19 years (n = 50,039)	≥20 years (n = 38,000)
Tokyo	12,844 (14.6%)	9236 (18.5%)	3608 (9.5%)
Kanagawa	6036 (6.9%)	3751 (7.5%)	2285 (6.0%)
Aichi	5506 (6.3%)	3926 (7.8%)	1580 (4.2%)
Osaka	5328 (6.1%)	3984 (8.0%)	1344 (3.5%)
Chiba	4187 (4.8%)	2672 (5.3%)	1515 (4.0%)
Hokkaido	3979 (4.5%)	1486 (3.0%)	2493 (6.6%)
Saitama	3650 (4.1%)	2555 (5.1%)	1095 (2.9%)
Hyogo	3537 (4.0%)	2292 (4.6%)	1245 (3.3%)
Nagano	2507 (2.8%)	919 (1.8%)	1588 (4.2%)
Fukuoka	2416 (2.7%)	1555 (3.1%)	861 (2.3%)
Shizuoka	2415 (2.7%)	1219 (2.4%)	1196 (3.1%)
Gifu	1937 (2.2%)	1050 (2.1%)	887 (2.3%)
Tochigi	1702 (1.9%)	867 (1.7%)	835 (2.2%)
Hiroshima	1643 (1.9%)	848 (1.7%)	795 (2.1%)
Miyagi	1635 (1.9%)	755 (1.5%)	880 (2.3%)
Kyoto	1608 (1.8%)	893 (1.8%)	715 (1.9%)
Niigata	1533 (1.7%)	718 (1.4%)	815 (2.1%)
Ibaragi	1501 (1.7%)	752 (1.5%)	749 (2.0%)
Fukushima	1499 (1.7%)	451 (0.9%)	1048 (2.8%)
Gunma	1472 (1.7%)	807 (1.6%)	665 (1.8%)
Okayama	1241 (1.4%)	668 (1.3%)	573 (1.5%)
Iwate	1162 (1.3%)	349 (0.7%)	813 (2.1%)
Shiga	1143 (1.3%)	865 (1.7%)	278 (0.7%)
Mie	1099 (1.2%)	591 (1.2%)	508 (1.3%)
Kumamoto	1069 (1.2%)	411 (0.8%)	658 (1.7%)
Shimane	948 (1.1%)	160 (0.3%)	788 (2.1%)
Toyama	865 (1.0%)	426 (0.9%)	439 (1.2%)
Nara	849 (1.0%)	437 (0.9%)	412 (1.1%)
Yamagata	808 (0.9%)	275 (0.5%)	533 (1.4%)
Aomori	802 (0.9%)	219 (0.4%)	583 (1.5%)
Kagoshima	776 (0.9%)	275 (0.5%)	501 (1.3%)
Yamaguchi	772 (0.9%)	404 (0.8%)	368 (1.0%)
Yamanashi	768 (0.9%)	343 (0.7%)	425 (1.1%)
Akita	757 (0.9%)	281 (0.6%)	476 (1.3%)
Miyazaki	715 (0.8%)	162 (0.3%)	553 (1.5%)
Kagawa	700 (0.8%)	464 (0.9%)	236 (0.6%)
Ehime	675 (0.8%)	257 (0.5%)	418 (1.1%)
Oita	672 (0.8%)	261 (0.5%)	411 (1.1%)
Okinawa	671 (0.8%)	392 (0.8%)	279 (0.7%)
Wakayama	653 (0.7%)	332 (0.7%)	321 (0.8%)
Tokushima	627 (0.7%)	236 (0.5%)	391 (1.0%)
Nagasaki	606 (0.7%)	283 (0.6%)	323 (0.9%)
Ishikawa	584 (0.7%)	281 (0.6%)	303 (0.8%)
Kochi	580 (0.7%)	248 (0.5%)	332 (0.9%)
Tottori	565 (0.6%)	221 (0.4%)	344 (0.9%)
Saga	503 (0.6%)	231 (0.5%)	272 (0.7%)
Fukui	494 (0.6%)	231 (0.5%)	263 (0.7%)

AAI prescriptions per person

A total of 88,039 patients were prescribed 116,758 AAIs during the study period (1.33 AAIs per patient per year). Figure 3 shows the counts for AAI prescriptions per patient according to age. The counts for prescribed AAIs per year were higher in children than in adults. Specifically, 28,338 patients received 46,156 AAIs among those aged 0–9 years (1.63 AAIs per patient per year), and 21,701 patients received 30,607 AAIs among those aged 10–19 years (1.41 AAIs per patient per year) (Fig. 3). We did not observe any statistically significant sex differences. The AAIs prescription rates per patient per year for males and females of all ages were 1.31 and 1.33, respectively. The rates for males and females aged 0–19 years were 1.54 and 1.52, while those for males and females over age 20 years were 1.05 and 1.06.

Discussion

To the best of our knowledge, this is the first epidemiologic study in the field of allergic diseases that was conducted using the NDB, one of the largest medical record databases on a global scale. This database collects over 1.6 billion electronic medical receipts every year, thus comprising almost all medical database information in Japan. Given the current circumstances of medical care for allergic diseases, we focused on anaphylaxis (a fatal allergic disease) as promoted and implemented by the aforementioned Basic Law and by Strategy 2030. To provide basic statistics for the standardization of medical care on a country-wide basis and to evaluate and analyze the distributions of these statistics across regions, we evaluated AAI prescription counts along with patient background and regional disparities in clinical practices. The present study revealed that approximately 90,000 patients were prescribed AAIs during the course of one representative year and that the overall prescription rate of AAIs in Japan was 69.5 per 100,000 population-years. We also found that prescription rates varied by age and geographic region and that children had higher prescription rates than adults.

To our knowledge, there are no reports on the prevalence of anaphylaxis or on AAI prescription in Japan to date. It has been recognized that prescription patterns for adrenaline are indicative of secular trends in anaphylaxis.[17] Herein, we investigated AAI prescription data within a large and comprehensive medical database. We found that a total of 88,039 patients per year were prescribed AAIs (69.5 for every 100,000 subjects; 0.0695%). The UK study using ICD coding observed rates ranging from 1.0 to 7.0 per 100,000 person-years.[18] In the European population, the incidence rate for anaphylaxis has similarly ranged from 1.5 to 7.9 per 100,000 person-years in prior research.[3] In contrast, recent reports have shown a global incidence of anaphylaxis ranging between 50 and 112 episodes per 100,000 person-years.[2,19,20] This number of AAI prescriptions is reasonable given that the prevalence of anaphylaxis varies widely due to different study methods and data coding practices.[1] In Japan, a total of 52 cases of fatal anaphylaxis occurring due to food, medication, serum, or venom exposure as well as unspecified causes (0.041 per 100,000 population) occurred as of 2017 (Supplementary Table 1). There were a recorded 52–71 annual cases of fatal anaphylaxis due to these causes that occurred each year from 2015 to 2019.

A recent study reported AAI prescription trends through a US-based outpatient population-based study conducted in Minnesota from 2014 to 2016. This study evaluated the first AAI prescription for each patient per year, as well as the first prescription per patient during the entire study period in order to calculate incidence rates.[17] The overall incidence rate for AAI prescriptions during this period was 757 per 100,000 population-years.[17] Although the actual number of prescribed devices cannot be solely predicted based on the number of prescriptions, the number of prescribed

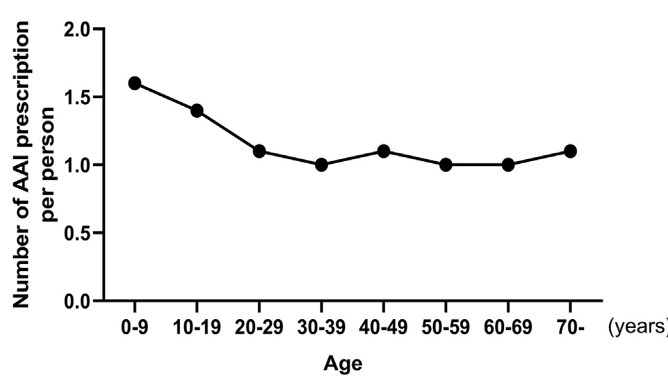

Fig. 3. The number of adrenaline auto-injector prescriptions per person by age group within the National Insurance Claims Database of Japan. AAI, adrenaline auto-injector.

AAIs in Japan seems to be less than that in the US. The underlying reason is likely that food-allergic patients are routinely prescribed two AAIs in the US.[21]

Moreover, a prior study reported that the burden of anaphylaxis was lower in Asia than in the US and that this burden differed from that observed in the West in terms of age distribution. Nevertheless, the low rates of adrenaline use as a first-line intervention for diagnosed anaphylaxis are concerning.[22] A recent analysis of health insurance claims data within the Japan Medical Data Center database (JMDC, Tokyo, Japan), which enrolled 5.6 million individuals registered in health insurance programs as of 2018, reported that AAI prescription rates were low even among patients who had experienced severe anaphylaxis.[12] A recent study conducted in the UK likewise reported prescription data for AAIs and found that AAI prescriptions increased by 336% from 1998 to 2018.[23] Epidemiological studies of anaphylaxis over time are essential for standardizing treatments, informing medical guidelines, and improving health policy. Additional highly-powered long-term studies are needed to evaluate these questions more thoroughly.

We found that the rate of AAI prescriptions was 231.8 per 100,000 population-years in patients aged 0–19 years, whereas the rate for patients aged ≥20 years was 36.1 per 100,000 population-years; prescription rates decreased continuously in the latter age group. Additionally, we found a prescription rate of 278.9 per 100,000 population-years in patients aged 0–9 years, and a prescription rate of 189.9 per 100,000 population-years in patients aged 10–19 years. These rates likewise decreased with age. The prevalence of anaphylaxis was highest in children aged 0–19 years,[24] and the most frequent trigger of anaphylaxis was food.[25]

In general, the prevalence of food allergies is highest among infants, and is also high among younger children; the prevalence of food allergies decreases with age.[26] In Japan, current medical guidelines recommend prescribing AAIs for children with food allergies who are at risk of experiencing anaphylaxis.[27] It is well known that patients with food allergies are at risk of developing allergic reactions, including anaphylaxis. Guidelines for the management of allergic diseases in schools and daycare centers advise the use of AAIs to treat allergic reactions caused by accidental exposures. AAIs may be prescribed for patients with no history of anaphylaxis, given that 11% of 51,531 children were prescribed AAIs in a study conducted among Japanese nursery schools.[28] Moreover, many children receive AAIs at no cost due to the national subsidy system for medical treatment fees for infants and children in Japan. These factors may influence the varying number of AAI prescriptions by age.

A recent study of AAI prescription trends in the US demonstrated that boys were more likely to receive AAI prescriptions than girls, but that this trend was reversed at later ages.[17] A similar tendency was observed in our study. Males are more often affected by allergic asthma during childhood. However, after puberty, females are predominantly affected by allergic asthma as compared with males until around the time of menopause. These changes are considered to be mainly regulated by sex hormones that act on various types of cells, such as dendritic cells, mast cells, eosinophils, group 2 innate lymphoid cells, and epithelial cells.[29,30] In anaphylaxis, boys under 10 years of age have been reported to have a higher anaphylaxis incidence than girls,[31] which is in line with our findings. We also found that food allergies were more prevalent in boys than in girls. Although gender dominance in the prevalence or incidence of anaphylaxis after puberty was not clear in the current study, in contrast to studies of gender differences in asthma[32–35] (presumably because of difference in the target populations as well as the definition of anaphylaxis in each study), some reports have demonstrated comparable or higher rates in females. These results were similar to our findings.[33–35] We found that in those over 50 years of age, there was a marked increase in AAI prescriptions in males only (Fig. 1(B)). This may be due to the loss of female sex hormones as well as the age and gender distribution of the number of forestry workers at risk of Hymenoptera sting.[36]

In our study, we found that the AAI prescription rates per population varied widely by geographic region. Although the uneven distribution of allergists may have influenced some of these regional differences, the number of allergists certified by the Japanese Society of Allergology per population in 2017 did not correlate with the AAI prescription rates by geographic region ($p = 0.384$, Supplementary Fig. 3). AAI prescription rates by geographic region differed between children and adults. The number of patients with food allergies treated in facilities within each geographic region may affect AAI prescription rates for children, given that food is the most common cause of anaphylaxis in children.[4] In adults, drugs and venom are the most common causes of anaphylaxis.[5] Prior research has demonstrated that forestry workers and electrical facility field workers experience systemic reactions to Hymenoptera stings with a higher frequency as compared with office workers,[37] and that beekeepers often experience systemic reactions to honey bee stings.[38] In this study, the AAI prescription rates in Tohoku, Chubu, and Southern Kyushu were higher than in urban areas, possibly due to regional differences in industrial factors. Thus, we recommend that physicians receive more extensive training on the use and prescription practices for AAIs as part of their medical training and continuing education.

In the present study, we found a total prescription rate of 1.33 AAIs per person per year for patients of all ages. We found that the number of prescribed AAIs per year was higher in patients aged 0–9 years (1.63 AAIs per patient per year) than in those aged 10–19 years (1.41 AAIs per patient per year). Among patients with food-related anaphylaxis treated with adrenaline, 12–17% received a second dose or higher.[39,40] Therefore, in the US, all AAIs are exclusively dispensed as twin packs, and patients are advised to have two AAI devices available. In the UK, prescribers are required to provide two AAIs for each patient according to the Medicines and Healthcare Products Regulatory Agency. However, in Japan, the guidelines for anaphylaxis do not mention that multiple AAIs should be prescribed for all patients. Hence, multiple AAIs may or may not be prescribed depending on the physician's clinical judgment. In younger children, AAIs are often prescribed at no cost (i.e., prescriptions are covered by the national subsidy system for medical treatment fees for infants and children). A second AAI may be prescribed to store at school or daycare. Research suggests that the higher number of AAI prescriptions for children does not seem to occur simply due to the varying severity of the disease across age groups. For example, a recent cost-effectiveness analysis for AAIs suggested that limiting prescriptions of a second AAIs to patients with a history of anaphylaxis was more cost-effective than routinely prescribing two AAIs to all food-allergic patients.[21] Hence, the optimal number of prescribed AAIs needs to be investigated, including with respect to the medical economic/healthcare cost aspects of this clinical decision-making process in Japan.

In addition to the substantial strengths of this investigation, we acknowledge several potential limitations of our study. First, each observation period was limited to one year, and thus we could not estimate the gross number of episodes of anaphylaxis within the NDB. Thus, in order to take advantage of the NDB data that have already been and will be registered every year, it is desirable to continuously and rigorously follow up on these trends within future investigations. Moreover, we were not able to distinguish between cases where the second AAI was prescribed due to medical history and cases where a second AAI was prescribed as a matter of course. Thus, future highly-powered studies on the clinical characteristics of patients who have been prescribed AAIs are needed.

In conclusion, in this comprehensive evaluation within a national medical insurance claims database conducted in Japan, we found that 88,039 patients of all ages were prescribed AAIs in the year 2017. Patients 0–10 years of age received 1.5 AAIs per year. The number of prescriptions declined after the age of 10. Males were more likely to be prescribed AAIs than females in all age groups, with the exception of those aged 20–24 years. We also note differences in AAI prescription rates according to geographic region. This comprehensive evaluation regarding AAI prescriptions helps develop preventive strategies with respect to anaphylaxis in Japan and informs both research directions and medical guidelines. Future studies on longitudinal changes and clinical features of prescribed patients are necessary to improve the understanding and effective management of anaphylaxis.

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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.2022.02.002.

Conflict of interest

SS and ME reports lecture fees from the Mylan EPD. TIn reports consulting fees from Santen Pharmaceutical and InnoJin. YN reports consulting fees from Novo Nordisk. These sources had no role in the design, conduct, preparation, or writing of this manuscript. The rest of the authors have no conflict of interest.

Authors' contributions

SS, KKai and ENGAGE NDB Task Force designed the study. SS and KKai performed data analysis, and wrote the manuscript. TN, TIm and YN contributed to data acquisition and analysis. ME, MF, AM, SN, YO, and MT contributed to data interpretation and revised the manuscript critically for important intellectual content. HM and TA contributed to study management and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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