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ORIGINAL PAPER

Allergic rhinitis and asthma comorbidity: ARIA classification of rhinitis does not correlate with the prevalence of asthma

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Clinical and Experimental Allergy

Summary

Background Allergic rhinitis and asthma comorbidity is supported by both the similar underlying pathogenesis and immunologic mechanisms. The aim of this study was to verify whether the characteristics of rhinitis classified according to the new Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines correlate with the prevalence of asthma.

Methods From 1 March to 30 June 2002, a multi-centre cross-sectional study was conducted by 154 allergists chosen from throughout Italy. Duration, severity of rhinitis (according to the ARIA classification) and the type of allergic sensitizations were compared with the prevalence of asthma.

Results One thousand three hundred and twenty-one consecutive rhinitis-allergic patients aged 18 years or older were enrolled for the study. The majority of patients, 1060 (80.24%), were on medication at the time of their specialist visit. Mild intermittent rhinitis was diagnosed in 7.7% of patients, moderate/severe intermittent in 17.1%, mild persistent in 11.6%, and moderate/severe persistent in 63.6%. The prevalence of asthma was 48% in patients with mild intermittent rhinitis, 49.6% in moderate–severe intermittent rhinitis, 36.6% in mild persistent rhinitis and 47.5% in moderate severe persistent patients. No correlation between the ARIA categories of rhinitis and the prevalence of asthma was found.

A multivariate analysis, after adjustment for age, sex, type of sensitization, level of severity and duration of rhinitis classified according to the ARIA guidelines, demonstrated that age, over 41 years [risk ratio (RR) 1.260, 95% confidence interval (CI) 1.072–1.482] and especially over 51 years (RR 1.460, 95% CI 1.237–1.723), sensitization to indoor allergens (mite and cat), (RR 1.203, 95% CI 1.060–1.366), and polysensitization (RR 1.178, 95% CI 1.004–1.383) are significant risk factors for asthma.

Conclusion In allergic rhinitis (AR) patients referred to a specialist, the features of AR as defined by the ARIA classification are not able to predict the presence of asthma, therefore all such patients should be assessed for asthma.

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Introduction

The link between rhinitis and asthma is supported by anatomical and epidemiological evidence; moreover the involvement of the same causative agents (allergens, anti-inflammatory drugs, etc.) and the demonstration of 'bidirectional' allergic inflammation between the upper and lower airways have been shown [1–6]. As a direct result of this evidence it has been proposed that rhinitis and asthma are manifestations of a single chronic inflammatory syndrome, in which the mildest and earliest forms primarily affect the upper airway [1–6].

The severity of rhinitis may therefore correlate with the increased prevalence of asthma.

Some studies confirm this and demonstrate that the severity of rhinitis is a risk factor for asthma irrespective of the presence of allergy [7]. Moreover, a significant relationship between the severity of rhinitis and the prevalence of

asthma in allergic patients has been documented both in patients suffering from perennial-allergic rhinitis (PAR) [8] and in patients suffering from pollen-sensitive rhinitis and asthma [9].

Severity is a subjective factor and the most reliable method of assessment is the daily symptom/medication score [10, 11], which is labuorious, particularly in an epidemiological setting.

Recently the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines redefined the old nomenclature (seasonal/perennial), and proposed that rhinitis should be classified according to both its duration (intermittent and persistent) and severity, evaluated as the impact on patient quality of life (QOL) (mild and moderate–severe) [3].

This new classification makes it possible to assess rhinitis through a series of few and simple questions, making its use of value in epidemiological studies.

Two studies, which used the ARIA categories to investigate the relationship between allergic rhinitis (AR) and the prevalence of asthma yielded contrasting results. One large cross-sectional study carried out in the general population in six European countries reported the proportions of intermittent and persistent rhinitis in the general population as being 71% and 29%, respectively, though the prevalence of asthma was similar in both populations (21% in intermittent and 20% in persistent subjects) [12].

A French survey enrolling patients with AR referred by general practitioners (GPs) to specialists documented a distribution of rhinitis which is almost the inverse (27% of intermittent rhinitis and 63% of persistent rhinitis subjects) thus confirming the selection bias towards severity of patients studied in a specialist practice. However, it is surprising that in this study, where a significant association between the duration and severity of AR and the prevalence of asthma were demonstrated, the overall prevalence of asthma (24%) was slightly higher than in the general population study [13].

Finally, a third very recent study, performed in France, confirms the latter finding, though an ARIA category-to-category comparison revealed no significant differences in the prevalence of asthma [14].

The aim of the study was to verify whether the clinical features of AR classified according to the ARIA guidelines correlate with the prevalence of asthma.

Patients and methods

Study design

A multi-center observational cross-sectional study was carried out from 1 March to 30 June 2002 on a sample of 1610 AR patients referred by their GP to an allergist.

The study was conducted by 154 allergists selected from throughout Italy.

Consistent with the protocol, a specific questionnaire was administered by each allergist to the first 12 consecutive patients who had been referred by their GPs to a specialist for a rhinitis evaluation.

The inclusion criteria were as follows:

(1) Age 18 years or older.
(2) Presence of rhinitis symptoms at the time of the hospital visit.
(3) History of rhinitis >1 year.
(4) Positive skin test for inhalant allergens.
(5) Written informed consent.

If the patient had not performed a skin prick test (SPT) in the previous year, SPTs were done during the visit with commercially available standardized extracts in Italy (Stallergenes-France, ALK-Abello Denmark, Lofarma, Italy) to assess allergic sensitization.

The allergens tested were: mites (*Dermatophagoides pteronissynus and Dermatophagoides farinae*), animal dander (cat, dog, horse), pollens (grass, pellitory, olive, cypress, birch, hazelnut, mugwort, ragweed), fungal allergens (*Alternaria*, *Cladosporium*, *Aspergillus*) and latex; a negative and positive control (histamine 10 mg/mL) was also included. Skin tests were done following a standard procedure; patients who had used antihistamines during the 3 days before the test were excluded [15].

If sensitization to different allergens was detected, the patient was classified as being polysensitive. Sensitization to a single allergen or the simultaneous sensitization to *D. pteronissynus* and *D. farinae* meant patients were monosensitive.

Questionnaire for diagnosis of AR and asthma

Patients were surveyed on socio-demographic data and on their rhinitic and asthmatic status.

The clinical diagnosis of AR was confirmed by the answer 'yes' to the question: 'In the last year, have you had a runny or stuffy nose or episodes of sneezing apart of cold?' and who had positive skin test results.

Patients with AR were classified according to the ARIA guidelines [3], and in particular, on the basis of the duration of their symptoms, rhinitis was divided into intermittent (<4 days/week or <4 weeks/year) and persistent (>4 days/week and >4 weeks/year).

Rhinitis was moderate–severe in those patients who replied 'yes' to one or more of the following items: abnormal sleep; impairment of daily work or school; impairment of leisure activities; and presence of troublesome symptoms. The rhinitis was classified as mild in those patients who replied 'no' to all previous items.

A positive diagnosis of conjunctivitis was made when patients replied 'yes' to the question: 'In the last 12 months, together with your nasal symptoms have you experienced itchy-watery eyes?'

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A selection of questions from the ISAAC questionnaire was used to evaluate respiratory symptoms. A diagnosis of current asthma was made when patients gave affirmative answers to the following question: 'Have you ever experienced asthma?' and to at least one of the questions below:

- In the past 12 months, have you experienced wheezing or whistling in your chest?
- In the last 12 months, have you ever had an asthma attack during the day, which occurred at least once a week?
- In the last 12 months, have you had night-time asthma symptoms more than twice a month?
- In the last 12 months, have you taken asthma medication?

As the study was performed in a clinical setting, clinical judgement was involved to rule out any misunderstanding between a clinical- and questionnaire- related diagnosis.

Statistical analysis

For all analyses, *P*-values <0.05 were regarded as statistically significant. Chi-square tests were used to compare categorical characteristics between groups. A binomial regression model was applied to identify independent risk factors for asthma: the risk measure computed was the risk ratio (RR) with a 95% confidence interval (95% CI). All statistical analyses were performed using SAS™ (Release 8.2, Procedures: FREQ, GENMOD).

Results

Classification of rhinitis

One hundred and thirty-nine of the 154 allergists completed the study. Owing to unavailable questionnaires and/or skin test data, out of the 1610 patients recruited only 1321 (84%) were eligible.

The sample was made up of adults, slightly more females than males, the majority were non-smokers and fairly well distributed throughout the country (Table 1).

The majority of patients (73.4%) were polysensitive, the most prevalent allergens being grass pollen, mite and pellitory pollen (Table 2).

A high prevalence of rhino-conjunctivitis (84%) was documented, and this result probably mirrors both the high percentage of sensitization to pollens within our sample and the time of year (spring) when the study was carried out.

The vast majority of patients were suffering from moderate/severe persistent rhinitis, in particular mild intermittent rhinitis was diagnosed in 102 patients (7.7%), moderate/severe intermittent in 226 patients (17.1%), mild persistent in 153 (11.6%) and moderate/severe persistent in 840 (63.6%) (Table 2).

Table 1. Demographic characteristics of rhinitic patients

Sample size	1321
Male gender	47.0%
Age (years)	
Mean (SD)	34 (12)
Range	18–80
Median	32
Geographic area	
North	43.9%
Centre	12.1%
South/Islands	43.9%
NR	28
Smoking status	
Never smoked	73.1%
Former	9.0%
Current	17.9%

NR, not recorded; SD, standard deviation.

Table 2. Allergic sensitization and aria rhinitis classification

Sample size	1321
Number of allergens	
One	26.6%
Two or more	73.4%
Allergens	
Grass pollen	57.6%
House dust mite	47.2%
Pellitory	41.3%
Olive	26.6%
Birch	24.6%
Cupressacee	16.4%
Mugwort	15.6%
Hazelnut	15.6%
Cat	14.7%
Dog	9.4%
Ambrosia	8.3%
Alternaria	5.8%
Others	4.1%
Skin positivity	
+	1.9%
++	10.5%
+++	44.0%
++++	43.6%
Rhinitis classification (ARIA)	
Mild intermittent	7.7%
Moderate/severe intermittent	17.1%
Mild persistent	11.6%
Moderate/severe persistent	63.6%

ARIA, Allergic Rhinitis and its Impact on Asthma.

The comparison between monosensitized and polysensitized rhinitis patients revealed some significant differences (Table 3): on the whole, monosensitized patients had a milder form of the disease and the prevalence of pollen sensitization was found to be higher than for polysensitized patients.

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Table 3. Comparison between monosensitive and polysensitive patients

	Monosens (%) ($n = 351$)	Polysens (%) ($n = 970$)	P
Age >40 years	30.2	22.5	0.004
Indoor allergens	30.2	61.2	< 0.001
Rhinitis classification (ARIA)			
Mild intermittent	12.0	6.2	< 0.001
Moderate/severe intermittent	17.7	16.9	
Mild persistent	14.2	10.6	
Moderate/severe persistent	56.1	66.3	

P-values from χ^2 test.
ARIA, Allergic Rhinitis and its Impact on Asthma.

Table 4. The most common drug or drugs associations within rhinitic patients

Class of drugs	No. of patients	(%)
Oral anti-H1+intranasal steroid	303	28.58
Oral anti-H1	261	24.60
Intranasal steroid	149	14.05
Decongestant	53	5.00
Others	294	27.70

The group 'others' collects several further therapies (single drug or associations) taken by groups of patients, each of which was smaller than 5% (number of patients = 1060).

Table 5. Adjusted rate ratios and confidence intervals derived from multivariate binomial regression model

	Unadjusted prevalence		Adjusted RR	(95% CI)	P
Sex					
Female	334/702	47.6%	1.045	(0.932–1.171)	0.453
Male	282/619	45.6%	1.000		
Age (years)					
> 50	73/122	59.8%	1.460	(1.237–1.723)	< 0.001
41–50	105/202	52.0%	1.260	(1.072–1.482)	0.005
31–40	177/393	45.0%	1.066	(0.925–1.228)	0.377
18–30	261/604	43.2%	1.000		
Current or previous smoker					
Yes	176/357	49.3%	1.051	(0.928–1.190)	0.431
No	440/964	45.6%	1.000		
Polysensitive					
Yes	478/970	49.3%	1.178	(1.004–1.383)	0.045
No	138/351	39.3%	1.000		
Indoor allergens (mite or cat)					
Yes	354/700	50.6%	1.203	(1.060–1.366)	0.004
No	262/621	42.2%	1.000		
Moderate/severe persistent	399/840	47.5%	0.935	(0.760–1.150)	0.525
Mild persistent	56/153	36.6%	0.755	(0.569–1.003)	0.053
Moderate/severe intermittent	112/226	49.6%	1.000	(0.791–1.263)	0.997
Mild intermittent	49/102	48.0%	1.000		

CI, confidence interval; RR, risk ratio.

The majority of patients, [1060 (80.24%)], were on medication at the time of their specialist visit (Table 4).

Comorbidity with asthma

Although our survey reported a high prevalence of rhinitis and asthma comorbidity (616/1321 = 46.6%), no correlation between the ARIA categories of rhinitis and the prevalence of asthma was found.

There was a 48% prevalence rate of asthma in patients with mild intermittent rhinitis, 49.6% in moderate–severe intermittent rhinitis patients, 36.6% in mild persistent rhinitis and 47.5% in moderate–severe persistent patients. The prevalence of asthma does not present significant variations between intermittent (49.1%) and persistent (45.8%) rhinitis ($P = 0.304$) and between mild (41.2%) and moderate–severe (47.9%) rhinitis ($P = 0.052$), even though the severity seems to have more impact than the duration of rhinitis.

Analysis of the relationship between the presence of asthma and allergic sensitization revealed that the prevalence of asthma was significantly higher in polysensitized (49.3%) than in monosensitized patients (39.3%) ($P = 0.002$) and also in rhinitics monosensitized to indoor allergens [house dust mites (HDMs) and cat dander] (50.6%) compared with individuals sensitized to pollens (42.2%) ($P = 0.002$).

In the polysensitized group, the role of indoor allergens remains relevant: the prevalence of asthma was higher in patients sensitized to several allergens including HDM and cat dander (306/592 = 51.7%) as opposed to patients sensitized to several pollens only (182/403 = 45.2%) ($P = 0.047$).

A multivariate analysis, after adjustment for age, sex, type of sensitization, level of severity and frequency of rhinitis symptoms classified according to the ARIA guidelines, demonstrates that sensitization to indoor allergens and polysensitization represent significant risk factors for asthma (Table 5).

Moreover, the analysis revealed a significant association between the age of rhinitic patients and asthma: in particular the prevalence of asthma was stable in individuals up to 40 years, while it increased significantly above that age (Table 5).

Discussion

The findings of the present survey show that in patients with AR, the classification of rhinitis, according to the ARIA

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guidelines [3], does not correlate with the prevalence of asthma, while age, sensitization to indoor allergens (HDM and cat), as well as the presence of polysensitization, in descending order, represent risk factors for asthma.

The results concerning the role of sensitization to indoor allergens and to several allergens confirm well-known data [3, 16, 17] whereas the association between age and asthma seems more unusual.

Indeed the timeframe of this relathionship in our study (Table 5) is quite similar to the findings of another survey, which demonstrated that the prevalence of asthma in AR patients did not correlate with age until 50 years and only increased in older age groups [7].

Observational studies have documented the presence of allergic asthma in adults and older age subjects [18], and the association between age and asthma in the subset of AR patients [19–21], moreover prospective studies have demonstrated the late development of asthma in patients who in younger age were afflicted with AR alone [2, 22, 23].

Moreover the absence of correlation between age and smoking habit (data not shown) seems to confirm that this result is not due to smoking.

In conclusion, we think that our results reveal the cumulative effect of two issues: first, the association between the new onset of allergic disease in older age and the long lasting increasing prevalence of the disease in the subset of the AR patients, and second: the selection bias of the specialist setting, which collects the majority of allergic patients spanning the whole age spectrum.

On the whole, our results provide evidence that, the role of the underlining atopic status is prevalent with respect to the severity of rhinitis, evaluated according to the ARIA classification, in the relationship between asthma prevalence and AR. Even though a trend between the severity of rhinitis and prevalence of asthma was documented, this trend disappeared when the four ARIA categories of rhinitis were evaluated (Table 4).

As the studies performed recording the symptom score provide evidence of a relationship between the severity of rhinitis and prevalence of asthma [7–9] we believe that our results can be attributed to the parameters the ARIA classification is based on.

In our opinion the interplay between duration and severity, which provides the framework for the classification, does not seem to be sufficiently sensitive to identify the allergen-specific risk for the development of asthma [1, 17, 24].

With regard to the duration, comparison of our results with those of a survey conducted in France [13], in rhinitic patients presenting similar features described in the ARIA categories, revealed a significant variation of allergic sensitizations within the same ARIA category.

The allergic sensitization profile, we found is consistent with the findings of another recent Italian study and so seems to be representative of the characteristic features of the mediterranean area [25].

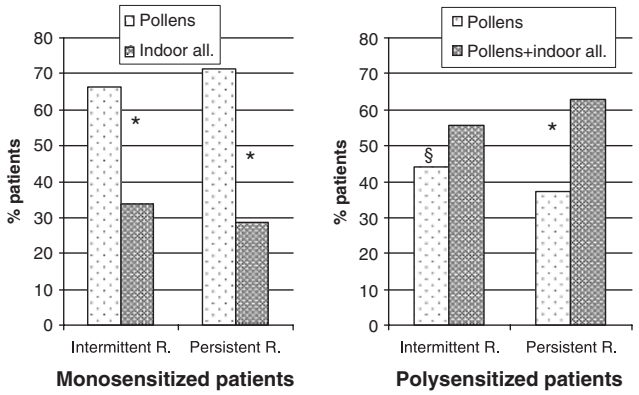


Fig. 1. Skin tests positivity in monosensitized (no. 351) and polysensitized patients (no. 970) with intermittent and persistent rhinitis according to Allergic Rhinitis and its Impact on Asthma (ARIA) classification. The indoor allergens category includes mite and cat skin test positivity. In the group of polysensitized patients were compared with patients polysensitized to several pollens without indoor allergens vs. patients polysensitized to pollens and indoor allergens $^{*}P < 0.001$; $^{\S}P = 0.082$.

In monosensitive patients, the predominance of pollen allergy in intermittent rhinitis was documented in this and the French study, albeit with a difference in the relative percentages between pollens and indoor allergens. In France, the percentage of pollen-sensitized individuals is very high (87%) while sensitization to indoor allergens (HDM and cat) is low (8%); in Italy, the percentage of patients allergic to indoor allergens is as high as 33% (Fig. 1).

Moreover, in the French study, in polysensitive patients, a considerably higher number of HDM sensitizations (72%) in patients with persistent rhinitis compared with those with intermittent rhinitis (35%) was found, whereas in our survey the prevalence of indoor sensitization was similar both in intermittent and persistent categories (Fig. 1).

Even though no data are available for mite contamination, the different household environments (carpeting, insulation, etc.) and climates were probably involved in the classification of the vast majority of mite-allergic patients in the persistent category in the French survey, whereas in Italy a relative large group of such patients fell into the intermittent category.

The independence of the duration of rhinitis from the type of sensitization, but not from its ability to induce asthma, was confirmed by a European polycentric study, where several environments were mixed [12].

A higher prevalence of mite sensitization in intermittent (52.4%) than in persistent rhinithis patients (41.3%) has been demonstrated, but consistent with the asthmogenic capacity of this allergen, a similar prevalence of asthma in both groups has been documented (21% in intermittent and 20% in persistent) [12].

Also, with regard to severity, the interplay between the type of allergen and the assessment of symptoms should be considered.

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In pollen allergic patients a more relevant impact of the allergen in the nose than in the bronchi is well known [1, 3]. Moreover, the association between rhinitis and asthma, if present, is related to the pollen season and is closer than in mite-allergic patients.

In these latter patients even though the exacerbations of allergic symptoms are related to mite environmental contamination [17], the prevalence of asthma appeared independent from the level of mite contamination [26]. A recent Australian 1-year study monitored 37 HDM rhinitic patients daily (of which 43% were monosensitive) in an environment with a high presence of mites and underlines that half of bronchial symptoms occur when nasal symptoms are absent [8]. Indeed, irrespective of the severity of the AR, the presence of bronchial minimal persistent inflammation in asymptomatic mite rhinitic patients could be involved in asthma exacerbations, favouring both the role of aspecific triggers and the role of rhinovirus infections through the up-regulation of ICAM 1 [27, 28].

Moreover, the ISAAC study demonstrated that the assessment of rhinitis symptoms, compared with those of asthma and eczema, seem to reflect the more recent symptomatology, in particular the seasonal trends, while the assessment of asthma symptoms is reliable for the last 12 months [29].

As a result, the simple evaluation of the most recent rhinitis severity is not sufficiently able to evaluate the different impact of allergens in the upper and lower airways in the last year.

Therefore, we think that the ARIA classification method can determinate a relevant variability of the allergenic case mix in the same category of rhinitis, which is likely related to different environments.

In order to better understand the role of the ARIA classification in exploring the relationship between upper and lower airways and the interplay with the allergy further studies will be necessary to assess the features of rhinitis in different countries [30, 31].

A number of methodological aspects of our survey deserves discussion.

The ARIA guidelines should be used in non-treated patients but several studies, both in the specialist and primary care setting, documented the majority of patients were already being treated when they consulted their doctor. As a result, the severity of rhinitis and its relationship with asthma may have been affected by the enrolment of treated patients.

In our survey, the prevalence of current asthma (46.5%) was found at higher levels of the comorbidity between AR and asthma, which ranges from 18% to 40% [6].

In a recent epidemiological survey performed in Italy, the prevalence of asthma comorbidity in rhinitis allergic patients was 26%, even though the possibility of recording symptoms linked with asthma is as high as 51% [32].

We think that the most important reasons that can explain the high level of asthma in our survey are the selection bias due to an imbalance towards severe patients studied in the specialist practice and to the diagnosis based on the use of multiple questions [33].

Moreover, we believe that, even though the patients were enrolled because of an exacerbation of rhinits, a certain level of overlap between 'patients suffering from AR without a previous diagnosis of asthma' and 'patients suffering from AR and asthma' certainly occurred.

As the main goal of the our study was not to evaluate the prevalence of asthma in AR, but to assess whether the features of rhinitis, classified according to the ARIA guidelines, correlates with the prevalence of asthma we believe that this assessment should not necessarily be limited to rhinitis patients without any previous diagnosis of asthma.

However, a very recent study specifically designed for rhinitis patients with no prior diagnosis of asthma demonstrated that severity and duration of rhinitis according to the ARIA guidelines are a risk factor for asthma [21].

In our study, we did not set a recruitment age limit, which may have produced a misleading result in the prevalence of asthma due to the presence of COPD. Indeed, the epidemiological studies carried out through the administration of a questionnaire are limited to younger age groups (<40 years) but the clinical setting of our survey should nevertheless prevent, or minimize, this risk.

The imbalance between the number of patients enrolled in each ARIA category may not have provided a reliable assessment of the relationship between rhinitis and asthma but our results reflect the findings of the other surveys carried out in the clinical setting [13, 14].

In conclusion, our study demonstrates that in AR patients referred to a specialist, the features of AR as defined by the ARIA classification are not able to predict the presence of asthma.

Therefore, our results confirm and strengthen the most relevant ARIA recommendation, that all patients with AR should be assessed for asthma.

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References

1 Leynaert B, Neukirch C, Kony S *et al.* Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol* 2004; 113:86–93.

2 Linneberg A, Nielsen N, Frolund L, Madsen F, Dirksen A, Jorgensen T. The link between allergic rhinitis and allergic

© 2007 The Authors

asthma: a prospective population-based study. The Cophenhagen Allergy Study. *Allergy* 2002; **57**:1048–52.
3 Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma: comorbidity and complications. *J Allergy Clin Immunol* 2001; **108**:S198–207.
4 Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003; **111**:1171–83.
5 Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy* 2003; **58**:691–706.
6 Braunstahl GJ, Fokkens W. Nasal involvement in allergic asthma. *Allergy* 2003; **58**:1235–43.
7 Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002; **109**:419–25.
8 Downie SR, Andersson M, Rimmer J *et al*. Association between nasal and bronchial symptoms in subjects with persistent allergic rhinitis. *Allergy* 2004; **59**:320–6.
9 Bousquet J, Boushey HA, Busse WW *et al*. Characteristics of patients with seasonal allergic rhinitis and concomitant asthma. *Clin Exp Allergy* 2004; **34**:897–903.
10 Downie SR, Andersson M, Rimmer J *et al*. Symptoms of persistent allergic rhinitis during a full calendar year in house dust mite-sensitive subjects. *Allergy* 2004; **59**:406–14.
11 Juniper EF, Ståhl E, Doty RL, Simons FER, Allen DB, Howarth PH. Clinical outcomes and adverse effect monitoring in allergic rhinitis. *J Allergy Clin Immunol* 2005; **115**:S390–413.
12 Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy* 2005; **60**:350–3.
13 Bousquet J, Annesi-Maesano I, Carat F *et al*. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. *Clin Exp Allergy* 2005; **35**:728–32.
14 Bousquet J, Neukirch F, Bousquet PJ *et al*. Severity and impairment of allergic rhinitis in patients consulting in primary care. *J Allergy Clin Immunol* 2006; **117**:158–62.
15 Position Paper. Allergen standardization and skin test EAACI. *Allergy* 1993; **48** (Suppl. 14):48–82.
16 Postma DS, Bleecker ER, Amelung PJ *et al*. Genetic susceptibility to asthma–bronchial hyperresponsiveness coinherited with a major gene for atopy. *N Engl J Med* 1995; **333**:894–900.
17 Platts-Mills TAE, De Weck AL. Dust mite allergens and asthma – a worldwide problem. *J Allergy Clin Immunol* 1989; **83**:416–27.
18 Raherison C, Nejjari C, Marty ML *et al*. IgE level and Phadiatop in an elderly population from the PAQUID cohort: relationship to respiratory symptoms and smoking. *Allergy* 2004; **59**:940–5.
19 Bozkurt B, Karakaya G, Kalyoncu AF. Seasonal rhinitis, clinical characteristics and risk factors for asthma. *Int Arch Allergy Immunol* 2005; **138**:73–9.
20 Litonjua AA, Sparrow D, Weiss ST, O'Connor GT, Long AA, Ohman JL. Sensitization to cat allergen is associated with asthma in older men and predicts new-onset airway hyperresponsiveness: the Normative Aging Study. *Am J Respir Crit Care Med* 1997; **156**:23–7.
21 Demoly P, Bozonnat MC, Dacosta P, Daures JP. The diagnosis of asthma using a self-questionnaire in those suffering from allergic rhinitis: a pharmaco-epidemiological survey in everyday practice in France. *Allergy* 2006; **61**:699–704.
22 Huovinen E, Kaprio J, Laitinen LA, Koskenvuo M. Incidence and prevalence of asthma among adult Finnish men and women of the Finnish Twin Cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. *Chest* 1999; **115**:928–36.
23 Settipane GA, Greisner WA III, Settipane RJ. Natural history of asthma: a 23-year followup of college students. *Ann Allergy Asthma Immunol* 2000; **84**:499–503.
24 Guerra S, Allegra L, Blasi F, Cottini M. Age at symptom onset and distribution by sex and symptoms in patients sensitized to different allergens. *Allergy* 1998; **53**:863–9.
25 Olivieri M, Verlato G, Corsico A *et al*. Italian European Community Respiratory Health Survey group. Prevalence and features of allergic rhinitis in Italy. *Allergy* 2002; **57**:600–6.
26 Vervloet D, de Andrade AD, Pascal L *et al*. The prevalence of reported asthma is independent of exposure in house dust mite-sensitized children. *Eur Respir J* 1999; **13**:983–7.
27 Ciprandi G, Buscaglia S *et al*. Minimal persistent inflammation is present at mucosal level in patients with asymptomatic rhinitis and mite allergy. *J Allergy Clin Immunol* 1995; **96**:971–9.
28 Friedlander SL, Busse WW. The role of rhinovirus in asthma exacerbations. *J Allergy Clin Immunol* 2005; **116**:267–73.
29 Stewart AW, Asher MI, Clayton TO *et al*. The effect of season-of-response to ISAAC questions about asthma, rhinitis and eczema in children. *Int J Epidemiol* 1997; **26**:126–36.
30 Sunyer J, Jarvis D. European Community Respiratory Health Survey Study Group. *et al*. Geographic variations in the effect of atopy on asthma in the European Community Respiratory Health Study. *J Allergy Clin Immunol* 2004; **114**:1033–9.
31 Zock JP, Heinrich J. Indoor Working Group of the European Community Respiratory Health Survey II. *et al*. Distribution and determinants of house dust mite allergens in Europe: the European Community Respiratory Health Survey II. *J Allergy Clin Immunol* 2006; **118**:682–90.
32 Bugiani M, Carosso A. ISAYA (ECRHS Italy) Study Group. *et al*. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. *Allergy* 2005; **60**:165–70.
33 Pekkanen J, Sunyer J, Anto JM, Burney P.European Community Respiratory Health Study. Operational definitions of asthma in studies on its aetiology. *Eur Respir J* 2005; **26**:28–35.

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