

creased prevalence of BA, allergic rhinitis (AR), and allergic conjunctivitis (AC) and a decreased prevalence of atopic dermatitis (AD) from 1982 to 2002,<sup>17</sup> while more recent data showed a decreased prevalence of AD and no significant changes in prevalence of BA, AR, and AC from 1996 to 2006.<sup>18</sup> ATS-DLD questionnaires were used to obtain the data, and neither severity nor past disease history were analyzed. In 1996, we conducted a large-scale population-based survey of allergic diseases among more than 50,000 schoolchildren between the ages of 7 to 15 years in Kyoto and its suburban areas<sup>19</sup> of which 16,176 children lived in Kyoto City, one of the largest cities in Japan with a typical urban lifestyle. The questionnaires were based on and comparable with the questionnaire used in ISAAC,<sup>20</sup> and not only prevalence but also the past history and severity of the diseases were evaluated. In 2006, to observe changes in the recent trends of the childhood allergy epidemic, a survey using the identical scale and questionnaire was repeated in the same region in 2006. The results of the 2 surveys were compared in order to clarify any changes in the prevalence, past history, or severity of allergic diseases between 1996 and 2006.

## METHODS

### EPIDEMIOLOGICAL STUDIES ON THE PREVALENCE OF ALLERGIC DISEASES IN SCHOOLCHILDREN

A questionnaire survey dealing with the prevalence of 4 allergic diseases (BA, AD, AR, and AC) was administered to the parents of schoolchildren aged 7 to 15 years. The questionnaire was based on and comparable with that used by the ISAAC<sup>20</sup> and was prepared and validated by the Study Group of Epidemiology of Allergic Diseases founded by the Japanese Ministry of Health and Welfare in 1993.<sup>21</sup> This study was designated as the Allergic Schoolchildren in Kyoto (ASK) study, and was approved by the Ethics Committee of Kyoto University Graduate School of Medicine.

Details of the questionnaire, in addition to the definitions and severity of the diseases have been previously published.<sup>22</sup> In brief, BA was defined as repeated episodes of wheezing with dyspnea during the preceding 2 years. AD was defined as chronic eczema having more than 3 typical symptoms of AD. AR was defined as the presence of at least 3 of the 4 chronic nasal symptoms: sneezing, rhinorrhea, scratching around the nose, and nasal obstruction. AC was defined as the presence of bilateral itchy-watery eyes. BA severity was defined as mild, moderate, or severe according to the number of absences from school due to asthmatic symptoms, i.e., 3 days or less, 4 to 6 days, or more than 7 days, respectively. AD severity was defined as mild, moderate, or severe, according to the sum of the symptom scores.<sup>22</sup> AR severity was defined as mild, moderate, or severe when nasal

symptoms were experienced sometimes, often, or so often as to disturb quality of life, respectively. AC severity was defined as mild, moderate, or severe, when itchy eyes were experienced sometimes, always, or always in combination with sleep disturbances due to symptoms, respectively.

A past history of each disease was defined as the previous presence of each symptom but not during the preceding 2 years. Suspected Japanese cedar pollinosis (SJCP) was defined as having both AR and AC with aggravated symptoms during the spring season in which Japanese cedar pollinosis is prevalent.

In June 1996 and 2006, schoolteachers distributed the questionnaire to parents of schoolchildren aged 7 to 15 years of the same 30 randomly-selected schools in Kyoto City, which were filled out and returned to the school. A total of 16,176/17,906 questionnaires were collected (response rate, 90.3%) in 1996 and 13,215/14,669 questionnaires (response rate, 90.1%) in 2006. There was no significant difference in the age distribution, sex ratio or birth order distribution, among children in 1996 and 2006 (unpublished data).

### STATISTICAL ANALYSIS

Univariate and multivariate logistic regression analysis were performed to determine the differences between data from 1996 and 2006, using SAS software (Version 9.1; SAS Institute Inc. Cary, NC, USA). *P* values less than 0.05 were considered to indicate a statistically significant difference.

## RESULTS

### CHANGE IN THE PREVALENCE AND SEVERITY OF BA

No significant changes were found in the current prevalence of BA, from 5.1% to 5.0% ( $p = 0.58$ ) (Table 1A). Among those with current BA, the prevalence of severe cases was 12.4% to 10.2% ( $p = 0.21$ ) and showed no significant change, while that of mild cases increased from 73.7% to 81.5% ( $p < 0.0001$ ) (Table 2). Meanwhile, the prevalence of a past history of BA increased in 2006, resulting in a statistically significant increase in lifetime prevalence (current prevalence and past history combined) from 6.5% to 7.6% ( $p < 0.0001$ ) (Table 1B).

### CHANGE IN THE PREVALENCE AND SEVERITY OF AD

The current prevalence of AD increased from 4.2% to 5.6% ( $p < 0.0001$ ) (Table 1A). Among those with current AD, a significant increase was found in severe cases, from 38.2 to 44.5% ( $p = 0.02$ ), while mild cases decreased from 25.6% to 17.0% ( $p < 0.0001$ ) (Table 2). Prevalence of a past history of AD also increased in 2006, resulting in an increase in lifetime prevalence from 10.1% to 13.6% ( $p < 0.0001$ ) (Table 1B).

**Table 1**

(A) Current prevalence of allergic diseases among schoolchildren in Kyoto, Japan

	Year		p-Value
	1996 (n = 16,176)	2006 (n = 13,215)	
BA	829 ( 5.1%)	664 ( 5.0%)	0.58
AD	685 ( 4.2%)	735 ( 5.6%)	< 0.0001
AR	3279 (20.3%)	3621 (27.4%)	< 0.0001
AC	2158 (13.3%)	3324 (25.2%)	< 0.0001
sJCP	495 ( 3.1%)	1059 ( 8.0%)	< 0.0001

(B) Lifetime prevalence of allergic diseases among schoolchildren in Kyoto, Japan

	Year		p-Value
	1996 (n = 16,176)	2006 (n = 13,215)	
BA	1055 ( 6.5%)	1005 ( 7.6%)	< 0.0001
AD	1636 (10.1%)	1803 (13.6%)	< 0.0001
AR	3525 (21.8%)	3838 (29.0%)	< 0.0001
AC	3971 (24.5%)	3959 (30.0%)	< 0.0001

Lifetime prevalence is defined as current prevalence and past history combined.

BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis; AC, allergic conjunctivitis; sJCP, suspected Japanese cedar pollinosis.

**Table 2** Distribution of disease severity among children with current allergic diseases

		Year		p-Value
		1996	2006	
BA	mild	611 (73.7%)	541 (81.5%)	< 0.0001 <sup>†</sup>
	moderate	115 (13.9%)	55 ( 8.3%)	
	severe	103 (12.4%)	68 (10.2%)	0.21 <sup>‡</sup>
AD	mild	175 (25.6%)	125 (17.0%)	< 0.0001 <sup>†</sup>
	moderate	248 (36.2%)	283 (38.5%)	
	severe	262 (38.2%)	327 (44.5%)	0.02 <sup>‡</sup>
AR	mild	1632 (49.8%)	1463 (40.4%)	< 0.0001 <sup>†</sup>
	moderate	1192 (36.4%)	1506 (41.6%)	
	severe	455 (13.8%)	652 (18.0%)	< 0.0001 <sup>‡</sup>
AC	mild	1745 (80.8%)	2484 (74.7%)	< 0.0001 <sup>†</sup>
	moderate	146 ( 6.8%)	156 ( 4.7%)	
	severe	267 (12.4%)	684 (20.6%)	< 0.0001 <sup>‡</sup>

<sup>†</sup> Change in distribution of those with mild symptoms were compared.<sup>‡</sup> Change in distribution of those with severe symptoms were compared.

BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis; AC, allergic conjunctivitis.

**CHANGE IN THE PREVALENCE AND SEVERITY OF AR**

The current prevalence of AR increased from 20.3% to 27.4% ( $p < 0.0001$ ). Among those with current AR, there was an increase in severe cases from 13.8% to 18.0% ( $p < 0.0001$ ), while mild cases decreased from 49.8% to 40.4% ( $p < 0.0001$ ) (Table 2). The prevalence of a past history of AR showed no significant difference, resulting in an increase in lifetime prevalence from 21.8% to 29.0% ( $p < 0.0001$ ) (Table 1B).

**CHANGE IN THE PREVALENCE AND SEVERITY OF AC**

The current prevalence of AC increased from 13.3% to 25.2% ( $p < 0.0001$ ). Among those with current AC,

there was an increase in severe cases from 12.4% to 20.6% ( $p < 0.0001$ ), while mild cases decreased from 80.8% to 74.7% ( $p < 0.0001$ ) (Table 2). Although the prevalence of a past history of AC decreased, there was an increase in lifetime prevalence from 24.5% to only 30.0% ( $p < 0.0001$ ) (Table 1B).

**CHANGE IN THE PREVALENCE OF SUSPECTED JCP (sJCP)**

The current prevalence of sJCP, defined as having both presence of AR and AC symptoms plus aggravated symptoms during the spring cedar pollen season in Japan, increased from 3.1% to 8.0% ( $p < 0.0001$ ) (Table 1).

**Table 3** Differences in the prevalence of allergic diseases by sex (comparison between 1996 and 2006)

	1996		<i>P</i> value (univariate)	<i>P</i> value <sup>†</sup> (multivariate)	2006		<i>P</i> value (univariate)	<i>P</i> value <sup>†</sup> (multivariate)
	Male	Female			Male	Female		
	( <i>n</i> = 8,043)	( <i>n</i> = 8,036)			( <i>n</i> = 6,712)	( <i>n</i> = 6,482)		
BA	504 ( 6.3%)	320 ( 4.0%)	< 0.0001	< 0.0001	401 ( 6.0%)	260 ( 4.0%)	< 0.0001	< 0.0001
AD	304 ( 3.8%)	377 ( 4.7%)	0.004	< 0.0001	369 ( 5.5%)	364 ( 5.6%)	0.767	0.24
AR	1875 (23.3%)	1390 (17.3%)	< 0.0001	< 0.0001	2028 (30.2%)	1567 (24.2%)	< 0.0001	< 0.0001
AC	1064 (13.2%)	1087 (13.5%)	0.562	< 0.0001	1688 (25.1%)	1633 (25.2%)	0.961	0.001

<sup>†</sup> adjusted for age, birth order, family history of allergy and presence of other allergic diseases.

BA, bronchial asthma; AD, atopic dermatitis; AR, allergic rhinitis; AC, allergic conjunctivitis.

### CHANGE IN THE SEX DIFFERENCE IN THE PREVALENCE OF ALLERGIC DISEASES

In accordance with previous reports,<sup>23</sup> a significant male predominance in the prevalence of BA and AR in both 1996 and 2006 was found (Table 3). Interestingly, however, the female predominance in the prevalence of AD observed in 1996, disappeared, and no sex differences were observed in 2006. This indicates the increased prevalence of AD particularly among boys during the 10-year period (Table 3).

### DISCUSSION

In this study, we set out to determine the changes in the recent trends seen in the childhood allergy epidemic in Japan. Using the same questionnaire and targeting the same population of schoolchildren in the corresponding area, we found that the prevalence of BA had reached a plateau, while that of AD, AR, and AC increased from 1996 to 2006. The results are in line with the Japanese data reported as part of the ISAAC survey of worldwide trends in the prevalence of allergic diseases,<sup>4,24</sup> in which the prevalence of BA plateaued or decreased, while that of AR and AC increased in the last 8 years. The data were further examined by evaluating the changes in severity, past history, and sex ratio for each disease.

No significant changes in BA prevalence have been found during the past 10 years. Moreover, there was a statistically significant reduction in the distribution of severe cases. There was no change in the sex ratio, with a higher prevalence in boys than in girls. Meanwhile, those with a past history of BA increased, and lifetime prevalence increased significantly. Given that a past history was defined as the existence of BA symptoms beyond the 2 most recent years, these results may indicate that the BA symptoms were better controlled during the 10-year period, probably due to improved long-term management plans and their spread among general practitioners. However, it is still uncertain whether those with a past history were actually cured or their symptoms had ceased due to medication, such as inhaled corticosteroids and/or leukotriene receptor antagonists. In fact, in children at high risk for asthma, 2 years of inhaled corticosteroid therapy showed no effect on the development of asthma symptoms during the following treatment-

free year.<sup>25</sup> This issue cannot be evaluated in the present study because the questionnaire did not question the use of such antiasthmatic medications.

Both the prevalence and severity of AD increased significantly over the decade, which may reflect the chronic nature of the disease and no notable improvement in treatment strategies, despite progress in understanding the disease's basic mechanisms.<sup>26</sup> A deep-rooted tendency to avoid steroid ointments among Japanese due to excessive concern about side effects, may exaggerate the rising trend in AD. More effort in educating patients and caregivers with accurate knowledge about the disease and its treatment are necessary. It should be noted that the prevalence increased more in boys than in girls in the past 10 years, resulting in the disappearance of the female predominance seen in 1996. The same trend has been observed in 13- to 14-year-old children in England from 1996 to 2002.<sup>6</sup> Although the reason for this is not clear, one might speculate that boys are less conscious of their appearance and less adherent to skin care and treatment, which makes them more susceptible than girls to the environmental influences that increase AD symptoms.

Dramatic increases in the prevalence and severity of both AR and AC were also found. In particular, the prevalence of AC almost doubled, from 13.3% to 25.2% over the 10-year period, while the number with a past history of AC dropped, which indicates that AC-like "itchy eye" symptoms became more persistent. Strikingly, the prevalence of sJCP, defined as the presence of both AR and AC symptoms plus aggravation during the spring cedar pollen season, increased by 2.6 times, from 3.1% to 8.0%. The data suggests that part of the reason for the increase in AR and AC is the increase in JCP, formerly regarded as an adult disease, among children. The increase in JCP prevalence cannot be explained by the increase in the amount of pollen because the average amount of JC pollen was greater between 1994 and 1996 (3,330/cm<sup>2</sup>/yr) than between 2004 and 2006 (1,617/cm<sup>2</sup>/yr) (data provided by the Kyoto Prefectural Pollen Information Center). The increase in JCP has become a serious social problem in Japan, and an increase in pediatric patients has also been noted in other reports.<sup>27</sup> On the other hand, the data should be carefully inter-

preted since JCP was not strictly defined in our questionnaire and overdiagnosis due to parents' increased awareness is possible, as those with both AR and AC who experienced aggravated symptoms during the spring season were regarded as having "suspected" JCP. In addition, not only Japanese cedar but also Japanese cypress and sweet vernal grass are the major causes for pollinosis in the spring season in Japan. These issues urgently require more elucidation.

Our findings should be interpreted within the inherent limitations. That is, we used self-reported questionnaires to measure the prevalence of allergic diseases. Although previously attested questionnaires were used, some misclassification would be inevitable. However, such misclassification would result in both overestimation and underestimation. Therefore, we can conclude that the prevalence is still valid based on the large sample size.

In conclusion, although the prevalence of BA appears to have reached a plateau and its severity has improved, both the prevalence and the severity have increased for other allergic diseases, including AD, AR, and AC, from 1996 to 2006 in Kyoto, Japan, with the cumulative prevalence of BA still increasing. Overall, the results indicate there is still a rising trend in allergic diseases in Japanese schoolchildren. Based on the present results, more attention should be paid to skin and nasooocular symptoms which are increasing and becoming more aggravated. In order to develop better management and prevention strategies, it is also important to constantly monitor the changing trends in the prevalence of these diseases and to evaluate possible factors responsible for changes, such as alterations in lifestyle, environmental factors, and general awareness and management of symptoms.

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