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Allergen sensitization affected the change trend of prevalence of symptoms of rhinitis co-existing with wheeze among adolescents in Guangzhou city from 1994 to 2009.

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Short title: Prevalence of rhinitis with wheeze and allergen sensitization

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Abstract

Background: Few studies have assessed the time trends of prevalence of symptoms of rhinitis (SR) with wheezing and their associations in Chinese adolescents.

Objective: To explore the trend of prevalence of SR with wheezing and allergen sensitization in adolescents during the past 15 years.

Methods: A total of 7165 adolescents aged 13–14 years in 2009 were recruited for the study using the Phase III Protocol of the International Study of Asthma and Allergic disease in Childhood (ISAAC) and allergic sensitization to seven inhalant allergens in 2531 was assessed by skin prick test in 2010. The results were compared to those obtained in the Phase I (1994/95) and III (2001/02) ISAAC studies.

Results: The prevalence of “SR ever” and “current symptoms of rhino-conjunctivitis” increased from 46.3% and 8.7% in 1994 to 53.2% and 11.1% in 2001 ($P<0.001$), respectively, and remained stable at 52.6% and 10.4% in 2009 ($P>0.05$). The prevalence of “SR ever and wheeze ever” and “SR ever and current wheeze” increased from 6.2% and 3.4% in 1994 to 8.6% and 4.8% in 2001 ($P<0.001$) to 10.9% and 5.9 % ($P<0.001$). The sensitization rate to common inhaled allergens was higher in 2010 than in 2002 ($P<0.001$). Sensitization to house dust mites (HDMs) was

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associated with increases in the prevalence of SR (*OR*, 2.06-2.86), especially with coexistence of wheeze (*OR*, 6.07–7.43).

Conclusion: The prevalence of symptoms of rhinitis and coexistence with wheezing has increased significantly since 1994. Sensitization to HDMs is the main risk factor associated with this increase.

Introduction

Rhinitis, with the symptoms of sneezing, runny nose or nasal obstruction, is the most common upper airway disease among children all over the world (1), numerous studies have shown various associations between rhinitis and asthma. Children suffering with rhinitis may increase the risk of asthma or impairs the clinical management of asthma because of the “allergic march” (2-4), and poses a significant burden on both the individual and society (2, 5, 6). Due to their associations, the prevalence of rhinitis and asthma has often been surveyed together in epidemiological studies.

After decades of an increase in the global prevalence of rhinitis (7-9), a few recent studies reported no further increase or even a reverse trend in some areas since the mid-2000s (10, 11). The same changes were also observed in allergic sensitization (12). Two cross-sectional studies were conducted following the International Study of Asthma and Allergic disease in Childhood (ISAAC) protocol in 1994 (Phase I) and in 2001 (Phase III) in Guangzhou. Results showed that the

prevalence rates of physician-diagnosed allergic rhinitis in the past 12 months in 13- to 14-year-old secondary schoolchildren in Guangzhou increased from 17.4% in 1995 and to 22.7% in 2001 (13).

Among all risk factors, allergen sensitization, as measured by skin prick test (SPT), has been indicated as one of the strongest and most consistent relationships with the development of rhinitis (14, 15). A previous study showed that multiple sensitizations are common, and house dust mites (HDMs) are the most prevalent allergens in patients with rhinitis, asthma, or both in China (16). It is hypothesized that dramatic environmental changes, such as rapid urbanization, and increases in the temperature and humidity in many parts of China over the past decade may have facilitated the growth of HDM populations. This change could be associated with increase in HDM sensitization in Chinese schoolchildren and may contribute to further increases in the prevalence of allergic diseases. For this reason, in 2009-2010, a follow-up cross-sectional study on the prevalence of AR, specifically symptoms of rhinitis (SR) with lower airway symptoms and skin sensitization, was conducted in secondary schoolchildren aged 13–14 years from the same schools in Guangzhou using the ISAAC Phase III protocol. The results were compared with those in Phase I and III surveys, which used the same ISAAC core questionnaires and were conducted in 1995 and 2001, respectively. Associations between prevalence of SR, SR with lower airway symptoms, and aeroallergen sensitization were also taken into consideration.

Methods

Sampling and questionnaire

Ten secondary schools in four central districts of Guangzhou were randomly selected and approached for participation in accordance with the ISAAC protocol (17). All first- and second-year students in these schools with the highest proportion of children aged 13–14 years in participating schools were invited to participate in this survey. Each participating student was asked to fill out a questionnaire which had been translated into Chinese in accordance with the ISAAC protocol (18). In 1994, a total of 3868 students were invited, with a response rate of 99.6%. In 2001 for Phase III, 3675 children were invited, with a response rate of 96%. In 2009, 7165 students were invited, with a response rate of 96.7% (Table 1).

SR included “sneezing, runny nose or nasal obstruction unrelated to a cold or the flu,” and those of rhino-conjunctivitis were “SR accompanied by itchy, watery eyes,” Symptoms of dermatitis were defined by “itching rash longer than 6 months” “current” symptoms were considered symptoms in the past 12 months, and “ever” symptoms referred to symptoms that the patient had experienced at any point in his or her lifetime.

All the surveys were approved by the Ethics Review Board of Guangzhou Educational Department and the First Affiliated Hospital of Guangzhou Medical University.

Skin prick test

A random subgroup of 1543 students from the Phase III during April and May of 2002 was invited to have SPT and 1187 (77%) students agreed to participate. Between March and June of 2010, a random subgroup of 3086 students was recruited for SPT, and 2531 (82%) students agreed to participate. All the participants were asked to refrain from any antihistaminic medication 72 hours before receiving SPT. The SPT was conducted using a standard allergen extract panel (ALK, Horsholm, Denmark) and comprised histamine and diluent as positive and negative controls. Seven common aeroallergens, including *Dermatophagoides pteronyssinus* (Der-p), *Dermatophagoides farinae* (Der-f), cat, German cockroach, *Alternaria alternata* (a fungus species), mixed grass pollens (*Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Phleum pratense*, and *Poa pratensis*) and mixed tree pollens (*Ulmus americana*, *Platanus acerifolia*, *Salix caprea*, and *Populus deltoids*) were tested in both surveys. A positive reaction was recorded if the mean wheal size, (largest diameter + perpendicular diameter)/2 $\geq$ 3 mm after 15 min, and after subtraction of the negative control. Skin index (SI) (19) and atopic index (AI)(20) were then calculated. Skin index was calculated by the ratio of weal diameter of each allergen to that induced by histamine, and graded by following criteria: 0: SI=0; 1: 0<SI<0.5; 2: 0.5 $\leq$ SI<1.0; 3: 1.0 $\leq$ SI<2.0; 4: SI $\geq$ 2.0. The degree of atopy was graded by AI which was the sum of the number of the allergens that give a positive response plus the largest skin weal size (1 $\leq$ 4 mm, 2 $\geq$ 4 mm). AI 0 was considered as normal, 2 and 3 as mild, 4 and 5 as moderate, $\geq$ 6 as severe.

Statistical analysis

The prevalence of various symptoms and positive skin tests to allergens was calculated as crude rates with 95% confidence intervals (CIs). The time differences in the prevalence of the change trend and between years were compared by chi-square tests. Logistic regression analyses were performed to test the associations between various degrees of SI of each allergen and the prevalence of rhinitis and adjusted for sex and age. The results are given with adjusted odds ratios (OR with 95% CI). A *P*-value of ≤ 0.05 was considered significant. All data were categorized and analyzed using the Statistical Package for the Social Sciences (SPSS Inc. Chicago, IL, USA) for Windows Release 13.0

Results

Characteristics of study sample

The study sample comprised 3855 children (1891 boys and 1964 girls) in Phase I, 3516 (1699 boys and 1817 girls) in Phase III and 6928 (3504 boys and 3424 girls) in 2009. The percentage of children aged 13–14 years was 87.5%, 87.2%, and 87.5%, respectively. With regard to the allergen skin prick tests, 1187 children (613 boys and 574 girls) from Phase III participated in 2002, and 2531 (1386 boys and 1145 girls) from the present survey participated in 2010 (Table 1).

Prevalence of SR and co-existing wheeze

The prevalence of physician-diagnosed-rhinitis and hay fever and SR showed an overall increase trend from 1994 to 2009 (P for trend <0.05). Similar trends were found in the prevalence of SR co-existing wheeze (P for trend <0.05). But the trend for related symptoms of rhinitis showed a slightly change in the last two surveys: The prevalence of “SR ever” and “current symptoms of rhino-conjunctivitis” remained stable from 2001 to 2009. The prevalence of “current SR” and “SR interfering with daily activities” decreased from 45.5% and 34.5% in 2001 to 43.2% and 26.2% in 2009 ($P<0.05$).

Prevalence of allergic sensitization

The prevalence of atopy increased from 46.3% in 2002 to 62.3% in 2010 ($P<0.001$). The pattern of allergic sensitization in 2002 and 2010 was similar, and sensitization to Der-p and Der-f was most common in both years, followed by German cockroach and cats. Sensitization to Der-p, Der-f, cats, and mixed grass pollen significantly increased from 43.1%, 44.9%, 4.8%, and 0.5% in 2002 to 55%, 55%, 17%, and 3.7% in 2010, especially the degree of 3-4 skin sensitization to Der-p, Der-f and cats. The prevalence of sensitization to German cockroach decreased significantly from 16.0% in 2002 to 7.6% in 2010 ($P<0.001$; Fig. 1).

SR and co-existing wheeze in subjects with and without sensitization

The prevalence of SR increased significantly from 2002 to 2010 in all subjects (57.8% to 71.1% for SR+/All) and those without sensitization to tested allergens ($P<0.05$), whereas prevalence with SR were at a very high level (71.1–82.1%) and remain unchanged in the subjects with sensitization to specific allergens (Fig. 2). Meanwhile, from 2002 to 2010, the prevalence of co-existing wheezing increased significantly in subjects with sensitization.

Allergen sensitization in subjects with and without SR

From 2002 to 2010, the prevalence of sensitization to any tested allergen, Der-p, Der-f increased significantly in subjects without SR and in subjects with SR and co-existing wheeze. Sensitization to cat dander increased over time in subjects both with and without SR or co-existing wheeze. However, sensitization to German cockroach decreased significantly in subjects with SR whereas it remained unchanged in subjects without SR (Fig. 3).

Association between allergen sensitization and SR

The positive skin reactivity to Der-p and Der-f showed significantly positive associations with SR with multivariate logistic analysis in 2010 (Table 3). The odd ratios increased with increasing degrees of positive skin test results, and steeply

increased from only SR (OR, 2.26 for Der-p; 2.91 for Der-f) to co-existing wheezing (OR, 8.22 for Der-p; 5.95 for Der-f). All the subjects with sensitization to mixed grass pollen or mixed tree pollen reported SR, and 66.7% and 25% of them had co-existing wheezing.

Discussion

The current work used the same questionnaire and targeted schoolchildren of the same age in the same geographic area as in two previous studies. Its purpose was to measure the time trends of the prevalence of symptoms of rhinitis and sensitization to aeroallergens among adolescents in Guangzhou. To our knowledge, this is the first epidemiology study of prevalence on rhinitis and coexisting wheeze in 13- to 14-yr-old children in a long period from 1994 to 2009 in China.

Despite an overall increase trend of the prevalence of doctor-diagnosed-rhinitis and symptoms of rhinitis from 1994 to 2009, the present survey showed a conflicting result between the prevalence of physician-diagnosed-rhinitis and symptoms of rhinitis from 2001 to 2009: The prevalence of physician-diagnosed rhinitis and hay fever increased continuously by 10.6% and 29.3% , respectively, while the prevalence of “SR ever” and “current rhino-conjunctivitis” were stable, and the prevalence of “current SR” and “SR interfering with daily activities” slightly declined. Although those conflicting results make it difficult to estimate the real change of SR prevalence in the last two surveys,

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“current rhino-conjunctivitis” was found to be the best predictor of rhinitis in children in Phase I ISAAC studies: Its prevalence remained unchanged(1). To reduce the possible bias in the self-reported questionnaires, the participating children were subdivided into sensitized and non-sensitized groups, and no change was found in the prevalence of SR in participants with positive SPT, while a significant increase in subjects without positive SPT between the last two surveys (Fig. 2), which indicated that the prevalence of “real allergic rhinitis” (combined rhinitis symptoms and allergen sensitization) might plateau. The increase in the prevalence of physician-diagnosed-rhinitis and hayfever might have reflected increased professional awareness of diagnosis and increased public awareness. Such changes in the trends in the prevalence of rhinitis and allergic disease have been reported in some studies: No increase in clinical rhinitis symptoms was observed in schoolchildren from 1996 to 2006 in Northern Sweden(12). In England, decreases in the trend of symptoms of rhino-conjunctivitis were observed in 12- to 14-year-old children, from 18% in 1995 to 15% in 2002 (21). The prevalence of rhino-conjunctivitis symptoms in 13- to 15-year-old Maltese children showed a decrease trend from 29% in 1995 to 21.8% in 2002 (22).

This study showed the prevalence of co-existing wheezing to increase continually in these three surveys (Table 2), particularly in subjects with positive SPT in the last two surveys (Fig. 2). In these surveys, HDMs were the main allergen and the prevalence of sensitization was found to have increased 1.25-fold from 2002 to 2010. The intensity of sensitization also increased significantly (Fig. 1). This may be

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attributed to Guangzhou's tropical climate, whose warm and humid environment facilitated the growth and proliferation of HDMs. Previous local surveys have found the concentration of HDMs to be high in Guangzhou families (23), especially in rooms equipped with air conditioners (24). In the current survey, the concentration of HDMs was also measured at relatively high level (median = 1.6 $\mu\text{g}/\text{m}^2$) in bed (25). Many studies have shown that the enzymatic activity of HDMs body and fecal pellets can initiate apoptosis of epithelial cells (26), damage epithelial tight junction (27), which can trigger the lower airways and elicit not only rhinitis symptoms but also asthma symptoms. In these cases, the appearance of asthma and rhinitis in the same subjects was a manifestation of a single inflammatory process, particularly in its more severe form (28). Our previous study also reported that the prevalence of wheezing in adolescents in Guangzhou has increased since 1994 and sensitization to HDMs is an important risk factor associated with this increase (29). In line with those findings, results showed that sensitization to Der-p and Der-f to be strongly associated with rhinitis symptoms in the multivariate logistic regression analysis, and the odd ratios increased with increasing degrees of positive skin test results. This increasing trend was particularly pronounced when rhinitis symptoms co-existed with wheezing (Table 3). These results suggesting that sensitization to HDMs is a risk factor for the development of SR, especially with co-existing wheezing (29).

Trends of prevalence of SR and allergic sensitization were diverse in the last two surveys ostensibly. However, when the participating children were subdivided into SR and non-SR groups (Fig. 3), the prevalence of sensitization to HDMs only

increased in subjects without SR. It was stable in subjects with SR. It was parallel to the change in prevalence of rhinitis symptoms in the same period. It is here assumed that that the families with SR children are more likely to take measures to control their environment to prevent of allergen exposure, while a general increase in the concentration of HDMs in indoor environments in the same geographic area. Although there were little accurate data regarding environment controls, cockroaches served as indicators of hygiene conditions. Sensitization to German cockroach showed a marked decrease in subjects with SR.

Another strong relationship between allergens and SR was found in pollen: all the subjects with sensitization to pollen reported the rhinitis symptoms. This relationship less close in cases with both SR and wheezing: only 66.7% of subjects with mixed grass pollen sensitization and 25% with mixed tree pollen sensitization reported co-existing wheezing. These findings support the fact that pollen is mainly deposited in upper airway, where it induces local inflammatory or pathological changes because it is larger than other allergen, such as HDMs(30). In addition, sensitization to pollen differs widely in different parts of China. The current and previous surveys all found the prevalence of sensitization to pollen to be very low in Guangzhou ($\leq 3.7\%$), which only slightly affected the prevalence of SR and co-existing wheezing.

Conclusion

In conclusion, the prevalence of symptoms of rhinitis increased from 1994 to 2001 and remained steady from 2001 to 2009, while the prevalence of co-existing wheezing increased continuously across all three surveys. Sensitization to HDMs was found to be the main risk factor of rhinitis, especially for co-existing wheezing, and the large increase in sensitization may predict a continuous increase in clinical manifestations of rhinitis and co-existing wheezing. However, other factors, such as climate change and air pollution may also play important roles in this process and merit further investigation.

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Figure legends

Fig. 1. Prevalence of degree of allergen sensitivity in children of the surveys in 2002 and 2010.

The degree of atopy was graded by atopic index (AI) which was the sum of the number of the allergens that give a positive response plus the largest skin weal size ($1 \leq 4$ mm, $2 \geq 4$ mm). The degree of allergen skin testing was graded by skin index (SI) which was calculated by the ratio of weal diameter of each allergen to that induced by histamine.

Mixed grass pollen[†] included *Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Phleum pratense*, and *Poa pratensis*.

Mixed tree pollen[‡] included *Ulmus americana*, *Platanus acerifolia*, *Salix caprea*, and *Populus deltoids*.

Fig. 2. Prevalence of symptoms of rhinitis (SR) or combined SR and wheezing (any positive response to questions regarding history of asthma or wheezing) in all subjects who had received allergen skin prick test (SR+/All) and those with or without positive reaction to any tested allergen, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, Cockroach, or cat (SR+/SPT+ or SR+/SPT-, SR+/Der-p+ or SR+/Der-p-, SR+/Der-f+ or SR+/Der-f-, SR+/Cockroach+ or SR+/Cockroach-, SR+/Cat+ or SR+/Cat-, SR&wheeze+/SPT+ or SR&wheeze+/SPT-, SR&wheeze+/Der-p+ or SR&wheeze+/Der-p-, SR&wheeze+/Der-f+ or SR&wheeze+/Der-f-, SR&wheeze+/Cockroach+ or SR&wheeze+/Cockroach-, SR&wheeze+/Cat+ or SR&wheeze+/Cat-, respectively) during surveys in 2002 and 2010.

***: $P < 0.001$, **: $P < 0.01$, *: $P < 0.05$

Fig. 3. Prevalence of positive skin reaction to any tested allergen in all subjects who received allergen skin prick tests (SPT+/All) and prevalence of positive skin reaction to any tested allergen, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blattella germanica*, or cats in subjects with or without any positive response to symptoms of rhinitis (SPT+/SR+ or SPT+/SR-, Der-p+/SR+ or Der-p+/SR-, Der-f+/SR+ or Der-f+/SR-, Cockroach+/SR+ or Cockroach+/SR-, Cat+/SR+ or Cat+/SR-, SPT+/ SR&wheeze+ or SPT+/ SR&wheeze-, Der-p+/ SR&wheeze+ or Der-p+/ SR&wheeze-, Der-f+/ SR&wheeze+ or

Der-f+/ SR&wheeze- , Cockroach+/ SR&wheeze+ or Cockroach+/ SR&wheeze-, Cat+/ SR&wheeze+ or Cat+/ SR&wheeze-, respectively) during surveys in 2002 and 2010.

***: $P < 0.001$, **: $P < 0.01$, *: $P < 0.05$

Table 1. Demographic data of recruited subjects in questionnaire surveys in 1994, 2001 and 2009, and allergy skin prick tests in 2002 and 2010

	Questionnaire surveys			Skin prick tests	
	1994	2001	2009	2002	2010
N	3868	3675	7165	1543	3086
Response rate (%)	99.6	96	96.7	77	82.1
Sex,%					
Boys	1891 (49.1)	1699 (48.3)	3504 (50.6)	613 (51.6)	1386 (54.8)
Girls	1964 (50.9)	1817 (51.7)	3424 (49.4)	574 (48.4)	1145 (45.2)
Average age (years, mean $\pm$ SD)	13.40 $\pm$ 0.64	13.30 $\pm$ 0.69	13.30 $\pm$ 0.64	13.13 $\pm$ 0.71	13.60 $\pm$ 0.65
Age group, n (%)					
$\leq$ 12 years	305 (8.0)	411 (11.7)	823 (11.9)	156 (13.1)	278 (11.0)
13–14 years	3374 (87.5)	3067 (87.2)	6062 (87.5)	1019 (85.8)	2142 (84.6)
$\geq$ 15 years	176 (4.5)	38 (1.1)	43 (0.6)	12 (1.0)	111 (4.4)

Table 2. Comparison of prevalence of rhinitis and related symptoms of surveys in 1994, 2001 and 2009.

	1994 n = 3855	2001 n = 3516	2009 n = 6928			<i>P for trend</i>
	% (95% CI)	% (95% CI)	% (95% CI)	P_1^*	$P_2^†$	
Physician-diagnosed allergic rhinitis	17.4 (16.2–18.6)	22.7 (21.3–24.1)	25.1 (24.5–25.6)	0.000	0.008	0.000
Physician-diagnosed hayfever	2.9 (2.4–3.4)	4.1 (3.4–4.8)	5.3 (5.1–5.6)	0.006	0.007	0.000
SR ever	46.3 (44.7–47.9)	53.2 (51.6–54.8)	52.6 (52.0–53.2)	0.000	0.570	0.000
Current SR	39.5 (38.0–41.0)	45.5 (43.9–47.1)	43.2 (42.6–43.8)	0.000	0.023	0.002
Current symptoms of rhino-conjunctivitis [‡]	8.7 (7.8–9.6)	11.1 (10.0–12.1)	10.4 (10.0–10.7)	0.001	0.263	0.019
SR interfering daily activities	26.0 (24.6–27.4)	34.5 (32.9–36.1)	26.2 (25.7–26.7)	0.000	0.000	0.250
Slightly	24.5 (22.2–24.8)	30.8 (29.3–32.3)	23 (22–24)	0.000	0.000	0.062
Moderately	2.3 (1.9–2.8)	3.2 (2.7–3.9)	2.7 (2.3–3.1)	0.017	0.137	0.339
Severe	0.2 (0.1–0.4)	0.5 (0.4–0.8)	0.5 (0.3–0.7)	0.028	0.813	0.039
Physician-diagnosed asthma	3.9 (3.2–4.5)	4.6 (3.9–5.3)	6.9 (6.5–7.2)	0.000	0.000	0.000
Wheeze ever	6.2(5.4-7.0)	8.6(7.6-9.5)	14.6(14.1-15.0)	0.000	0.000	0.000

Current wheeze	3.4(2.8-3.9)	4.8(4.1-5.5)	6.1(5.8-6.4)	0.000	0.000	0.000
SR ever and wheeze ever	6.2 (5.4–7.0)	8.6 (7.6–9.5)	10.9 (10.6–11.2)	0.000	0.000	0.000
SR ever and current wheeze	3.4 (2.8–3.9)	4.8 (4.1–5.5)	5.9 (5.7–6.1)	0.000	0.021	0.000
SR ever and physician-diagnosed asthma	3.9 (3.2–4.5)	4.6 (3.9–5.3)	4.9 (4.7–5.1)	0.000	0.528	0.019
Symptoms of dermatitis ever	1.7(1.3-2.1)	3.0(2.4-3.6)	3.0(2.8-3.2)	0.000	0.908	0.000
Current symptoms of dermatitis	1.3(0.9-1.7)	2.2(1.7-2.7)	1.9(1.7-2.1)	0.003	0.326	0.050

* P_1 was compared by chi-square tests between 1996 and 2001; † P_2 was compared by chi-square tests between 2001 and 2009; ‡ Symptoms of rhino-conjunctivitis was defined as symptoms of rhinitis accompanied by itchy, watery eyes.

Table 3. Logistic regression analyses between the degree of allergen sensitivity and symptoms of rhinitis or combined wheezing in surveys in 2010.

	Degree	Symptoms of rhinitis					Combined symptoms of rhinitis and wheezing				
		% [§]	Univariate		Multivariate [¶]		% [§]	Univariate		Multivariate [¶]	
			OR ⁺ (95% CI)	<i>P</i>	OR ⁺ (95% CI)	<i>P</i>		OR ⁺ (95%CI)	<i>P</i>	OR ⁺ (95% CI)	<i>P</i>
<i>D. pteronyssinus</i>	0	61.5	1				4.7	1			
	1	80	2.37 (0.48–11.64)	0.287			20	4.58 (0.80–26.07)	0.261		
	2	72.5	1.59 (0.74–3.45)	0.238			17.5	4.09 (1.34–12.53)	0.014	3.33 (1.14–9.75)	0.028
	3–4	80.9	2.55 (1.47–4.44)	0.001	2.06 (1.17–3.62)	0.012	36.6	11.58 (4.97–27.04)	0.000	7.43 (3.32–16.63)	0.000
<i>D. farinae</i>	0	60.8	1				6.8	1			
	1	72.7	1.64 (0.42–6.48)	0.479			9.1	1.24 (0.14–10.74)	0.847		
	2	66.7	1.23 (0.57–2.67)	0.596			11.1	1.60 (0.46–5.49)	0.458		
	3–4	83.6	3.22 (1.82–5.69)	0.000	2.86 (1.61–5.09)	0.000	36.6	8.39 (3.97–17.75)	0.000	6.07 (3.50–12.07)	0.000

Cat	0	68.9	1				14.7	1			
	1–4	82.1	2.08 (1.00–4.32)	0.049	1.39 (0.63–3.06)	0.414	42.9	4.17 ((2.20–7.87)	0.000	1.86 (0.93–3.76)	0.082
German cockroach	0	71.1	1				18.8	1			
	1–4	72	0.99 (0.40–2.48)	0.986			28	1.55 (0.61–3.97)	0.356		
Mixed grass pollen	0	70	--				17.7	1			
	1–4	100 [‡]	--	-			66.7	9.63 (2.73–34.04)	0.000	5.36 (1.37–20.90)	0.016
Alternaria alternata	0	71	1				19.8	--			
	1–4	80	1.56 (0.17–14.33)	0.693			0 [‡]	--	-		
Mixed tree pollen	0	70.8	--				19.4	1			
	1–4	100 [‡]	--	-			25	1.29 (0.13–12.74)	0.830		

[§]Percentage of the subjects with only symptoms of rhinitis or combined wheeze in the respective degree of allergen sensitivity.

[¶]Factors were selected from those with $P < 0.1$ in univariate logistic regression analyses and were entered in the multivariable logistic analyses.

[†]Odds ratio adjusted for sex and age in a logistic regression model.

[‡]Analysis could not be performed because all or none of the subjects with sensitization to specific allergen have symptoms.

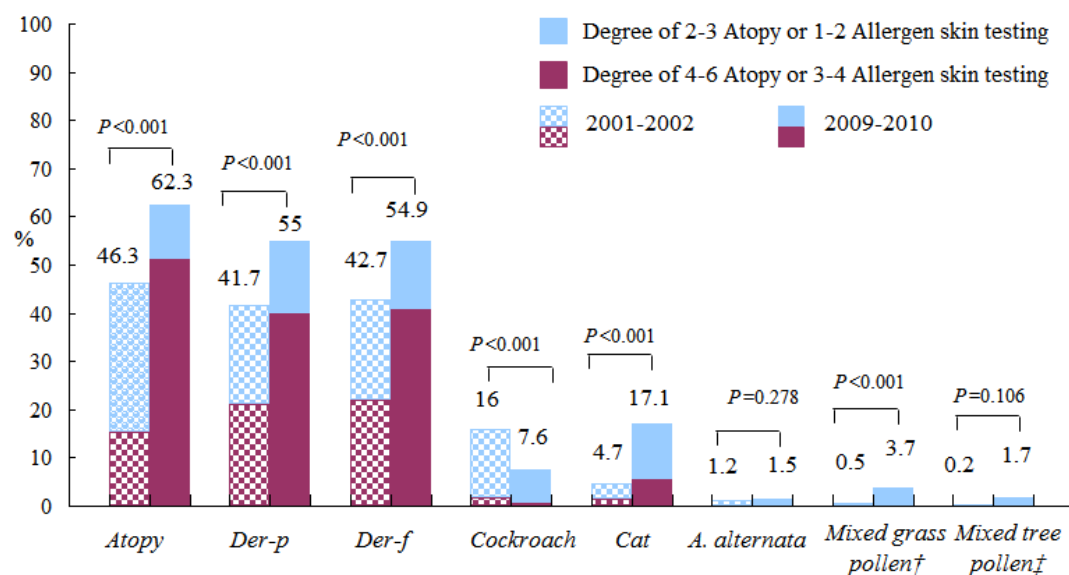


Fig.1

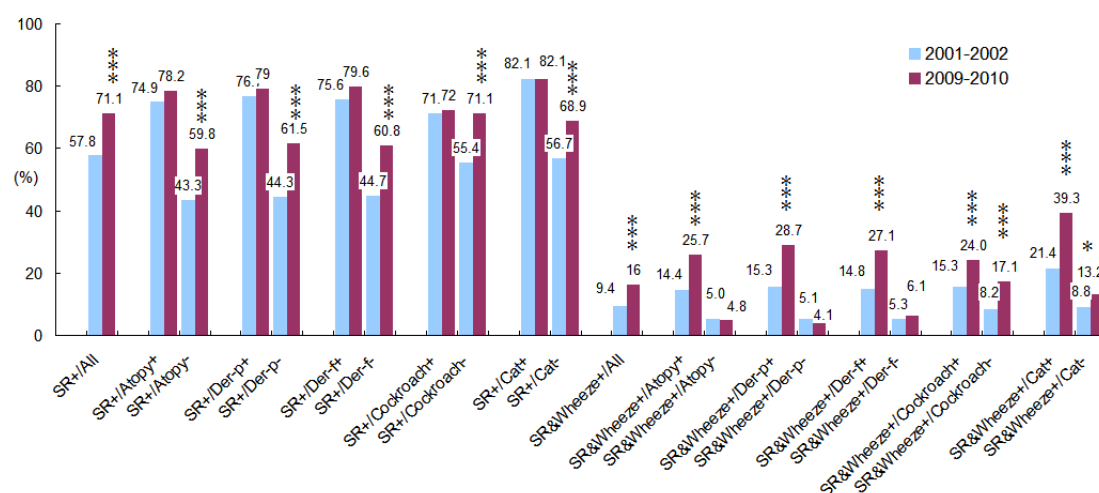


Fig. 2

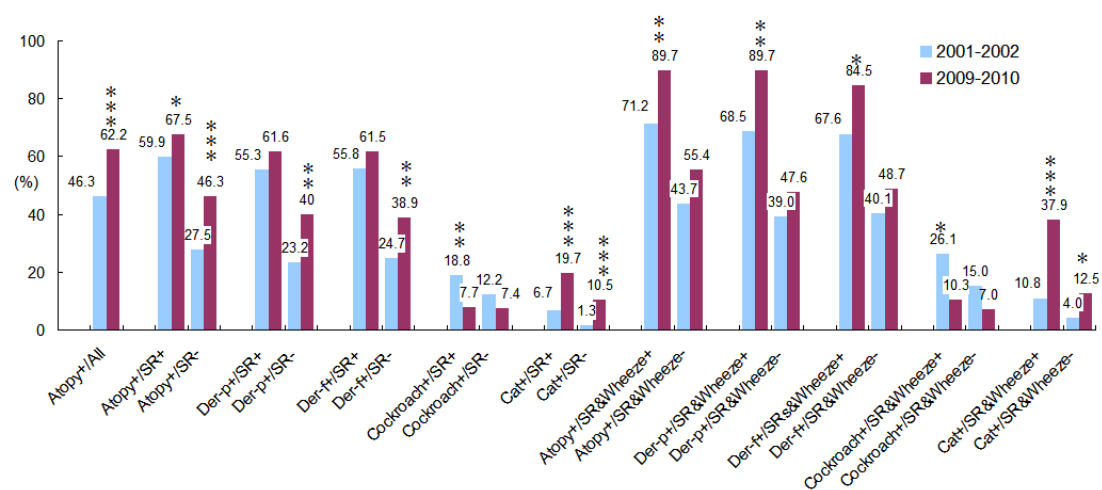


Fig.3.