

Characteristics of patients with seasonal allergic rhinitis and concomitant asthma

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Summary

Background Allergic rhinitis and asthma often co-exist and appear to produce a continuum of airway disease, but whether the clinical characteristics of asthma in patients with seasonal rhinitis differ from those of persistent asthma has not been examined.

Objective The aim of this retrospective study was to characterize the clinical features of patients with seasonal allergic rhinitis with concomitant asthma and to compare them with those in patients with persistent asthma.

Methods The patient populations for this study were derived from nine prospective, placebo-controlled planned clinical trials of similar design. Six studies (958 patients) enrolled patients with seasonal allergic rhinitis and concomitant asthma; three (607 patients) involved patients with persistent asthma. In all studies, patients were excluded from oral corticosteroid therapy in the preceding 3 months, and from inhaled corticosteroids in the preceding month.

Results Patients with seasonal rhinitis and asthma had a significantly ($P < 0.001$) higher total asthma symptom score than those with persistent asthma. In particular, cough was three times more severe. The need for β_2 -agonist as a rescue medication and the ratio of forced expiratory volume in 1 s/forced vital capacity (FVC) were similar in the two groups whereas forced expiratory fraction 25–75%/FVC was significantly ($P < 0.02$) reduced in the persistent asthmatics. Asthma and nasal symptom severity scores were correlated in patients with seasonal rhinitis and asthma ($P < 0.0001$).

Conclusions Patients with seasonal allergic rhinitis and concomitant asthma appear to differ from those with persistent asthma. A prospective study should be designed to discover whether patients with seasonal rhinitis and asthma may represent a distinct nosological entity, 'allergic airway disease'.

Keywords allergy, asthma, co-morbidity, pulmonary function, seasonal allergic rhinitis, symptom severity

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Introduction

Allergic rhinitis and asthma often co-exist and appear to produce a continuum of airway disease [1]. Despite increasing interest in the epidemiological, molecular, and environmental links between allergic rhinitis and asthma, there is a relative paucity of data in the literature describing the characteristics of asthma in patients with co-existing rhinitis and asthma symptoms. Seasonal exposure to pollens and/or moulds such as *Alternaria* and *Cladosporium* [2, 3] in allergic subjects induces intermittent or persistent rhinitis [1]. Some such patients present concomitant symptoms suggestive of asthma, like shortness of breath, wheezing and cough [4].

Much of our current understanding of the pathogenesis of seasonal asthma comes from mechanistic studies of the response to inhalation of allergen in the experimental or natural setting [5, 6]. In many patients with rhinitis, non-specific bronchial hyper-reactivity is seen during seasons of natural pollen or mould exposure and for some weeks thereafter [7, 8]. Bronchial inflammation has also been found to increase during the pollen season in patients with rhinitis [9], and true asthma exacerbations may occur in allergic patients naturally exposed to pollens [10, 11], especially during thunderstorms [12]. What is meant by 'seasonal asthma' is still unclear, however, since many patients with allergic rhinitis and chest symptoms (cough, wheeze, and/or shortness of breath) do not exhibit relevant airflow obstruction, do not demonstrate reversibility of forced expiratory volume in 1 s (FEV_1) following bronchodilator administration and do not have increased peak flow variability [13–15].

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Thus, despite the increased emphasis on the evaluation of rhinitis symptoms in patients with asthma and vice versa (as recommended by the allergic rhinitis and its impact on asthma (ARIA) guidelines), there is little information available regarding the phenotypic expression of asthma in patients with co-existing allergic rhinitis and asthma.

We performed the current retrospective study to compare the clinical features of patients with seasonal allergic rhinitis and concomitant asthma with those of patients with persistent asthma. The aim of this study was to assess whether asthma in patients with allergic rhinitis and concomitant asthma differed phenotypically from asthma in patients with persistent asthma. The patient populations for this study were derived from nine clinical trials of similar design. All studies were prospective, placebo-controlled planned analyses of symptoms and pulmonary function. Six studies (958 patients) enrolled patients with seasonal allergic rhinitis and concomitant asthma. The three remaining studies (607 patients) involved patients with persistent asthma, who were enrolled in the traditional manner irrespective of the presence of seasonal allergies. In all studies, patients were excluded from oral corticosteroid therapy in the preceding 3 months and from the use of any asthma 'controller' therapy (inhaled corticosteroids) in the previous month. The clinical features analysed included symptom scores, β_2 -agonist use and pulmonary function parameters. In patients with seasonal rhinitis and asthma, chest and rhinitis symptoms

were analysed statistically to assess whether any correlation existed between upper and lower airway symptom severity scores.

Methods

Patients

The entry criteria for the 958 patients with seasonal rhinitis and concomitant asthma were similar across studies (Table 1a). All patients had rhinitis and chest symptoms during the pollen or mould season. All patients had reversibility of airflow obstruction of at least an increase of 12% in FEV₁ over baseline values [16] assessed within the past 2 years. FEV₁ values ranged from 60% to 90% of predicted values [17]. Patients in one study had positive skin prick tests (SPTs) to seasonal allergens (pollens and/or moulds) prevalent during the study period, while patients in the other five studies had positive SPTs to pollens.

The entry criteria for the 607 patients with persistent asthma were similar across studies (Table 1b). All patients demonstrated reversibility of airflow obstruction with an increase in FEV₁ of $\geq 12\%$ over baseline values [16] within the past 2 years. FEV₁ values ranged from 55% to 85% of predicted values [17]. The presence of rhinitis or allergy was not an entry criterion for these persistent asthma studies and was not monitored.

Table 1. Entry criteria

Study	P95-090	P97-009	P95-233	P96-017	P00214	P00215
(a) Seasonal asthma and rhinitis (<i>n</i> = 958)						
Number of subjects	73	188	148	146	216	187
Enrolment date	August 1995	March 1997	April 1996	October 1996	Fall 1999	Fall 1999
Age	12–60	> 18	12–60	12–60	≥ 15	≥ 15
FEV ₁ (% predicted)	≥ 70%	70–90%	60–90%	60–90%	≥ 70%	≥ 70%
Nasal symptoms score	7.00	6.17	6.86	6.00	8.00	8.25
Smoking	Prohibited					
Skin prick tests	Pollens or molds	Pollens	Pollens	Pollens	Pollens	Pollens
ICS	Not allowed	Not allowed	Not allowed	Not allowed	Not allowed	Not allowed
Run-in	1 week	1 week	1 week	1 week	1 week	1 week
Bronchodilator/asthma*	≥ 2	≥ 1	≥ 2	≥ 2	≥ 2	≥ 2
Study	C96-136MF		C96-186MF		C98-475MF	
(b) Persistent asthma (<i>n</i> = 607)						
Number of subjects	185		257		165	
Enrolment date	October 1996		February 1997		December 1998	
Age	> 12		> 12		> 12	
FEV ₁ (% predicted)	55–85%		55–85%		55–85%	
Nasal symptoms score	Not evaluated		Not evaluated		Not evaluated	
Smoking	Prohibited		Prohibited		Prohibited	
Skin prick tests	Not done		Not done		Not done	
ICS	Not allowed		Not allowed		Not allowed	
Run-in	1–2 weeks		1–2 weeks		1–2 weeks	
Bronchodilator/asthma	Not specified		Not specified		> 3/week	

*Note: Daytime/nighttime frequency of asthma symptoms or frequency of bronchodilator use of a least 2, as based on the following scales.

Frequency of asthma symptoms: 0, none; 1, < weekly and/or on exercise only; 2, > weekly but not daily; 3, daily asthma symptoms or awakening due to asthma symptoms once per week; 4, daily asthma symptoms and/or awakening due to asthma symptoms > once per week.

Frequency of bronchodilator use: 0, none; 1, < weekly and/or for exercise induced bronchospasm only; 2, > weekly but not daily; 3, daily 1–4 puffs; 4, daily > 5 puffs.

ICS, inhaled corticosteroids; FEV₁, forced expiratory volume in 1 s.

Exclusion criteria for the study groups were as follows. Current smokers or ex-smokers who had smoked within the previous 6 months were excluded from the persistent asthma studies and from one of the six studies of seasonal rhinitis and concomitant asthma. Patients with a recent severe exacerbation of asthma or who required oral corticosteroids within the previous 3 months were excluded. In the month before enrollment none of the patients received inhaled corticosteroid controller therapy [16]. Specific immunotherapy was only allowed when the patients were on a stable maintenance schedule.

Ethics committees approved all studies and all patients gave their written informed consent.

Assessment of asthma severity

Airflow obstruction was assessed on day 1, and for 1 week thereafter patients were assessed using pulmonary function tests, symptoms scores and medication needs.

FEV₁, forced vital capacity (FVC) and forced expiratory fraction 25–75% (FEF_{25–75%}) were measured according to the American Thoracic Society guidelines. Because there was a gender difference between the two groups of patients, the results for FEV₁ were expressed both as absolute values and in percentages of predicted values. Peak expiratory flow (PEF) was measured using the Personal Best peak flow meter in the morning and the evening of each study day. The highest peak flow was recorded. PEF variability between morning and evening peak flow rates was assessed using the following formula:

$$\text{PEF variability} = \frac{\text{daily (max - min)} \times 100}{\text{daily mean}}$$

In all studies, symptoms of cough, wheezing, and shortness of breath and rescue use of β_2 -agonist were recorded. Chest symptoms were evaluated using a four-point scale from 0 (none) to 3 (severe). In the seasonal rhinitis and asthma group, rhinitis symptoms (nasal obstruction, rhinorrhea, sneezing, and nasal pruritus) were also recorded using a four-point scale from 0 (none) to 3 (severe). Total nasal symptom score (TNSS) was the sum of all four individual nasal symptom scores.

Statistical analysis

Data from the six studies of patients with seasonal rhinitis and asthma were pooled as the seasonal rhinitis and asthma group. The data from the three studies of persistent asthma were pooled as the control group for comparisons. All data were summarized by frequency or descriptive statistics.

For pulmonary function tests (FEV₁, FVC, forced expiratory fraction 25–75% (FEF_{25–75%}), and their derived ratios), baseline characteristics were defined as data recorded on day 1, while for patient diary data (PEF_{AM} and PEF_{PM}, β_2 -agonist use, severity of chest symptoms and severity of nasal symptoms), median weekly data were used.

We used non-parametric tests since the asthma symptoms were discrete variables (scale 0–3). The results are presented as medians and 25–75%. The differences between the seasonal rhinitis and asthma group and the persistent asthma population were compared using the Mann–Whitney *U*-test. The Spearman rank correlations of chest symptoms vs. pulmonary function were also tabulated.

Results

Demographics

Demographic results are presented in Table 2. Patients with seasonal rhinitis and asthma and those with persistent asthma had a similar age, weight, and duration of asthma. However, there was a significant difference in gender between groups.

Symptom severity

Patients with seasonal rhinitis and asthma had a significantly higher total chest symptom score than those with persistent asthma (Table 3). Median total chest symptoms normalized for FEV₁ were significantly higher in the seasonal rhinitis and asthma group than in the persistent asthma group (1.61 vs. 0.92, respectively; $P < 0.001$). The three individual chest symptoms (shortness of breath, wheeze, and cough) were significantly more severe in the seasonal rhinitis and asthma group than in the persistent asthma group ($P < 0.001$ for all scores). The largest difference was observed for cough, which was three times more severe in the seasonal rhinitis and asthma group than in the persistent asthma group. The interquartile range indicated that there was little overlap for cough severity between the two groups of patients. Cough symptom scores were not correlated with age in the seasonal rhinitis and asthma group ($\rho = 0.1$, NS).

Rescue medication

The need for β_2 -agonist as a rescue medication was similar in the two groups of patients (Table 3).

Table 2. Demographic summary

	Seasonal rhinitis and asthma	Persistent asthma	<i>P</i> -value
Gender			
Male	374 (39%)	286 (47%)	0.002
Female	584 (61%)	321 (53%)	
Age (years)			
Median	30	28	0.013
Q1–Q3	23–39	20–40	
Race			
Black	88 (9%)	60 (10%)	0.898
Caucasian	793 (83%)	499 (82%)	
Other	77 (8%)	48 (8%)	
Asthma duration (years)			
Median	14	13	0.284
Q1–Q3	7–24	7–22	
Rhinitis duration (years)			
Median	18	–	NA
Q1–Q3	10–26	–	
Height (in.)			
Median	66	66	0.215
Q1–Q3	64–69	64–70	
Weight (lb.)			
Median	164	164	0.734
Q1–Q3	135–198	136–194	

NA, not assessed.

Difference between two groups was compared using Mann–Whitney *U*-test.

Table 3. Symptoms and asthma medications

	Seasonal rhinitis and asthma	Persistent asthma	P-value
	Median (Q1–Q3)	Median (Q1–Q3)	
Shortness of breath	1.60 (1.00–2.00)	1.00 (0.50–1.50)	<.0001
Cough	1.33 (0.71–2.00)	0.43 (0.00–1.00)	<.0001
Wheezing	1.57 (1.00–2.00)	0.86 (0.33–1.29)	<.0001
Total chest score	4.46 (3.00–5.86)	2.43 (1.33–3.57)	<.0001
Total chest score/FEV ₁	1.61 (1.06–2.25)	0.92 (0.49–1.44)	<.001
β ₂ -Agonist use (puffs per day)	3.17 (1.71–4.86)	3.14 (1.86–5.00)	0.283

Difference between two groups was compared using Mann–Whitney *U*-test.

Pulmonary function tests

Pulmonary function parameters are presented in Table 4. The median percentage predicted FEV₁ was significantly lower in the persistent asthma group compared with the seasonal rhinitis and asthma group ($P < 0.001$), although the magnitude of the difference was small. Patients with persistent asthma also had significantly lower median FEF_{25–75%} ($P < 0.001$) compared with the seasonal rhinitis and asthma group. Similarly, the FEF_{25–75%}/FVC was significantly ($P = 0.019$) lower in the persistent asthma group vs. the seasonal rhinitis and asthma group, while the median ratio of FEV₁/FVC was similar between groups.

Median peak flow rates were significantly lower in patients with seasonal rhinitis and asthma than in those with persistent asthma (Table 4). Conversely, the median peak flow variability was slightly but significantly greater in patients with persistent asthma.

Correlation between nasal and chest symptoms in the seasonal rhinitis and asthma group

Correlations between nasal and non-nasal symptoms were studied in seasonal rhinitis and asthma patients. Asthma and nasal symptom severity scores were well correlated ($P < 0.0001$ for all individual and total symptom severity scores) (Table 5). The strongest correlation between asthma and nasal symptom severity scores was between total nasal and total asthma symptoms (Table 5 and Fig. 1).

Table 4. Pulmonary function parameters

	Seasonal rhinitis and asthma median (Q1–Q3)	Persistent asthma median (Q1–Q3)	P-value
FEV ₁ (% predicted)	77 (72–82)	74.7 (68.2–80.3)	<0.001
FEV ₁	2.65 (2.29–3.12)	2.59 (2.23–3.05)	0.016
FVC (l)	3.42 (2.9–4.18)	3.39 (2.85–4.16)	0.328
FEV ₁ /FVC	0.77 (0.71–0.84)	0.76 (0.69–0.84)	0.055
FEF _{25–75%} (l)	2.32 (1.88–2.91)	2.16 (1.70–2.79)	<0.001
FEF _{25–75%} /FVC	0.66 (0.51–0.88)	0.63 (0.47–0.84)	0.019
PEF am (l/min)	353 (301–418)	366 (316–437)	0.001
PEF pm (l/min)	365 (313–434)	387 (336–467)	<0.001
PEF variability (%)	8.0 (4.8–12.4)	8.5 (5.1–13.3)	0.044

Difference between two groups was compared using Mann–Whitney *U*-test. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF, forced expiratory fraction 25–75%; PEF, peak expiratory flow.

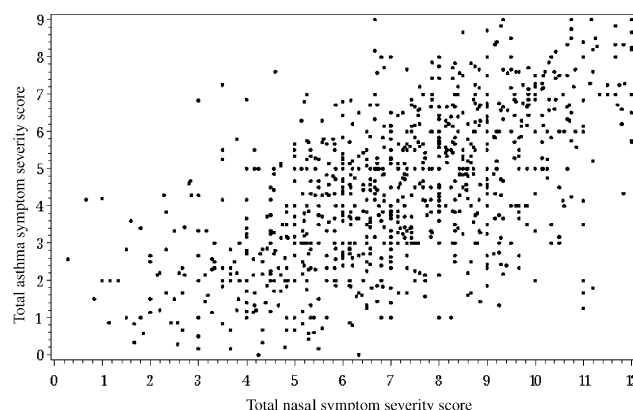
Table 5. Correlation coefficient between symptoms in patients with seasonal rhinitis and concomitant asthma

	Total chest symptom score	Cough	Wheeze	Shortness of breath
Total nasal symptom score	0.58	0.54	0.47	0.5
Rhinorrhea	0.49	0.45	0.39	0.43
Nasal obstruction	0.49	0.41	0.41	0.45
Sneezing	0.5	0.5	0.41	0.4
Pruritus	0.45	0.42	0.38	0.4
Total chest symptom score	1.0	0.81	0.89	0.88
Cough	0.81	1.0	0.55	0.53
Wheeze	0.89	0.55	1.0	0.76
Shortness of breath	0.88	0.53	0.76	1.0

Note: Correlation by Spearman's rank test, $P < 0.0001$ for all parameters.

Discussion

The current study shows that the clinical manifestations of asthma that occur concurrently with seasonal allergic rhinitis appear to differ from those with persistent asthma. Asthma symptoms scores, especially those for cough, are significantly higher and PEFs are lower in asthma associated with seasonal allergic rhinitis. In contrast to this, the percentage predicted FEV₁ and FEF_{25–75%} are significantly lower in those with persistent asthma. The essential difference between the groups in this study is that patients with seasonal allergic rhinitis and asthma have disproportionately severe symptoms for their degree of impairment of airflow obstruction. They exhibit significantly higher individual and total asthma symptom severity scores than do patients with persistent asthma. This difference in asthma symptoms, particularly cough, is not related to more severely impaired lung function, since FEV₁ and FEF_{25–75%} were significantly lower in the persistent asthma group. This observation suggests that the differences in symptom scores between them may be related to a poorer perception of symptoms – or a higher threshold for perception – in patients who have persistent disease [2, 18], in comparison with the keener discomfort provoked by relatively acute changes in airway calibre [19, 20]. Thus, the intermittent, short-lived disturbances in seasonal asthma and rhinitis patients may be perceived as being more severe than in persistent asthma for an equivalent degree of airway

**Fig. 1.** Correlation between total chest symptom scores and total nasal symptom scores. $\rho = 0.58$, $P < 0.0001$.

obstruction. An alternative explanation is that the site of obstruction may determine the severity of symptoms perceived by the patient; airflow obstruction in peripheral airways in persistent asthma could for some reason cause less distress than obstruction in larger calibre central airways.

As cough severity accounted for the largest symptomatic difference between the two groups, it deserves particular attention. Cough was three times more severe in the seasonal allergic rhinitis and asthma group as compared with the persistent asthma group, and there was little overlap between the two groups. Cough may result from rhinitis, sinusitis, post-nasal drip, asthma or gastroesophageal reflux [21] and in many patients, multiple causes of cough can be found [22]. Although the present study was not designed to address the cause of cough, our data showed that cough was approximately equally correlated with nasal symptoms as with wheezing or shortness of breath. It is possible, therefore, that the high cough symptom severity scores in patients with seasonal rhinitis and asthma occurred at least partly as a consequence of rhinitis. Interestingly, a recent study showed that capsaicin cough sensitivity was increased in allergic asthmatics during the birch pollen season [23], suggesting that the threshold for cough may be modulated by airway allergen exposure in allergic patients. Additionally, wheezing is not necessarily related to bronchial obstruction and may also arise from more proximal airways, such as, in tracheal obstructive diseases [24].

The clear-cut difference between the groups in terms of asthma symptom severity was not mirrored by their pulmonary function test profiles. Despite having higher asthma symptom scores than their persistent asthma counterparts, patients with seasonal rhinitis and asthma did not exhibit more profound airflow obstruction, as evidenced by a similar median FEV₁/FVC ratio in the two groups. However, the lower FEV_{25–75%}/FVC in patients with persistent asthma indicates that the site of airflow obstruction may differ between the groups, potentially being localized to peripheral airways in persistent asthma [25] and to proximal/central airways in seasonal rhinitis and asthma.

The strong correlation between chest symptoms and rhinitis (particularly between cough and rhinitis symptoms) in the seasonal rhinitis and asthma group suggests that a continuum of disease exists throughout the upper and the lower airways in these patients. The recent progress achieved in the cellular and molecular biology of airways diseases has clearly documented that inflammation plays a critical role in the pathogenesis of both asthma and rhinitis. The same inflammatory cells and mechanisms appear to be active in the nasal and bronchial mucosa [26]. Natural exposure to pollen during the season provokes an increase in airway responsiveness in non-asthmatic subjects with seasonal allergic rhinitis and also induces inflammatory cell recruitment and IL-5 expression, leading to bronchial inflammation [9]. Nasal allergen provocation induces inflammation in upper and lower airways [27]. Studies support the critical involvement of the bone marrow in the development of eosinophilic inflammation of the airways and emphasize the systemic nature of these conditions [28]. Allergens causing nasal allergic activity can induce post-nasal drip that seeds the airways – especially the large proximal airways – with inflammatory mediators, thus inducing symptoms through

irritant receptor stimulation [29]. Pollen particles have generally been considered too large to penetrate into the lower respiratory tract. Such grains were therefore believed to be unable to induce an immunological response in the lower respiratory tract. There is evidence, however, that a small percentage of large particles (20–30 µm) may penetrate into the peripheral areas of the lung [30]. It also appears that small airborne units of less than 5 µm with the same antigenic activity as pollen may contribute to inhaled allergen burden [12]. Pollen asthma probably results, therefore, from the gradual accumulation of small amounts of allergenic material deposited in lower airways [30].

While the findings of this study in terms of the apparent differences in asthma phenotypes between the study groups are novel and potentially important, some limitations to this study require discussion. The study is retrospective in design and suffers from the drawbacks of all similar studies, mainly in relation to difficulties in ensuring the homogeneity and comparability of the respective comparator groups. Such issues were overcome partly by constituting the study database purely from strictly designed, high-quality, prospective, placebo-controlled studies. The groups were well balanced for relevant demographic and asthma criteria, and a large total population was gathered (>1500 patients) to add robustness to the dataset. A specific confounding issue was the inclusion of smokers in the seasonal rhinitis and asthma group, and it could be suggested that higher cough symptom severity scores were due to smoking-induced cough caused by chronic bronchitis [21]. We note, however, that most patients were under 40 years of age and would, therefore, be unlikely to include many patients with established smoking-induced lung disease, and we found no correlation in the study between age and cough. Clearly, it would be important to exclude smokers from future studies examining upper-lower airway links to remove any possible confounding effect. The database purposely included patients with age and FEV₁ values that were comparable across the two groups of patients. While there was an age difference between the two groups, this was small and unlikely to be clinically significant (28 and 30 years). There was a difference in gender distribution between the groups, thus necessitating the expression of pulmonary function test data in terms of percentage of predicted values. Gender has been shown possibly to influence the reporting of symptoms [31], but the influence is small and could not account for the large magnitude of differences observed between the study groups. As symptoms were not recorded year-round, some patients with seasonal rhinitis and asthma may have had symptoms persisting throughout the year. Similarly, as pollen counts were not available for all centres in all studies, it was not possible to assess the potential impact of different levels of pollen exposure on symptomatology. Rhinitis and allergen skin test positivity were not assessed in the persistent asthma group. Given that most asthmatic patients have concomitant rhinitis [1], it appears likely that most patients in this group had either intermittent or persistent rhinitis. On the other hand, patients with seasonal rhinitis and asthma may not necessarily have intermittent disease. A recent study in over 3000 patients seen in general practice in France, found that approximately 50% of patients with seasonal allergic rhinitis have persistent rhinitis as defined by ARIA [32]. As the

studies included in the database were performed before the advent of ARIA, the presence, severity and chronicity of rhinitis in both study groups was not recorded under the reclassified system. We would argue, however, that the clear differences noted between the groups in terms of asthma symptom severity (chiefly, but not limited to, cough) and pulmonary function parameters in a large, well-defined population are valid and outweigh the inherent and specific limitations of this type of retrospective analysis.

The current study suggests strongly that the clinical characteristics of asthma associated with seasonal allergic rhinitis differ from persistent asthma. In asthma associated with seasonal rhinitis, the increase in chest symptoms, particularly cough, which was disproportionately larger than the objective lung function impairment, and the close association between asthma and nasal symptoms have three important implications. Firstly, they emphasize the close – possibly causal – association between rhinitis and asthma. Secondly, they raise the possibility that the course or natural history of asthma associated with seasonal allergic rhinitis is different from that of persistent asthma. Thirdly, they suggest that there may be heterogeneity in terms of responses to therapy, particularly with respect to treatments that control nasal inflammation. Our findings are in accord with the recent ARIA guidelines [1]; patients presenting with rhinitis should be assessed for asthma, and patients presenting with asthma should be assessed for rhinitis. The results of this study are novel and provide an important indication of a heterogeneity amongst asthma patients in terms of symptom severity that appears to be related to seasonality and/or concomitant upper airway allergic disease. We believe that the findings of this study warrant discussion among clinicians and researchers regarding the nature of future prospective studies designed to determine whether patients with seasonal rhinitis and concomitant asthma represent a specific nosologic entity, 'allergic airway disease.'

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