

Predictive value of respiratory symptoms for the diagnosis of pollen-induced seasonal asthma among children and adults in Inner Mongolia

Ting Ting Ma¹⁻³
 Yan Zhuang¹
 Hai Ying Gong⁴
 Anthony Chauang Yii⁵
 Xue Yan Wang¹
 Huan Zhong Shi^{2,3}

¹Department of Allergy, Beijing Shijitan Hospital, Capital Medical University, ²Department of Respiratory and Critical Care Medicine, Beijing Chao-Yang Hospital, Beijing Institute of Respiratory Medicine, Capital Medical University, ³Center of Medical Research, Beijing Institute of Respiratory Diseases, ⁴Fangshan District Center for Disease Control and Prevention, Beijing, China; ⁵Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore, Singapore

Background: The diagnosis of asthma is made on the basis of variable respiratory symptoms and supported by objective evidence of variable airflow limitation. However, spirometry and bronchoprovocation tests may not be routinely available in resource-scarce settings or in the context of large-scale epidemiological studies. There is a gap in knowledge about the predictive value of respiratory symptoms for the diagnosis of pollen-induced asthma.

Objective: The aim of this study was to investigate the predictive value of self-reported respiratory symptoms for diagnosing pollen-induced asthma.

Patients and methods: We recruited 1,161 patients with respiratory symptoms who presented to the respiratory medicine outpatient clinic of two central hospitals in Inner Mongolia during the pollen season of July–September 2015. All patients were interviewed by a respiratory physician and completed a questionnaire survey, lung function tests and skin prick tests for common inhaled allergens.

Results: A total of 392 patients (33.8%) were diagnosed with asthma and 292 (25.2%, 160 adults, 132 children) with pollen-induced asthma. Respiratory symptoms of cough, wheezing, dyspnea, chest pain and nocturnal awakenings due to breathlessness were all associated with increased odds of being diagnosed with pollen-induced asthma, with cough being the most common symptom in both adults and children, giving a sensitivity of 90.6% in adults and 88.6% in children. Wheezing was the most specific symptom (78% and 89.5% in adults and children, respectively) compared to other symptoms. Overall, the positive predictive value of respiratory symptoms was poor for diagnosing pollen-induced asthma, with the exception of wheezing in children which had a high positive predictive value of 72.7%.

Conclusion: Cough was the predominant symptom in adults and children with pollen-induced asthma. Wheezing was a reliable predictor of pollen-induced asthma in children. In adults, respiratory symptoms were not sufficiently reliable for diagnosing pollen-induced asthma.

Keywords: pollen-induced asthma, asthma symptoms, wheezing, cough, shortness of breath

Correspondence: Huan Zhong Shi
 Department of Respiratory and Critical Care Medicine, Beijing Chao-Yang Hospital, No 8, Workers Stadium South Road, Chaoyang District, Beijing 100020, China
 Tel +86 10 8523 1409
 Email ml3911612465_1@163.com

Xue Yan Wang
 Department of Allergy, Beijing Shijitan Hospital, No 10, Yang Fang Dian Road, Haidian District, Beijing 100038, China
 Tel +86 10 6392 6072
 Email wangxueyan2018@163.com

Introduction

Asthma is one of the most common chronic respiratory diseases worldwide and represents an important source of health care costs. In recent years, there has been a rise in the incidence and mortality of asthma. Globally, about 300 million people are afflicted with asthma, with 250,000 deaths every year.¹⁻³ Asthma poses a major burden not only on patients but also on health care systems.⁴⁻⁶ Identifying patients who suffer from asthma and preventing and controlling disease are major challenges faced currently.

Asthma is a highly heterogeneous disease with variable and diverse symptomatology, inflammatory phenotypes, airway physiology and pathobiologic pathways. Wheezing,

shortness of breath, chest tightness and cough are the most frequent symptoms of asthma,⁷⁻⁹ and symptoms are important for diagnosing asthma and monitoring disease activity. The Global Initiative for Asthma (GINA) has established criteria for the diagnosis of asthma which encompasses two components: a history of variable respiratory symptoms and evidence of variable expiratory airflow limitation.⁹ While important for providing supporting evidence for making the diagnosis of asthma, lung function tests such as spirometry, bronchodilator reversibility and bronchoprovocation testing are not specific for asthma, can be falsely negative and cannot be used as exclusive criteria for diagnosing asthma. In addition, lung function tests may not be available in resource-scarce settings where achieving a clinical diagnosis of asthma depends on careful history, examination and exclusion of other respiratory diseases. Global large-scale epidemiological surveys often rely on symptom questionnaires to diagnose asthma because of cost reasons, convenience and difficulty with standardizing and performing lung function tests. For example, in a largest worldwide collaborative research project of the International Study of Asthma and Allergies in Childhood (ISAAC),^{10,11} the core questionnaires are mainly concerned with the respiratory symptoms such as wheezing throughout the year, which implies the primary importance of respiratory symptoms.

The validity of using symptoms to distinguish between asthmatics and non-asthmatics is questionable. Symptoms and signs such as cough, rhonchi, wheezing, chest tightness and shortness of breath are nonspecific manifestations of a broad range of pulmonary and non-pulmonary diseases, including but not limited to asthma, chronic obstructive pulmonary disease (COPD), acute bronchitis, bronchiectasis¹¹⁻¹⁴ and cardiac disease. Little is known about the sensitivity, specificity and predictive values of these common respiratory symptoms in relation to asthma diagnosis, especially in seasonal pollen-induced asthma, a unique phenotype of asthma linked to high ambient concentrations of allergenic pollen which can occur as outbreaks/epidemics and has been described in various geographic regions worldwide.¹⁵⁻¹⁷ Hence, we performed a prospective study of pollen-induced asthma in a grassland area (Inner Mongolia Autonomous Region, China). High pollen counts of *Artemisia* species, *Humulus scandens* and *Chenopodiaceae* occur seasonally in July–September and are paralleled by increased numbers of patients presenting with asthma and other allergic diseases. The aim of this study was to investigate the relationship between the presence of common respiratory symptoms and clinically confirmed pollen-induced asthma in both adults and children.

We also aimed to evaluate the sensitivity, specificity and positive and negative predictive values of respiratory symptoms for diagnosing pollen-induced asthma.

Patients and methods

This was a cross-sectional study. Approval to conduct this study was obtained from the ethics committees of the Beijing Shijitan Hospital and the Tongliao City Hospital (China). All study participants provided written informed consent prior to recruitment.

From July to September 2015, all subjects who presented to the respiratory medicine outpatient clinics of two Tongliao City Hospitals with one or more symptoms of cough, wheezing, chest tightness or shortness of breath were invited to participate in the study. Following recruitment, subjects completed a standardized questionnaire administered by a respiratory physician asking about gender, age, place of residence (urban and rural), ethnic group (Han, Mongolian and others), body mass index (BMI), respiratory symptoms on a month-to-month basis in the past 12 months (wheezing, cough, shortness of breath, chest tightness and nocturnal awakenings), smoking history, allergy to food, family history of allergies/allergic diseases, living conditions, environmental exposure and others.

All participants underwent lung function tests and skin prick tests (SPTs) with a panel of common respiratory aeroallergens. Asthma was diagnosed according to GINA 2014 guidelines, requiring the history of both variable respiratory symptoms and variable expiratory airflow limitation (positive bronchodilator reversibility of >12% and 200 mL after 200–400 µg of salbutamol, or average diurnal peak flow variability >10% in adults or >13% in children).¹³ Pollen-induced asthma was diagnosed based on the history of onset of symptoms in relation to exposure of the pollen allergens which were reported by local pollen counts in time and with IgE-mediated sensitization confirmed by SPTs. Systematic assessment to exclude the following diseases was carried out before making a diagnosis of asthma or pollen-induced asthma: COPD, interstitial lung disease or pulmonary fibrosis, bronchiectasis, lung cancer, pneumonia, pneumothorax, pulmonary embolism, allergic bronchopulmonary aspergillosis, heart diseases and gastroesophageal reflux disease. Patients were excluded from the study if they had previously received immunotherapy.

SPTs

SPTs were conducted by trained allergy nurses or physicians. Oral antihistamines were discontinued for at least 3 days

prior to SPT. Ten respiratory aeroallergens such as *Artemisia* species, *Chenopodium*, *Humulus scandens*, *Salix*, *Zea mays*, *Juniperus chinensis* var. *chinensis*, *Ulmus pumila*, *Betula*, *Populus*, and *Dermatophagoides pteronyssinus* (DP) were tested using standardized allergen extracts (Macro-Union Pharmaceutical Co., Ltd., Beijing, China). The diluent was administered as negative control and histamine hydrochloride (1 mg/mL) as positive control. Allergen extracts were administered to the flexor side of forearm unilaterally after disinfection with alcohol at a distance of 1.5 cm using a disposal skin test needle. The reaction of patients was observed 15 min later. Wheal diameter of ≥ 3 mm for each of the allergens tested was considered as positive response.¹⁸

Statistical analysis

Epidate 3.1 (EpiData Association, Odense, Denmark) was used for data entry. Data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Data were reported as number (%) for categorical variables and mean \pm standard deviation for continuous data. Univariate comparisons were performed using independent-sample *t*-test as the continuous data were normally distributed. Binary logistic regression was used to assess the association between respiratory symptoms and pollen-induced asthma. A *P*-value of <0.05 was considered significant.

Results

A total of 1,161 patients, 770 adults (66.3%) and 391 children (33.7%), were recruited. Patient characteristics are shown in Table 1. A total of 392 patients (33.7%) were diagnosed as asthma. There was no statistical difference between asthmatic and non-asthmatic patients in terms of gender, age, ethnicity, area of residence, smoking and BMI.

Among the asthmatic patients, 292 patients (160 adults and 132 children) were confirmed to be pollen-induced asthma, and they were further analyzed for correlation between the presence of respiratory symptoms and diagnosis of pollen-induced asthma.

Respiratory symptoms

As shown in Table 2, the presence of each respiratory symptom was predictive of pollen-induced asthma in both adults and children. The presence of these symptoms reached a peak in July, August and September (Figure 1A and C), which were also the high pollen season as reported by daily local pollen counts (data not shown).

Cough was the most common symptom in both adults ($n=145$, 90.6%) and children ($n=117$, 88.6%) with pollen-induced asthma. In logistic regression analyses, the three most common symptoms (Table 3) associated with increased

Table 1 Demographic characteristics of the study subjects

Characteristics	Adults (n=770)			Children (n=391)			Total (n=1,161)
	Asthma (n=228)	Non-asthmatic (n=542)	P-value	Asthma (n=164)	Non-asthmatic (n=227)	P-value	
Gender			0.4457			0.2150	
Male	85 (37.3)	218 (40.2)		77 (47.0)	121 (53.3)		501 (43.2)
Female	143 (62.7)	324 (59.8)		87 (53.0)	106 (46.7)		660 (56.8)
Age (years)			0.0655			0.2030	
6–14	–	–		150 (91.5)	215 (94.7)		365 (31.4)
15–18	–	–		14 (8.5)	12 (5.3)		26 (2.2)
19–44	115 (50.4)	267 (49.3)		–	–		382 (32.9)
45–64	78 (34.2)	220 (40.6)		–	–		298 (25.7)
≥ 65	35 (15.4)	55 (10.1)		–	–		90 (7.8)
Ethnicity			0.2883			0.9592	
Han	141 (61.8)	302 (55.7)		89 (54.3)	122 (53.7)		654 (56.3)
Mongolian	80 (35.1)	222 (41.0)		66 (40.2)	91 (40.1)		459 (39.5)
Others	7 (3.1)	18 (3.3)		9 (5.5)	14 (6.2)		48 (4.2)
Area of residence			0.3557			0.0885	
Urban	119 (52.2)	303 (55.9)		90 (54.9)	144 (63.4)		656 (56.5)
Rural	109 (47.8)	239 (44.1)		74 (45.1)	83 (36.6)		505 (43.5)
Smoking			0.0600				
Current smoker	177 (77.6)	382 (70.5)		–	–		559 (48.1)
Never smoker	30 (13.2)	110 (20.3)		–	–		140 (12.1)
Ex-smoker	21 (9.2)	50 (9.2)		–	–		71 (6.1)
BMI	24.6 \pm 4.2	24.7 \pm 3.8	0.712	18.4 \pm 5.0	18.2 \pm 4.6	0.6891	22.5 \pm 5.2

Note: Data shown as number (%) or mean \pm standard deviation.

Abbreviation: BMI, body mass index.

Table 2 Common asthma characteristic symptoms in patients with pollen-induced asthma and non-asthmatic

Clinical symptoms	Pollen-induced asthma (n=160)	Adults (n=702)		Children (n=359)		P-value
		Non-asthmatic (n=542)	P-value	Pollen-induced asthma (n=132)	Non-asthmatic (n=227)	
Cough	145 (90.6)	355 (65.5)	<0.0001	117 (88.6)	159 (70.0)	<0.0001
Chest tightness	126 (78.8)	341 (62.9)	0.0001	55 (41.7)	54 (23.8)	0.0006
Shortness of breath	122 (76.3)	297 (54.8)	<0.0001	49 (37.1)	43 (18.9)	<0.0001
Wheezing	98 (61.3)	99 (18.3)	<0.0001	72 (54.5)	10 (4.4)	<0.0001
Nocturnal awakening due to breathlessness	89 (55.6)	155 (28.6)	<0.0001	43 (32.6)	39 (17.2)	0.0005

Note: Data shown as number (%).

odds of being diagnosed with pollen-induced asthma (with adjusted odds ratio [OR]; confidence interval [CI]) were wheezing (OR =7.8, 95% CI: 5–11.4), cough (OR =5.4, 95% CI: 3.2–9.6) and shortness of breath (OR =2.6, 95%

CI: 1.9–4.1) in adults and wheezing (OR =30.6, 95% CI: 14.4–65.7), cough (OR =4.4, 95% CI: 2.3–8.9) and shortness of breath (OR =2.7, 95% CI: 1.7–4.7) in children. In addition, the sensitivity and specificity, together with positive and

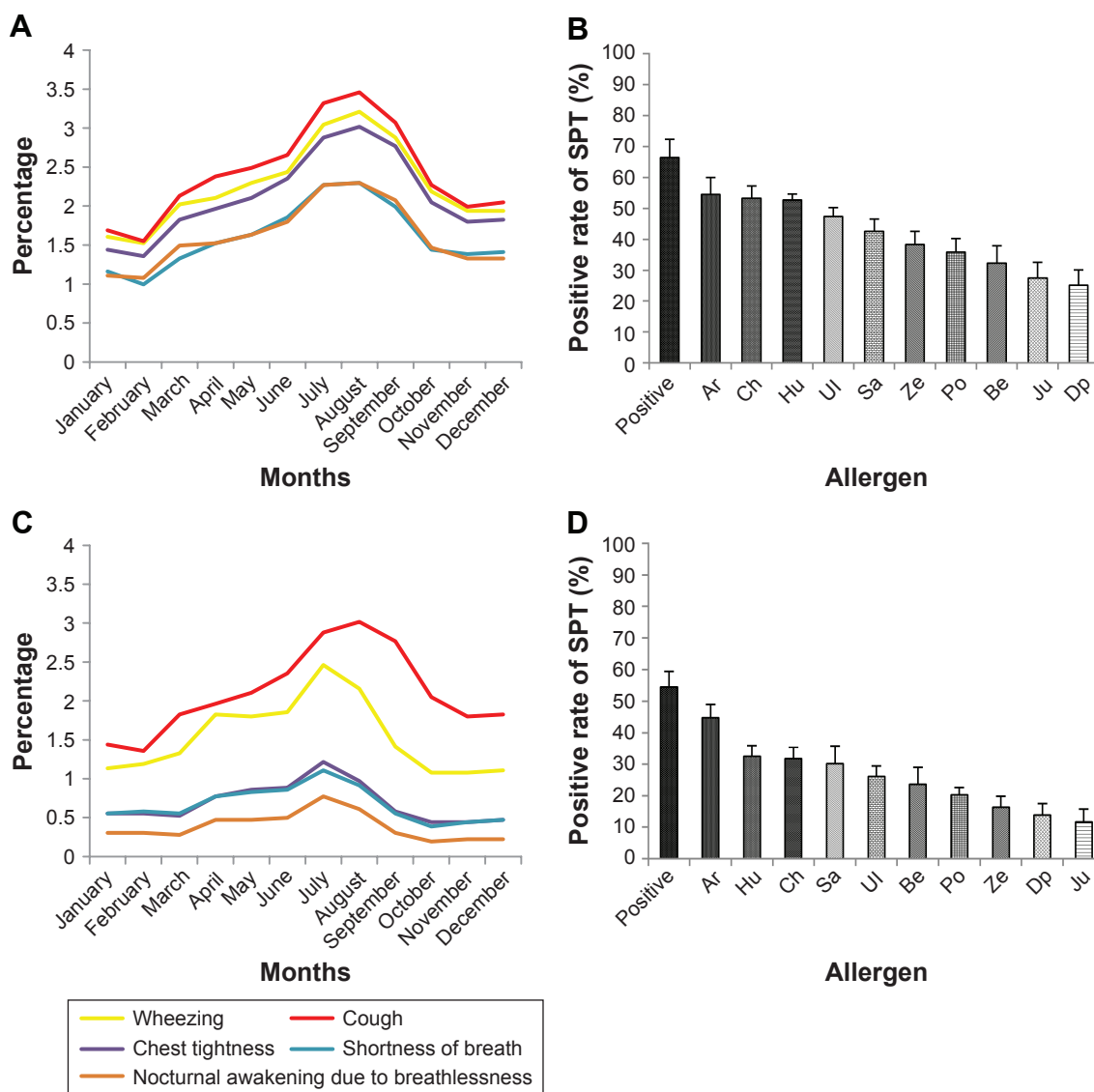


Figure 1 The frequency of appearance (%) of asthma characteristic symptoms throughout 12 months in adults (A) and children (C), and the positive rate (%) of common inhalant allergens tested (SPT) in adults (B) and children (D).

Abbreviations: Ar, *Artemisia species*; Be, *Betula*; Ch, *Chenopodium*; DP, *Dermatophagoides pteronyssinus*; Hu, *Humulus scandens*; Ju, *Juniperus chinensis var. chinensis*; Po, *Populus*; Sa, *Salix*; SPT, skin prick test; Ul, *Ulmus pumila*; Ze, *Zea mays*.

Table 3 The correlation between common asthma characteristic symptoms and seasonal asthma in adults and children

Clinical symptoms	Adults		Children	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Wheezing	7.1 (4.9–10.3)	7.8 (5.0–11.4)	30.2 (14.1–64.0)	30.6 (14.4–65.7)
Cough	5.2 (2.7–9.1)	5.4 (3.2–9.6)	4.4 (2.3–8.9)	4.4 (2.3–8.9)
Shortness of breath	2.5 (1.7–4.1)	2.6 (1.9–4.1)	2.8 (1.8–4.6)	2.7 (1.7–4.7)
Chest tightness	2.2 (1.6–3.6)	2.4 (1.6–3.4)	2.2 (1.4–3.7)	2.4 (1.4–3.8)
Nocturnal awakening due to breathlessness	2.8 (2.1–4.2)	3.0 (2.1–4.1)	2.6 (1.6–4.1)	2.3 (1.5–4.1)

Note: Adjusted for gender, age, smoking and BMI.

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

negative predictive values, of these respiratory symptoms for the diagnosis of pollen-induced seasonal asthma in adults and children have been calculated (Table 4). Wheezing had the highest specificity (adults: 78%, children: 89.5%) for pollen-induced asthma. However, all the respiratory symptoms had low positive predictive values in both children and adults, with the exception of wheezing in children which demonstrated a good positive predictive value of 72.7%.

The pattern of allergic sensitization

Based on SPT results, allergic sensitization (positive SPT) was 66.5% in adults (Figure 1B) and 54.5% in children (Figure 1D). The predominant sensitization patterns were *Artemisia* species, *Humulus scandens* and *Chenopodiaceae*, and most subjects were sensitized to at least three or more pollens (Figure 2), mirroring the pollen species count reported in the region. Interestingly, sensitization to house dust mite allergen (eg, DP) had a low prevalence compared to pollens.

Discussion

In the current study, we evaluated the predictive value of respiratory symptoms for the diagnosis of pollen-induced asthma in a cohort of adults and pediatric individuals experiencing respiratory symptoms during the pollen season of July–September 2015. Cough was the predominant symptom. Although wheezing, cough, shortness of breath, chest tightness and nocturnal symptoms were all associated with

pollen-induced asthma, respiratory symptoms had a poor positive predictive value for diagnosing pollen-induced asthma in adults, indicating that assessing symptoms alone is not sufficiently reliable to identifying pollen-induced asthma cases even in a high-prevalence setting. In contrast, wheezing demonstrated good positive predictive value of 72.7% for diagnosing pollen-induced asthma in children.

Epidemiological studies of asthma are valuable for advancing our knowledge in asthma prevalence and risk factors, as well as to investigate asthma as a risk factor for the development of other disease such as COPD, lung cancer and pulmonary infections. An accurate and validated instrument to identify asthma cases is therefore crucial. Most studies have used symptoms to define asthma cases. In the Phase III study reports (2006) of the ISAAC, the rise in the prevalence of asthma in many countries is documented on the basis of positive answers to the written question: “Have you (has your child) had wheezing or whistling in the chest in the past 12 months?”^{10,11} In that study, other common symptoms such as shortness of breath, chest tightness and cough were not included, and asthma diagnosis was not validated. In a Swiss population-based study reported by Sistek et al,¹⁹ wheezing was the most sensitive symptom (75%) for an asthma diagnosis, defined as positive self-reported history of doctor-diagnosed asthma. Wheezing with dyspnea had the best, albeit modest, positive predictive value (24%).

Table 4 Sensitivity and specificity, together with positive and negative predictive values, of these respiratory symptoms for the diagnosis of pollen-induced seasonal asthma in adults and children

Clinical symptoms	Adults (n=160)				Children (n=132)			
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cough	90.6	32.8	26.4	92.9	88.6	27.1	38.4	82.3
Chest tightness	78.8	35.8	24.6	86.3	41.7	74.4	45.4	71.4
Shortness of breath	76.2	41.8	25.8	86.8	37.1	79.5	48.0	71.2
Wheezing	61.2	78.0	29.9	88.3	54.5	89.5	72.7	79.4
Nocturnal awakening due to breathlessness	55.6	67.7	28.4	85.1	32.6	84.1	51.2	70.9

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

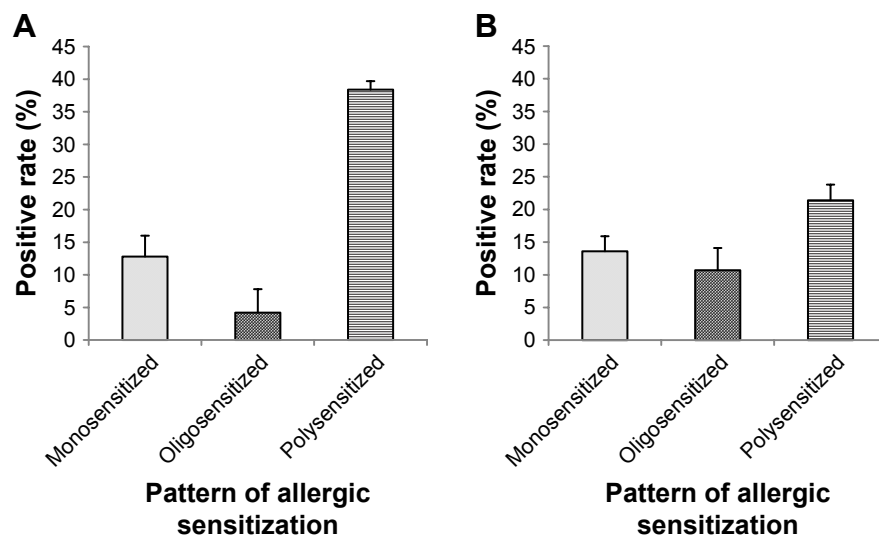


Figure 2 Pattern of allergic sensitization (by SPT) among adults (A) and children (B) sensitized to at least one allergen.

Notes: Monosensitized: sensitization to a single pollen allergen; oligosensitized: sensitization to two pollen allergens; polysensitized: sensitization to more than two pollen allergens.

Abbreviation: SPT, skin prick test.

Compared to the two studies described earlier, our study is novel because 1) it focuses on a unique phenotype of pollen-induced seasonal asthma, 2) patients were diagnosed with asthma by respiratory specialists using a careful, systematic approach combining symptoms, lung function and SPTs and 3) both adult and pediatric patients were included in the study. By including both children and adults, we found that wheezing was more specific for, and predictive of, pollen-induced asthma in children than in adults. One possible reason is that wheezing is a nonspecific symptom that can occur in a wide range of diseases, including COPD, bronchiectasis, endobronchial tumors, airway strictures, acute bronchitis and cardiac disease. These diseases increase in prevalence with increasing age and may explain the loss of specificity of wheezing for asthma in adults compared to children.

The optimal strategy for identifying pollen-induced asthma in adults in the setting of an epidemiological study remains unclear. The gold standard remains clinical assessment supplemented by spirometry and SPT positivity to pollen aeroallergens as in this study, but this approach is tedious and costly. Studies comparing symptoms versus symptoms supplemented by bronchoprovocation testing found that this led to increase in specificity but loss of sensitivity. Use of lung function tests and/or SPTs has important limitations: standardization is difficult especially in international studies, subjects may not be able to cooperate with the tests and their use may result in fewer participants. Future studies should take into account the potential pitfalls of using symptom questionnaires alone to identify asthma in adults,

who may require additional evaluation either clinically, with lung function tests or tests of allergic sensitization to reliably identify cases. Our results do indicate that wheeze is a good marker of disease in children and can be a useful measure in epidemiological studies.

In this study, we have also reported the profile of symptoms experienced by patients with pollen-induced asthma, and how the symptoms wax and wane over time. In both adults and children, cough was the most frequently reported symptom. Previous studies of asthma, but not specifically pollen-induced asthma, also found that cough was the most prevalent symptom. Zhang et al²⁰ surveyed children with asthma in 30 Chinese cities and found cough was the most predominant symptoms (91.3%), followed by wheezing (76.2%). Lin et al²¹ arrived at similar conclusions in adult patients, where cough was found in 66.3%. In a study involving multiple sites across six countries in the Asia-Pacific region, asthma accounted for one-third of patients seeking medical care for cough,⁸ confirming the magnitude of the burden of cough in asthma. Osman et al²² found that asthma patients rated cough as the symptom of the overriding concern. The current management for asthma emphasizes treating the underlying airway inflammation to reduce asthma symptoms but not specifically cough. Compared to other symptoms such as wheeze, chest tightness or dyspnea, cough may also respond less well to treatment with bronchodilators and cough is difficult to measure objectively in clinical practice. We propose that asthma patients may be well served by additional patient-centered interventions targeting cough.

This study has several limitations. First, response of symptoms to asthma treatment was not assessed due to cross-sectional design of the study. Second, severity and intensity of symptoms were not evaluated and therefore their association with indices of disease severity could not be determined. Third, the perception and reporting of symptoms may be culture specific and language specific and may not be generalizable to other populations. Fourth, there was a high prevalence of smoking among adults presenting with respiratory symptoms, a group which may represent the forme fruste of COPD. Fifth, our study preferentially selects asthmatics who seek contact with health services. In the literature, some studies have shown the influences of meteorological parameters and biological and chemical air pollutants to the incidence of asthma,^{23–26} which are not investigated in this study and must be considered in our future studies.

Conclusion

Cough was the predominant symptom in pollen-induced asthma. Wheezing had good positive predictive value for diagnosing pollen-induced asthma in children, but respiratory symptoms were poorly predictive of pollen-induced asthma in adults. In adults, a systematic approach integrating the analysis of symptoms, exposure to pollen, objective measurement on lung function and allergic sensitization is needed to accurately diagnose pollen-induced asthma.

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Author contributions

Conception and design: TTM, XYW and HZS. Data collection: TTM and YZ. Data analysis and interpretation: TTM and HYG. Drafting the manuscript: TTM and ACY. Editing and final approval of the manuscript: TTM, ACY, XYW and HZS. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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