

Original article

Rhinoconjunctivitis, bronchial responsiveness, and atopy as determinants for incident non-work-related asthma symptoms in apprentices exposed to high-molecular-weight allergens

Objective: The aim of this study was to explore the role of rhinoconjunctivitis (RC), taking into account atopy and the level of bronchial responsiveness to methacholine, on the incidence of respiratory symptoms and in the development and/or worsening of asthma.

Methods: We examined data from a prospective study in 769 students starting exposure to high-molecular-weight occupational allergens and who were serially followed for up to 44 months.

Results: The presence of RC symptoms at baseline was significantly associated with an increased risk of developing shortness of breath and wheezing in atopic subjects regardless of PC20 level and in subjects with a $PC20 \leq 32$ mg/ml regardless of atopic status. RC symptoms were significantly associated with the development of exercise-induced respiratory symptoms. Multivariate analyses indicated that having a measurable PC20 was significantly associated with the incidence of all respiratory symptoms studied, whereas baseline seasonal RC was associated only with incident exercise-induced respiratory symptoms; atopy played a minimal role, and only through an interaction with seasonal RC.

Conclusion: Of the three potential factors for the development of respiratory symptoms that we considered, i.e. RC symptoms, having a measurable PC20 and atopy, having a measurable PC20 is the most significant one.

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Recent reviews have covered the topic of the association between rhinitis and asthma (1, 2). There is evidence that 'rhinitis and asthma represent a continuum of disease' (3, 4). Prospective epidemiological studies have shown that hay fever (5) and perennial rhinitis (6, 7) or allergic rhinitis (seasonal and nonseasonal) (8, 9) are risk factors for the development of asthma.

Possible confounders in the association of rhinitis and asthma are atopy and the level of bronchial responsiveness. Atopy is an independent risk factor for rhinitis and asthma (10), but it is not known whether atopy modulates the association between rhinitis and asthma. Bronchial hyperresponsiveness is a key factor of asthma. A frequently used definition of asthma in epidemiological studies includes the association of asthma symptoms together with bronchial hyperresponsiveness (11, 12). Borderline or mild bronchial hyperresponsiveness can

also be associated with rhinitis (13, 14). It is unknown, however, whether rhinitis symptoms are a risk factor for the development of bronchial hyperresponsiveness or asthma defined by the association of symptoms and bronchial hyperresponsiveness. Nor do we know if the level of bronchial responsiveness and rhinitis are independent risk factors for the onset of respiratory symptoms and asthma. It has been shown that some subjects with apparently asymptomatic bronchial hyperresponsiveness develop asthma symptoms (15).

In recently published studies (16–19), we examined the development of immunological sensitization, occupational asthma and rhinitis in apprentices exposed to high-molecular-weight agents. The same apprentices were also serially questioned on general rhinoconjunctivitis (RC) and respiratory symptoms occurring in the general environment, i.e. out of the workplace; these data are being analysed here. We, therefore, sought to examine the development of asthma and its symptoms in subjects with prevalent RC symptoms according to the atopic status and the level of bronchial responsiveness.

Abbreviations: FEV1, forced expiratory volume in 1 s; PC20, concentration of methacholine in milligrams per millilitre causing a fall of 20% in FEV1; RC, rhinoconjunctivitis.

Material and methods

Subjects, study design and testing

The baseline characteristics of the apprentices, who started exposure to high-molecular-weight allergens between 1993 and 1995 as pastry-makers, animal health technicians and dental hygienists, have been described (20). Briefly, 769 students entered a training programme for these professions. These students were re-assessed 20, 32 and 44 months after beginning their programme in the case of animal health technology ($n = 417$), 20 and 32 months in the case of dental hygiene technology ($n = 122$), and 8 and 16 months for pastry-making ($n = 230$). On entry into the apprenticeship programme and at each follow-up visit, besides specific questions on occupational-related symptoms used in other studies (16–19), a standardized general respiratory questionnaire was administered (21). The recorded symptoms were sneezing; a runny or stuffy nose; itchy or watery eyes on exposure to house dust or pets, and the same symptoms during the pollen season; an itchy or runny nose in the absence of a cold; the nose blocked regularly in the morning or during the day; and episodes of shortness of breath, cough, wheezing and/or chest tightness. Skin tests with common inhalants were performed at baseline. In addition, bronchial responsiveness to methacholine was assessed at baseline in all students ($n = 689$) and at one or more follow-up visits in a subsample of 304 subjects (those who developed immunological sensitization to a work-related allergen and two controls per case matched on atopy, baseline PC20, i.e. ≤ 16 vs > 16 mg/ml, and school attended) using a standardized, though shortened methodology (output of the Wright's nebulizer = 0.14 ml/min) (22).

Analysis of results

Rhinitis was defined as *seasonal rhinitis* if one or more nasal symptom was present on exposure to pollen, as *animal rhinitis* if one or more nasal symptom was reported on exposure to pets, as *non-infectious rhinitis* when an itchy or runny nose occurred in the absence of a cold, and as *persistent rhinitis* when the nose was regularly blocked. *Seasonal conjunctivitis* and *animal conjunctivitis* were defined as the presence of itchy or watery eyes on exposure to pollen and pets, respectively. *Rhinoconjunctivitis* was defined as the presence of at least one symptom of rhinitis or of conjunctivitis. Bronchial hyperresponsiveness to methacholine was determined to be significant at a level of the provocative concentration causing a change in FEV1 of 20% (PC20) of ≤ 16 mg/ml (23), and a measurable PC20 at ≤ 32 mg/ml. Significant decrease in PC20 was set in the occurrence of a ≥ 3.2 -fold difference in PC20 (24) or, if subjects had a PC20 > 32 mg/ml, at the baseline visit and a change to a value ≤ 16 mg/ml. A positive skin test reaction was defined as a wheal ≥ 3 mm in the absence of reaction to the diluent and in the presence of a positive reaction to histamine phosphate. Atopy was present if there was an occurrence of two or more immediate reactions by prick testing to 11 common inhalants (16). Incident cases of asthma were identified if there was at least one incident symptom (shortness of breath, wheezing, chest tightness, exercise-induced respiratory symptoms) and significant changes in PC20, as proposed (11).

Cox proportional hazards models were used to evaluate the effect of a history of seasonal RC, animal RC, persistent rhinitis and noninfectious, nonallergic rhinitis (main risk factors) at entry in the cohort, on the risk of occurrence of shortness of breath, wheezing, exercise-induced respiratory symptoms or asthma; the time variable was defined as the difference between time of first occurrence of a given event and time of entrance into the programme. Use of the Cox model took into account the variable duration of follow-up

between the three groups. Fixed covariates in the analyses were assessed at baseline: atopy, PC20 (≤ 32 vs > 32 mg/ml) respiratory symptoms including shortness of breath, wheezing, exercise-induced respiratory symptoms and chest tightness. For these fixed covariates, the proportionality assumption was tested using Harrell's procedure on Schoenfeld residuals as provided in S-PLUS. A first series of analyses were performed for each form of RC symptoms separately and stratifying by one covariate at a time. A second series were used to estimate the effect of each type of RC symptoms on the occurrence of asthma stratifying for PC20 level and prevalence of respiratory symptoms at baseline. Subsequently, the effect of baseline seasonal RC, animal RC, nonallergic, noninfectious rhinitis on the occurrence of wheezing, shortness of breath or exercise-induced respiratory symptoms was assessed in three Cox proportional hazards models; in each model, atopy and PC20 level were taken into account and interactions between the main risk factors and the covariate were examined. Rate ratios and 95% confidence intervals were estimated. Statistical analyses were performed using the SPSS software package (version 9.1 for Windows, Chicago, IL, USA).

Results

Baseline characteristics of the subjects

Table 1 gives some baseline characteristics, relevant to the current study, for the 689 students who had the questionnaire, skin-prick tests, and assessment of bronchial responsiveness to methacholine on entry into the cohort and at least one follow-up assessment by questionnaire. The majority were young women and atopy was frequent. Nearly 35% of the subjects stated that they had RC symptoms on contact with pets. One type or another of RC symptoms was present in 44.4% of subjects. Respiratory symptoms at rest were present in 1.6–12.2% depending on symptoms, and respiratory symptoms on exercise were more frequent, occurring in almost one-fourth of subjects. Nearly one-third of subjects had what we considered a measurable PC20 (PC20 ≤ 32 mg/ml, the highest concentration administered) and slightly more than one-fourth, which has been considered as significant bronchial hyperresponsiveness, i.e. PC20 ≤ 16 mg/ml (23). Prevalence of atopy, atopic symptoms including rhinoconjunctivitis and bronchial responsiveness at baseline were not significantly different in the three programmes. The incidence of respiratory symptoms varied from 3.9% in the case of chest tightness to 12.0% in the case of wheezing. The incidence of symptoms (shortness of breath, wheezing and exercise-induced symptoms) expressed in person-years was as follows: animal technicians: 1.3, 1.78 and 1.57%; bakers: 5.36, 8.65 and 7.69%; dental hygienists: 1.92, 7.69 and 4.57%, respectively.

Association between baseline RC symptoms and incidence of respiratory symptoms according to the atopic status

Table 2 shows the association between prevalent seasonal and any type of RC symptoms at baseline and the

Table 1. Relevant baseline characteristics and incidence of respiratory symptoms at follow-up in the 689 participants

	Number	%
Sex (M/F)	100/589	14.5/85.5
Age (mean $\pm$ SD)	21.9 $\pm$ 6.8	—
Nonsmokers/smokers	587/102	85.2/14.8
Atopy	292	42.4
<i>Rhinoconjunctivitis symptoms</i>		
Seasonal rhinitis	152	22.1
Seasonal conjunctivitis	161	23.4
Seasonal rhinoconjunctivitis	183	26.6
Rhinitis symptoms out of the pollen season	74	10.7
Rhinitis symptoms in contact with pets	239	34.7
Conjunctivitis symptoms in contact with pets	30	4.4
Rhinoconjunctivitis symptoms in contact with pets	240	34.8
Any type of rhinoconjunctivitis symptoms	383	44.4
<i>Respiratory symptoms</i>		
Asthma (physician-based diagnosis)	72	10.4
Shortness of breath*	53	7.7
Chest tightness*	11	1.6
Wheezing*	84	12.2
Respiratory symptoms by inhaling cold air*	72	10.4
Respiratory symptoms on exercise*	94	24.2
<i>Levels of bronchial responsiveness</i>		
In all subjects		
PC20 $\leq$ 32 mg/ml	263	39.6
PC20 $\leq$ 16 mg/ml	202	30.4
In those with follow-up PC20 results ($n = 304$)		
PC20 $\leq$ 32 mg/ml	92	30.6
PC20 $\leq$ 16 mg/ml	80	26.6
<i>Incidence of respiratory symptoms</i>		
Shortness of breath	45	6.5
Chest tightness	27	3.9
Wheezing	83	12.0
Respiratory symptoms by inhaling cold air	59	8.6
Respiratory symptoms on exercise	67	9.7

* In the previous 12 months.

incidence of selected respiratory symptoms according to the atopic status. Any type of baseline RC symptom was associated with the incidence of shortness of breath and wheezing, with the risk being significant only in atopic subjects. Incident exercise-induced symptoms were significantly associated with seasonal and any type of RC at baseline in both atopic and nonatopic subjects. Significant rate ratios with the same order of magnitude were found when examining the effect of RC symptoms in contact with pets; the effect of atopy on the associations was comparable.

Association between baseline RC symptoms and incidence of respiratory symptoms according to bronchial responsiveness

In Table 3, we present the same association as in Table 2, but stratified for measurable PC20. It can be seen that RC symptoms were significantly associated with the incidence of shortness of breath and wheezing only in subjects with a measurable PC20. However, RC symptoms at baseline were significantly associated with the incidence of exercise-induced respiratory symptoms in subjects both with

and without a measurable PC20; when considering seasonal RC alone, the risk of developing this respiratory outcome was significantly increased only in subjects with a PC20 > 32 mg/ml.

Association between baseline RC symptoms and development or persistence of asthma

Table 4 shows that having RC symptoms slightly but significantly increased the risk for developing asthma in those with either PC20 ≤ 16 mg/ml or symptoms, and in those with PC20 > 16 mg/ml and without symptoms, but not in those subjects who had both features at baseline. Moreover (results not presented in Table 4), baseline RC symptoms were significantly associated with the incidence or worsening of asthma as defined by incident respiratory symptoms and change in bronchial responsiveness, this being the case for seasonal RC (RR = 2.01, 95%CI = 1.14–3.56) and any type of RC symptoms (RR = 3.57, 95%CI = 2.06–6.18). After stratifying the 304 apprentices according to their atopic status, RRs, although no longer significant, were higher in nonatopic than in atopic subjects.

Results of the multivariate analysis

A summary of the results of the multivariate Cox regression analysis is presented in Table 5, with RC symptoms divided into seasonal, animal-induced and nonallergic–noninfectious. Having a measurable PC20 at baseline remained significantly associated with the development of all symptoms considered. Having seasonal RC at entry was significantly associated with the development of symptoms on exercise. When considering possible interaction between factors (RC symptoms in contact with pets, seasonal RC, atopy, measurable PC20), we found that some factors significantly enhanced the risk for developing respiratory symptoms (over the effect of PC20 alone); however, having seasonal RC at baseline and a measurable PC20 yielded a risk that was significantly lower than the addition of the risks associated with the two factors considered by themselves (negative interaction).

Discussion

Atopy, RC and bronchial responsiveness are all known contributing factors for the development of asthma. Atopy and the level of IgE were long ago identified as risk factors, as reviewed in Ref. (25). Although it has also long been known that asthmatic subjects frequently have RC symptoms, their association has recently garnered greater interest in the context of prospective epidemiological studies, as reviewed in Ref. (3). Finally, publications on the role of bronchial hyperresponsiveness in the subsequent development of respiratory symptoms

Table 2. Association between baseline rhinoconjunctivitis (RC) symptoms and respiratory outcomes according to atopic status

		Respiratory outcome				
			Present			
Atopy	Seasonal RC	Absent	Baseline	F-up	RR	95% CI
<i>Shortness of breath</i>						
Present	Present	99	31	18	2.29	1.07–4.90*
Present	Absent	125	10	9		
Absent	Present	32	1	2	1.29	0.31–5.38
Absent	Absent	335	11	16		
<i>Wheezing</i>						
Present	Present	73	52	43	3.49	2.08–5.87*
Present	Absent	111	15	18		
Absent	Present	28	6	1	2.0	0.9–4.46
Absent	Absent	310	30	22		
<i>Exercise-induced respiratory symptoms</i>						
Present	Present	84	40	24	1.66	0.94–2.92
Present	Absent	110	17	17		
Absent	Present	26	4	5	2.53	1.02–6.23*
Absent	Absent	308	33	21		
Any type of RC						
<i>Shortness of breath</i>						
Present	Present	153	34	24	3.34	1.04–10.77*
Present	Absent	71	7	3		
Absent	Present	84	6	5	1.20	0.47–3.49
Absent	Absent	283	6	13		
<i>Wheezing</i>						
Present	Present	118	52	41	3.09	1.38–9.69*
Present	Absent	66	9	6		
Absent	Present	75	8	12	1.65	0.86–3.16
Absent	Absent	263	15	24		
<i>Exercise-induced respiratory symptoms</i>						
Present	Present	129	48	34	2.15	1.0–4.61*
Present	Absent	65	9	7		
Absent	Present	72	13	10	2.12	1.0–4.49
Absent	Absent	262	24	16		

Four groupings defined according to atopic status and baseline rhinoconjunctivitis symptoms. Estimates of rate ratios (RR) with 95% confidence intervals (CI). * $P \leq 0.05$. 'Any type of RC' stands for seasonal RC and/or animal RC, and/or nonspecific RC. F-up = follow-up.

were examined by Jansen and colleagues (26). Zhong and collaborators (27) found that 20% of adolescents with bronchial hyperresponsiveness developed asthmatic symptoms during 2 years of follow-up. Laprise and co-workers (15) found that 14% of 30 subjects with asymptomatic bronchial hyperresponsiveness developed asthmatic symptoms during 3 years of follow-up. A prospective study showed that airway hyperresponsiveness increased the likelihood for the development of respiratory symptoms by an OR of 3.67 (95%CI = 1.75–7.67), but only in the presence of significant blood eosinophilia.

We were interested in the possible interaction effect of RC symptoms and atopy, on the one hand, and of RC symptoms and bronchial responsiveness, on the other, on the incidence of respiratory symptoms suggestive of asthma. Results of the univariate analysis that we performed are in accordance with those published by others in which baseline RC symptoms have been

associated with incident respiratory symptoms both in atopic and nonatopic subjects (6, 7, 10). The fact that our results did not generally reach statistical significance in the cases of shortness of breath and wheezing, but did in the case of exercise-induced respiratory symptoms, might be explained by the clinical evidence that respiratory symptoms on exercise are a more sensitive marker for asthma than are symptoms at rest. Multivariate analysis carried out by incorporating RC, measurable PC20 and atopy in the model, which, to the best of our knowledge, was not done in other studies, showed that seasonal RC was significantly associated with the development of exercise-induced respiratory symptoms and that having both atopy and seasonal RC had an enhancing effect on the risk of developing shortness of breath and wheezing. Interestingly, the effect of these factors on the development of asthma symptoms is therefore not only additive but, in certain cases, it potentiates the effect of having a measurable PC20.

Table 3. Association between baseline rhinoconjunctivitis (RC) symptoms and respiratory outcomes according to baseline bronchial responsiveness status

Measurable PC20	Seasonal RC	Respiratory outcome			RR	95% CI
		Absent	Present			
			Baseline	F-up		
<i>Shortness of breath</i>						
Present	Present	56	24	17	2.08	1.10–3.92*
Present	Absent	119	17	15		
Absent	Present	63	7	2	0.99	0.22–4040
Absent	Absent	311	2	10		
<i>Wheezing</i>						
Present	Present	33	35	29	2.15	1.40–3.29*
Present	Absent	97	27	27		
Absent	Present	57	8	7	2.13	0.91–4.96
Absent	Absent	295	12	16		
<i>Exercise-induced respiratory symptoms</i>						
Present	Present	44	33	20	1.66	0.98–2.80
Present	Absent	95	33	22		
Absent	Present	56	10	6	2.98	1.12–7.80*
Absent	Absent	298	15	10		
	Any type of RC					
<i>Shortness of breath</i>						
Present	Present	91	31	25	2.80	1.27–6.19*
Present	Absent	84	10	7		
Absent	Present	129	8	3	0.64	0.18–2.33
Absent	Absent	245	1	9		
<i>Wheezing</i>						
Present	Present	59	48	40	2.20	1.33–3.63*
Present	Absent	71	14	16		
Absent	Present	118	11	11	1.75	0.79–3.85
Absent	Absent	234	9	12		
<i>Exercise-induced respiratory symptoms</i>						
Present	Present	70	47	30	1.89	1.06–3.39*
Present	Absent	69	19	13		
Absent	Present	117	13	10	3.19	1.19–8.57*
Absent	Absent	237	12	6		

Four groupings defined according to bronchial responsiveness status and baseline rhinoconjunctivitis symptoms. Estimates of rate ratios (RR) with 95% confidence intervals (CI).

* $P \leq 0.05$. 'Any type of RC' stands for seasonal RC and/or animal RC, and/or nonspecific RC. F-up = follow-up.

In analyses stratified according to whether or not there is a measurable PC20 at entry, seasonal RC or any type of RC at baseline was significantly associated with incident shortness of breath and wheezing in those with a PC20 ≤ 32 mg/ml at baseline, whereas a significant increased risk was present with exercise-induced symptoms regardless of the level of PC20 at baseline.

According to the multivariate analyses where all the studied factors were considered, the independent effect of seasonal RC remained present only for the incidence of exercise-induced respiratory symptoms, but the effect of RC was no longer significant for shortness of breath and wheezing after controlling for measurable PC20. In two cohorts of adults followed prospectively for 3 years, it was also found that higher degrees of bronchial responsiveness were associated with incident respiratory symptoms (28, 29). However, in these studies, RC symptoms and atopy were not examined concomitantly.

When considering interaction between factors (RC symptoms in contact with pets, seasonal RC, atopy, measurable PC20), we found that some provided an enhancement (significantly more than the effect of PC20 alone) of the risk for developing respiratory symptoms with one exception, that is, having seasonal RC at baseline and a measurable PC20 yielded a risk that was significantly lower than the addition of the risks associated with the two factors considered by themselves. The only explanation for the significantly reduced effect of these two factors combined might be that seasonal RC symptoms play an intermittent role whereas RC symptoms in contact with pets have a year-round effect, thus making them more likely to interact.

In a subgroup of subjects, we examined the incidence and/or worsening of asthma using the proposed epidemiological definition of asthma (11), that is, a combination of a respiratory symptom and increased bronchial responsiveness to assess the effect of RC symptoms. By

Table 4. Association between baseline rhinoconjunctivitis (RC) symptoms and development or persistence of asthma* in a subgroup of 304 subjects with a follow-up assessment of PC20, by distinguishing those with either bronchial hyperresponsiveness or asthma symptoms at baseline assessment, those with both features and those with neither feature

	Asthma*		PC20 Not done	RR	95% CI
	Present	Absent			
<i>Seasonal RC</i>					
PC20 ≤ 16 mg/ml or one or more symptoms					
Present	19	19	41	1.55	1.10–2.19
Absent	14	48	95		
PC20 ≤ 16 mg/ml and presence of symptoms				1.02	0.79–1.31
Present	11	31	21		
Absent	10	30	24		
PC20 > 16 mg/ml and absence of symptoms				1.30	1.02–1.66
Present	6	17	50		
Absent	4	95	234		
<i>Any type of RC</i>					
PC20 ≤ 16 mg/ml or one or more symptoms					
Present	27	30	63	1.63	1.24–2.15
Absent	6	37	73		
PC20 ≤ 16 mg/ml and presence of symptoms				1.07	0.83–1.38
Present	15	40	29		
Absent	6	21	16		
PC20 > 16 mg/ml and absence of symptoms				1.22	1.04–1.43
Present	8	32	101		
Absent	2	80	183		

* Asthma defined as at least one incident respiratory symptom and PC20 ≤ 16 mg/ml at follow-up. Estimates of rate ratios (RR) with 95% confidence intervals (CI).

Table 5. Results of the multivariate Cox regression analyses to estimate rate ratios (RR) and 95% confidence intervals (CI) for the incidence of three selected respiratory symptoms suggestive of asthma according to RC symptoms, measurable PC20 and atopy

	Symptom incidence estimated by RR with 95% CI		
	Shortness of breath	Wheezing	Exercise-induced respiratory symptoms
Number of subjects (%) with symptoms	113 (16.4%)	187 (27.1%)	177 (25.7%)
Factors			
Measurable PC20	2.50 (1.56–4.01)	2.36 (1.64–3.40)	2.58 (1.70–3.90)
Seasonal RC	NS	NS	2.48 (1.58–3.89)
Atopy	NS	NS	NS
Interaction terms			
RC in contact with pets × measurable PC20	1.53 (0.92–2.52)	1.81 (1.22–2.69)	1.73 (1.14–2.63)
Seasonal RC × measurable PC20	0.47 (0.21–1.02)	NS	0.56 (0.31–0.99)
Atopy × seasonal RC	2.44 (1.62–3.69)	2.02 (1.47–2.79)	NS

taking a more stringent approach to defining asthma than had been used in the studies cited above, we confirmed that RC symptoms had a significant impact on the development of asthma in the whole population, with the risk of developing asthma greater in nonatopic than in atopic subjects (although the RRs were not significantly increased in either group). As regards the development of asthma alone, RC symptoms represented a small though significant risk factor only among those with either increased bronchial responsiveness or respiratory symptoms and in those with neither feature at baseline, with the latter subjects showing a lower risk.

Our sample was not randomly selected from the general population. We acknowledge that there is a possibility of an enhancing effect of developing symptoms

due to the general environment in subjects exposed to sensitizing agents at work. There could also be a possibility of contamination in answering questions related to the general environment, on the one hand, and to the workplace environment, on the other. Prevalence rates of RC symptoms, atopy and bronchial responsiveness were similar on entry in the three programmes. However, respiratory symptoms on entry into the cohort were commoner in apprentices in baking (20), possibly because the subjects attending this programme were older and included fewer nonsmokers. If the incidence of wheezing and exercise-induced symptoms was not significantly different in the baking programme than within dental hygienists, animal handlers developed significantly fewer incident symptoms than the two other

groups. These differences in incidence of respiratory symptoms according to the programmes, though significant, are difficult to interpret and might just reflect the small number of incident cases when the analysis is carried out for each programme and/or the different idiosyncrasies of students selecting heterogeneous programmes.

In conclusion, this study confirms the role of RC in the development of asthmatic symptoms and of asthma. Its interaction with bronchial responsiveness, more than with atopy, is significant. Paying attention to atopy and RC symptoms is surely justified in the course of prospective epidemiological studies of asthma and clinical management of patients who may present with isolated atopy

and/or RC symptoms; however, our results suggest that assessing bronchial responsiveness seems even more relevant.

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