



Contents lists available at ScienceDirect

Allergology International

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

Original Article

Nationwide survey of the prevalence of wheeze, rhino-conjunctivitis, and eczema among Japanese children in 2015

Emi Morikawa^{a, b, *}, Mari Sasaki^a, Koichi Yoshida^a, Yuichi Adachi^c, Hiroshi Odajima^d, Akira Akasawa^a^a Division of Allergy, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan^b Clinical Research Support Center, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan^c Department of Pediatrics, University of Toyama, Toyama, Japan^d Department of Pediatrics, National Hospital Organization Fukuoka National Hospital, Fukuoka, Japan

ARTICLE INFO

Article history:

Received 11 April 2019

Received in revised form

15 August 2019

Accepted 23 August 2019

Available online xxx

Keywords:

Allergic disease

Child

Cross-sectional studies

Epidemiology

Prevalence

Abbreviations:

PS primary school students

MS middle school students

ISAAC International Study of Asthma and Allergies in Childhood

ABSTRACT

Background: Global surveys and cohort studies have been conducted to evaluate the prevalence of allergic disease in childhood, but only a few nationwide surveys have been conducted in Japan. We aimed to report the prevalence of childhood allergic disease in Japan and determine the prevalence distribution by sex and prefecture.

Methods: In 2015, we conducted a school-based questionnaire survey using the Japanese version of the International Study of Asthma and Allergies in Childhood questionnaire among two age groups: primary school students (PS, 6–8 years old) and middle school students (MS, 13–15 years old). The schools were randomly selected from each prefecture.

Results: Valid responses were obtained from 42,582 PS and 36,638 MS. Among PS and MS, the prevalence of wheeze was 10.2% and 8.2%, that of allergic rhino-conjunctivitis was 18.7% and 26.7%, and that of eczema was 14.6% and 9.7%, respectively. In terms of sex, the prevalence of wheeze and rhino-conjunctivitis was higher in male PS while that of rhino-conjunctivitis and eczema was higher in female MS. In terms of prefecture, there was a two-fold difference in the prevalence of wheeze and eczema and a four-fold difference in the prevalence of rhino-conjunctivitis, with each disease showing different distribution patterns.

Conclusions: We demonstrated the prevalence of allergic disease among PS and MS in 2015. The prevalence tended to be higher in male PS and female MS. Each disease exhibited different prevalence ranges and distributions. Identifying the factors behind these differences is a topic for future research.

Copyright © 2019, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Wheeze, rhino-conjunctivitis, and eczema are common chronic diseases worldwide. Their prevalence differs by region, age, and sex, and is thought to be influenced by a variety of factors, including climate, living environment, and exposures, including antibiotic use.^{1–5} Understanding the distribution of prevalence not only helps us understand the factors involved in its onset but can also help in determining the preventive measures that can be adopted in local health policies. In Japan, only a few studies have been conducted to

evaluate the distribution of allergy prevalence rates among children on a national scale.

In 2005 and 2008, we conducted national surveys of the prevalence of pediatric allergies using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, which is used in epidemiological surveys of allergies worldwide.^{6–9} We repeated this study using the same method in 2015 and reported the prevalence-related time trend.¹⁰ Herein, we report the prevalence of allergic disease from the third study we conducted in 2015, with further investigation into the prevalence distribution by sex and prefecture.

* Corresponding author. Clinical Research Support Center & Department of Allergy, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan, 2-8-29 Musashidai, Fuchu, Tokyo 183-8561, Japan.

E-mail address: emi08071-o-lzz@hotmail.co.jp (E. Morikawa).

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2019.08.010>

1323-8930/Copyright © 2019, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Methods

Study design

In July 2015, we conducted a school-based questionnaire survey targeting two age groups: students in grades 1–2 of primary school (6–8 years old) and students in grades 7–8 of middle school (13–15 years old). We randomly selected schools in each prefecture using a table of random numbers. Recruitment of schools was continued until the total number of students in the target grade reached 1000 for both age groups per prefecture. Questionnaires were distributed in the schools. Respondents aged 13–15 old years were asked to fill out the questionnaire by themselves, and the guardians of participants aged 6–8 years old were asked to complete the survey on behalf of the subjects. The completed forms were each returned in a sealed envelope to the school to ensure anonymity, then sent to the research center.

Definitions

The Japanese version of the ISAAC questionnaire was used to evaluate the prevalence of wheeze, rhino-conjunctivitis, and eczema. Students with current wheeze, rhino-conjunctivitis or eczema were defined as shown below.¹¹

Current wheeze: Students who answered “yes” to the following two questions:

“Have you (or your child) ever had wheezing or whistling in the chest at any time in the past?”

“Have you (or your child) had wheezing or whistling in the chest in the past 12 months?”

Current rhino-conjunctivitis: students who answered “yes” to the following three questions:

“Have you (or your child) ever had a problem with sneezing, or a runny or blocked nose even if you did not have a cold or a flu?”

“In the past 12 months, have you (or your child) had a problem with sneezing, or a runny or blocked nose even if you (or your child) did not have a cold or a flu?”

“In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?”

Current eczema: subjects who answered “yes” to the following three questions:

“Have you (or your child) ever had an itchy rash which was appearing and disappearing for at least 6 months?”

“Have you (or your child) had this itchy rash at any time in the past 12 months?”

“Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?”

We geographically divided Japan into the following areas based on the categories of the Meteorological Agency of Japan as shown in [Supplementary Table 1](#): East and West, the Sea of Japan coast and Pacific Ocean coast, and inland and coastal areas.

Statistical analysis

Responses were excluded if the subject's age was not indicated or differed from the participant's grade level or when the sex was

not indicated. Valid responses were those that included answers to questions on at least one of the three diseases. The prevalence estimate for each disease by age, sex, and prefecture was calculated as the observed proportion with the 95% confidence interval (CI).

Prevalence between male and female subjects and among the regions was compared using a chi-square test. The prevalence in each prefecture was categorized and color-coded to explore the geographical distribution of the prevalence of each disease on the map of Japan then compared by area (see above) using the chi-square test. A two-sided P value <5% was considered significant. IBM SPSS Statistics Version 25 (IBM Corp, Armonk, NY, USA) was used for the statistical analysis.

Ethical considerations

The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labour and Welfare of Japan. The study was approved by our ethics review board (ID: H26-123).

The questionnaire contained an explanation of the objective and scope of the study and indicated that participation was voluntary. Therefore, participants were considered to have provided their consent if they returned the questionnaire to the school.

Results

Number of responses

Questionnaires were sent to 635 primary schools and 293 middle schools, with responses obtained from 625 primary schools (98.4% response rate) and 276 middle schools (94.2%). A total of 50,392 6–8-year-old subjects and 51,442 13–15-year-old subjects were eligible, and responses were obtained from 43,493 [overall response rate: 86.3%, range: 65.3% (Nara)–95.6% (Iwate)] and 37,513 [overall response rate: 72.9%, range 43.0% (Kyoto)–90.5% (Toyama)] of these subjects, respectively. Of these, valid responses were obtained from 42,582 (84.5%), 6–8-year-old subjects and 36,638 (71.2%), 13–15-year-old subjects and used in the analysis ([Fig. 1](#)).

Prevalence of each disease and male-female ratio

[Table 1](#) shows the prevalence of each disease stratified by sex.

The prevalence of current wheeze

The overall prevalence among 6–8-year-old subjects was 10.2% (95% CI: 9.9–10.5), with males showing a higher prevalence (males vs females: 11.6%, 11.1–12.0% vs. 8.7%, 8.4–9.1, $p < 0.001$). The overall prevalence among 13–15-year-old subjects was 8.2% (7.9–8.4), with no clear difference between the sexes (males vs females: 8.3%, 7.9–8.7% vs. 8.0%, 7.7–8.4, $p = 0.434$). Prevalence decreased by age for both sexes, with males showing a larger decline (males vs females: 3.3% vs. 0.7%).

The prevalence of current rhino-conjunctivitis

The overall prevalence among 6–8-year-olds was 18.7% (18.3–19.1), with males showing a higher prevalence (males vs females: 19.9%, 19.4–20.4% vs. 17.5%, 17.0–18.0%, $p < 0.001$). The overall prevalence among the 13–15-year-olds was 26.7% (26.2–27.2), with females showing a higher prevalence (males vs females: 25.2%, 24.6–25.8% vs. 28.1%, 27.5–28.8%, $p < 0.001$). Prevalence increased with age for both sexes, with females showing a larger increase (males vs females: 5.3% vs. 10.6%).

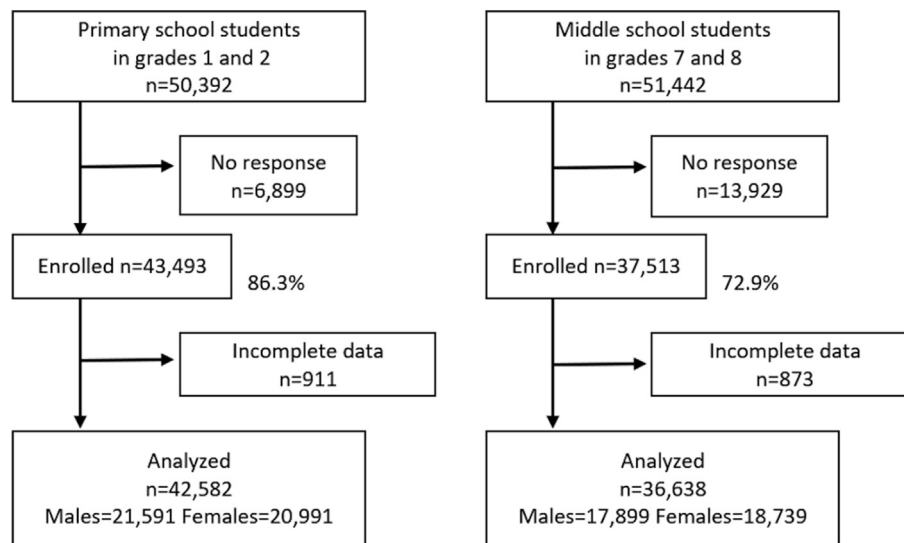


Fig. 1. Overview of analysis.

Table 1

Prevalence of current symptoms of wheeze, rhino-conjunctivitis, and eczema per age group.

	Total			Males			Females			p
	n	%	95%CI	n	%	95%CI	n	%	95%CI	
Wheeze										
6 to 8-year-olds	42,176	10.2	(9.9–10.5)	21,384	11.6	(11.1–12.0)	20,792	8.7	(8.4–9.1)	<0.001*
13 to 15-year-olds	36,243	8.2	(7.9–8.4)	17,694	8.3	(7.9–8.7)	18,549	8.0	(7.7–8.4)	0.434
Rhino-conjunctivitis										
6 to 8-year-olds	42,215	18.7	(18.3–19.1)	21,415	19.9	(19.4–20.4)	20,800	17.5	(17.0–18.0)	<0.001*
13 to 15-year-olds	35,999	26.7	(26.2–27.2)	17,584	25.2	(24.6–25.8)	18,415	28.1	(27.5–28.8)	<0.001*
Eczema										
6 to 8-year-olds	42,351	14.6	(14.3–14.9)	21,470	14.4	(13.9–14.9)	20,881	14.8	(14.3–15.3)	0.296
13 to 15-year-olds	36,229	9.7	(9.4–10.0)	17,692	8.5	(8.1–9.0)	18,537	10.8	(10.3–11.2)	<0.001*

Data are presented as a percentage and 95% confidence interval (95% CI). Prevalence among males and females was compared using a chi-square test.

*P value from chi-squared test of the proportion of males to females <0.05.

Due to missing data, the number of responses varied for each disease.

The prevalence of current eczema

The overall prevalence among 6–8-year-olds was 14.6% (14.3–14.9), with no clear sex difference (males vs females: 14.4%, 13.9–14.9 vs. 14.8%, 14.3–15.3%, $p = 0.296$). The overall prevalence among 13–15-year-olds was 9.7% (9.4–10.0), with females showing a higher prevalence (males vs females: 8.5%, 8.1–9.0% vs. 10.8%, 10.3–11.2, $p < 0.001$). Prevalence decreased by age for both sexes, with males showing a larger decline (males vs females: 5.9% vs. 4.0%).

Range and distribution of prevalence by prefecture

The prevalence of each disease per age group was calculated for each prefecture (Supplementary Table 2). The prevalence data were then categorized and each category color-coded to explore the geographical prevalence distribution of each disease on the map of Japan (<5%: purple, 5%–10%: blue, 10%–15%: green, 15%–20%: yellow, 20%–25%: orange, and $\geq 25\%$: red), (Figs. 2–4). The results of the statistical analysis of the regional differences in the prevalence of each disease are listed in Supplementary Table 3.

The prevalence of current wheeze by prefecture ranged from 7.5% (5.7–9.2, Niigata) to 13.9% (11.8–16.1, Kagoshima) for 6–8-year-old subjects and from 4.5% (2.2–6.5, Osaka) to 13.8% (11.6–16.0, Fukushima) for 13–15-year-old subjects

(Supplementary Table 2). The prevalence in West Japan was higher among 6–8-year-old subjects, with the regional difference being less evident among 13–15-year-old subjects. The prevalence of rhino-conjunctivitis ranged from 8.1% (5.7–10.4, Okinawa) to 30.1% (26.8–33.3, Shizuoka) for 6–8-year-old subjects and from 10.3% (7.8–12.7, Okinawa) to 40.1% (36.1–44.1, Gifu) for 13–15-year-old subjects (Supplementary Table 2). The prevalence in the inland areas was higher than in coastal areas among 6–8-year-old subjects while the prevalence in areas along the Pacific Ocean coast was higher among 13–15-year-old subjects. The prevalence of eczema ranged from 9.9% (8.1–11.7, Ibaraki) to 18.8% (16.1–21.6, Nara) among 6–8-year-old subjects and from 6.4% (4.5–8.4, Okinawa) to 13.2% (10.3–16.0, Tokyo) among 13–15-year-old subjects (Supplementary Table 2). There was a similarity in the prevalence distribution between both age groups, but no characteristics of the distribution were clearly identifiable.

Discussion

In the present study, we conducted a nationwide survey of allergy prevalence among primary and middle school students in 2015 using the ISAAC questionnaire. The results showed that in Japan, approximately one in ten children had current wheeze or current eczema, and one in four had current rhino-conjunctivitis.

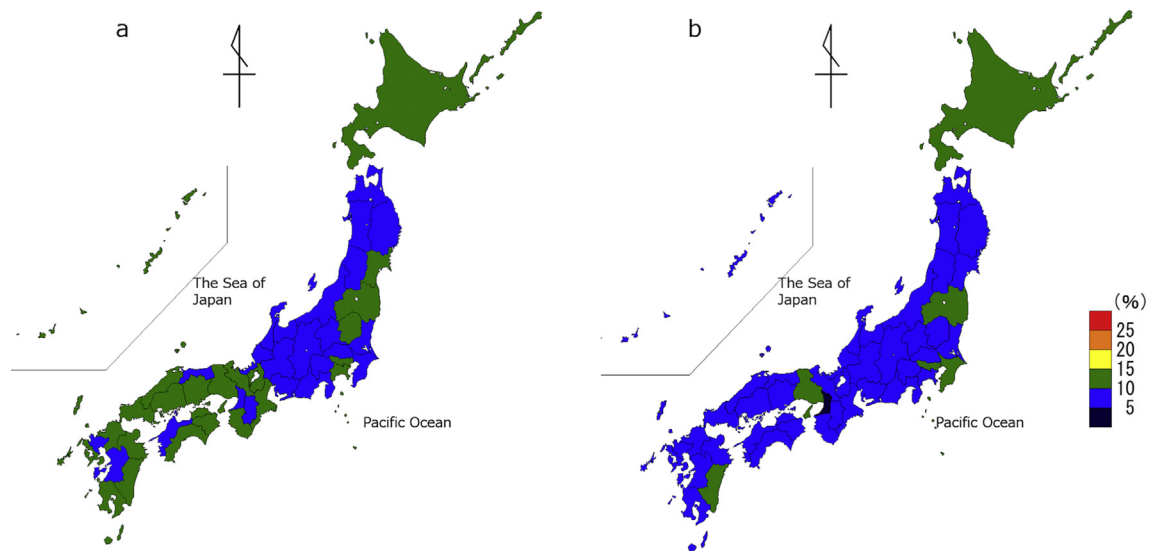


Fig. 2. Map of prevalence of current symptoms of wheeze. (a) 6–8-year-old. (b) 13–15-year-old. Each prevalence category was assigned a different color: $\geq 20\%$ (red), ≥ 15 to <20 (orange), ≥ 10 to <15 (yellow), ≥ 5 to <10 (green), ≥ 5 to <10 (blue), and <5 (purple).

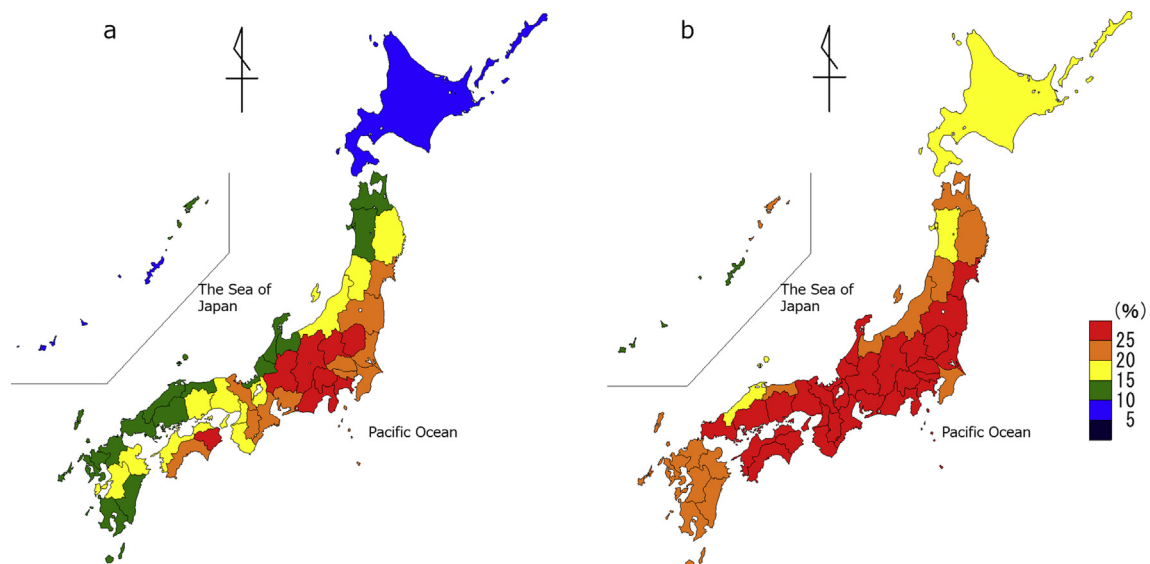


Fig. 3. Map of prevalence of current symptoms of rhino-conjunctivitis. (a) 6–8-year-old. (b) 13–15-year-old. Each prevalence category was assigned a different color: $\geq 20\%$ (red), ≥ 15 to <20 (orange), ≥ 10 to <15 (yellow), ≥ 5 to <10 (green), ≥ 5 to <10 (blue), and <5 (purple).

In terms of sex, current wheeze and current rhino-conjunctivitis were more prevalent in 6–8-year-old males while current rhino-conjunctivitis and current eczema was more prevalent in 13–15-year-old females. When the prevalence between the two age groups was compared, males exhibited a larger decrease in the prevalence of current wheeze and eczema than females while the latter exhibited a larger increase in the prevalence of current rhino-conjunctivitis than males. Osman *et al.* conducted a survey of allergic disease (asthma, allergic rhinitis, and eczema) among individuals aged 0–65 years to examine sex- and age-based differences and showed that males and females exhibited different courses for each disease.¹² In their study, asthma and allergic rhinitis were more prevalent among males during childhood but were more prevalent among females in adolescence, and eczema was more prevalent among females of reproductive age. Similarly, other cross-sectional surveys using the ISAAC questionnaire and

some birth cohorts have reported a tendency for the prevalence of allergic diseases to be higher among males during childhood and higher among females during adolescence.^{13–16} These gender differences in prevalence suggest the role of hormones, particularly female sex hormones (estrogen and progesterone), in the development of allergic diseases.^{12,13,17}

In wheeze, low maximum ventilation with respect to lung volume in males during childhood was also thought to be one of the reasons for the difference in prevalence.¹⁸ In contrast to studies showing female predominance in wheeze during adolescence,^{13–16} we failed to find any gender difference among the 13–15-year-old group. In the ISAAC Phase 1 study, while the overall prevalence of wheeze was higher among females at ages 13–15 years, there was considerable regional variation suggesting an association with differences in physical maturation.¹³ Sexual maturation in Asians occurs later than in other ethnic groups, possibly explaining the

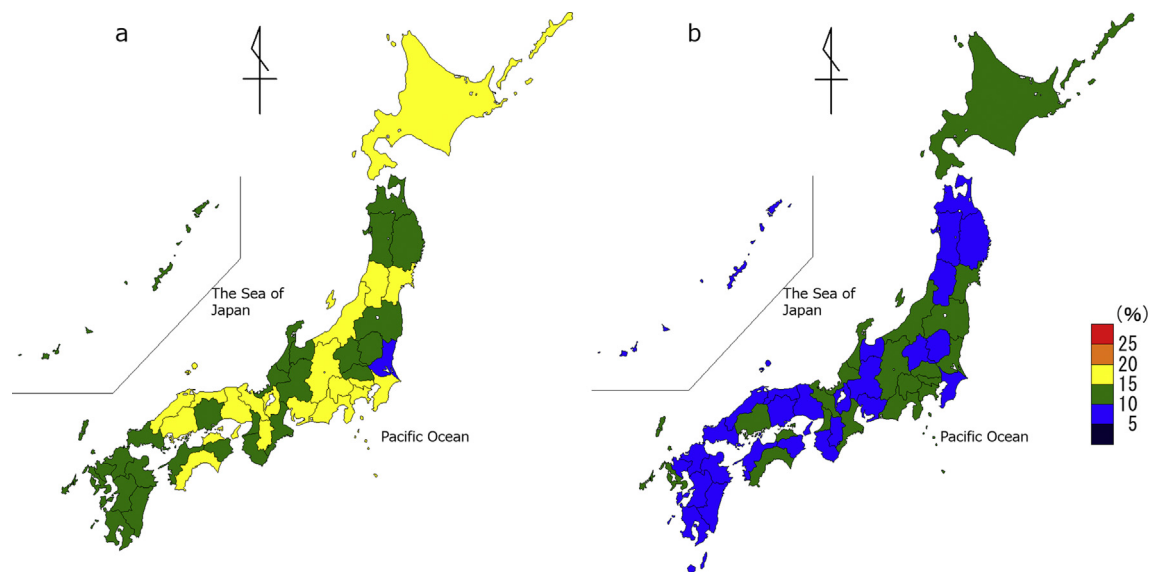


Fig. 4. Map of prevalence of current symptoms of eczema. (a) 6–8-year-old. (b) 13–15-year-old. Each prevalence category was assigned a different color: $\geq 20\%$ (red), ≥ 15 to <20 (orange), ≥ 10 to <15 (yellow), ≥ 5 to <10 (green), ≥ 5 to <10 (blue), and <5 (purple).

absence of observable differences by sex in the 13–15-year-old group.¹⁹ The prevalence of eczema was higher among 13–15-year-old females in the present study. In addition to the possible increase in prevalence under the influence of sex hormones, misclassification of irritant contact dermatitis, which is reportedly more common in adolescent females, may have occurred.²⁰ While we found the prevalence of rhino-conjunctivitis to be higher among 6–8-year old males and 13–15-year-old females, few studies have investigated the sex difference in rhino-conjunctivitis. An analysis of sensitization data from an Isle of Wight cohort (4–18 years old) showed that allergic rhinitis was more common among males while nonallergic rhinitis was more common among females.²¹ Further investigation is necessary to determine whether sex hormones play a role here as in the other diseases described above.

Prevalence by prefecture showed a different range and distribution pattern for each disease. An approximately two-fold difference was observed for current wheeze and eczema while an approximately four-fold difference was observed for rhino-conjunctivitis in both age groups.

While the prevalence of current wheeze among 6–8-year-old subjects was higher in West Japan, it was lower among 13–15-year-old subjects, and the regional differences were also smaller. Possible reasons for the high prevalence in West Japan include climatic conditions, such as temperature and humidity and the effects of the so-called, 'yellow sand'.²² However, it is not clear why this tendency was observed only among 6–8-year-old subjects. The prevalence of rhino-conjunctivitis was higher in inland areas, particularly among 6–8-year-old subjects. Inland areas are mountainous and forested with cedar, Japanese cypress, and other trees that produce a large amount of pollen. This may partly explain our finding, since the prevalence of rhino-conjunctivitis is known to be associated with the pollen count.²³ Areas of high and low prevalence of eczema exhibited a similar distribution for both age groups, but there were no clearly discernible pattern of distribution. Eczema prevalence reportedly differs between urban and rural areas.²⁴ We may not have observed any pattern in the prevalence of eczema by prefecture due to the varying degree of urbanization both between and within prefectures. Determining the role of factors such as climatic conditions or urbanization in these findings requires further investigation.

Previous studies have suggested that climatic conditions, including temperature, humidity, and the UV index, affect the prevalence of allergic diseases.^{25,26} Geographically, Japan extends from the subarctic to subtropical zones, with a corresponding diversity of climates. Moreover, the coastal regions abutting the Pacific Ocean and Japan Sea differ in humidity and rainfall due to meteorological conditions. How this complex climatic picture may affect the prevalence of allergic diseases in Japan is a topic for future research.

The strength of this study lies in the large size of the survey, which used a randomly selected sample of schools on a national level and achieved a high response rate. To assess for possible selection bias resulting from selecting approximately 1000 children per prefecture regardless of the population of resident children, we calculated the adjusted prevalence by the size of the target population in each prefecture, giving more weight to prefectures with a larger number of children of the relevant ages. The overall adjusted prevalence was similar to the unadjusted values, suggesting that our study population was representative of the general child population. Furthermore, our study was the first to report the prevalence by prefecture and to identify the geographical differences in prevalence. However, several limitations need to be considered. First, because we based the definition of target diseases on the questionnaire responses, possible misclassification of the diseases should be considered. However, we used the ISAAC questionnaire, which has been validated for worldwide use in epidemiological studies of allergic disease. Second, it is possible that the subjects were not representative of children in their respective prefecture in terms of gender, family structure, socio-economic status or other factors that may contribute to the development of allergic diseases. However, we tried to minimize the potential for selection bias by selecting the target schools in each prefecture randomly. Additionally, the response rates differed between prefectures, ranging from 43.0% to 95.6%. This may have affected the prefecture-based prevalence estimates for some prefectures with a low response rate and the analysis in the distribution of prevalence.

In conclusion, we used the ISAAC questionnaire to conduct a national survey in Japan to describe the prevalence of childhood allergic diseases and to investigate the differences by age, sex, and prefecture. Different factors may greatly impact the prevalence of

each disease. How these factors contribute to changes in the prevalence rates is a topic for future research.

Acknowledgements

We thank the officials of the Japanese Ministry of Education, Culture, Sports, Science, and Technology; the staff at the various boards of education; the teachers at the participating schools; and the guardians and students who responded to the survey for their cooperation.

We thank Mr. James Robert Valera for his assistance with editing the manuscript.

This study was conducted as part of a research project funded by the Japan Agency for Medical Research and Development's 2015 practical research project for immune, allergic, and other diseases aimed at establishing a continuous epidemiological survey system for understanding allergic disease across all age groups and using the findings in cohort analyses of factors responsible for causing and exacerbating the allergic march.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.08.010>.

Conflicts of interest

The authors have no conflict of interest to declare.

Authors' contributions

AA, HO, YA, KY, MS, and EM designed the study. EM performed the statistical analysis and wrote the first draft of the manuscript. All the other authors contributed to data collection and interpretation and critically reviewed the manuscript. All the authors approved the final version of the manuscript.

References

- Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998;**351**: 1225–32.
- Ellwood P, Asher MI, Garcia-Marcos L, Williams H, Keil U, Robertson C, et al. Do fast foods cause asthma, rhinoconjunctivitis and eczema? Global findings from the International Study of Asthma and Allergies in Childhood (ISAAC) phase three. *Thorax* 2013;**68**:351–60.
- Foliaki S, Nielsen SK, Bjorksten B, Von Mutius E, Cheng S, Pearce N. Antibiotic sales and the prevalence of symptoms of asthma, rhinitis, and eczema: the International Study of Asthma and Allergies in Childhood (ISAAC). *Int J Epidemiol* 2004;**33**:558–63.
- Mitchell EA, Beasley R, Keil U, Montefort S, Odhiambo J. The association between tobacco and the risk of asthma, rhinoconjunctivitis and eczema in children and adolescents: analyses from Phase Three of the ISAAC programme. *Thorax* 2012;**67**:941–9.
- Stewart AW, Mitchell EA, Pearce N, Strachan DP, Weiland SK. The relationship of per capita gross national product to the prevalence of symptoms of asthma and other atopic diseases in children (ISAAC). *Int J Epidemiol* 2001;**30**:173–9.
- Futamura M, Ohya Y, Akashi M, Adachi Y, Odajima H, Akiyama K, et al. Age-related prevalence of allergic diseases in Tokyo schoolchildren. *Allergol Int* 2011;**60**:509–15.
- Higuchi O, Adachi Y, Itazawa T, Ito Y, Yoshida K, Ohya Y, et al. Relationship between rhinitis and nocturnal cough in school children. *Pediatr Allergy Immunol* 2012;**23**:562–6.
- Higuchi O, Adachi Y, Itazawa T, Ito Y, Yoshida K, Ohya Y, et al. Rhinitis has an association with asthma in school children. *Am J Rhinol Allergy* 2013;**27**:e22–5.
- Okabe Y, Itazawa T, Adachi Y, Yoshida K, Ohya Y, Odajima H, et al. Association of overweight with asthma symptoms in Japanese school children. *Pediatr Int* 2011;**53**:192–8.
- Sasaki M, Morikawa E, Yoshida K, Adachi Y, Odajima H, Akasawa A. The change in the prevalence of wheeze, eczema and rhinoconjunctivitis among Japanese children: findings from 3 nationwide cross-sectional surveys between 2005 and 2015. *Allergy* 2019;**74**:1572–5.
- Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483–91.
- Osman M, Hansell AL, Simpson CR, Hollowell J, Helms PJ. Gender-specific presentations for asthma, allergic rhinitis and eczema in primary care. *Prim Care Respir J* 2007;**16**:28–35.
- Worldwide variations in the prevalence of asthma symptoms: the international study of asthma and allergies in childhood (ISAAC). *Eur Respir J* 1998;**12**: 315–35.
- Keil T, Bockelbrink A, Reich A, Hoffmann U, Kamin W, Forster J, et al. The natural history of allergic rhinitis in childhood. *Pediatr Allergy Immunol* 2010;**21**:962–9.
- Ballardini N, Kull I, Lind T, Hallner E, Almqvist C, Ostblom E, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12: data from the BAMSE birth cohort. *Allergy* 2012;**67**:537–44.
- Ziyab AH, Raza A, Karmaus W, Tongue N, Zhang H, Matthews S, et al. Trends in eczema in the first 18 years of life: results from the Isle of Wight 1989 birth cohort study. *Clin Exp Allergy* 2010;**40**:1776–84.
- Leffler J, Stumbles PA, Strickland DH. Immunological processes driving IgE sensitisation and disease development in males and females. *Int J Mol Sci* 2018;**19**.
- Osman M, Tagiyeva N, Wassall HJ, Ninan TK, Devenny AM, McNeill G, et al. Changing trends in sex specific prevalence rates for childhood asthma, eczema, and hay fever. *Pediatr Pulmonol* 2007;**42**:60–5.
- Biro FM, Greenspan LC, Galvez MP, Pinney SM, Teitelbaum S, Windham GC, et al. Onset of breast development in a longitudinal cohort. *Pediatrics* 2013;**132**:1019–27.
- Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009;**124**:1251–8. e23.
- Kurukulaaratchy RJ, Karmaus W, Raza A, Matthews S, Roberts G, Arshad SH. The influence of gender and atopy on the natural history of rhinitis in the first 18 years of life. *Clin Exp Allergy* 2011;**41**:851–9.
- Watanabe M, Noma H, Kurai J, Shimizu A, Sano H, Kato K, et al. Association of sand dust particles with pulmonary function and respiratory symptoms in adult patients with asthma in western Japan using light detection and ranging: a panel study. *Int J Environ Res Public Health* 2015;**12**:13038–52.
- Yoshida K, Adachi Y, Akashi M, Itazawa T, Murakami Y, Odajima H, et al. Cedar and cypress pollen counts are associated with the prevalence of allergic diseases in Japanese schoolchildren. *Allergy* 2013;**68**:757–63.
- Schram ME, Tedja AM, Spijker R, Bos JD, Williams HC, Spuls PI. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. *Br J Dermatol* 2010;**162**:964–73.
- Weiland SK, Husing A, Strachan DP, Rzehak P, Pearce N, Group IPOS. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med* 2004;**61**:609–15.
- Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in the United States. *J Invest Dermatol* 2013;**133**: 1752–9.

Supplementary Table1. The definitions of each area on the map of Japan

East Japan	Hokkaido, Aomori, Akita, Iwate, Yamagata, Miyagi, Fukushima, Tokyo, Tochigi, Gunma, Saitama, Ibaraki, Chiba, Kanagawa, Nagano, Yamanashi, Shizuoka, Gifu, Mie, Aichi, Niigata, Toyama, Ishikawa, Fukui
West Japan	Shiga, Kyoto, Osaka, Hyogo, Nara, Wakayama, Tottori, Shimane, Okayama, Hiroshima, Yamaguchi, Tokushima, Kagawa, Ehime, Kochi, Fukuoka, Saga, Nagasaki, Kumamoto, Oita, Miyazaki, Kagoshima, Okinawa
Sea of Japan coast	Aomori, Akita, Niigata, Toyama, Ishikawa, Fukui, Kyoto, Tottori, Shimane, Yamaguchi, Fukuoka, Saga, Nagasaki, Kumamoto, Oita
Pacific Ocean coast	Hokkaido, Iwate, Miyagi, Fukushima, Ibaraki, Tochigi, Gunma, Saitama, Chiba, Tokyo, Kanagawa, Yamanashi, Nagano, Gifu, Shizuoka, Aichi, Mie, Shiga, Osaka, Hyogo, Nara, Wakayama, Okayama, Hiroshima, Tokushima, Kagawa, Ehime, Kochi, Miyazaki, Kagoshima, Okinawa
Inland areas (non-coastal prefectures)	Tochigi, Gunma, Saitama, Yamanashi, Nagano, Gifu, Shiga, Nara
Coastal areas	Hokkaido, Aomori, Iwate, Miyagi, Akita, Yamagata, Fukushima, Ibaraki, Chiba, Tokyo, Kanagawa, Niigata, Toyama, Ishikawa, Fukui, Shizuoka, Aichi, Mie, Kyoto, Osaka, Hyogo, Wakayama, Tottori, Shimane, Okayama, Hiroshima, Yamaguchi, Tokushima, Kagawa, Ehime, Kochi, Fukuoka, Saga, Nagasaki, Kumamoto, Oita, Miyazaki, Kagoshima, Okinawa

Supplementary Table 2. The prevalence of current symptoms of wheeze, rhino-conjunctivitis, and eczema per age group by prefecture

Prefecture	6-8-year-olds								
	Wheeze			Rhino-conjunctivitis			Eczema		
	n	%	95%CI	n	%	95%CI	n	%	95%CI
Hokkaido	842	12.7	(10.5–15.0)	836	9.3	(7.4–11.3)	840	18.6	(15.9–21.2)
Aomori	897	7.7	(5.9–9.4)	898	13.9	(11.7–16.2)	903	14.1	(11.8–16.3)
Iwate	1,051	8.9	(7.2–10.7)	1,047	19.2	(16.8–21.6)	1,052	12.1	(10.1–14.0)
Miyagi	849	13.3	(11.0–15.6)	844	22.7	(19.9–25.6)	847	17.7	(15.1–20.3)
Akita	850	9.8	(7.8–11.8)	854	12.9	(10.6–15.1)	856	14.4	(12.0–16.7)
Yamagata	977	8.9	(7.1–10.7)	983	15.2	(12.9–17.4)	991	18.3	(15.9–20.7)
Fukushima	1,097	11.4	(9.5–13.3)	1,103	23.7	(21.2–26.2)	1,109	12.9	(10.9–14.9)
Ibaraki	1,056	9.2	(7.4–10.9)	1,062	21.8	(19.4–24.3)	1,061	9.9	(8.1–11.7)
Tochigi	934	10.5	(8.5–12.5)	938	26.9	(24.0–29.7)	941	14.7	(12.4–16.9)
Gunma	1,280	9.5	(7.8–11.1)	1,281	27.7	(25.3–30.2)	1,280	14.8	(12.8–16.7)
Saitama	1,011	9.8	(8.0–11.6)	1,012	23.7	(21.1–26.3)	1,008	12.8	(10.7–14.9)
Chiba	1,219	9.6	(7.9–11.3)	1,216	21.3	(19.0–23.6)	1,226	16.2	(14.1–18.2)
Tokyo	994	10.8	(8.8–12.7)	990	24.5	(21.9–27.2)	996	16.0	(13.7–18.2)
Kanagawa	1,127	12.9	(10.9–14.8)	1,122	25.6	(23.0–28.1)	1,130	16.5	(14.3–18.6)
Niigata	868	7.5	(5.7–9.2)	865	15.4	(13.0–17.8)	869	15.0	(12.6–17.3)
Toyama	1,003	8.0	(6.3–9.7)	1,010	13.9	(11.7–16.0)	1,011	13.7	(11.6–15.9)
Ishikawa	1,161	9.0	(7.3–10.6)	1,167	12.1	(10.2–14.0)	1,166	13.8	(11.8–15.8)
Fukui	1,102	7.8	(6.2–9.4)	1,105	14.8	(12.7–16.8)	1,111	14.6	(12.5–16.7)
Yamanashi	1,102	8.1	(6.5–9.7)	1,102	30.0	(27.3–32.7)	1,110	15.0	(12.9–17.2)
Nagano	671	8.8	(6.6–10.9)	671	25.0	(21.8–28.3)	672	16.5	(13.7–19.3)
Gifu	372	9.1	(6.2–12.1)	372	29.6	(24.9–34.2)	369	14.6	(11.0–18.3)
Shizuoka	771	9.1	(7.0–11.1)	775	30.1	(26.8–33.3)	777	15.6	(13.0–18.1)
Aichi	1,343	8.3	(6.9–9.8)	1,341	23.9	(21.7–26.2)	1,345	15.8	(13.8–17.7)
Mie	78	11.5	(4.3–18.8)	75	24.0	(14.1–33.9)	77	14.3	(6.3–22.3)
Shiga	321	13.1	(9.4–16.8)	325	16.9	(12.8–21.0)	323	17.3	(13.2–21.5)
Kyoto	1,008	12.5	(10.5–14.5)	1,004	20.4	(17.9–22.9)	1,012	16.6	(14.3–18.9)
Osaka	1,099	8.3	(6.6–9.9)	1,094	18.7	(16.4–21.1)	1,098	13.8	(11.7–15.8)
Hyogo	638	11.4	(9.0–13.8)	638	16.3	(13.4–19.2)	638	15.0	(12.3–17.8)
Nara	770	9.9	(7.8–12.0)	773	22.9	(19.9–25.9)	770	18.8	(16.1–21.6)
Wakayama	950	10.7	(8.8–12.7)	954	18.6	(16.1–21.0)	952	13.7	(11.5–15.8)
Tottori	892	7.7	(6.0–9.5)	894	10.2	(8.2–12.2)	895	15.5	(13.2–17.9)
Shimane	549	11.5	(8.8–14.1)	549	13.7	(10.8–16.5)	552	17.4	(14.2–20.6)
Okayama	879	10.8	(8.8–12.9)	879	16.2	(13.7–18.6)	880	13.9	(11.6–16.2)
Hiroshima	960	10.3	(8.4–12.2)	960	13.2	(11.1–15.4)	968	16.0	(13.7–18.3)
Yamaguchi	759	10.0	(7.9–12.1)	752	14.4	(11.8–16.9)	760	12.8	(10.4–15.1)
Tokushima	764	11.3	(9.0–13.5)	766	25.2	(22.1–28.3)	767	14.1	(11.6–16.5)
Kagawa	883	11.9	(9.8–14.0)	882	19.2	(16.6–21.8)	887	15.1	(12.7–17.5)

Ehime	1,126	9.4	(7.7 – 11.1)	1,128	18.9	(16.6–21.2)	1,128	12.4	(10.5–14.3)
Kochi	553	12.1	(9.4 – 14.8)	556	20.1	(16.8–23.5)	560	17.0	(13.8–20.1)
Fukuoka	988	11.2	(9.3 – 13.2)	995	14.9	(12.7–17.1)	997	14.0	(11.9–16.2)
Saga	1,012	9.8	(7.9 – 11.6)	1,022	14.3	(12.1–16.4)	1,020	13.4	(11.3–15.5)
Nagasaki	1,149	10.7	(8.9 – 12.5)	1,152	11.9	(10.0–13.8)	1,153	13.9	(11.9–15.9)
Kumamoto	890	9.3	(7.4 – 11.2)	892	16.0	(13.6–18.4)	894	11.5	(9.4 – 13.6)
Oita	1,007	11.1	(9.2 – 13.1)	1,009	16.0	(13.7–18.2)	1,018	13.6	(11.4–15.7)
Miyazaki	772	13.3	(10.9–15.7)	766	13.1	(10.7–15.4)	773	13.6	(11.2–16.0)
Kagoshima	1,033	13.9	(11.8–16.1)	1,037	12.1	(10.1–14.0)	1,042	12.3	(10.3–14.3)
Okinawa	519	12.9	(10.0–15.8)	519	8.1	(5.7–10.4)	517	10.8	(8.1 – 13.5)

Prefecture	13-15-year-olds								
	Wheeze			Rhino-conjunctivitis			Eczema		
	n	%	95%CI	n	%	95%CI	n	%	95%CI
Hokkaido	745	13.2	(10.7 – 15.6)	741	18.9	(16.1 – 21.7)	748	12.0	(9.7 – 14.4)
Aomori	837	8.0	(6.2 – 9.8)	827	21.2	(18.4 – 24.0)	833	9.6	(7.6 – 11.6)
Iwate	931	6.6	(5.0 – 8.1)	918	22.7	(19.4 – 25.9)	940	8.5	(6.7 – 10.3)
Miyagi	720	9.6	(7.4 – 11.7)	726	27.1	(23.9 – 30.4)	723	12.7	(10.3 – 15.2)
Akita	1167	9.8	(8.1 – 11.5)	1154	19.4	(17.1 – 21.7)	1164	8.2	(6.7 – 9.8)
Yamagata	404	7.4	(4.9 – 10.0)	397	24.9	(20.7 – 29.2)	405	8.4	(5.7 – 11.1)
Fukushima	947	13.8	(11.6 – 16.0)	940	28.8	(25.9 – 31.7)	942	10.7	(8.7 – 12.7)
Ibaraki	1103	8.3	(6.7 – 10.0)	1097	30.9	(28.2 – 33.6)	1107	11.1	(9.3 – 13.0)
Tochigi	1105	8.3	(6.7 – 10.0)	1101	29.3	(26.6 – 32.0)	1107	9.8	(8.0 – 11.5)
Gunma	1267	6.7	(5.3 – 8.1)	1259	34.4	(31.8 – 37.0)	1264	9.7	(8.0 – 11.3)
Saitama	667	8.2	(6.2 – 10.3)	662	31.6	(28.0 – 35.1)	668	10.0	(7.7 – 12.3)
Chiba	871	10.2	(8.2 – 12.2)	869	24.3	(21.4 – 27.1)	869	7.4	(5.6 – 9.1)
Tokyo	551	10.5	(8.0 – 13.1)	544	28.3	(24.5 – 32.1)	547	13.2	(10.3 – 16.0)
Kanagawa	596	8.2	(6.0 – 10.4)	594	26.3	(22.7 – 29.8)	592	11.0	(8.5 – 13.5)
Niigata	787	7.4	(5.5 – 9.2)	786	22.1	(19.2 – 25.0)	795	10.7	(8.5 – 12.8)
Toyama	956	6.4	(4.8 – 7.9)	947	23.3	(20.6 – 26.0)	953	9.0	(7.2 – 10.8)
Ishikawa	728	7.0	(5.1 – 8.9)	718	26.7	(23.5 – 30.0)	728	11.8	(9.5 – 14.2)
Fukui	1003	5.9	(4.4 – 7.3)	998	27.0	(24.2 – 29.7)	1000	11.3	(9.3 – 13.3)
Yamanashi	1129	8.2	(6.6 – 9.8)	1116	37.6	(34.8 – 40.5)	1127	10.2	(8.4 – 12.0)
Nagano	226	7.1	(3.7 – 10.4)	222	27.9	(22.0 – 33.9)	223	12.1	(7.8 – 16.4)
Gifu	572	5.9	(4.0 – 7.9)	574	40.1	(36.0 – 44.1)	576	9.9	(7.4 – 12.3)
Shizuoka	1151	7.2	(5.7 – 8.7)	1142	33.5	(30.7 – 36.2)	1148	10.1	(8.4 – 11.9)
Aichi	751	6.7	(4.9 – 8.4)	740	30.1	(26.6 – 33.6)	747	9.4	(7.3 – 11.1)

Mie	297	7.1	(4.1 - ^{10.} ₀)	294	30.6	(⁸ ₃ - ⁴ ₉)	294	10.5	(7.0 - ⁵ ₁)
Shiga	405	8.9	(6.1 - ^{11.} ₇)	404	27.5	(^{23.} ₁ - ^{31.} ₈)	406	9.9	(6.9 - ^{12.} ₈)
Kyoto	338	7.1	(4.3 -9.9)	333	30.9	(^{25.} ₉ - ^{35.} ₉)	339	10.6	(7.3 - ^{13.} ₉)
Osaka	336	4.5	(2.2 -6.7)	333	26.7	(^{21.} ₉ - ^{31.} ₅)	338	10.4	(7.1 - ^{13.} ₆)
Hyogo	506	10.9	(8.1 - ^{13.} ₆)	503	25.2	(^{21.} ₄ - ^{29.} ₁)	506	9.7	(7.1 - ^{12.} ₃)
Nara	658	5.9	(4.1 -7.7)	650	34.3	(^{30.} ₆ - ^{38.} ₀)	657	7.6	(5.6 -9.6)
Wakayama	872	7.0	(5.3 -8.7)	870	32.0	(^{28.} ₈ - ^{35.} ₁)	872	9.1	(7.2 - ^{11.} ₀)
Tottori	548	5.3	(3.4 -7.2)	554	20.4	(^{17.} ₀ - ^{23.} ₈)	552	9.4	(7.0 - ^{11.} ₉)
Shimane	418	6.9	(4.5 -9.4)	413	18.2	(^{14.} ₄ - ^{21.} ₉)	415	9.2	(6.4 - ^{11.} ₉)
Okayama	513	7.2	(5.0 -9.5)	511	28.6	(^{24.} ₆ - ^{32.} ₅)	515	9.7	(7.1 - ^{12.} ₃)
Hiroshima	696	9.3	(7.2 - ^{11.} ₅)	698	30.2	(^{26.} ₈ - ^{33.} ₆)	706	11.3	(9.0 - ^{13.} ₇)
Yamaguchi	804	7.8	(6.0 -9.7)	804	28.1	(^{25.} ₀ - ^{31.} ₂)	804	8.5	(6.5 - ^{10.} ₄)
Tokushima	902	8.4	(6.6 - ^{10.} ₂)	895	30.1	(^{27.} ₀ - ^{33.} ₁)	903	8.9	(7.0 - ^{10.} ₇)
Kagawa	1171	8.1	(6.5 -9.7)	1164	25.6	(^{23.} ₁ - ^{28.} ₁)	1169	10.9	(9.1 - ^{12.} ₇)
Ehime	861	7.5	(5.8 -9.3)	850	30.6	(^{27.} ₅ - ^{33.} ₇)	864	9.6	(7.6 - ^{11.} ₆)
Kochi	671	7.2	(5.2 -9.1)	665	26.2	(^{22.} ₈ - ^{29.} ₅)	665	10.5	(8.2 - ^{12.} ₉)
Fukuoka	873	8.9	(7.0 - ^{10.} ₈)	863	24.6	(^{21.} ₇ - ^{27.} ₄)	873	8.6	(6.7 - ^{10.} ₅)
Saga	991	9.1	(7.3 - ^{10.} ₉)	982	22.1	(^{19.} ₅ - ^{24.} ₇)	992	8.7	(6.9 - ^{10.} ₄)
Nagasaki	1008	7.5	(5.9 -9.2)	1003	22.5	(^{19.} ₉ - ^{25.} ₁)	1011	11.0	(9.0 - ^{12.} ₉)
Kumamoto	824	6.9	(5.2 -8.7)	820	21.5	(^{18.} ₆ - ^{24.} ₃)	818	7.3	(5.5 -9.1)
Oita	888	8.8	(6.9 - ^{10.} ₆)	879	23.0	(^{20.} ₂ - ^{25.} ₈)	890	8.8	(6.9 - ^{10.} ₆)
Miyazaki	520	11.5	(8.8 - ^{14.} ₃)	521	23.2	(^{19.} ₆ - ^{26.} ₉)	519	7.3	(5.1 -9.6)
Kagoshima	1338	9.1	(7.6 - ^{10.} ₇)	1333	21.9	(^{19.} ₇ - ^{24.} ₁)	1325	8.0	(6.5 -9.5)
Okinawa	591	7.3	(5.2 -9.4)	585	10.3	(7.8 - ^{12.} ₇)	590	6.4	(4.5 -8.4)

Supplementary Table 3. Prevalence of current symptoms of wheeze, rhino-conjunctivitis, and eczema per age group in each region

	East Japan		West Japan		p	The Sea of Japan coast		Pacific Ocean coast		p	Inland areas		Coastal areas		p
	%	95%CI	%	95%CI		%	95%CI	%	95%CI		%	95%CI	%	95%CI	
Wheeze															
6-8y	9.6	9.2-10.0	10.8	10.4-11.3	<0.001*	9.5	9.0-10.0	10.5	10.2-10.9	0.001*	9.6	8.9-10.3	10.3	10.0-10.6	0.082
13-15y	8.3	7.9-8.7	8.0	7.6-8.4	0.353	7.7	7.2-8.1	8.4	8.1-8.8	0.013*	7.5	6.8-8.2	8.3	8.0-8.6	0.031*
Rhino-conjunctivitis															
6-8y	20.9	20.4-21.5	16.1	15.6-16.7	<0.001*	14.4	13.8-14.9	21.1	20.7-21.6	<0.001*	26.1	25.0-27.2	17.4	17.0-17.8	<0.001*
13-15y	27.9	27.3-28.5	25.3	24.6-26.0	<0.001*	23.3	22.5-24.0	28.5	27.9-29.1	<0.001*	33.6	32.4-34.8	25.3	24.8-25.8	<0.001*
Eczema															
6-8y	14.9	14.4-15.3	14.3	13.8-14.8	0.093	14.5	13.9-15.0	14.7	14.2-15.1	0.616	15.3	14.4-16.2	14.5	14.1-14.8	0.087
13-15y	10.2	9.7-10.8	9.2	8.8-9.7	0.001*	9.4	8.9-9.9	9.8	9.5-10.2	0.209	9.7	9.0-10.5	9.7	9.3-10.0	0.918

Data are presented as a percentage and 95% confidence interval (95% CI).

Prevalence among regions was compared using a chi-square test.

* P value from chi-squared test of the proportion of East to West Japan, Pacific Ocean to on the Sea of Japan side or inland to coastal areas < 0.05.