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Recent prevalence of allergic rhinitis caused by house dust mites among the pediatric population in Fukui, Japan

Yoshimasa Imoto, MD, PhD[a]*, Masafumi Sakashita, MD, PhD[a], Takahiro Tokunaga, MD, PhD[b], Masafumi Kanno, MD, PhD[a], Kyoko Saito, MD[a], Anna Shimizu, MD[a], Ayako Maegawa, MD[a] and Shigeharu Fujieda, MD, PhD[a]

ABSTRACT

Background: Allergic rhinitis (AR) is an IgE-mediated type I allergic chronic nasal disease common among all age groups, including the pediatric population. House dust mites (HDMs) are globally ubiquitous and the most important indoor aeroallergen. However, the recent prevalence of HDM-caused AR (AR-HDM) in Japan remains unknown, especially after the COVID-19 pandemic.

Objective: The objective of this study was to investigate the current prevalence of AR-HDM, its clinical features, and the current status of medical examinations in elementary school students.

Methods: A survey of 41,000 elementary school students was conducted during July 2021 in Fukui Prefecture, Japan. Parents were asked to complete a questionnaire that examined allergic disease history and clinical background.

Results: A total of 17,974 subjects were analyzed in the study. The results showed that the current prevalence of AR-HDM in elementary school children is 18.8%. We found that AR-HDM had already developed before entrance into elementary school in 68.3% of affected subjects. Among these subjects, 82.3% had received some form of treatment, such as prescription medications, whereas 4.2% were treated by allergen immunotherapy. Multiple logistic regression analysis of the onset of AR-HDM revealed that male sex, being the first-born child, comorbidity of bronchial asthma, atopic dermatitis, food allergy, and allergic conjunctivitis are associated with development of AR-HDM.

Conclusions: The present study revealed the prevalence of AR-HDM in elementary school children. The results emphasize the importance of appropriate diagnosis and treatment from infancy through early childhood.

Keywords: Allergic rhinitis, House dust mites, Elementary school children, Onset of allergic rhinitis, Atopic march

[a]Department of Otorhinolaryngology, Head & Neck Surgery, Faculty of Medical Sciences, University of Fukui, Fukui, Japan
*Corresponding author. Department of Otorhinolaryngology, Head & Neck Surgery, Faculty of Medical Sciences, University of Fukui, 23-3 Shimoaizuki, Matsuoka, Eiheiji, Yoshida, Fukui, 910-1193, Japan. E-mail: yimoto@u-fukui.ac.jp
Full list of author information is available at the end of the article

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INTRODUCTION

Allergic rhinitis (AR), an IgE-mediated type I allergic, chronic inflammatory disorder affecting the nasal mucosa, is characterized by episodes of repeated sneezing, rhinorrhea, and nasal congestion. Allergic rhinitis is a common chronic nasal disease in all age groups, including the pediatric population. As the prevalence of AR is increasing worldwide, its associated social and economic problems remain to be resolved.[1-3]

Unlike in adults, AR is often underdiagnosed in children because they frequently do not report nasal symptoms of the illness to their parents and/or physicians, resulting in a lack of appropriate treatment. Although AR is not associated with severe morbidity and mortality, nasal symptoms caused by AR can affect the health-related quality of life (QOL) of children going through the process of growth and development by substantially interrupting their daily activities.[4-6] This reduction in QOL can be due to the severity of nasal symptoms, which can cause sleep disorders, emotional problems, fatigue, irritability, and impairment of activities and social functioning.[7-9]

The International Study of Asthma and Allergies in Childhood (ISAAC) reported that the current overall worldwide prevalence of rhino-conjunctivitis symptoms ranges from 4.2 to 12.7% in children aged 6–7 years and to 45.1% in those aged 13–14 years.[10] Another study from Australia reported that the prevalence of AR was approximately 12.9% in children aged 6–7 years and 19.3% in children aged 13–14 years,[11] whereas other data showed a higher prevalence.[12] Although there are some regional differences, it is thought that the prevalence of AR in children is progressively increasing, raising concerns that it is a health issue that can have an effect on child development.[13]

We previously investigated the prevalence of AR among various age groups, including children aged 18 months,[14] high-school students aged 15–18 years,[15] and adults aged 20–59 years.[16] In the survey of children aged 18 months, 44 subjects (10.7%) tested positive for Japanese cedar pollen (JCP), mites, or cat antigen–specific IgE, which indicated that sensitization to inhalant antigens had already occurred before 18 months of age, although a definite diagnosis of AR may be difficult.[3] In contrast, a survey involving 19,461 high-school students revealed an AR prevalence rate of 19.2% in 2012,[15] with the prevalence of perennial AR similar to that of adults (18.8%).[17] These results indicate that the onset of perennial AR may accelerate from toddler to elementary school age.

House dust mites (HDMs) are globally ubiquitous and are considered the most important indoor aeroallergen. HDMs can cause conditions related to airway allergic inflammation, including AR and asthma.[18-20] A previous report showed that sensitization to inhaled perennial allergens associated with impaired lung function at school age, which is affected by chronic allergic airway inflammation beginning in the first 3 years of life,[21] sensitization to mite allergens in early life may be of significant clinical importance. Large-scale epidemiologic surveys of elementary students in Japan were conducted in 1982, 1992, and 2002.[22] The latest survey in Japan showed that the prevalence of rhino-conjunctivitis was 18.7% in 2015 for 6- to 8-year-old children.[23] As the current prevalence of HDM-caused AR (AR-HDM) in Japan remains unknown, we investigated the current prevalence of AR-HDM, clinical features of the condition, and frequency of medical reviews for AR-HDM in elementary school students.

METHODS

A survey of 41,000 elementary school students was conducted during July 2021 to assess the status of allergic diseases in Fukui Prefecture, Japan. Parents were asked to complete a questionnaire regarding their child's age, sex, height, weight, number of siblings, and birth order. To assess obesity, we grouped the subjects into 3 categories based on body mass index (BMI) and defined obesity as at or above the 95th percentile of BMI for age; overweight as between 85th to 95th percentile of BMI for age; and the others according to the previous reports.[24-26]

The questionnaire included several items regarding allergic diseases, as follows (Supplementary Fig. 1): 1.) Has your child been diagnosed by a physician with any of the following illnesses: AR-HDM, seasonal AR (SAR) caused by JCP (SAR-JCP), bronchial asthma, atopic dermatitis,

food allergy, or allergic conjunctivitis? [multiple answers] 2.) When does your child show AR-HDM symptoms? [multiple answers] 3.) At what age did your child's symptoms of AR-HDM begin? 4.) Does your child visit a hospital or clinic for nasal conditions caused by AR-HDM? 5.) Has your child received any treatments for AR-HDM, such as prescription medications from a clinic or hospital, over-the-counter (OTC) medications, or allergen immunotherapy (AIT) such as subcutaneous or sublingual immunotherapy ? [multiple answers] Cumulative incidence rate is defined as the cumulative number of persons who have onset of disease by that age divided by the total number of persons in the study. We also defined new onset rate as the number of new cases at that age divided by the number of cases that had not yet onset by the previous year.

This study was performed in compliance with the Declaration of Helsinki and Good Clinical Practice, with prior approval from the Ethics Committee of University of Fukui, Japan (20210027).

Statistical analysis

Both the cumulative incidence rate and new onset rate of AR-HDM according to age were calculated with the 95% confidence interval (CI). Differences between AR-HDM patients and non–AR-HDM subjects were examined using the $\chi 2$ test for categorical variables and the *t*-test for quantitative variables. Missing values were not imputed.

Multivariable logistic-regression models were prepared to estimate the risk of AR-HDM associated with potential predictors, adjusting for back ground characteristics (age, sex, residence area, student's birth order, obesity, and comorbidity of allergic diseases). Inclusion of these variables in the models was based on existing knowledge of risk factors for AR-HDM. The odds ratio (OR) with 95% CI were calculated. Inclusion of variables in the models was based on existing knowledge of risk factors for AR-HDM. We followed standard methods to estimate the sample size for multiple logistic regression, with at least 10 outcomes needed for each included independent variable. Considering the number of AR-HDM patients analyzed in this study, the number of variables used was appropriate, and considerably lower than the upper limit.

Analyses were performed using Stata software, version 18.0 (STATA Data Analysis and Statistical Software, Stata Corp LP, College Station, TX, USA. www.stata.com). The significance level was set at 0.05.

RESULTS

All elementary school children (total of 41,000) were surveyed, and 22,082 (53.9%) parents responded to the questionnaires. We excluded 4108 children because of inappropriate answers. There were no missing values regarding the diagnosis of AR-HDM, and finally, a total of 17,974 (43.8%) subjects were analyzed (Fig. 1). There were 8013 (49.9%) boys and 8047 (50.1%) girls included in the study. There were no significant differences in terms of grade level in school (Table 1). Of all school children included, 3381 (18.8%) were previously diagnosed with AR-HDM. The prevalence of SAR-JCP was 16.6%, atopic dermatitis 12.9%, asthma 8.3%, food allergy 5.9%, and allergic conjunctivitis 4.9% (Table 1).

The age at which allergic nasal symptoms due to AR-HDM appeared is shown in Fig. 2A. The cumulative incidence rate of AR-HDM gradually

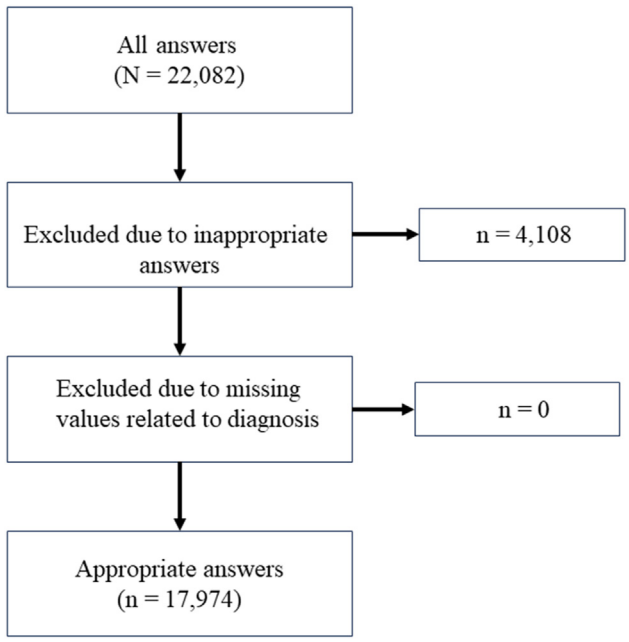

Fig. 1 Flowchart of the survey. A total of 22,082 children were surveyed, and 4108 children were excluded because of inappropriate answers. There were no missing values regarding the diagnosis of AR-HDM. Finally, 17,974 (43.8%) subjects were analyzed in the study

	N = 17,974
Sex	
Male	8013 (44.6%)
Female	8047 (44.8%)
Unknown	1914 (10.7%)
Elementary school grade	
1st	2807
2nd	2800
3rd	2606
4th	2659
5th	2588
6th	2616
Unknown	1898
Number of siblings	2 ± 0.8
Birth order	
1st	7329 (46.4%)
2nd	5913 (37.4%)
3rd	2155 (13.6%)
4th	343 (2.2%)
5th and above	72 (0.5%)
Obesity	
Overweight	1427 (9.7%)
Obese	776 (5.3%)
Others	12,459 (85.0%)
Comorbidity	
AR-HDM	3381 (18.8%)
Japanese cedar pollinosis	2981 (16.6%)
Atopic dermatitis	2319 (12.9%)
Bronchial asthma	1492 (8.3%)
Food allergy	1065 (5.9%)
Allergic conjunctivitis	889 (4.9%)

Table 1. Subject characteristics

increased at approximately 3 years of age. The new onset rate of AR-HDM also peaked at approximately 3 years of age and remained high until approximately 6 years of age (Fig. 2B). In total, 68.3% of AR-HDM subjects had developed the condition before entering elementary school.

As for AR symptoms related to HDM, 1610 children (47.6%) had persistent nasal symptoms, and the frequency of nasal symptoms was higher in March–April and May–June than in other periods (March–April, 16.2%; May–June, 10.3%). These results could be indicative of overlap with SAR caused by JCP or Japanese cypress pollen, which are dispersed around the same time (Table 2).

We also examined frequency of medical reviews for AR-HDM. Among children with AR-HDM, 23.6% (768/3263) visited a clinic for regular medical examinations and medications, whereas 66.9% (2175) occasionally visited a clinic when they showed nasal symptoms, and the remaining 310 (9.5%) students did not see a physician (Table 3). Although 2783 students (82.3%) had received some kind of treatment, such as prescription medications from a clinic or hospital, only 141 students (4.2%) were treated using AIT.

Next, we examined whether there were any differences between AR-HDM students and non–AR-HDM students by comparing details of their characteristics. As shown in Table 4, boys had a significantly higher rate of AR-HDM (58.6%, $P < 0.001$) than girls (41.4%). Regarding the number of siblings, students with AR-HDM had

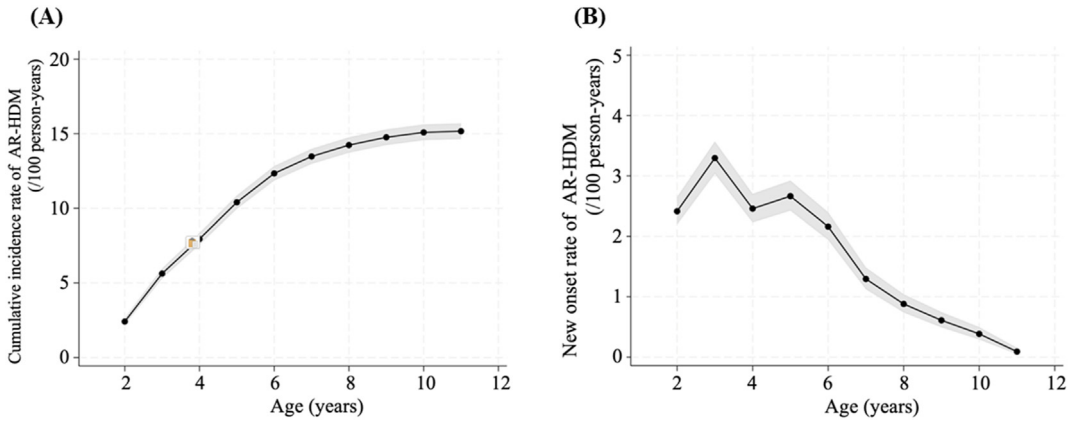

Fig. 2 The cumulative incidence rate and new onset rate of AR-HDM. (A) The cumulative incidence rate of AR-HDM increased gradually and reached a plateau at 10 years of age. The prevalence and 95% 95% CI were calculated. (B) The new onset rate of AR-HDM peaked at 3 years of age, whereas the rate of new cases decreased after 7 years of age. The prevalence and 95% 95% CI were calculated

All year round	1610 (47.6%)
January–February	145 (4.3%)
March–April	549 (16.2%)
May–June	349 (10.3%)
July–August	94 (2.8%)
September–October	222 (6.6%)
November–December	155 (4.6%)
Unknown	875 (25.9%)

Table 2. Periods when children show nasal symptoms

slightly fewer siblings compared to non-AR-HDM students ($P < 0.001$). Interestingly, first-born children had a higher incidence of AR-HDM than non–AR-HDM students ($P < 0.001$), suggesting that the incidence of AR-HDM varies by birth order. In comparison to non–AR-HDM students, AR-HDM students had significantly higher past diagnosis of SAR-JCP (46.5%, $P < 0.001$), atopic dermatitis (22.4%, $P < 0.001$), bronchial asthma (17.2%, $P < 0.001$), food allergy (13.1%, $P < 0.001$), and allergic conjunctivitis (13.4%, $P < 0.001$).

According to a previous report, obesity is a risk factor for development of allergic airway disease.[27] We therefore examined the relationship between obesity and AR-HDM according to the previous reports based on BMI.[24–26] There was no significant difference between three groups in terms of AR-HDM among all subjects (Table 5).

Clinic visits	Regular	768 (23.6%)
	Occasional	2175 (66.9%)
	Never	310 (9.5%)
	Unknown	128
Medication	Prescription medication	2783 (82.3%)
	OTC	300 (8.9%)
	AIT	141 (4.2%)
	Never treated	291 (8.6%)
	Others	38 (1.1%)

Table 3. Medical examination status for AR-HDM

Interestingly, children with bronchial asthma were more likely to be obese (asthmatic subjects, 7.0%; non-asthmatic subjects, 5.1%, $P < 0.001$; Supplementary Table 1). Furthermore, the proportion of obesity differed depending on comorbidities with AR-HDM (obese subjects with AR-HDM: asthmatic subjects, 6.1%; non-asthmatic subjects, 5.4%, $P = 0.53$; obese subjects without AR-HDM: asthmatic subjects, 7.5%; non-asthmatic subjects, 5.1%, $P < 0.001$).

Multiple logistic regression analysis of the onset of AR-HDM revealed that male sex (odds ratio [OR]: 1.53, 95% confidence interval [95% CI]: 1.41–1.65, $P < 0.001$), being the first-born child (OR: 1.36, 95% CI: 1.26–1.48, $P < 0.001$), bronchial asthma (OR: 2.11, 95% CI: 1.87–2.37, $P < 0.001$), atopic dermatitis (OR: 1.59, 95% CI: 1.43–1.76, $P < 0.001$), food allergy (OR: 2.24, 95% CI: 1.95–2.58, $P < 0.001$), and allergic conjunctivitis (OR: 3.62, 95% CI: 3.31–4.18, $P < 0.001$) were associated with the risk of developing AR-HDM (Table 6).

DISCUSSION

In the present study, we examined the recent cumulative incidence rate of AR-HDM in elementary school children using a parents-based questionnaire. The results showed that 18.8% of the children surveyed had been diagnosed with AR-HDM. As we were able to evaluate a total of 17,974 children without any significant differences in age or sex, the results reflect the present cumulative incidence rate of AR-HDM. With regard to risk factors for AR-HDM, our results showed that there was a significant difference in sex; AR-HDM is more common in males among elementary school children (OR: 1.53, $P < 0.001$). We then determined that the cumulative incidence rate and new onset rate of AR-HDM are dependent on age and sex. As shown in Supplementary Fig. 2A, the cumulative incidence rate of AR-HDM in boys is higher than in girls across all ages. The present study also revealed that 13.4% of children aged 2 years had already developed AR-HDM–related nasal symptoms. Interestingly, the cumulative incidence rate of AR-HDM increased gradually with age, plateauing at 10 years of age; by age 6 years, 68.3% of the children surveyed had already developed AR symptoms (Fig. 2A). As shown in Fig. 2B and

	Non-AR-HDM subjects n = 14,593	AR-HDM patients n = 3381	*P*-value
Sex			
Male	6034 (41.3%)	1979 (58.5%)	<0.001***
Female	6651 (45.6%)	1396 (41.3%)	
Unknown	1908 (13.1%)	6 (0.2%)	
Number of siblings	2.4 ± 0.9	2.3 ± 0.8	<0.001***
Birth order			
1st	5569 (44.5%)	1760 (53.3%)	<0.001***
2nd	4780 (38.2%)	1133 (34.3%)	
3rd	1802 (14.4%)	353 (10.7%)	
4th	296 (2.4%)	47 (1.4%)	
5th and above	64 (0.5%)	8 (0.2%)	
Comorbidity			
Japanese cedar pollinosis	1516 (12.4%)	1465 (46.5%)	<0.001***
Atopic dermatitis	1563 (10.7%)	756 (22.4%)	<0.001***
Bronchial asthma	909 (6.2%)	583 (17.2%)	<0.001***
Food allergy	622 (4.3%)	443 (13.1%)	<0.001***
Allergic conjunctivitis	435 (3.0%)	454 (13.4%)	<0.001***

Table 4. Comparison of characteristics between Non-AR-HDM subjects and AR-HDM patients

Supplementary Fig. 2B, the new onset rate of AR-HDM peaked at 3 years of age, whereas the incidence of new cases decreased after 7 years of age in both boys and girls.

Compared with the ISAAC study, which reported that AR tends to first develop in children younger than 5 years and increases at approximately age 6–7 years, our results are not only consistent but

	Non-AR-HDM subjects n = 14,593	AR-HDM patients n = 3381	*P*-value
Obesity			
Overweight	1132 (9.8%)	295 (9.5%)	
Obese	605 (5.2%)	171 (5.5%)	
Others	9813 (85.0%)	2646 (85.0%)	0.750

Table 5. Subject characteristics related to obesity

	Odds Ratio [95% CI]	*P*-value
Sex (reference: female)		
Male	1.53[1.41–1.65]	<0.001***
Unknown	1.01 [0.41–2.49]	0.979
Birth order (reference: 2nd or above)		
1st	1.36 [1.26–1.48]	<0.001***
Comorbidity		
Atopic dermatitis	1.58 [1.42–1.76]	<0.001***
Bronchial asthma	2.12 [1.88–2.38]	<0.001***
Food allergy	2.25 [1.96–2.58]	<0.001***
Allergic conjunctivitis	3.62 [3.13–4.18]	<0.001***

Table 6. Multiple logistic regression analysis of the onset of AR-HDM

also suggest that a significant proportion of younger children around age 3 years may have already developed AR-HDM nasal symptoms.[28] Although the onset of new AR-HDM cases was relatively low in children aged 10–11 years, the new onset rate was higher in girls than boys (Supplementary Fig. 2B). Keller et al. reported that AR is more common in males prior to puberty and more common in females after puberty, indicating that a "sex-switch" from male to female predominance in rhinitis prevalence occurs around puberty.[29] To elucidate the changes in the incidence of AR-HDM around puberty in more detail, a continuous observation study will be necessary.

Allergic rhinitis in children may contribute to low productivity in school, sleep disturbances, and decreased involvement in outdoor activities.[3,30] Despite the presence of significant comorbidities and the adverse effects of childhood AR on QOL and school performance, the condition is often misunderstood and therefore mistreated. Several reports have highlighted pediatric AR by updating existing guidelines.[31–34] AR can be effectively treated using pharmacotherapy with H1-antihistamines or intranasal corticosteroids, in addition to allergen-specific immunotherapy (including subcutaneous or sublingual immunotherapy). Our present data showed that 23.6% of AR-HDM children see their physician regularly, compared with 66.9% who see a physician occasionally when they have symptoms necessitating medical treatment (Table 3). Although details regarding the severity of AR-HDM symptoms remain unclear, these results may reflect a relatively high medical examination rate in Japan. By contrast, 9.5% of AR-HDM children did not see a physician, which suggests that their symptoms may not have been severe. As the present survey was conducted during the COVID-19 pandemic, it is possible that some parents refrained from taking their children to see a physician when they otherwise would have.

Our results also revealed that the most frequently used medications include intranasal sprays prescribed by a medical institution (82.3%), whereas the rate of OTC or nonprescription medication use was relatively low (8.9%) (Table 3). AIT is an effective treatment modality that can suppress nasal symptoms to achieve remission.[35–37] As expected, the current proportion of subjects who had received AIT was relatively low, at only 4.2%. To avoid bothersome symptoms and maintain school performance, we believe that AIT against AR-HDM should be recommended more frequently in Japan, which may also lead to the prevention against the development of asthma and new sensitizations.

Airway allergic diseases such as asthma may be related to systemic conditions such as obesity.[38] Regarding AR, the potential associations with overweight and obesity remain unclear.[27] The present results revealed that children with bronchial asthma are typically obese. However, this did not find no significant difference between obese, overweight, and the other children in terms of AR-HDM incidence among all subjects (Table 5). Among children with AR-HDM, no significant difference in terms of obesity was found, similar to asthma as a comorbidity, although the relationship between AR-HDM severity and overweight/obesity is unclear. On the other hand, the finding that a higher proportion of non-AR children with bronchial asthma were obese suggests that there might be pathologic differences between bronchial asthma and AR-HDM. Further studies are needed to address this possibility.

Multiple logistic regression analysis also indicated that the onset of AR-HDM is closely related to bronchial asthma, atopic dermatitis, food allergy, and allergic conjunctivitis (Tables 4 and 6). Although residual confounding by unmeasured factors may influence results in our study, previous cross-sectional and longitudinal studies revealed that these allergic diseases are closely related to AR.[39,40] Of note, both atopic dermatitis and food allergy occur in younger children.[41–43] As the present study revealed that 13.4% of children aged 2 years old had already developed AR-HDM and that the new onset rate of AR-HDM peaked at 3 years of age, early IgE responses to allergens, as well as the presence of other atopic diseases, may be key factors in the development of AR-HDM.

With regard to the limitations of the present study, the results were based on questionnaire responses provided by parents, we can't rule out any possibilities of bias or inaccuracies, and whether all of the children who were reported as having AR-HDM were diagnosed by skin testing or measurement of specific IgE against HDM remains

unclear. Allergic rhinitis is caused by inhalation of antigens such as mites, fungi, and pollen. In order to distinguish AR caused by mites from seasonal AR, we clarified the term "AR-HDM" in the questionnaire, in contrast with previous reports.[23,44] Furthermore, we defined the cumulative incidence rate of AR-HDM from patients' response regarding diagnosis of their child with AR-HDM by a physician. Therefore, we believe that the results reflect the current cumulative incidence rate of AR-HDM among elementary school children in Japan.

In conclusion, we revealed that the current cumulative incidence rate of AR-HDM among elementary school children in Japan is 18.8%, and 68.3% of children with AR-HDM developed the condition by 6 years of age. Sex (male), being the first-born child, and the presence of comorbidities such as bronchial asthma, atopic dermatitis, food allergy, and allergic conjunctivitis are risk factors for the development of AR-HDM. It may be necessary for clinicians to reconsider the therapeutic strategy and provide more information regarding AIT to both children and their parents in Japan. Changes in the prevalence of AR-HDM should also be closely monitored in the future.

Abbreviations
AR, allergic rhinitis; HDM, house dust mites; AR-HDM, HDM-caused AR; SAR, seasonal allergic rhinitis; OTC, over-the-counter medication; AIT, allergen immunotherapy.

Author contributions
Concept and design: Yoshimasa Imoto, Masafumi Sakashita, and Shigeharu Fujieda.

Collection of data: Yoshimasa Imoto, Masafumi Sakashita, and Shigeharu Fujieda.

Data analysis: Yoshimasa Imoto, Masafumi Sakashita, Takahiro Tokunaga, Masafumi Kanno, Kyoko Saito, Anna Shimizu, and Ayako Maegawa.

Manuscript writing: All authors.
Final approval of manuscript: All authors.

Ethics statement
This study was performed in compliance with the Declaration of Helsinki and Good Clinical Practice, with prior approval from the Ethics Committee of the University of Fukui (20210027).

Authors' consent for publication
All authors have approved the final version of this manuscript and have been asked to give their consent to publication.

Submission declaration
The work presented herein is original, has not been previously published in whole or in part, and is not under consideration for publication in any other journal. If accepted, the authors agree that the paper will not be published elsewhere in the same or similar form, in English or in any other language, without written consent of the copyright holder. All authors listed have contributed sufficiently to the project to be included as authors, and all those qualified to be authors are listed in the author byline. All authors listed on the title page have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to *World Allergy Organization Journal*.

Declaration of competing interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100932.

Author details
[a]Department of Otorhinolaryngology, Head & Neck Surgery, Faculty of Medical Sciences, University of Fukui, Fukui, Japan. [b]Department of Otorhinolaryngology, Shinseikai Toyama Hospital, Japan.

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