

Original article

Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy

Background: Several studies have provided evidence of a strong association between asthma and allergic or nonallergic rhinitis, leading to the hypothesis that allergic rhinitis (AR) and asthma represent a continuum of the same disease.

Aim: The aims of our study were: (i) to measure the comorbidity of AR and asthma and asthma-like symptoms and (ii) to assess whether asthma, AR, and their coexistence share a common pattern of individual risk factors.

Methods: The subjects are participants from the Italian multicentre, cross-sectional survey on respiratory symptoms in the young adult general population (Italian Study of Asthma in Young Adults, ISAYA). The relationship between individual risk factors and asthma, AR and their coexistence, was studied by means of a multinomial logistic regression.

Results: About 60% of asthmatics reported AR. On the other hand, subjects with AR presented an eightfold risk of having asthma compared to subjects without AR. Age was negatively associated with asthma [OR = 0.89, 95% confidence interval (CI): 0.82–0.96], AR (OR = 0.92, 95% CI: 0.86–0.98), and asthma associated with AR (OR = 0.83, 95% CI: 0.79–0.88). The risk of AR without asthma was significantly higher in the upper social classes (OR = 1.23, 95% CI: 1.08–1.39). Active current smoking exposure was positively associated with asthma alone (OR = 1.24, 95% CI: 1.09–1.41) and negatively associated with AR with (OR = 0.69, 95% CI: 0.54–0.88) or without (OR = 0.76, 95% CI: 0.69–0.84) asthma.

Conclusions: Asthma and AR coexist in a substantial percentage of patients; bronchial asthma and AR, when associated, seem to share the same risk factors as AR alone while asthma without AR seems to be a different condition, at least with respect to some relevant risk factors.

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Rhinitis is one of the most common respiratory disorders affecting individuals, particularly atopic subjects, during their most productive years of life (1, 2). Although rhinitis is not usually a severe disease, it significantly alters the social life of patients and affects school learning performance as well as work productivity (1, 3). Chronic rhinitis is also associated with significant comorbidity states such as sinusitis, nasal polyps, chronic otitis, lymphoid hypertrophy with obstructive sleep apnoea and disordered sleep. Moreover, several epidemiological studies in the general population have provided evidence of a strong association between asthma and allergic or nonallergic rhinitis. The prevalence of allergic rhinitis (AR) in asthmatic patients has been estimated as about 80% (3) and several studies have identified rhinitis as a risk factor for asthma (4–8). Indeed, as many as 19–38% of patients with AR may have asthma (9–11), which is much more than the 3–5% prevalence among the general population (12). As rhinitis

is known to occur more often in atopic than in nonatopic subjects, the association between AR and asthma could be due to the common atopic status. In any case, some authors (13) have been able to demonstrate that rhinitis is a significant risk factor for developing asthma also in nonallergic subjects, suggesting that the association might not be due only to atopy but also to other risk factors (14).

It has even been proposed that AR and allergic asthma are manifestations of the same disease and that they represent a continuum (15–18), sharing common pathological and physiological characteristics (19). In this way, subjects with less severe disease express only rhinitis, while subjects with more severe disease express both rhinitis and asthma. This has been labelled ‘one airway, one disease’ or ‘united airways disease’ or ‘allergic rhinobronchitis’ (9, 20, 21).

The aims of our study were: (i) to measure the comorbidity of AR and asthma and asthma-like

symptoms (ALS) in a general population sample of young adults and (ii) to evaluate whether asthma, AR, and the coexistence of asthma and AR share a common pattern of individual risk factors.

Methods

Study design

For the purpose of the study the data of the Italian Study of Asthma in Young Adults (ISAYA) were used. The ISAYA is a multicentre, cross-sectional survey on the young adult general population aimed at assessing the variations of asthma, ALS and chronic bronchitis prevalence in Italy, and it was carried out between February 1999 and June 2000. Nine Italian centres were involved in the study (Verona, Pavia, Turin, Udine, Sassuolo, Ferrara, Pisa, Sassari and Siracusa).

The design of the study was the same as the one used in the first European Community Respiratory Health Survey (ECRHS) stage 1 and described in detail elsewhere (22, 23). Briefly, each centre identified an up-to-date sampling frame of the residents of the target area, from which a random sample of 3000 people aged 20–44 years (men/women ratio = 1 : 1) was selected. A two-page screening questionnaire was sent by post to each subject up to three times in the case of nonresponse; finally the questionnaire was administered by phone to the remaining nonresponders (24).

The questionnaire used is a modified version of the short questionnaire of ECRHS, enquiring about the subject's past and present history of asthma, ALS and AR and its validation criteria have been published elsewhere (25). The questionnaire concerns also some personal characteristics (age, sex, smoking behaviour and profession). A validated visual analogue score (pollution annoyance score) aimed at measuring the subjective perception of air pollution (26) was also administered as a part of the questionnaire. Study subjects self-assessed their degree of annoyance on an 11-point scale. Possible scores on the scale range from 0 (no disturbance at all) to 10 (intolerable disturbance). A picture of the Annoyance Scale in the form of a thermometer was presented and the participant was asked, 'How much are you annoyed by outdoor air pollution (from traffic and industry) at your actual home, if you keep the windows open'?

Definitions and statistical analysis

Subjects were classified as having: AR, in the case of a positive response to the question: 'Do you have any nasal allergies including hay fever?'; asthma (ever) in the case of a positive response to the question 'Have you ever had asthma'?

Regarding other ALS, the subjects were classified as having wheeze, tightness in the chest in the case of a positive response to the following questions respectively: 'Have you had wheezing or whistling in your chest at any time in the last 12 months?', 'Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?', asthma attacks, in the case of a positive response to the question: 'Have you had an attack of asthma in the last 12 months?'; drugs for asthma, in the case of a positive response to the question: 'Are you currently taking any medicines (including inhalers, aerosols or tablets) for asthma; chronic cough and phlegm, in the case of a positive response to the question: 'Have you had cough and phlegm on most days for a minimum of 3 months a year and for at least 2 successive years'?

Subjects were classified according to their smoking habits (smoke) as: smokers, if they were current smokers and had smoked at least one cigarette per day or one cigar a week for 1 year; ex-smokers, if

they had smoked for at least 1 year (as defined above) but not during the last month; all the other subjects were considered non-smokers.

As the centres had different response rates the prevalence rates were adjusted for the response rate, and for age and sex. Adjusted prevalence rates were then obtained through a logistic regression model, considering symptoms as the dependent variable (present *vs* absent) and sex, age, response rate, and type of interview as the covariates. Moreover, subjects were classified according to their profession as proxy for socio-economic status into three groups: high social class (managers, entrepreneurs and businessmen); middle (white collars, craftsmen, dealers) and lower social class (salesmen, blue collar workers), other conditions (retired and unemployed persons, housewives and students).

Response time was defined as mail wave (1–3) or phone response. The Cohen Kappa statistic was used to measure the association between AR, asthma and ALS. To study the relationship between individual risk factors and AR, asthma and their coexistence, a multinomial logistic regression was fitted to the data, using as dependent variable a four-level indicator classifying all subjects as having: (i) no symptoms; (ii) AR only; (iii) asthma only; (iv) both asthma and AR. Age, social class, smoking habits and subjective pollution score were used as potential predictors while response time was considered as a potential confounding variable.

For analysis the STATA 8.0 (27) package and svymlogit procedure was used to estimate multinomial logistic regression (or polytomus logistic regression) for complex survey data, setting sex as a strata identifier variable, centres as a cluster identifier variable and the inverse of the sample base population of the centre as the sampling weight variable.

Symptoms (asthma, AR, as previous defined, and their association) were used as response polytomus variables using no symptom (intended as not asthma or AR) as reference category.

Smoking habits, social status, response status were used as categorical.

The pollution annoyance score was divided by 10 to obtain a 0–1 scale.

Following an initial analysis result, predictive variables not significant at the 5% level were removed from the model; categories of predictive variables with an effect not significant different from other were collapsed.

Results

Of 23 506 eligible subjects 17 666 filled in the questionnaire. The overall response rate was 72.7% (Table 1), ranging from 48.7 (Siracusa) to 82% (Pavia). The mean age of the studied sample was 33 years (SD: 6.9) and the percentage of women was 49.1%. The reported AR prevalence in the whole sample was 18.7% (Table 1), ranging from 14.9 (Sassari) to 23.3% (Pisa).

Table 1 shows also the rates of prevalence of AR, asthma, and both asthma and AR by city, adjusted for age, sex and response rates. Table 2 shows the agreement between AR and asthma and other ALS: the agreement was significantly > 0 for all symptoms. The prevalence of AR in subjects reporting asthma was about 60%. The probability of having AR conditional to having other ALS ranged from 70.6% for subjects who reported asthma attacks in the last 12 months to 31.1% for subjects with chronic cough and phlegm, and it was 13%

Table 1. Number of eligible subjects, proportion (%) of responders, prevalence of allergic rhinitis (AR, total or without asthma), asthma (A) and of the coexistence of AR and asthma (AR and A) by centres adjusted for sex, age and response rate

Characteristics (centre)	Eligible* (N)	Response rate (%)	Prevalences				
			AR (%)	A (%)	AR without A (%)	A without AR (%)	AR and A (%)
Ferrara	3000	70.1	15.3	8.3	10.5	3.5	4.8
Pavia	2981	82.0	17.0	7.4	13.0	3.4	4.0
Sassuolo	2869	74.7	15.7	8.5	10.3	3.1	5.4
Torino	2892	78.2	19.6	8.4	14.9	3.7	4.7
Udine	2936	70.9	20.3	7.7	15.5	2.8	4.9
Verona	2927	74.0	21.4	11.1	15.0	4.7	6.4
Pisa	2976	81.0	23.3	10.7	17.3	4.7	6.0
Sassari	2925	70.3	14.9	8.4	10.0	3.6	4.8
Siracusa	2463	48.7	20.0	9.4	14.4	3.8	5.6
Total	25 969	72.7	18.7	8.9	13.7	3.7	5.2

Table 2. Prevalence percentage asthma-like symptoms in subjects with allergic rhinitis (ALS/AR) and of allergic rhinitis in subjects with asthma-like symptoms (AR/ALS) and Cohen K coefficient of agreement (Kappa) between AR and ALS

	Prevalence (%)	ALS/AR (%)	AR/ALS (%)	Kappa	Z	Probability > Z
Wheezing	12.3	26.3	40.8	0.20	28.6	0.000
Tightness	8.1	16.7	38.9	0.14	20.9	0.000
Asthma attacks	3.8	14.7	70.6	0.18	35.8	0.000
Drugs for asthma	2.8	10.3	68.7	0.14	29.7	0.000
Chronic cough	12.2	20.5	31.1	0.12	16.2	0.000
Asthma (ever)	8.3	26.0	58.7	0.28	42.1	0.000
Any AL symptom	22.7	51.5	38.1	0.23	33.9	0.000
No AL symptom	77.3	48.5	13.2	-0.08	-27.3	0.000

Table 3. Odds ratios (OR) and 95% confidence intervals for the association of allergic rhinitis with asthma-like symptoms mutually adjusted

	OR	LL	UL	P-value > t
Wheezing	1.65	1.43	1.90	0.000
Dyspnoea	1.43	1.17	1.74	0.001
Tightness on the chest	1.59	1.32	1.92	0.000
Drugs for asthma	1.17	0.89	1.53	0.252
Chronic cough	2.37	1.52	3.71	0.001
Asthma attacks	3.06	1.83	5.12	0.000
Asthma (ever)	7.89	7.07	8.08	0.000

LL, lower limit; UL, upper limits of 95% confidence intervals.

among asymptomatic subjects. Fifty-one percentage of subjects with AR reported at least one ALS. The probability of having ALS conditional to having AR ranged from 26% for wheezing in the last year and asthma to 10% among subjects taking drugs for asthma. The probability of having had asthma (ever) among subjects with AR was 26%. When mutually adjusting for all the considered ALS (Table 3), AR was significantly and independently associated with all ALS, particularly with asthma attacks in the last 12 months, chronic cough and asthma (ever).

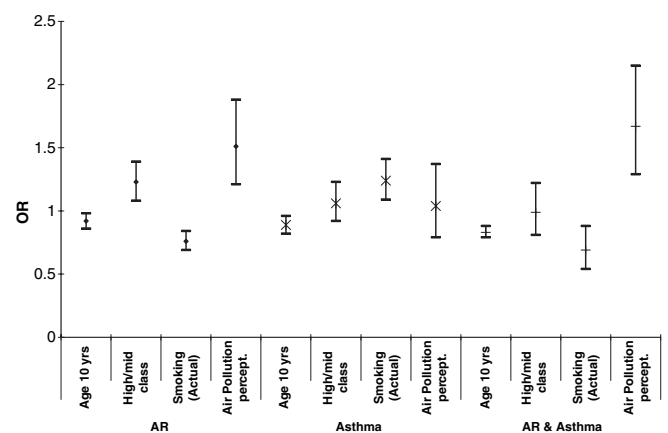


Figure 1. Odds ratio for allergic rhinitis (AR), asthma and comorbidity (with 95%) confidence interval (CI) by predictive variables.

Figure 1 shows the results of multinomial logistic regression analysis using an outcome variables AR alone, asthma alone, and asthma with AR. Following an initial analysis some multicategorical predictive variables were grouped as binary, grouping the similar categories: current smoking *vs* past and nonsmokers, high and middle social class *vs* low and unemployed. Age was negatively associated with asthma (OR = 0.89, 95% CI: 0.82–0.96), AR (OR = 0.92, 95% CI: 0.86–0.98), and asthma and AR (OR = 0.83, 95% CI: 0.79–0.88). The risk of having AR without asthma was significantly higher in upper social classes (OR = 1.23, 95% CI: 1.08–1.39), while asthma alone (OR = 1.06, 95% CI: 0.92–1.23) or with AR (OR = 0.99, 95% CI: 0.81–1.22) was not statistically associated with social class. Active actual smoking exposure was positively associated with asthma alone (OR = 1.24, 95% CI: 1.09–1.41) and negatively associated with rhinitis with (OR = 0.69, 95% CI: 0.54–0.88) or without (OR = 0.76, 95% CI: 0.69–0.84) asthma. The pollution annoyance score showed an opposite pattern and was positively associated with AR alone

(OR = 1.51, 95% CI: 1.21–1.88) and with asthma (OR = 1.67, 95% CI: 1.29–2.15) but not with asthma alone (OR = 1.04, 95% CI: 0.79–1.37).

Discussion

The ISAYA is the largest epidemiological study on adult asthma ever to have been carried out in Italy (14). The response rate was quite high (72.7%), very similar to those obtained in other multicentre studies on young adults (23), and nonresponse was mainly due to organizational problems (wrong addresses or the use of not completely updated sampling frames), rather than to refusal to answer the questionnaire (25). Only the Siracusa response rate is particularly low (48.7%), with the next lowest being Ferrara (70.1%) that is instead very near the average.

The strength of our analysis is the use of the multinomial logistic regression model (MLRM) in order to prevent bias due to nonindependence between the outcomes, i.e. asthma and rhinitis (28). The MLRM is the extension of the standard logistic regression model (SLRM) to the case where the dependent variable has more than two categories (asthma, AR, asthma and AR). The simple SLRM requires AR or asthma to be considered separately as dependent variables, and this greatly limits the efficacy and the robustness of the model. For example, when considering asthma, the reference category (i.e. not asthma) will consist of subjects without asthma but who may suffer from AR, and this will often produce a bias in the estimation of risk factor effects if AR and asthma share (or have the opposite effect for) the same risk factor. Instead, the more sophisticated MLRM allows us to estimate simultaneously the effect of risk factors both on the condition and on their association, without bias in the estimation of the common risk factors.

Asthma and rhinitis coexist in a substantial percentage of patients; nearly 60% of asthmatics also have AR and people affected by AR have an eightfold risk of having asthma compared to subjects without AR. These results are in agreement with previous ones, as asthma symptoms may be mimicked by symptoms of rhinitis, such as cough and postnasal drip (6, 29), leading to a misclassification. Besides exacerbating asthma, AR may also play a causal role by either inciting or inducing asthma. From this point of view we could simply consider AR to be an atopy proxy or atopy marker (2, 30, 31). However, some authors (13) have demonstrated that rhinitis is a significant risk factor for developing asthma also in nonallergic subjects, suggesting that the association may not be due only to atopy.

Our finding that older subjects had a lower risk of AR, asthma and their association is in agreement with other studies (7), although other authors have demonstrated the opposite pattern (22, 32).

The higher prevalence of AR, but not of asthma, in the higher social class is in agreement with previous findings

(30, 33, 34). This may be due to the better availability of therapy and detailed education on how to correctly treat rhinitis in that class, thus reducing the risk of developing bronchial asthma (35, 36).

In this study a new finding (thanks to the MLRM) is the differential behaviour of asthma alone *vs* rhinitis with or without asthma with regard to smoking habits and subjects' perception of air pollution. With regard to smoking, we found that the risk of having AR with or without asthma is lower in smokers than in non- or ex-smokers: the lower prevalence in smokers could be explained by a selective effect (subjects with AR either do not start smoking or they stop smoking sooner) (37). Also in other studies smoking was associated with a lower prevalence of AR in adults (30) and this finding was attributed to an effect of selection (38, 39). However, in the absence of longitudinal studies, it is difficult to establish whether smoking is a protective factor of allergy or not (40). The possible selective effect seems to act only on subjects with AR and not on asthmatic subjects without AR: it is likely that some of the asthmatic subjects without AR have a smoking-related chronic bronchitis that has been misclassified as asthma.

With regard to the effect of the perception of pollution, which is positively associated with AR but not with asthma without AR, this is a very complex matter concerning subjective sensitivity to the smell of traffic or industry and the objective presence of outdoor pollution. The nose is the detector and the target of such pollution. Exposure to irritants can induce symptoms in asthmatic subjects with AR (41, 42) more than in subjects without AR; it is well-known that environmental pollution exposure affects allergic subjects in different ways to non allergic subjects, probably due to synergism or effect modification between allergens and pollutants, particularly oxidants and particulates (14, 43).

A possible limitation of this study is that it was based only on a screening questionnaire: in this study phase we performed no allergy skin tests or immunoglobulin E (IgE) measurements. The classification of rhinitis as allergic was made only using a subjective response; however, this response seems to be, albeit with some obvious imprecision, very specific for AR (2, 31). The risk factor panel is, of course, very restricted and does not consider the potential contribution of many other relevant variables such as number of siblings, presence of household pets, family history of atopy (1, 3, 32). Consequently our results have to be considered as an attempt to generate hypotheses for subsequent work using a more extensive clinical questionnaire and some objective tests for allergy and asthma severity (44).

In conclusion, this study suggests that the association between asthma and AR is epidemiologically significant as most young adults in Italy with bronchial asthma also have AR and, conversely, the risk of asthma in subjects with AR is significantly higher than the risk in subjects

without AR. Bronchial asthma and AR, when associated, seem to share the same risk factors as AR alone while asthma without AR seems to be a different condition, at least with respect to some relevant risk factors.

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