

A population-based 5-year follow-up of allergic rhinitis in Chinese children

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ABSTRACT

Background: There have been few longitudinal investigations of allergic rhinitis (AR) in Chinese children. We previously conducted an investigation of the prevalence of AR in 3- to 6-year old children for the year of 2005–2006. The aim of this study was to observe the natural course of AR in children in the previously investigated population during a cohort study for 5 years.

Methods: A total of 1211 children in the previously investigated population were included in this study. Telephone interviews were conducted three times during the 1st, 3rd, and 5th year from the previous study.¹⁴ Questions including duration, severity of nasal symptoms, asthma, and related problems of allergy were examined. Skin-prick tests (SPTs) were performed again on those children who had done SPTs in the previous study¹⁴ after the last follow-up (i.e., after 5 years).

Results: Of the 1211 children, 870 (71.8%) completed the 5-year observation period. In the 5th year, the prevalence of positive nasal symptoms was 29.4% (256 of the 870 children), including 64/70 (91.4%) of those who were formerly symptom positive and SPT⁺, 45/104 (43.3%) of those who were formerly symptom positive and SPT[−], 40/66 (60.6%) of those who were formerly symptom positive with SPTs not performed (SPTs[x]), and 107/630 (17.0%) of those who were formerly symptom negative. SPT results showed that 96.1% (73/76) of previous SPT⁺ children remained SPT⁺; only 3.9% (6/154) became SPT⁺ in previous SPT[−] children.

Conclusion: We concluded that the natural course of AR (symptom positive and SPT⁺) and non-AR (symptom positive and SPT[−]) children were quite different.

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Allergic rhinitis (AR) is a common disease that has great economic and health burdens for society.^{1–3} Epidemiological studies showed that the prevalence of AR in children was high and increasing in many countries.⁴ Nevertheless, AR has often been defined simply as the presence of nasal symptoms (symptom positive) based on questionnaire findings in many epidemiological studies, which may have overestimated the prevalence of the diseases.^{5–8} Meanwhile, the variation of AR was often estimated depending on cross-sectional investigations within different populations, making it difficult to describe the natural history of AR.^{9–13}

There are few longitudinal study reports of AR in children, especially using population-based observations. In our previous study¹⁴ in year 2005–2006, 1211 children were investigated using questionnaires and skin-prick tests (SPTs). All children were living in urban areas of Wuhan, an important metropolis in central China. It was found that the prevalence of positive nasal symptoms was ~27.1% in 3- to 6-year-old children. However, the prevalence of AR was ~10.8% when using the diagnostic criteria of positive nasal symptoms and positive SPTs (SPT⁺).¹⁴ The aim of the current study was to perform a population-based longitudinal investigation to observe the variation of nasal symptoms and to investigate the natural course of AR in the children initially observed in our previous study.¹⁴

METHODS

Study Population and Study Design

All subjects enrolled were from the previous study¹⁴ investigating the prevalence of AR in 3- to 6-year-old children in Wuhan of

China and have been described in detail.¹⁴ The flowchart is shown in Fig. 1.

Informed consent was obtained from legal guardians before the follow-up study. Telephone interviews were then conducted after 1, 3, and 5 years during the same month that the previous study¹⁴ was performed. Approval was obtained through the Ethics Committee of Huazhong University of Science and Technology.

Content of Telephone Interviews

Telephone interviews were the primary method of acquiring information. Because the children attended different primary schools, it was difficult to conduct written questionnaires. We compared the answers of the core questions asked in the written questionnaire from the previous study¹⁴ and from the telephone interviews. We found a high level of coincidence (99.3% of all questions, 100% of questions determining grouping) in the observed population. Therefore, the telephone interviews were performed by the same persons in charge of the telephone interviews in a previous study.¹⁴ The major questions were similar to those used in the previous investigations, which were referred by the Allergic Rhinitis and Its Impact on Asthma (ARIA) and International Study of Asthma and Allergy in Childhood studies.^{3,15} The core questions are shown in Table 1. Treatment of rhinitis except for cold or flu during the past year of the telephone interviews were also inquired (including immunotherapy, medicine, etc.).

The children for whom “yes” was selected in either of the first two questions were considered to be nasal symptom positive, and the others were considered to be nasal symptom negative. Nasal symptom-positive children were classified into intermittent mild (IM), persistent mild (PM), intermittent moderate–severe (IMS), or persistent moderate–severe (PMS) according to ARIA guidelines:

IM—Answer “<4 days a week” or “<4 weeks a year” in question 3 and answer “no” in question 4.

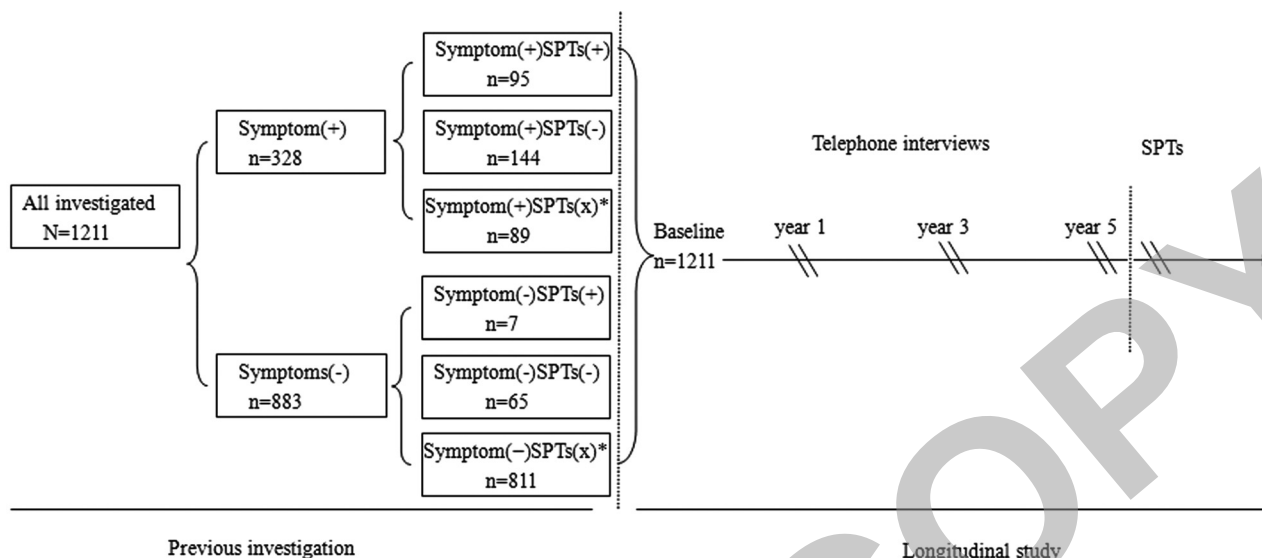
IMS—Answer “<4 days a week” or “<4 weeks a year” in question 3 and answer “yes” in question 4.

PM—Answer “≥4 days a week” and “≥4 weeks a year” in question 3 and answer “no” in question 4.

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* SPTs (x): SPTs not done.

Figure 1. The flowchart of the study.

Table 1 Core questions of telephone interview

1. In the past 12 mo, has your child had a problem with sneezing, a runny, or blocked nose when he/she DID NOT have a cold or the flu? Yes [] No []
(Nasal symptoms caused by cold or flu were carefully inquired and distinguished. Characteristics of cold or flu were described as the nasal symptoms were caused by definitive reasons (cold or flu) and often disappeared after ~1 wk, the accompanied symptoms often included coughing and sore throat. Systemic symptoms such as headache, muscle pain, weakness, and fever might be comparably serious with flu.)
2. In the past 12 mo, has your child ever had hay fever? Yes [] No []
3. The duration of nasal symptoms: <4 days a wk [] ≥4 days a wk [] <4 wk a yr [] ≥4 wk a yr []
4. Any impairment of daily activities or sleep caused by nasal symptoms: Yes [] No []
5. Severity of each symptom when nasal problems occur:
(1) Blocked nose: absence [] mild [] moderate [] severe []
(2) Itchy nose: absence [] mild [] moderate [] severe []
(3) Runny nose: absence [] mild [] moderate [] severe []
(4) Sneezing: absence [] mild [] moderate [] severe []
6. Physician-diagnosed asthma: Yes [] No []
7. Asthma attack in the past 12 mo: Yes [] No []

PMS—Answer “≥4 days a week” and “≥4 weeks a year” in question 3 and answer “yes” in question 4.

The severity of each symptoms was calculated as 0 = absence, 1 = mild, 2 = moderate, and 3 = severe.

Skin-Prick Tests

SPTs were performed again at the end of the last follow-up. Standardized extracts for SPTs were from Allergopharma (Hamburg, Germany) similar to our previous investigation.¹⁴ The tests were performed and read by the same nurse as in a previous study.¹⁴ The allergens were selected based on the common allergens for 8- to 11-year-old children of the local area.¹⁶ The allergens included house-dust mites (HDMs), a mixture of molds, ragweed and a tree mixture, egg, and milk, which were tested during a previous investigation. Because sensitization percentages to cats and dogs were very low in our area, we had not selected the allergens in previous investigations. However, cats and dogs were strong indoor allergens elsewhere and

we want to explore if there were any changes after 5 years, so cat and dog dander were added in the current test. Saline and histamine (10 mg/mL) were used as negative and positive controls, respectively. The reaction was considered positive with a mean weal size equal to or greater than histamine (given a negative reaction to saline). The SPTs were considered positive (SPT⁺) when any inhalant allergen was positive. The SPTs were thought negative (SPT⁻) when no inhalant allergen was positive.

Statistical Analysis

Values of $p < 0.05$ were regarded as statistically significant for all analyses. Nasal symptom scores were described as means $\pm$ SD. The χ^2 -test and t -test were used to compare the sex, age, and clinical characteristics of the children that completed the follow-up or not to assess the likelihood of a selection bias. The prevalence of positive nasal symptoms was presented with their 95% CI. The statistical analysis was performed using SPSS 17.0 for Microsoft Windows (SPSS, Inc., Chicago, IL).

Table 2 Nasal symptoms of the children grouped according to the baseline study at 1-, 3-, and 5-yr follow-up

Different Symptoms and SPT Results According to Previous Investigation	Previous Investigation Symptom Positive n/N (%) [*]	1 yr Symptom Positive n/N (%) [*]	3 yr Symptom Positive n/N (%) [*]	5 yr Symptom Positive n/N (%) [*]
Symptom-positive SPT ⁺	95/95 (100)	90/92 (97.8)	79/84 (94)	64/70 (91.4)
Symptom-positive SPT ⁻	144/144 (100)	116/138 (84.1)	67/125 (53.6)	45/104 (43.3)
Symptom-positive SPT(x)	89/89 (100)	71/81 (87.7)	50/75 (66.7)	40/66 (60.6)
Symptom-negative SPT ⁺	0/7 (0)	1/7 (14.3)	2/7 (28.6)	2/6 (33.3)
Symptom-negative SPT ⁻	0/65 (0)	4/63 (6.3)	9/58 (15.5)	7/50 (14)
Symptom-negative SPT(x)	0/811 (0)	52/791 (6.6)	134/690 (19.4)	98/574 (17.1)
Total	328/1211 (27.1)	334/1172 (28.5) [#]	341/1039 (32.8) [§]	256/870 (29.4) [¶]

^{*}n/N (%): n represents the number of the children with positive nasal symptoms and N represents the number of the children who had completed the follow-up in each group.

[#]95% CI was 28.5 (25.9–31.1).

[§]95% CI was 32.8 (27.8–37.8).

[¶]95% CI was 29.4 (26.4–32.5).

SPT = skin-prick test; SPT(x) = SPTs not performed.

Table 3 Comparison of children completing follow-up with dropout children

Different Symptoms and SPT Results According to Previous Investigation	Average Age			Sex (% male)			Symptom Score [*]		
	Complete (yr)	Dropout (yr)	p Value	Complete n/N (%)	Dropout n/N (%)	p Value	Complete	Dropout	p Value
Symptom-positive SPT ⁺	4.7 (3.7–5.8)	4.5 (3.5–5.5)	0.37	48/70 (68.6)	16/25 (64.0)	0.43	5.3 (3.8–6.9)	5.0 (3.3–6.7)	0.40
Symptom-positive SPT ⁻	4.5 (3.4–5.6)	4.4 (3.5–5.3)	0.66	55/104 (52.9)	21/40 (52.5)	0.56	4.4 (2.7–6.1)	4.0 (2.2–5.8)	0.17
Symptom-positive SPT(x)	4.6 (3.5–5.6)	4.4 (3.5–5.3)	0.52	35/66 (53.0)	11/23 (47.8)	0.43	4.6 (3.0–6.2)	4.4 (2.5–6.3)	0.57
Symptom-negative SPT ⁺ [#]	—	—	—	4/6 (66.7)	1/1 (100)	—	—	—	—
Symptom-negative SPT ⁻	4.7 (3.6–5.7)	4.4 (3.4–5.5)	0.45	31/50 (62.0)	10/15 (66.7)	0.50	—	—	—
Symptom-negative SPT(x)	4.5 (3.5–5.5)	4.6 (3.5–5.7)	0.34	301/574 (52.4)	123/237 (51.9)	0.48	—	—	—

^{*}The total scores of blocked nose, itchy nose, runny nose, and sneezing were calculated.

[#]Data of symptom-positive SPT⁺ children were not analyzed because of inadequate numbers.

SPT = skin-prick test; SPT(x) = SPTs not performed.

Table 4 Classification of symptom-positive SPT⁺ and symptom-positive SPT⁻ children according to ARIA guidelines and treatment of nasal symptoms

ARIA Classification	Symptom Positive SPT ⁺				Symptom Positive SPT ⁻			
	Baseline [*] (n = 95) No (%)	1st yr (n = 92) No (%)	3rd yr (n = 84) No (%)	5th yr (n = 70) No (%)	Baseline [*] (n = 144) No (%)	1st yr (n = 138) No (%)	3rd yr (n = 125) No (%)	5th yr (n = 104) No (%)
No symptoms	0 (0)	1 (1.1)	5 (6)	6 (8.6)	0 (0)	21 (15.2)	58 (46.4)	59 (56.7)
IM	17 (17.9)	28 (30.4)	31 (36.9)	39 (55.7)	46 (31.9)	45 (32.6)	24 (19.2)	27 (26.0)
IMS	19 (20)	18 (19.6)	12 (14.3)	5 (7.1)	43 (29.9)	31 (22.5)	14 (11.2)	3 (2.9)
PM	24 (25.3)	16 (17.4)	11 (13.1)	5 (7.1)	26 (18.1)	19 (13.8)	11 (8.8)	4 (3.8)
PMS	35 (36.8)	29 (31.5)	25 (29.8)	15 (21.4)	29 (20.1)	22 (15.9)	18 (14.4)	11 (10.6)
Treatment	77 (81.1)	63 (68.5) [#]	53 (63.1) [§]	41 (58.6) [¶]	99 (68.8)	71 (51.4)	48 (38.4)	30 (28.8)

^{*}Baseline data obtained during a previous investigation and not published.

[#]There was one child on whom immunotherapy was performed.

[§]There were three children on whom immunotherapy was performed (one old patients and two new patients).

[¶]There were three children on whom immunotherapy was performed (two old patients and one new patients).

ARIA = Allergic Rhinitis and Its Impact on Asthma; IM = intermittent mild; IMS=intermittent moderate-severe; PM = persistent mild; PMS = persistent moderate-severe; SPT = skin-prick test.

RESULTS

Study Population

Of the 1211 children of the previous study,¹⁴ 8 (0.7%) children were refused by their legal guardian to have long-term follow-up interviews. All of these children were in the symptom-negative group and were regarded as having dropped out. Other children lost in the follow-up

were because of losing contact. No children were initiatively withdrawn during the follow-up. The number of children successfully followed up are shown in Table 2. There were 870 (71.8%) children that completed the full 5 years of follow-up. These children were grouped according to their different symptoms and SPT results from the previous study.¹⁴

There were no significant differences in age, sex, and severity of nasal symptoms between the children that were successfully followed

up and those that dropped out before the three interviews were completed. The data compared the children successfully followed up and those that dropped out by the 5th year are shown in Table 3.

Prevalence of Nasal Symptoms

The prevalence of nasal symptoms during each round of telephone interviews is shown in Table 2. As for the whole population, the prevalence of positive nasal symptoms in the 1-, 3-, and 5-year follow-up was 28.5% (25.9–31.1%), 32.8% (27.8–37.8%), and 29.4% (26.4–32.5%), respectively, compared with 27.1% (24.6–29.6%) at baseline. During the final telephone interviews, it was found that 91.4% of children that were originally symptom positive and SPT⁺ remained symptom positive, compared with only 43.3% of those children who were originally symptom positive and SPT⁻. Meanwhile, there were 17.0% new symptom-positive children who were originally symptom-negative children.

Severity of Nasal Symptoms

We compared the impairment of daily activities or sleep caused by nasal symptoms and the severity of each nasal symptom between symptom-positive SPT⁺ and symptom-positive SPT⁻ children.

The classification of nasal symptom-positive SPT⁺ and symptom-positive SPT⁻ children according to ARIA guidelines is shown in Table 4. The level of impairment was found to be decreased in both groups, particularly in the latter group. The percentage of children with moderate–severe impairment decreased from 56.8% at baseline to 28.5% at the 5th year of follow-up in the symptom-positive SPT⁺ group ($p < 0.001$) and decreased from 50.0 to 13.5% in the symptom-positive SPT⁻ group ($p < 0.001$). Similarly, the percentage of the children with persistence duration also decreased in both groups: decreased from 62.1 to 28.5% in the symptom-positive SPT⁺ group ($p < 0.001$) and decreased from 38.2 to 14.4% in the symptom-positive SPT⁻ group ($p < 0.001$). Four children did immunotherapy in the symptom-positive SPT⁺ group altogether. Others in the symptom-positive SPT⁺ group and all those in the symptom-positive SPT⁻ group were treated with medicine or physical therapies. The percentage of rhinitis treatment also decreased with time in both groups (Table 4).

The nasal symptom scores also decreased with age in both groups compared with baseline (Fig. 2). In symptom-positive SPT⁺ children, the total scores were significantly decreased compared with baseline (4.2 versus 5.1; $p = 0.02$). Both the single symptom scores and the total scores decreased sharply in symptom-positive SPT⁻ children at all three follow-up time points.

Asthma

In the 70 symptom-positive SPT⁺ children who finished all three follow-up interviews, there were 13 (18.6%) children who had been diagnosed with asthma at baseline. Meanwhile, another 8 (11.4%) children were diagnosed with asthma by physicians during follow-up. At the final time point, there were 14 (20%) children who still had asthmatic attacks; 7 (10%) children had not had any asthma attack in the preceding 12 months. In the 104 symptom-positive SPT⁻ children who had finished all three follow-up interviews, there were 6 (5.8%) who were diagnosed with asthma at baseline. Another 3 (2.9%) children had at some point been diagnosed with asthma by physicians during the investigation. At the final time point, only 2 (1.9%) children had asthma attacks in the preceding 12 months (Table 5).

Skin-Prick Tests

Three hundred eleven children had SPTs performed in a previous study,¹⁴ among whom 230 children were successfully followed up. SPTs were performed again in all 230 children in the current investigation. The results of SPTs are shown in Table 5. No child was found sensitized to cat or dog dander alone, so the positive rate of SPTs

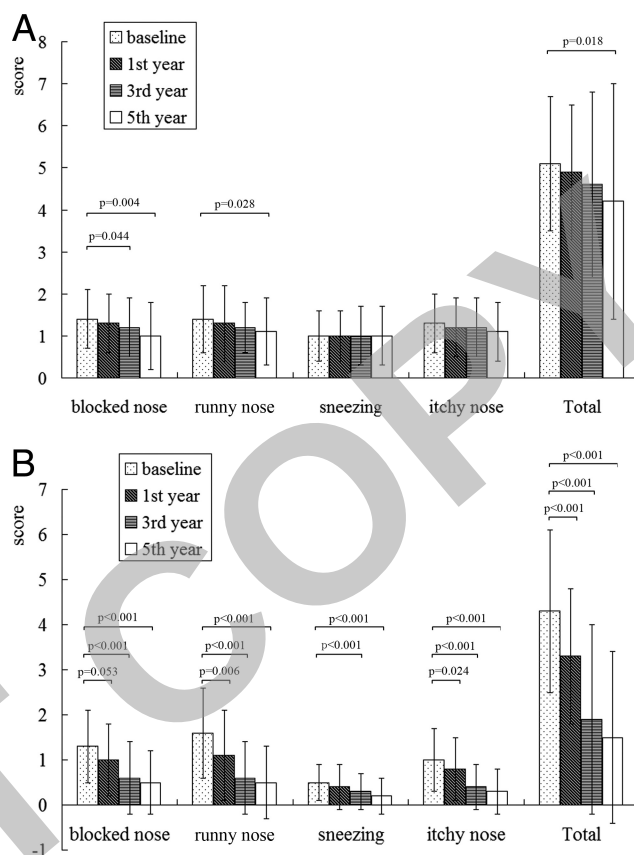


Figure 2. Symptom scores of symptom-positive skin-prick-positive (SPT⁺) and symptom-positive SPT⁻ children at 1-, 3-, and 5-year follow-up. (A) Symptom scores of symptom-positive SPT⁺ children. (B) Symptom scores of symptom-positive SPT⁻ children.

could be compared directly with that of the previous study.¹⁴ SPTs remained positive in 97.1% (68/70) of previous symptom-positive SPT⁺ children. Only 5.2% (4/104) became SPT⁺ in previous symptom-positive SPT⁻ children. In all SPT⁺ children, HDMs were still found to be the most important allergen: 96.2% (76/79) of SPT⁺ children sensitized to HDMs in current tests compared with 95.1% (97/102) in previous study.¹⁴ Interestingly, there was a decreased tendency of the SPT positivity for molds mixture (16.7% versus 28.4%; $p = 0.053$), eggs (8.9% versus 16.7%; $p = 0.11$), and milk (10% versus 22.5%; $p = 0.02$) compared with baseline levels, although only SPT positivity of milk was statistically different ($p < 0.05$). SPT positivity of ragweed (6.3% versus 6.9%; $p = 0.808$) and trees mixture (6.3% versus 5.9%; $p = 0.424$) did not change significantly. SPT positivities of cat and dog dander were 5.1% (4/79) and 3.8% (3/79), respectively.

DISCUSSION

The current work was the first population-based longitudinal study of AR in Chinese children. Our results showed that the prevalence of nasal symptoms was similar across the 5-year study period (27.1% versus 29.4%), and the composition of the nasal symptom-positive children changed significantly. Nasal symptoms remained in most of the original symptom-positive SPT⁺ children (64/70, 91.4%), but only in less than half of original symptom-positive SPT⁻ children (45/104, 43.3%). Of the original symptom-positive children, 107/630 (17.0%) became symptom positive after 5 years.

Most nasal symptom-positive children were distinguished by nasal symptoms and SPT results in the beginning, which made it possible to observe the natural course of AR. In retrospect, it was disappoint-

Table 5 Asthma and SPTs results at last follow-up

Different Symptoms and SPT Results According to Previous Investigation	Physician-Diagnosed Asthma			SPT ⁺ after Last Follow-Up. n/N (%)
	Baseline* n/N (%)	Current# n/N (%)	Total§ n/N (%)	
Symptom-positive SPT ⁺	13/70 (18.6)	14/70 (20)	21/70 (30)	68/70 (97.1)
Symptom-positive SPT ⁻	6/104 (5.8)	2/104 (1.9)	9/104 (8.7)	4/104 (5.2)
Symptom-negative SPT ⁺	0/6 (0)	0/6 (0)	0/6 (0)	5/6 (83.3)
Symptom-negative SPT ⁻	1/50 (2)	0/50 (0)	2/50 (4)	2/50 (4)

*Children who had physician-diagnosed asthma at baseline of the investigation.

#Children who ever had asthma attack during the last 12 mo of the 5-yr follow-up.

§Children who ever had physician-diagnosed asthma during all 5 yr of follow-up including baseline condition.

SPT = skin-prick test.

ing that most of the former symptom-negative children did not have SPTs performed at baseline, because this made it difficult to evaluate the influence of allergen sensitization to symptoms occurrence in this group. Bodtger reported an annual incidence rate of 5% for the onset of symptoms in a symptom-negative pollen sensitization adult population.¹⁷ Westman found that 56.3% of asymptomatic sensitization children developed AR after 4 years.¹⁸ However, the major allergens were both pollens in these two studies, which were much different from the current investigation. The influence of allergen sensitization to symptom occurrence needed more research.

The severity of nasal symptoms were found to be dramatically alleviated with age in symptom-positive SPT⁻ children in this study, half of whom reported no symptoms after 5 years. Although most symptom-positive SPT⁺ children still had nasal symptoms, their severity was also alleviated to a certain extent. In addition, the alleviation of the severity of nasal symptoms was not much influenced by the treatment, because most children had been treated very early and the percentage of treatment was also decreased with time. The exact reasons needs further investigation.

In contrast with our current study, Keil reported an increasing incidence and greater severity of AR in children aged 3–13 years old, with more than half of AR children being categorized as PM or PMS.¹⁹ However, he observed this variation across a whole population, not different subgroups based on symptoms and SPTs. In addition, the criteria of “<4 days a week” or “≥4 days a week” was not included, which might have led to more children being classified into the “persistent” group.

Peat reported that atopy acquired at an early age (before 6 years) is an important predictive factor for asthma continuing into late childhood.²⁰ We also found a higher incidence of asthma in symptom-positive SPT⁺ children than that in symptom-positive SPT⁻ children in our previous study (20% versus 5.6%).¹⁴ In contrast with the report of Chawes, who showed that children with allergic and non-AR have a similar risk of asthma at 7 years of age (21% versus 20%).²¹ In addition, it was found that both the incidence of newly diagnosed asthma and the asthma attacks in the preceding 12 months were much higher in the symptom-positive SPT⁺ children than that in the symptom-positive SPT⁻ children in our current study. The reasons for the discrepancy between our current study and Chawes's report might be caused by the inclusion of different major allergens, the environment, and the study population.

SPTs were performed again in all 230 children who had SPTs performed in a previous study¹⁴ and completed the follow-up as well in the current investigation. Although 26% (81/311) of children did not have the second SPTs performed because of losing contact, characteristics such as age, sex, and severity of nasal symptoms were not significantly different between the children who had the second SPTs performed or not in each group (Table 3). SPT positivity did not change in most children after 5 years, which implied that allergy was not easily attenuated with time. Rondón reported that 24% of non-AR patients could have allergen sensitization after 3 years.²² We found

that only 5.3% of the original symptom-positive SPT⁻ children became SPT⁺. The subjects Rondón studied were adult patients with severe clinical symptoms, which was different from our study and might result in different conclusions. The most important allergen was still found to be HDMs after 5 years of follow-up. The SPT positivity of molds, milk, and eggs decreased with age, although only sensitization to milk was statistically different. This tendency was similar to our clinical observations.¹⁶ It was reported that spontaneous clinical tolerance did develop in some food-allergic individuals, especially for egg, milk, wheat, and soy allergens. The reason was not very reliable, perhaps because of immune tolerance.²³

In conclusion, the current study showed similar prevalence of nasal symptoms during the 5 years of follow-up. The natural course of symptom-positive SPT⁺ and symptom-positive SPT⁻ children was much different, which implied the importance of allergen examination in epidemiological studies of AR. Nevertheless, longer observation are needed to know more about the regularity of AR.

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