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SUPPORTING INFORMATION

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The change in the prevalence of wheeze, eczema and rhino-conjunctivitis among Japanese children: Findings from 3 nationwide cross-sectional surveys between 2005 and 2015

To the Editor,

It has been suggested that the global increase in prevalence of allergic disease since the 1980s, also observed in Japan, may have reached a plateau or even decreased in some areas.¹ The analysis of time trends in the prevalence requires the use of the same methodology at each time point. We have carried out a nationwide study in 2005, 2008 and 2015 using a validated questionnaire and a similar sampling method at each time point to investigate the changing prevalence of allergic disease among Japanese children.

The method of this study has been described in detail elsewhere.² Briefly, in 2005, 2008 and 2015, we conducted a school-based questionnaire survey among two age groups: students in years 1-2 (age 6-8 years old) and in years 8-9 (age 13-15 years old). Schools were randomly selected to have a total of 1000 students for both age groups from each and all 47 prefectures in Japan. Questionnaires with an information sheet for parents were distributed through schools, and students returning their questionnaires to schools were judged as giving consent to participate. We used the Japanese version of ISAAC (International Study of Asthma and Allergies in Childhood) core questions for asthma, allergic rhinitis and eczema to identify children with current and severe wheeze, rhino-conjunctivitis and eczema³ (Table S1). Responses for age, sex and status of either current wheeze, current rhino-conjunctivitis or current eczema completed were included for analysis. The prevalence estimate for each allergic disease was calculated as the observed proportion with 95% confidence interval (CI) for each age group. Generalized linear model was employed to assess the change in the prevalence in each 2008 and 2015 by estimating a relative risk ratio (RR) using 2005 as baseline category. All statistical analysis was undertaken using Stata version 15.1 (StataCorp, College Station, TX, USA). The study protocol was approved by the Institutional Review Board of Tokyo Metropolitan Children's Medical Center (ID: H26-123).

Table S2 describes the participation for each study. The response rate was over 70% among both age groups for all 3 years. Over the 3 years, a total of 138 017 children aged 6-8 years old and 134 402 children aged 13-15 years old were included in the analysis.

As described in Table 1, the prevalence of current wheeze among 6- to 8-year-olds was stable between 2005 and 2008 (13.6% in both years), followed by a decrease to 10.2% in 2015 (RR 0.75, 95% CI 0.72-0.77). A similar but weaker trend was found for 13- to 15-year-olds between 2005 and 2015 (8.7% and 8.2%, respectively, RR 0.94, 95% CI 0.90-0.98). Severe wheeze almost halved in the 10 years for 6- to 8-year-olds (4.8%-2.9%, RR 0.60, 95% CI 0.56-0.64) and showed a slight decrease for 13- to 15-year-olds (3.6%-3.1%, RR 0.85, 95% CI 0.79-0.92). Rhino-conjunctivitis increased continuously for both age groups between the three study years, 14.8% in 2005 to 18.7% in 2015 (RR 1.27, 95% CI 1.23-1.30) for 6- to 8-year-olds and 20.5%-26.7% among 13- to 15-year-olds (RR 1.30, 95% CI 1.27-1.33). Severe rhino-conjunctivitis showed an increase only in 13- to 15-year-olds (5.8%-7.1%, RR 1.21, 95% CI 1.15-1.27). Current eczema decreased slightly in 6- to 8-year-olds (15.8%-14.6%, RR 0.92, 95% CI 0.89-0.95) and was stable for 13- to 15-year-olds between 2005 and 2015 (9.9%-9.7%, RR 0.98, 95% CI 0.94-1.02), while there was a slight decrease in severe eczema among 13- to 15-year-olds (1.9%-1.6%, RR 0.83, 95% CI, 0.74-0.92) but no change among 6- to 8-year-olds.

The overlap of the three allergic diseases among the two age groups in 2005 and 2015 is described in Figure 1, by means of proportional Venn diagrams. Among 6- to 8-year-olds, although the prevalence of children with wheeze, eczema or both decreased between 2005 and 2015, the overall proportion with any allergic disease was similar (33.7% and 34.7%), due to the increase in children with rhino-conjunctivitis only (8.5%-12.5%). Similarly, among 13- to 15-year-olds, the increase in rhino-conjunctivitis only (15.3%-20.3%) or with comorbid wheeze or eczema (5.2%-6.5%) resulted in an overall increase in children with any allergic disease (31.9%-36.5%).

Our results suggest that the prevalence of wheeze and eczema has stabilized or declined in Japanese children. It has been speculated that the plateau in prevalence is showing that the saturation level, determined by the genetic composition of the population, has been achieved.⁴ However, we found that the prevalence of rhino-conjunctivitis was still rising, in

TABLE 1 Prevalence of wheeze, rhino-conjunctivitis and eczema at 2005, 2008 and 2015

	Age 6-8			Age 13-15									
	n/N	%	P value	RR ^a	(95% CI)	(95% CI)	P value	n/N	%	(95% CI)	RR ^a	(95% CI)	P value
Wheeze													
Current wheeze													
2005	6987/51 258	13.6	(13.3-13.9)	1				4239/48 729	8.7	(8.5-9.0)	1		
2008	5970/43 784	13.6	(13.3-14.0)	1.00	(0.97-1.03)	0.985		4630/48 450	9.5	(9.3-9.8)	1.10	(1.06-1.14)	<0.001
2015	4288/42 176	10.2	(9.9-10.5)	0.75	(0.72-0.77)	<0.001		2957/36 243	8.2	(7.8-8.5)	0.94	(0.90-0.98)	0.005
Severe wheeze													
2005	2446/51 203	4.8	(4.6-5.0)	1				1764/48 677	3.6	(3.5-3.8)	1		
2008	2046/43 723	4.7	(4.5-4.9)	0.98	(0.93-1.04)	0.480		1995/48 391	4.1	(3.9-4.3)	1.14	(1.07-1.21)	<0.001
2015	1209/42 126	2.9	(2.7-3.0)	0.60	(0.56-0.64)	<0.001		1116/36 197	3.1	(2.9-3.3)	0.85	(0.79-0.92)	<0.001
Rhino-conjunctivitis													
Current rhino-conjunctivitis													
2005	7549/51 064	14.8	(14.5-15.1)	1				9885/48 184	20.5	(20.2-20.9)	1		
2008	6959/43 575	16.0	(15.6-16.3)	1.08	(1.05-1.11)	<0.001		10 289/47 896	21.5	(21.1-21.9)	1.05	(1.02-1.07)	<0.001
2015	7897/42 215	18.7	(18.3-19.1)	1.27	(1.23-1.30)	<0.001		9611/35 999	26.7	(26.2-27.2)	1.30	(1.27-1.33)	<0.001
Severe rhino-conjunctivitis													
2005	1235/51 038	2.4	(2.3-2.6)	1				2811/48 137	5.8	(5.6-6.1)	1		
2008	1054/43 555	2.4	(2.3-2.6)	1.00	(0.92-1.08)	0.999		2633/47 838	5.5	(5.3-5.7)	0.94	(0.90-0.99)	0.025
2015	958/42 199	2.3	(2.1-2.4)	0.94	(0.86-1.02)	0.134		2535/35 952	7.1	(6.8-7.3)	1.21	(1.15-1.27)	<0.001
Eczema													
Current eczema													
2005	8094/51 146	15.8	(15.5-16.1)	1				4822/48 598	9.9	(9.7-10.2)	1		
2008	7202/43 725	16.5	(16.1-16.8)	1.04	(1.01-1.07)	0.007		5203/48 293	10.8	(10.5-11.1)	1.09	(1.05-1.13)	<0.001
2015	6178/42 351	14.6	(14.3-14.9)	0.92	(0.89-0.95)	<0.001		3509/36 229	9.7	(9.4-10.0)	0.98	(0.94-1.02)	0.252
Severe eczema													
2005	923/51 108	1.8	(1.7-1.9)	1				927/48 553	1.9	(1.8-2.0)	1		
2008	860/43 686	2.0	(1.8-2.1)	1.09	(0.99-1.20)	0.066		860/48 257	1.8	(1.7-1.9)	0.93	(0.85-1.02)	0.142
2015	780/42 336	1.8	(1.7-2.0)	1.02	(0.93-1.12)	0.679		571/36 207	1.6	(1.5-1.7)	0.83	(0.74-0.92)	<0.001

CI, confidence interval, RR, risk ratio.

^aRR is calculated using 2005 as baseline for each 2008 and 2015.

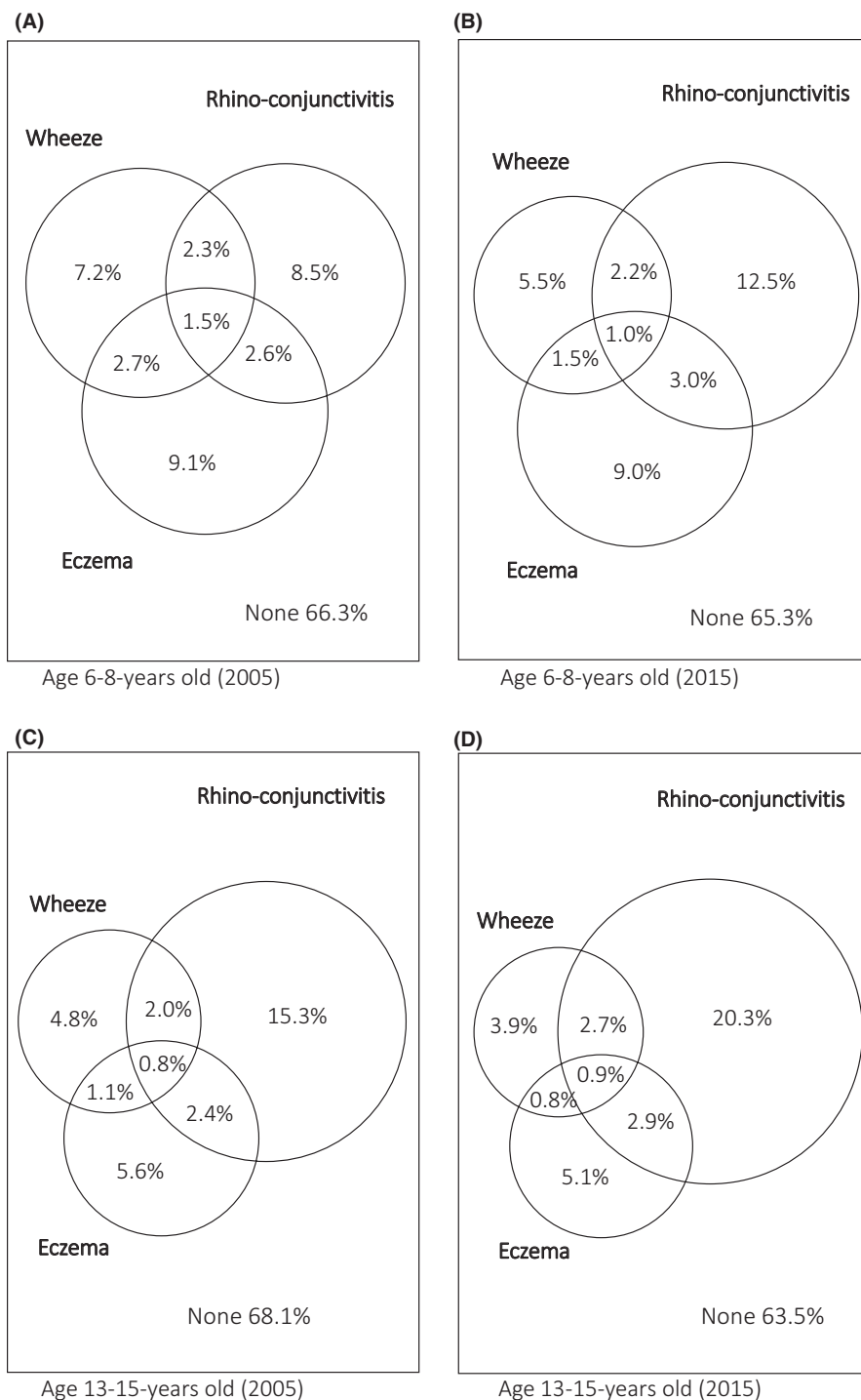


FIGURE 1 The distribution of children with current wheeze, rhino-conjunctivitis and eczema for 2005 and 2015 in the two age groups

contrast with the change in wheeze or eczema. This trend was similar to results from studies conducted in other countries or regions, including well-developed areas in Asia.^{1,5,6} Japanese cedar pollen allergy is known to be increasing in Japan, due to the higher pollen counts from the matured trees planted after World War II with possible influence of climate change.⁷ Whether the trend we found can be explained by Japanese cedar pollen allergy or other previously suggested environmental factors^{8,9} needs exploration in future studies using sensitization data.

One of the limitations of this study is that we have not employed objective measures to define the status of allergic diseases, which may have led to misclassification of the outcome. We have

tried to minimize this by using the ISAAC questionnaire which has been validated and widely used in large-sized epidemiological studies. Another limitation is the possibility of selection bias due to the rather lower participation rate in the 13- to 15-year-old group and the different participation rate between study years and prefectures. Furthermore, different schools were selected and not matched for socio-demographic or other environmental factors between study years, which may have affected our prevalence estimates. However, we were able to achieve a large sample size and the prevalence estimate was similar when reweighting the prevalence using the participating rate for each prefecture (data not shown).

In conclusion, we have found reversing trends in the prevalence of wheeze and eczema but not in rhino-conjunctivitis among Japanese children. One in three children still had one or more allergic disease, underlining the importance of further research into the risk factors and possible prevention strategies.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

Keywords

asthma, atopic dermatitis, epidemiology, pediatrics, rhinitis

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Birch pollen allergen-specific immunotherapy with glutaraldehyde-modified allergoid induces IL-10 secretion and protective antibody responses

To the Editor,

Allergen immunotherapy (AIT) is the only disease-modifying therapy for immediate-type allergies with long-lasting effects.¹ Nonetheless, IgE-mediated side effects, potentially leading to severe anaphylactic

reactions, can occur during therapy. To improve the safety of AIT, chemically modified allergen extracts (so-called allergoids) are generated by either formaldehyde or glutaraldehyde (GA)-treatment of native allergens leading to inter- and intramolecularly cross-linked, high-molecular-weight allergen polymers.² By this means, the

Abbreviations: AIT, allergen immunotherapy; BPE, birch pollen extract; FAB, facilitated allergen binding; GA-BPE, glutaraldehyde-modified birch pollen extract; Tr1, type-1 regulatory T cells.

Supplementary table 1. Definitions of current and severe wheeze, allergic rhino-conjunctivitis and eczema

	Definition
Current wheeze	Positive response to “Have you (has your child) had wheezing or whistling in the chest in the past 12 months?”
Severe wheeze	Children with current wheeze and a positive response to one or more of the following questions: wheezing severe enough to limit the child’s speech to only one or two words at a time between breaths, more than 12 attacks in the past 12 months, or child’s sleep disturbed due to wheezing more than one night per week.
Current rhino-conjunctivitis	Positive response to both “In the past 12 months, have you (has your child) had a problem with sneezing or a runny or blocked nose when you (he/she) did not have a cold or the flu?” and “In the past 12 months, has this nose problem been accompanied by itchy watery eyes?”
Severe rhino-conjunctivitis	Children with current ARC and answering “a lot” to how much the nose problems interfered with the child’s daily activities.
Current eczema	Positive response to the following three questions, “Have you (has your child) ever had a skin rash which was coming and going for at least 6 months?”, Have you (has your child) had this itchy rash at any time in the past 12 months?” and, “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.”
Severe eczema	Children with current eczema and child’s sleep disturbed due to the rash more than one night per week.

Supplementary table 2. Participation for each study in 2005, 2008 and 2015

	2005	2008	2015
Primary school, Grade 1-2 (Age 6-8)			
Total number of eligible students	64,424	47,915	50,392
Children with valid response*	51,463(79.8%)	43,972 (91.8%)	42,582 (84.5%)
% boys**	50.7	51.0	50.7
Secondary school, Grade 8-9 (Age 13-15)			
Total number of eligible students	70,006	63,359	51,442
Children with valid response*	49,018 (70.0%)	48,746 (76.9%)	36,638 (71.2%)
% boys**	49.4	49.1	48.9

* Valid responses were defined as having response for age, sex and status of either current wheeze, current rhino-conjunctivitis or current eczema.

** Proportion of boys among the children aged those with valid response.