Aeroallergen IgE profile, adenoid hypertrophy, and childhood allergic rhinitis in urban China

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Abstract

Background: Adenoid hypertrophy (AH) is a common comorbidity in pediatric allergic rhinitis (AR). The role of the sensitization to aeroallergens in AR children with AH is still unclear. Methods: 5307 children (2-8 years) with nasal complaints were enrolled in our study to identify the prevalence of AR and the incidence of AH complicated by AR. A smaller cohort including 2292 children was recruited for further confirmation. Basic information, serum total and specific immunoglobulin E (tIgE, sIgE) test, physical examination, and fluoroscopy evaluation were obtained for each patient. Risk factors for AH were estimated by logistic regression analysis. Results: We found that 3066 of 5307 children with nasal complaints had an elevated sIgE for at least one aeroallergen. House dust mites (HDMs) were the most common aeroallergen with a prevalence of 65.7%. Of 3066 children with AR, 1440 developed a moderate to severe AH. AR children with AH had a significantly higher tIgE level compared with those without AH (178IU/ml [interquartile range, IQR: 61.2-423.8] vs. 102IU/ml [IQR: 60.0-303.8], p<0.001). Sensitivity to Aspergillus fumigatus (Odds ratio [OR]: 1.687; 95% confidence interval [95%CI]: 1.199-2.373, p=0.003) and cockroaches (OR: 2.295, 95%CI: 1.263-4.170, p=0.006) was statistically significant in the logistic regression model after adjusting for several likely confounders. Conclusions: HDMs are the most common causes among sensitized children with nasal discomforts. AR children with higher tIgE may have higher likelihood of developing AH. AR children with AH have a distinct sensitization profile, and Aspergillus fumigatus and cockroaches could be the main triggers in urban China.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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65.7%. Of 3066 children with AR, 1440 developed a moderate to severe AH. AR children with AH had a significantly higher tIgE level compared with those without AH (178IU/ml [interquartile range, IQR: 61.2-423.8] vs. 102IU/ml [IQR: 60.0-303.8],p <0.001). Sensitivity to *Aspergillus fumigatus*(Odds ratio [OR]: 1.687; 95% confidence interval [95%CI]: 1.199-2.373, p =0.003) and cockroaches (OR: 2.295, 95%CI: 1.263-4.170, p =0.006) was statistically significant in the logistic regression model after adjusting for several likely confounders.

Conclusions: HDMs are the most common causes among sensitized children with nasal discomforts. AR children with higher tIgE may have higher likelihood of developing AH. AR children with AH have a distinct sensitization profile, and *Aspergillus fumigatus* and cockroaches could be the main triggers in urban China.

K E Y W O R D S

allergic rhinitis, adenoid hypertrophy, immunoglobulin E, aeroallergen

Key Message

There have been few studies that focused on the sensitivity manifestations of AR and AR complicated by AH in China. We conducted a population-based, observational and prospective cohort study involving children aged 2-8 years with nasal complaints in a large urban academic pediatric facility in urban China. Basic information was collected and immunoglobulin E measurements were taken and comprehensively analyzed. We found that allergic rhinitis children with a higher total immunoglobulin E level may have higher chance of developing adenoid hypertrophy. Allergic rhinitis children with adenoid hypertrophy have a distinct sensitization profile, and *Aspergillus fumigatus* and cockroaches could be the main triggers.

Main Text

1 INTRODUCTION

Allergic rhinitis (AR), as a critical public health and economic problem, affects about 10% of children in urban China[1]. Children with AR usually suffer from a series of discomforts such as cough, sneezing, nasal pruritus, nasal congestion, sore throat, and behavioral problems. Adenoid hypertrophy (AH) is a common comorbidity in pediatric AR with a frequency of 12%-21.2%[2-4]. Previous analysis of the incidence of AH in allergic children hypersensitive to dust mite found that the chance of AH was greater only in children with AR[5]. However, the etiology of AH in children with AR has not yet been clearly explained.

Aeroallergens are known risk factors for the development and triggering of AR[6]. In central China, house dust mites (HDMs) are the most common indoor allergen[7]. Identification of causative aeroallergens is essential for prevention, diagnosis, and management of AR[8]. It has been reported that sensitization to aeroallergens is associated with the presence of AH[3, 5, 9, 10]. In America and Europe, sensitivity to mold spores and pollen was found more frequently in AR children with AH[5, 9]. Nevertheless, different populations have different sensitization patterns based on age, gender, race, region, climate, life style and other exposure factors. Thus, an accurate description of aeroallergen sensitization patterns in AR and AH children are necessary.

Few studies have focused on the sensitivity manifestations of AR and AH-complicated AR in China. We described the aeroallergen sensitization profile of patients with nasal complaints in urban China and tried to identify possible characteristics specific to AR with AH in children. The intention is to provide suggestions for the early diagnosis and appropriate management of AH children with AR.

2 METHODS

2.1 Study design andpopulation

We designed a population-based, observational prospective cohort study involving 2-8 years children at Shanghai Children's Medical Center of Shanghai Jiao Tong University School of Medicine, a large urban academic pediatric facility in China. Between January 2016 and December 2018, 5307 children who visited the ear, nose and throat (ENT) clinic due to nasal complaints lasting for several weeks or months were enrolled. Children with autoimmune diseases, craniofacial deformity, abnormal of anatomic structure of nasal

cavity, congenital malformation syndromes, such as Down's syndrome, mucopolysaccharidosis syndrome, Hemifacial Microsomia, were excluded.

Basic information including age, gender, and clinical symptoms, was obtained for each patient. Tests for serum total IgE (tIgE) and specific IgE (sIgE) level were performed with their suspicious allergic symptoms. Moderate-to-severe AH was identified by admitting physicians based on patients' history, physical examination and fluoroscopy evaluation. We defined children with AR as the AR group, children without AR as the non-AR (nAR) group, AR children with moderate-to-severe AH as the AH-AR group, and AR children without AH as the non-AH-AR (nAH-AR) group.

For further investigation, 2292 children with nasal complaints were recruited in our clinic in 2019, and each of them was assessed through the same detections. The Shanghai Children's Medical Center of Shanghai Jiao Tong University School of Medicine Ethics Committee approved the study.

2.2 Diagnosis ofAR

Children were diagnosed with AR if they met the following criteria[11]: (1) Typical symptoms (water-like tears, nasal itching, congestion, or sneezing) existed more than a year; with [?]2 persistent symptoms lasting for more than one hour per day; (2) at least one serum aeroallergen-sIgE was positive.

2.3 Evaluation ofmoderate-to-severe AH

The adenoid size of each child was evaluated using fluoroscopy. Those whose choanae were over 50% obstructed by hyperplastic adenoid tissue were classified as moderate-to-severe AH (moderate: 50%-75% of choanae, free only in inferior area; severAHe: >75% of choanae, practically complete)[12]. Any of the clinical manifestations of the nasal airway obstruction-by adenoid tissue, such as obstructive breathing, obstructive sleep apnea symptoms, and chronic mouth breathing (which could result in palatal and dental abnormalities), recurrent or persistent otitis media and recurrent and/or chronic sinusitis, were also considered in the classification.

2.4 Serum total and specific IgE

Peripheral venous blood of children was collected and examined by western blot using the AllergyScreen™ (MEDIWISS Analytic GmbH, Germany) human serum sIgE allergen detection kit for aeroallergens (HDMs, cat/dog hair, molds, mixed grass/tree pollen, cockroaches,*Amaranthus retroflexus* , house dust and mulberry). sIgE levels of*Dermatophagoides pterronyssinu* s (*Der p*), *Dermatophagoides farina*(*Der f*),*Blomia tropicalis,* molds, dog/cat hair,*Aspergillus fumigatues* , cockroaches, silk, and mixed grass/tree pollen were detected using the same kit in the cohort from 2019. According to the instructions, the positive standard for tIgE [?]60 IU/mL and for sIgE is [?]0.35 IU/mL.

2.5 Statistical analysis

The statistical analysis was performed using IBM SPSS statistics for MacOS, version 26.0 (Armonk, NY: IBM Corp). Continuous variables were described either as mean and standard deviation (SD) or as median and interquartile ratio (IQR), depending on the normality of distribution. Measurements of tIgE were log-transformed to conform to normal distribution. Categorical variables were described with percentages. Student's t test was used for the comparison of continuous variables. The chi-square test was used for comparison of categorical variables. Binary logistic regression analysis was used to adjust for confounding factors. Significance was defined as p <0.05. The statistical power for this study was calculated using G*Power 2 software (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/). The statistical power for the comparison of two cohorts was both over 90% with the current sample size; the α was 0.05 and the β was 0.2.

3 Results

3.1 Overall constitution

5307 subjects aged 2-8 years were enrolled in our cohort in the period from 2016 to 2018. The mean age was 4.74±1.53 years, and 3298 (62.1%) were boys and 2009 (37.9%) were girls. AR children was significantly elder than non-AR children (4.91±1.54 vs. 4.49±1.47,p <0.001). AR was diagnosed in 3066 (57.8%, 95% confidence interval [95%CI]:56.4%-59.1%) children (1943 [63.4%] boys and 1123 [36.6%] girls). Boys with nasal complaints were more likely to be diagnosed with AR than girls (58.9% vs 55.9%, p =0.03). The incidence of moderate-to-severe AH was 55.7% (2957/5307, 95%CI: 54.4%-57.1%), including 1440 AR children and 1517 non-AR children. The prevalence of moderate-to-severe AH in AR children was 47.0% (1440/3066, 95%CI: 45.2%-48.7%) (Table 1).

3.2 Sensitization profile of pediatric AR

Overall, 57.8% (3066/5307) of children with nasal complaints had an elevated sIgE to at least one aeroallergen. The sensitization rates to aeroallergens in the general population increased with age (Fig 2a). tIgE level of sensitized children was elevated compared with that of unsensitized children. Among all sensitized children, 1732 (56.2%) were sensitized to one aeroallergen, 820 (26.7%) to two aeroallergens, 322 (10.5%) to three aeroallergens, 137 (4.5%) to four aeroallergens, and 65 (2.1%) to five aeroallergens or more. HDMs were the most common aeroallergen with a prevalence of 65.7% (Fig 2b). There were no significant differences between males and females except for dog/cat hair, to which more boys than girls were sensitized (33.7% vs. 29.4%, p =0.013) (Fig 2c).

3.3 Sensitization characteristics of moderate-to-severe AH and pediatric AR

In AR children, 1440 (47.0%) showed moderate-to-severe AH (960 boys, 480 girls). Boys were more likely to suffer from AH than girls (66.7% vs. 60.5%,p <0.001). Younger children developed moderate-to-severe AH more easily on the basis of AR (4.64±1.45 vs. 5.15±1.59,p <0.001). The AH-AR group had significantly higher tIgE than those without AH (178IU/mL [IQR: 61.2-423.8] vs. 102IU/mL [IQR: 60.0-303.8],p <0.001). HDMs were also the most common aeroallergen in AH-AR group. We compared the sensitization to six main aeroallergens between the two groups and found that HDMs (58.2% vs. 72.4%, p <0.001) and house dust (13.0% vs. 19.5%,p <0.001) were less common in AH-AR group (Table 2). Sensitivity to dog/cat hair, molds, pollens, and cockroaches did not differ significantly.

For further investigation, we established a new cohort in 2019. A total of 2292 children were involved. AR was diagnosed in 1301 children, and 984 children were excluded after a series of laboratory examinations. 499 (34.3%) AR children were comorbid with moderate-severe AH following the fluoroscopy. Age and gender showed the same trend between AH-AR and nAH-AR group, though they did not reach statistical significance. In surprising consensus with our first cohort, tIgE level was significantly higher in AH-AR group than in nAH-AR group (187IU/mL [IQR: 71.0-435.0] vs. 102IU/mL [IQR: 46.0-259.5],p <0.001).

Consistently, HDMs allergens (*Der f* and *Der p*), aeroallergens with the highest sensitization rate, were less common in AH-AR group. We also found that sensitivity to *Blomia tropicalis* as lower in AH-AR group, while sensitivity to molds, dog/cat hair, *Aspergillus fumigatus* , and cockroaches was higher (Table 3). In the logistic regression models, for the effect of the presence of AH, we adjusted for several likely confounders (gender, age, sensitivity to *Der f* , *Der p* , molds,*Blomia tropicalis* , dog/cat hair,*Aspergillus fumigatus* , and cockroaches). The results showed that sensitivity to*Aspergillus fumigatus*(Odds ratio [OR]: 1.687, 95%CI: 1.199-2.373, p =0.003) and cockroaches (OR: 2.295, 95%CI: 1.263-4.170, p =0.006) were statistically significant (Table 4).

4 Discussion

The prevalence of AR has been increasing continuously all over the word[1]. To build up an accurate profile of the current situation of pediatric AR in urban China, our study focused on 2-8-year-old children with allergy-like nasal complaints. It was based on a large pediatric population in a single advanced clinical center in Shanghai, China. Among 5307 children between 2016 and 2018, the definite diagnosis rate of AR was 57.8%, demonstrating that AR was still the main cause of nasal symptoms as a joint result of aeroallergens, IgE antibodies, immune cells, chemical mediators, sensory nerves, and blood vessels[8]. Thus, AR should be

first considered, and tIgE and sIgE should be tested when children visit an ENT clinic for nasal complaints. Interestingly, we found that the positive rate of aeroallergen sIgE increased with age, reaching a maximum of 71.9% (252/352) at the age of eight. A study on the natural history of AR concluded an increasing prevalence throughout childhood, which might be attributed to more time and chances to be exposed to diverse allergens as children grow up[13].

We found a significant male preponderance of pediatric AR. The incidence of AR was significantly higher in boys (58.9%) than in girls (55.9%). Many studies have presented the similar results[13, 14]. This could partly reflect that defference in anatomy, immune response profile, and sex hormones [14]. Sensitization profile of aeroallergens varies widely among the regions[15, 16]. In China, HDMs (*Der f* and *Der p*) sensitization is the highest in the southern and central regions, and the lowest in the northern and northwest regions[17]. In our study, HDMs were the most common aeroallergen in AR children, and the sensitization proportion of*Der p* (59.0%) was higher than that of *Der f*(47.4%). We also found a higher sensitization rate to dog/cat hair in boys than in girls. Different aeroallergens sensitization plays different roles in the occurrence and development of AR[18]. Therefore, individual analysis of sensitization is essential for children with suspected AR.

Persistent upper airway allergic reaction may cause lymphoid hyperplasia, leading to increased volume of adenoid tissue[3]. Several studies have found that AR is an important factor in AH[10, 19]. Dogru et al. found that the presence of AH increased AR severity and prolonged disease duration[4]. In our cohort, boys at a younger age were more likely to develop AH in the presence of AR. The age difference may be important because of rapidly growth of adenoid tissue in 3-5 years of age[20]. Most researches didn't show gender differences in the prevalence of AH in AR children, but Wang et al. found more boys among AH-AR children with sensitization to molds[21]. Since we focused on the prevalence of moderate-to-severe AH, our findings raise the question of whether gender differences are associated with the severity of AH in AR children. Further study should be conducted to further exploration.

Another novel finding of our study was that elevated tIgE may be a risk factor in the development of AH. AR is a typical type I allergic disease of the nasal mucosa, mediated by IgE produced within the lymphatic tissue of Waldeyer's ring[22]. An inappropriate IgE-mediated immune response against normally tolerated antigens represents a crucial pathogenic process in the development of AR[23]. Atopic individuals, who show increased levels of tIgE and sIgE to aeroallergens, are predisposed to be sensitized to harmless allergens through an IgE immune response[23, 24]. Recent research has demonstrated that general tissue inflammation enhances the level of polyclonal natural IgE via FcεRI signaling and potently promotes epidermal hyperplasia[25]. Therefore, we suppose that the production of IgE in children with AR accelerates the adenoid tissue inflammation and drives to epidermal hyperplasia, eventually resulting in AH.

We demonstrated a unique sensitization profile of AH-AR children in the population of urban China. In the AH-AR group, HDMs were the most common aeroallergen, but its prevalence was significantly lower than in the nAH-AR group. These results are consistent with previous studies and hints that mites are not at least the main causative allergens of AH[4, 5, 9, 10]. Molds are another aeroallergen associated with AH[9, 26]. In our first cohort, the difference in the sensitization rate difference to molds between the AH-AR and nAH-AR group was borderline. But in cohort 2019, we found that molds and*Aspergillus fumigatus* were more common in the AH-AR group. In the logistic regression model, AR children with sensitivity to*Aspergillus fumigatus* were 1.687 times (95%CI: 1.199-2.373) more likely to develop AH. Sahin et al. reported that children with molds exposure had a significantly increased rate of AH[26]. Sensitivity to*Alternaria alternata* was also considered as risk aeroallergen of AH[5]. Both*Alternaria alternata* and *Aspergillus fumigatues* were the main components of sensitization to molds, which has a long associative history with atopy[27]. Since molds include heterogeneous allergen proteins and taxonomy, it is valuable to evaluate their diverse effects on AR and AH. Unexpectedly, we found that cockroaches' sensitization could be a risk factor for AH in AR children. It's probably due to the glycans and complex allergen proteins[28]. However, the results were not completely the same between our two cohorts. Environmental exposure, interacting with genetic factors, might cause bias in the sensitization to cockroaches in our cohorts.

There are some limitations to our study. First, the impact of season was not considered. Nevertheless, tIgE measurements are relatively stable and vary little with changes in season[29]. Additionally, we didn't investigate the personal environment, such as mode of delivery, family atopic history, economic income, and passive cigarette smoking. In a published systematic review and meta-analysis study, data showed that environmental smoke exposure increased the risk of allergic sensitization but the effect was borderline[30]. In our study, all children came from the surrounding cities around our clinic in East China, which share similar living environments and economic development. Therefore, our study has satisfactory consistency and may leave little bias. Further studies will focus on the biological mechanism of sensitized molds' chemical composition to determine the pathogenesis of AH with AH.

5 Conclusion

In our study, sensitivity to aeroallergens was the main cause of nasal congestion and runny nose with HDMs being the most common aeroallergen. AR children with a higher tIgE may have higher chance of developing AH.*Aspergillus fumigatus* and cockroaches are the main inhalant allergens associated with AH in children with AR in urban China.

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References

1. Zhang Y, Zhang L. Increasing Prevalence of Allergic Rhinitis in China. *Allergy Asthma Immunol Res* . Mar 2019;11(2):156-169.

2.Ibáñez MD, Valero AL, Montoro J, et al. Analysis of comorbidities and therapeutic approach for allergic rhinitis in a pediatric population in Spain. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology* . Nov 2013;24(7):678-84.

3.Mariño-Sánchez F, Valls-Mateus M, de Los Santos G, Plaza AM, Cobeta I, Mullol J. Multimorbidities of Pediatric Allergic Rhinitis. *Curr Allergy Asthma Rep* . Feb 22 2019;19(2):13.

4.Dogru M, Evcimik MF, Calim OF. Does adenoid hypertrophy affect disease severity in children with allergic rhinitis? *Eur Arch Otorhinolaryngol* . Jan 2017;274(1):209-213.

5.Modrzynski M, Zawisza E. An analysis of the incidence of adenoid hypertrophy in allergic children. *Int J Pediatr Otorhinolaryngol* . May 2007;71(5):713-9.

6.Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* . Nov 2001;108(5 Suppl):S147-334.

7.Lou H, Ma S, Zhao Y, et al. Sensitization patterns and minimum screening panels for aeroallergens in self-reported allergic rhinitis in China. *Sci Rep* . Aug 24 2017;7(1):9286.

8.Okubo K, Kurono Y, Ichimura K, et al. Japanese guidelines for allergic rhinitis 2017. *Allergol Int* . Apr 2017;66(2):205-219.

9.Huang SW, Giannoni C. The risk of adenoid hypertrophy in children with allergic rhinitis. *Ann Allergy Asthma Immunol* . Oct 2001;87(4):350-5.

10.Evcimik MF, Dogru M, Cirik AA, Nepesov MI. Adenoid hypertrophy in children with allergic disease and influential factors. *Int J Pediatr Otorhinolaryngol* . May 2015;79(5):694-7.

11.Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* . Sep 2010;126(3):466-76.

12.Ysunza A, Pamplona MC, Ortega JM, Prado H. Video fluoroscopy for evaluating adenoid hypertrophy in children. *Int J Pediatr Otorhinolaryngol* . Aug 2008;72(8):1159-65.

13.Kurukulaaratchy RJ, Karmaus W, Raza A, Matthews S, Roberts G, Arshad SH. The influence of gender and atopy on the natural history of rhinitis in the first 18 years of life. *Clin Exp Allergy* . Jun 2011;41(6):851-9.

14.Pinart M, Keller T, Reich A, et al. Sex-Related Allergic Rhinitis Prevalence Switch from Childhood to Adulthood: A Systematic Review and Meta-Analysis. *Int Arch Allergy Immunol* . 2017;172(4):224-235.

15.Tao XY, Ng CL, Chen D, et al. Clinical Characteristics and Allergen Sensitization Patterns of Patients with Local Allergic Rhinitis in Southern China. *Int Arch Allergy Immunol* . 2018;175(1-2):107-113.

16.Heinzerling LM, Burbach GJ, Edenharter G, et al. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. *Allergy* . Oct 2009;64(10):1498-506.

17.Li H, Chen S, Cheng L, et al. Chinese guideline on sublingual immunotherapy for allergic rhinitis and asthma. *J Thorac Dis* . Dec 2019;11(12):4936-4950.

18.Yang Y, Zhu R, Huang N, et al. The Dermatophagoides pteronyssinus Molecular Sensitization Profile of Allergic Rhinitis Patients in Central China. *Am J Rhinol Allergy* . Sep 2018;32(5):397-403.

19.Lou Z. Adenoid hypertrophy in children and allergic rhinitis.*Eur Arch Otorhinolaryngol* . Mar 2018;275(3):831-832.

20. Wang DY, Bernheim N, Kaufman L, Clement P. Assessment of adenoid size in children by fibreoptic examination. Clin Otolaryngol Allied Sci. Apr 1997;22(2):172-177.

21.Wang ZX, Lin F, Li LS, Cui L, Guan K, Pang C. [Analysis of sensitization spectrum and clinical features of children with adenoid hypertrophy and perennial rhinitis]. *Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery* . Apr 2019;33(4):351-353.

22.Scadding G. Non-surgical treatment of adenoidal hypertrophy: the role of treating IgE-mediated inflammation. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology* . Dec 2010;21(8):1095-106.

23.Ciprandi G, Marseglia GL, Castagnoli R, et al. From IgE to clinical trials of allergic rhinitis. *Expert Rev Clin Immunol* . 2015;11(12):1321-33.

24.von Bubnoff D, Scheler M, Hinz T, Matz H, Koch S, Bieber T. Comparative immunophenotyping of monocytes from symptomatic and asymptomatic atopic individuals. *Allergy* . Sep 2004;59(9):933-9.

25.Hayes MD, Ward S, Crawford G, et al. Inflammation-induced IgE promotes epithelial hyperplasia and tumour growth. *Elife* . Jan 14 2020;9

26.Atan Sahin O, Kececioglu N, Serdar M, Ozpinar A. The association of residential mold exposure and adenotonsillar hypertrophy in children living in damp environments. *Int J Pediatr Otorhinolaryngol* . Sep 2016;88:233-8.

27.Barnes C. Fungi and Atopy. *Clin Rev Allergy Immunol* . Dec 2019;57(3):439-448.

28.Do DC, Yang S, Yao X, Hamilton RG, Schroeder JT, Gao P. N-glycan in cockroach allergen regulates human basophil function. *Immun Inflamm Dis* . Dec 2017;5(4):386-399.

29.Carlsson M, Thorell L, Sjölander A, Larsson-Faria S. Variability of total and free IgE levels and IgE receptor expression in allergic subjects in and out of pollen season. *Scand J Immunol* . Apr 2015;81(4):240-8.

30. Feleszko W, Ruszczyński M, Jaworska J, Strzelak A, Zalewski BM, Kulus M. Environmental tobacco smoke exposure and risk of allergic sensitisation in children: a systematic review and meta-analysis. Arch Dis Child. 2014;99(11):985-992.

Tables

Table 1 Characteristics of children with nasal complaints from 2016 to 2018

	All (n=5307)	AR (n=3066)	nAR (n=2241)	*P-value*
Gender, n (%)* Male Female	3298 (62.1) 2009 (37.9)	1943 (63.4) 1123 (36.6)	1355 (60.5) 886 (39.5)	0.033
Age+ (mean±SD) (years) *** Total IgE++ (IU/mL) [median (IQR)] *** Moderate-to-severe AH prevalence, n (%)***	4.74±1.53 62.50 (42.00-211.00) 2957 (55.7)	4.91±1.54 141.00 (60.00-369.00) 1440 (47.0)	4.49±1.47 59.70 (29.60-62.45) 1517 (67.7)	< 0.001 < 0.001 < 0.001

Abbreviation: IgE, Immunoglobulin E; AH, adenoid hypertrophy; AR, allergic rhinitis

+Continuous variables; ++ Student's t-test after log transformation; * *P* -value of <0.05;** *P* -value of <0.01;*** *P* -value of <0.001

Table 2 Characteristics and sensitivity to main aeroallergens in children with AR from 2016 to 2018

	AH-AR (n=1440)	nAH-AR (n=1626)	*P-value*
Gender, n (%)*** Male Female	960 (66.7) 480 (33.3)	983 (60.5) 643 (39.5)	<0.001
Age+ (mean±SD) (years) ***	4.64±1.45	5.15±1.59	<0.001
Total IgE++ (IU/mL) [median (IQR)] ***	178 (61.2-423.8)	102 (60.0-303.0)	<0.001
Sensitized to aeroallergen, n (%)			
HDMs*** Dog/cat hair	838 (58.2) 471 (32.7)	1177 (72.4) 514 (31.6)	<0.001 0.516
Molds House dust***	454 (31.5) 187 (13.0)	465 (28.6) 317 (19.5)	0.077 <0.001 0.836
Mixed tree/grass pollen	178 (12.4)	197 (12.1)	
Cockroaches	56 (3.9)	71 (4.4)	0.508

Abbreviation: IgE, Immunoglobulin E; AH, adenoid hypertrophy; AR, allergic rhinitis; HDMs, house dust mites

+Continuous variables;++Student's t-test after log transformation; * *P* -value of <0.05; ** *P* -value of <0.01; *** *P* -value of <0.001

Table 3 Characteristics and sensitivity to main aeroallergens in children with AR in 2019

	AH-AR (n=449)	nAH-AR (n=859)	χ^2	*P-value*
Gender, n (%) Male Female	281 (62.6) 168 (37.4)	526 (61.2) 333 (38.8)	0.227	0.634
Age+ (mean±SD) (years)	4.72±1.42	4.89±1.76	1.800	0.072

	AH-AR (n=449)	nAH-AR (n=859)	χ^2	*P-value*
Total IgE^{++} (IU/mL) [median (IQR)]***	187 (71.0-435.0)	102 (46.0-259.5)	-	<0.001
Sensitized to aeroallergen, n (%) *Der p**** *Der f* *** Molds* *Blomia tropicalis** Dog/cat hair* *Aspergillus fumigatus**** Cockroaches**	265 (59.0) 213 (47.4) 145 (32.3) 102 (22.7) 101 (22.5) 71 (15.8) 26 (5.8)	593 (69.0) 519 (60.4) 231 (26.9) 249 (29.0) 152 (17.7) 79 (9.2) 20 (2.3)	13.102 20.160 4.201 5.904 4.354 12.713 10.418	< 0.001 < 0.001 0.040 0.015 0.037 < 0.001 0.001

Abbreviation: IgE, Immunoglobulin E; AH, adenoid hypertrophy; AR, allergic rhinitis;*Der p, Dermatophagoides pterronyssinu* s; *Der f* ,

Dermatophagoides farina

$^{+}$Continuous variables; $^{++}$ Student's t-test after log transformation;* *P* -value of <0.05;** *P* -value of <0.01;*** *P* -value of <0.001

Table 4 Risk factors associated with the presence of AH in AR children in 2019

	Odds ratio	95% confidence interval	*P-value*
Aspergillus fumigatus** Cockroaches**	1.687 2.295	1.199-2.373 1.263-4.170	0.003 0.006

Likely confounders included gender, age, sensitivity to *Der f, Der p,* molds*, Blomia tropicalis,* dog/cat hair, *Aspergillus fumigatus* and cockroaches; * *P* -value of <0.05; ** *P* -value of <0.01;*** *P* -value of <0.001

Figure Legends

Fig 1 Composition of the cohort

Fig 2 Basic characteristics of aeroallergen sensitivity in 2-8- year-old children

Fig2a. The sensitization rates to aeroallergens in the general population increased with age. Fig2b. The sensitization rates of eight main aeroallergens were shown in descending order. Fig2c. Differences of sensitization rates between males and females were shown.

Author Contributions

Youjin Li contributed to the study concept, design and acquisition of data and conducted analysis and interpretation of data. Jie Chen helped to our study conduction in study design and data collection. Yihang Lin and Xiaoqing Rui contributed to the data collection, reduction, and analysis. Junyang Li helped to the data analysis and verification. All authors were involved in the preparation and review of the manuscript and approved the submitted version.

Conflict of Interest statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval and Trail Registration Statements

The Shanghai Children's Medical Center of Shanghai Jiao Tong University School of Medicine Ethics Committee approved the study.