

Determinants of bronchial responsiveness in the European Community Respiratory Health Survey in Italy: evidence of an independent role of atopy, total serum IgE levels, and asthma symptoms

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Allergy 1998; 53: 673–681. © Munksgaard 1998.

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The aim of the analysis was to test whether total serum IgE levels, specific serum IgE levels, and asthma symptoms are independent predictors of bronchial hyperresponsiveness (BHR), after controlling for known risk factors or potential confounders. The study was carried out on a sample of 875 young adults, 20–44 years old, who took part in the European Community Respiratory Health Survey in Italy. The subjects underwent a dose-response methacholine challenge test. We also measured airway caliber as the baseline FEV₁ in absolute terms and as percentage of forced vital capacity (FVC); skin wheal response to 11 common environmental allergens; and total and specific serum IgE levels to mites, molds, pets, and respiratory symptoms by means of a standardized questionnaire. Atopy (positive skin prick test and/or positive specific IgE assay), total IgE, asthma symptoms, airway caliber, and age appeared to be independent predictors of BHR. When all the other risk factors were taken into account, atopy and total IgE were associated with a threefold increase in BHR risk and thus emerged as the main determinants of BHR. The importance of symptom status as a determinant of BHR decreased remarkably after controlling for atopy and IgE: the odds ratio of current asthmatics to asymptomatic subjects decreased from 15.3 to 8.8. When controlling for symptoms and atopy, a family history of allergic diseases and early respiratory infections was not found to be associated with BHR. Both FEV₁ and FEV₁/FVC were strongly and inversely associated with BHR. When airway caliber was taken into account, older age was associated with decreased responsiveness, and the level of responsiveness did not differ significantly between males and females and between smokers and nonsmokers. The results from this analysis indicate that at any given age, irrespective of sex and smoking habits, total serum IgE, specific IgE, airway caliber, and asthma symptoms are the main independent factors influencing the occurrence of BHR in a young adult sample.

Key words: airway caliber; asthma epidemiology; bronchial hyperresponsiveness; IgE levels; skin test reactivity.

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Accepted for publication 13 February 1998

Epidemiologic and clinical studies on the biologic characteristics associated with bronchial hyperresponsiveness (BHR) have demonstrated that increased airway responsiveness is a common, though nonspecific, feature of subjects with bronchial asthma (1–3). In addition to respiratory

diseases, various other factors may be associated with BHR. Previous reports have almost invariably shown that sensitization to common allergens is a strong predictor of BHR (4–6). Furthermore, recent population studies have demonstrated an association between prevalence of asthma (defined

by symptoms and BHR) and total immunoglobulin E (IgE) serum levels, independent of specific IgE (7), suggesting a close interrelationship between total IgE and BHR, even in nonatopic subjects.

The prevalence of BHR is also influenced by sex, age (8, 9), cigarette smoking (10, 11), and airway caliber (8, 12). These observations are a proof of the complex, multifaceted, pathogenetic mechanism which contributes to the development of increased BHR.

In most of the studies on factors associated with bronchial responsiveness, either the effects of various determinants were evaluated separately, or the study was not designed to check all the relevant confounders (2, 12, 13). Furthermore, no previous investigation has looked at the potential independent role of total and specific IgE.

The aim of this analysis was to evaluate the independent role of different clinical or physiologic factors in explaining individual variability in methacholine-induced bronchoconstriction in young adults. In particular, we tested whether total IgE, atopy, and asthma symptoms are independent predictors of BHR, after controlling for known risk factors and potential confounders. The data presented were collected within the European Community Respiratory Health Survey (ECRHS), in a population sample from Verona, Pavia, and Turin, three cities in northern Italy.

Material and methods

Subjects

The ECRHS is an international, multicenter survey of the prevalence, determinants, and management of asthma (14). In Italy, the ECRHS involved three cities: Pavia, Turin, and Verona.

The design of the ECRHS involved two stages. In the first stage (15, 16), a screening questionnaire on respiratory symptoms was mailed to a random

sample of 20–44-year-old men and women. In the second stage (17), a 20% random sample of those who had answered the mailed questionnaire were invited to the local chest clinic, where they underwent a standardized clinical interview, allergic skin tests, and bronchial challenge with methacholine. Subjects who, in the screening questionnaire, had reported asthma attacks, taking medicine for asthma, or waking up because of breathlessness, were also asked to attend stage 2.

Of the 6031 subjects who had returned the questionnaire, 1835 were invited to the clinical centers. Of these, 899 agreed to take part in stage 2, and there was a 49% attendance rate. In addition, the clinical centers recruited a further 190 subjects who had reported asthma-like symptoms in the screening questionnaire and 15 subjects who had refused to attend stage 1; a total number of 1104 ECRHS stage 2 attenders was thus reached. Of these, 229 subjects (20.8%) either were not eligible for the challenge, refused to undergo the test, or were excluded from the analysis because of incomplete information.

Therefore, a total of 875 subjects formed the study group.

Questionnaire and interview information

Data on age, sex, smoking habits, early respiratory infections, family history of asthma/allergy, and symptoms were collected by means of the ECRHS standardized clinical interview (18) administered by medical doctors.

According to the symptoms reported, subjects were classified into six mutually exclusive subgroups:

- 1) “current asthma”, comprising subjects who reported having had an asthma attack during the previous 12 months and/or who were using asthma drugs at the time of the interview
- 2) “past asthma”, comprising subjects not belonging to group 1 but reporting asthma attacks at any time during their life
- 3) “wheezing and shortness of breath”, comprising subjects who had not been included in groups 1 and 2 but who reported at least one of the following symptoms: wheezing or whistling in the chest, awakening with a feeling of chest tightness, shortness of breath at rest or after strenuous activity, and awakening because of an attack of breath shortness during the previous 12 months
- 4) “allergic rhinitis/eczema”, comprising subjects not belonging to groups 1–3 but reporting at least one of the following symptoms: nasal allergy, including hay fever, eczema, and difficulty with breathing after taking medicines

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These results are from a local analysis of data collected for the European Community Respiratory Health Survey (ECRHS). Any final international comparison may use a different form of analysis.

- 5) "cough and phlegm", comprising subjects not included in groups 1–4 but who reported at least one of the following symptoms: waking up because of an attack of coughing during the last 12 months, habitual cough in the morning or during the day, and habitual phlegm during winter
- 6) "no symptoms", comprising the remaining subjects, who had reported no symptoms in the ECRHS clinical interview.

The subjects' smoking habits were classified into the following mutually exclusive groups:

- 1) "nonsmokers" – subjects who had not smoked for as long as 1 year; i.e., subjects who had not smoked at least 20 packs of cigarettes or 360 g of tobacco in their lifetime, or at least one cigarette a day or one cigar a week for 1 year
- 2) "ex-smokers" – subjects who had smoked for at least 1 year but not during the last month
- 3) "smokers" – subjects who had smoked for at least 1 year and also during the last month.

A family history of asthma/allergy was considered to be present when subjects declared that their mother, father, brothers, or sisters had had asthma or eczema, skin or nasal allergy, or hay fever.

The question to detect early respiratory illness was as follows: "Did you have a serious respiratory infection before the age of five?"

Total and specific IgE and skin prick test

Serum IgE was measured by taking 10 ml of venous blood from each subject who consented. The sample was then sent on dry ice to a central laboratory at Pharmacia Diagnostics AB (Uppsala, Sweden), according to the European protocol (14).

Specific and total IgE was measured by the Pharmacia CAP System. The working range for the assay of total IgE was 2 kilounits per liter (kU/l) to 2000 kU/l. For this analysis, total IgE was categorized into the following three levels: <150 kU/l; ≥150 kU/l; and unknown (for missing data).

All assays for specific IgE were judged to be positive if they were greater than 0.35 kU/l (i.e., the lower limit of detection of the assay) for the specific allergen. Specific IgE was measured against *Dermatophagoides pteronyssinus*, timothy grass, cat, *Cladosporium herbarum*, and *Parietaria judaica*.

Skin testing was done with Phazets (Pharmacia Diagnostics AB, Uppsala, Sweden).

The allergens selected for use in all ECRHS areas were those of *D. pteronyssinus*, cat, *Alternaria alternata*, *C. herbarum*, timothy grass, birch, *P. judaica*, olive, ragweed, and, in Italy, *D. farinae* and *Artemisia vulgaris*.

Fifteen minutes after the application of allergens, wheal size was recorded as the mean of the long axis and its perpendicular. The skin prick test was judged to be positive in the case of one or more wheal diameters of ≥3 mm.

Atopy was considered to be present when the skin prick test and/or the specific IgE assay were positive; to be absent if both the skin prick test and specific IgE were negative; and to be unknown in the remaining cases.

Bronchial responsiveness

One-second forced expiratory volume (FEV₁) and forced vital capacity (FVC) were measured with a water-sealed spirometer (Biomedin, Padova, Italy), according to the recommendations of the European Respiratory Society (19). All subjects who were suffering from heart disease or epilepsy, were pregnant or breast-feeding, or were taking beta-blockers were excluded from the methacholine challenge. Subjects with the best initial FEV₁ lower than 70% of the predicted value or postdiluent FEV₁ lower than 90% of the initial FEV₁ were also excluded.

The methacholine challenge (20) (Provocholine, Hoffman La Roche, Basel, Switzerland) was carried out with an ampoule-dosimeter device with an output of 10 µl/breath, triggered by an inspiration-activated solenoid valve (Mefar, Brescia, Italy). Five solutions of methacholine (0.39, 1.56, 6.25, 12.5, and 25 mg/ml, respectively) in a phosphate buffer were prepared daily. A separate solution containing a phosphate buffer was available to allow a buffer challenge before beginning the test. Methacholine was inhaled by the subjects in doses ranging from 7.8 µg up to a total cumulative dose of 2000 µg. The dose was increased by changing the methacholine concentration and/or the number of breaths. FEV₁ was determined 2 min after administration of the buffer and 2 min after each dose of methacholine. The methacholine test was stopped if there was a ≥10% fall in FEV₁ from baseline value after inhalation of the buffer, or when FEV₁ fell more than 20% as compared with the value measured after the buffer challenge, or when the highest dose of methacholine was reached. The results were expressed as the dosage of methacholine causing a 20% fall in FEV₁ (PD₂₀). Subjects were classified as reactive to methacholine if they had a PD₂₀ of <2000 µg.

Statistical analysis

Logistic regression was used to assess the likelihood of variables being independently associated with BHR and to determine unadjusted and adjusted odds ratios and their 95% confidence intervals (CI) (21).

A dummy variable indicating the occurrence of a 20% fall in initial FEV₁ was used as a dependent variable, whereas age, sex, smoking habits, early respiratory infections, asthma/allergy in the family, symptom groups, FEV₁, FEV₁/FVC%, atopy, and total IgE were considered explanatory variables. Age, baseline FEV₁, and FEV₁/FVC% served as continuous variables. The odds ratios for age, FEV₁, and FEV₁/FVC were computed on the basis of one standard deviation increase in the values.

The relative weight of each covariate in explaining the variations in BHR (explanatory weight) was measured as the percent ratio of the conditional deviance of that covariate to the deviance explained by the full model (the model including all covariates). The conditional deviance is the change in deviance due to the removal of a given covariate when all the others are included in the model.

Statistical analysis was performed with the EGRET program (22).

Results

The distribution of the potential determinants in the sample is shown in Table 1. Table 2 shows the percentage of subjects who had a 20% fall in FEV₁ in the different levels of the studied factors; the

unadjusted risk estimates (crude odds ratio) are also reported. When considered alone, age and smoking habits did not seem to affect the response to the challenge test. Sex, early respiratory infection, family history of asthma/allergy, symptoms, atopy, and total IgE significantly increased the occurrence of BHR whereas baseline airway caliber (both FEV₁ and FEV₁/FVC) was negatively associated with BHR.

When baseline airway caliber, atopy, and total serum IgE were not taken into account (Table 3), the main determinant of BHR was the respiratory-allergic symptom status, which alone accounted for 67% of the deviance explained by all the covariates in the model. For asymptomatic subjects, current and past asthmatics showed an odds ratio of 19.9 (95% CI 8.8–45.1) and 5.8 (2.7–12.4), respectively. Sex emerged as the second relevant covariate (see last column of Table 3). When adjusting for the symptom status, the odds ratios of early respiratory infections and of family history of asthma/allergy were no longer statistically significant.

After allowing for the effect of baseline airway caliber, the goodness of fit of the model improved by 26.7%: the explained deviance increased from 105.6 with 13 degrees of freedom (d.f.) to 134.1 with 15 d.f. Symptoms were again the main determinant of BHR (Table 4, last column), but baseline airway

Table 1. Potential risk factors for BHR in 875 subjects undergoing methacholine challenge test during ECRHS in Italy. Results are summarized through mean (SD) for continuous variables and through absolute and percent frequencies for categoric variables

		Men (n=445)		Women (n=430)	
Age (years)		34.1	(7.0)	33.5	(6.9)
Basal FEV ₁ (l)		4.36	(0.70)	3.21	(0.48)
FEV ₁ /FVC%		84.2	(6.3)	86.0	(6.5)
Smoking habits	Nonsmokers	166	(37.3%)	204	(47.4%)
	Smokers	191	(42.9%)	145	(33.7%)
	Ex-smokers	88	(19.8%)	81	(18.8%)
Early respiratory infections	No	363	(81.6%)	338	(78.6%)
	Yes	47	(10.6%)	54	(12.6%)
	Unknown	35	(7.9%)	38	(8.8%)
Family history of asthma/allergy	No	258	(58.0%)	208	(48.4%)
	Yes	150	(33.7%)	196	(45.6%)
	Unknown	37	(8.3%)	26	(6.0%)
Symptom status	No symptoms	139	(31.2%)	106	(24.7%)
	Current asthma	18	(4.0%)	25	(5.8%)
	Past asthma	28	(6.3%)	26	(6.0%)
	Wheezing/breath shortness	100	(22.5%)	109	(25.3%)
	Allergic rhinitis/eczema	95	(21.3%)	118	(27.4%)
	Cough and phlegm	65	(14.6%)	46	(10.7%)
Atopy	No	220	(49.4%)	256	(59.5%)
	Yes	166	(37.3%)	112	(26.0%)
	Unknown	59	(13.3%)	62	(14.4%)
IgE kU/l	<150	285	(64.0%)	306	(71.2%)
	≥150	81	(18.2%)	57	(13.3%)
	Unknown	79	(17.8%)	67	(15.6%)

Table 2. Number of subjects who reacted to methacholine, with percentage in parentheses, in different level of potential risk factors, and unadjusted risk estimates (odds ratios and 95% confidence intervals) of having 20% fall in FEV₁ during challenge test

		number of reactives	(%)	Unadjusted odds ratios	(95% CI)
Age (years)	<30	59	(18.3%)	1.00	
	30–38	45	(16.0%)	0.85	(0.5–1.3)
	>38	40	(14.8%)	0.77	(0.5–1.2)
Sex	M	50	(11.2%)	1.00	
	F***	94	(21.9%)	2.21	(1.5–3.2)
Smoking habits	Nonsmokers	63	(17.0%)	1.00	
	Smokers	51	(15.2%)	0.87	(0.6–1.3)
	Ex-smokers	30	(17.8%)	1.05	(0.6–1.7)
Early respiratory infections	No	108	(15.4%)	1.00	
	Yes*	24	(23.8%)	1.71	(1.0–2.8)
	Unknown	12	(16.4%)	1.08	(0.5–2.0)
Family history of asthma/allergy	Absent	55	(11.8%)	1.00	
	Present***	79	(22.8%)	2.21	(1.5–3.2)
	Unknown	10	(15.9%)	1.41	(0.7–2.9)
Symptom status	No respiratory symptoms	19	(7.8%)	1.00	
	Current asthma***	28	(65.1%)	23.5	(10.8–11.5)
	Past asthma***	18	(33.3%)	6.32	(3.0–13.1)
	Wheezing/breath shortness**	37	(17.7%)	2.72	(1.5–4.9)
	Allergic rhinitis/eczema*	32	(15.0%)	2.56	(1.4–4.7)
Baseline FEV ₁ (l)	Cough and phlegm	10	(9.0%)	1.15	(0.5–2.5)
	<3.29	78	(27.6%)	1.00	
	3.29–4.08***	42	(14.5%)	0.45	(0.3–0.7)
	>4.08***	24	(7.9%)	0.23	(0.1–0.4)
FEV ₁ /FVC%	<82.8	61	(20.9%)	1.00	
	82.8–87.9	45	(15.4%)	0.69	(0.4–1.0)
	>87.9*	38	(13.1%)	0.57	(0.4–0.9)
Atopy	No	34	(7.1%)	1.00	
	Yes	85	(30.6%)	5.73	(3.7–8.8)
	Unknown	25	(20.7%)	3.39	(1.9–5.9)
IgE (KU/e)	<150	60	(10.2%)	1.00	
	≥150	42	(30.4%)	3.87	(2.5–6.1)
	Unknown	42	(28.8%)	3.57	(2.3–5.6)

*, **, *** refer to significance of odds ratios: * $P<0.05$; ** $P<0.01$; *** $P<0.001$; Age, FEV₁, and FEV₁/FVC classes refer to tertiles.

caliber played an important role as an explanatory variable. After its introduction in the model, the twofold increase in risk of BHR for women (see Table 2) disappeared completely. Furthermore, a significant negative association between age and BHR emerged, so that BHR decreased with advancing age.

The odds ratios for current and past asthma showed a slight decrease after the introduction of the FEV₁/FVC ratio, suggesting that the narrowing of baseline airway caliber partly explains the enhanced response of asthmatic subjects to bronchoconstrictor agents.

Table 5 shows the adjusted odds ratios when total serum IgE and atopy were taken into account. When these variables were added, they improved the fit of the model by another 50%: the explained deviance increased from 134.1 with 15 d.f. to 201.3 with 17 d.f. When the effect of atopic status was allowed for, it was found to be the covariate with the highest explanatory power (see last column).

Both atopy and IgE increased, significantly and independently, the risk of BHR. The odds ratios for the other covariates were virtually unchanged except for the symptoms, which showed a substantial reduction in the risk estimates. The odds ratios for current asthmatics decreased from 15.3 to 8.8 and those for past asthmatics from 4.9 to 3.2. The odds ratios for the other symptomatic groups were no longer significant. Nevertheless, asthma symptoms were, to a large extent, an independent determinant of reactivity, as suggested by the adjusted odds ratios for asthmatic subjects, which remained significantly higher than 1, even if adjusted for atopy and IgE.

There was no statistical evidence of multiplicative interactions between any of these variables.

Discussion

The present analysis of ECRHS stage 2 data in Italy was conducted to establish the relative impor-

Table 3. Adjusted odds ratios (OR), 95% confidence intervals (CI), and explanatory weight (%)¹ for effect of age, sex, smoking habit, early respiratory infections, family history of asthma/allergy, and respiratory-allergic symptom status on odds of reacting to methacholine. Odds ratio for age was computed on basis of increase in values of one standard deviation

	OR	95% CI	Explanatory weight (%)
Age (SD=7.0 years)	1.01	(0.8–1.2)	0.001
Sex			
F***	2.06	(1.4–3.2)	12.8
Smoking habits			
Smokers	0.83	(0.5–1.3)	0.01
Ex-smokers	1.01	(0.6–1.7)	
Early respiratory infections			
Yes	1.23	(0.7–2.2)	1.3
Unknown	1.02	(0.5–2.1)	
Family history of asthma/allergy			
Present	1.46	(0.9–2.2)	4.0
Unknown	1.20	(0.5–2.6)	
Symptom status			
Current asthma***	19.90	(8.8–45.1)	67.0
Past asthma***	5.82	(2.7–12.4)	
Wheezing/tightness**	2.54	(1.4–4.6)	
Allergic rhinitis/eczema*	2.21	(1.2–4.0)	
Cough	1.20	(0.5–2.6)	

¹Explanatory weight is conditional change in deviance due to each term in model, divided by deviance explained by full model.

*, **, *** refer to significance of odds ratios: * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

tance and independent effects of self-reported asthma symptoms, atopy, and total serum IgE on the occurrence of BHR, after controlling for the main known determinants of BHR.

Our sample of young adults was not a genuine random sample from the general population, because of selection processes concerning the attendance at stage 2 (i.e., the clinical stage) of the ECRHS (15), the eligibility criteria for the challenge test (14), and the addition of symptomatic subjects. If this precludes inference of the true prevalence of BHR in specific populations, it does not limit in any way the assessment of the risk factors (23).

We chose to classify subjects as either reactive or not reactive, rather than to use a measure such as PD₂₀, mainly to make comparison with previous studies easier. This simple way of summarizing the individual response to the challenge test yields results that are very consistent with those obtained through other methods, such as the slope of O'Connor (24).

The results of our study show that atopy, total IgE level, self-reported asthma, and airway caliber are the main independent determinants of BHR. Other variables considered in the analysis such as sex, age, and smoking habits were confounders or were less powerful predictors of BHR.

In atopic subjects, as defined according to specific IgE and/or skin prick test, there was a more

Table 4. Adjusted odds ratios (OR), 95% confidence intervals (CI), and explanatory weight (%)¹ for effect of age, sex, smoking habit, early respiratory infections, family history of asthma/allergy, respiratory-allergic symptom status, baseline FEV₁, and baseline FEV₁/FVC (%) on odds of reacting to methacholine. Odds ratios for age, FEV₁, and FEV₁/FVC were computed on basis of increase in values of one standard deviation

	OR	95% CI	Explanatory weight %
Age (SD=7.0 years)*	0.79	(0.6–1.0)	3.0
Sex			
F	0.96	(0.5–1.7)	0.01
Smoking habits			
Smokers	0.75	(0.5–1.2)	1.0
Ex-smokers	1.03	(0.6–1.8)	
Early respiratory infections			
Yes	1.17	(0.7–2.0)	0.1
Unknown	1.01	(0.5–2.2)	
Family history of asthma/allergy			
Present	1.40	(0.9–2.1)	2.0
Unknown	1.12	(0.5–2.5)	
Symptom status			
Current asthma***	15.30	(6.6–35.6)	42.0
Past asthma***	4.93	(2.3–10.6)	
Wheezing/tightness**	2.28	(1.3–4.3)	
Allergic rhinitis/eczema*	2.19	(1.2–4.1)	
Cough	1.01	(0.4–2.3)	
Baseline FEV ₁ (l)***	0.51	(0.4–0.7)	9.0
FEV ₁ /FVC%***	0.72	(0.6–0.9)	7.0

¹Explanatory weight is conditional change in deviance due to each term in model, divided by deviance explained by full model.

*, **, *** refer to significance of odds ratios: * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

than threefold increase in BHR risk, even in the absence of respiratory symptoms. A more than threefold increase in BHR risk was also associated with high total IgE serum levels, independently of the presence of specific IgE or of asthma symptoms.

The role of total IgE in bronchial impairment has been reported in previous studies (2, 6, 25), but this one is the first to demonstrate that the effect on airway responsiveness is not related to atopy as detected by skin prick tests or by specific IgE, and is independent of the presence of asthma symptoms. Thus, our data indirectly confirm previous findings of a relationship between total IgE and asthma in nonatopic subjects (7, 26). Moreover, the present study adds further evidence of the association between airway responsiveness and IgE reported by Sears et al. both in children with asthma and in apparently normal children (13).

One might suspect that our results reflect the gross inadequacy of the testing of allergens by skin test or by specific IgE. But this was not the case, since both tests were done with various allergens very common in northern Italy. In addition, very

Table 5. Adjusted odds ratios (OR), 95% confidence intervals (CI), and explanatory weight¹ for effect of age, sex, smoking habit, early respiratory infections, family history of asthma/allergy, respiratory-allergic symptom status, baseline FEV₁, baseline FEV₁/FVC (%), atopy, and total IgE on odds of reacting to methacholine. Odds ratios for age, FEV₁, and FEV₁/FVC were computed on basis of increase in values of one standard deviation

	OR	95% CI	Explanatory weight %
Age (SD=7.0 years)*	0.80	(0.6–1.)	2.0
Sex			
F	1.29	(0.7–2.4)	0.3
Smoking habits			
Smokers	0.74	(0.4–1.2)	0.8
Ex-smokers	0.97	(0.5–1.7)	
Early respiratory infections			
Yes	1.26	(0.7–2.3)	0.3
Unknown	1.11	(0.5–2.4)	
Family history of asthma/allergy			
Present	1.21	(0.7–1.8)	0.2
Unknown	1.04	(0.4–2.3)	
Symptom status			
Current asthma***	8.84	(3.5–21.2)	13.0
Past asthma**	3.19	(1.4–7.1)	
Wheezing/tightness	1.79	(0.9–3.5)	
Allergic rhinitis/eczema	1.77	(0.9–3.6)	
Cough	1.20	(0.5–2.9)	
Baseline FEV ₁ ***	0.50	(0.3–0.7)	8.0
FEV ₁ /FVC***	0.71	(0.5–0.8)	6.0
Atopy			
Yes***	3.49	(2.0–5.8)	11.0
Unknown	1.50	(0.6–3.6)	
IgE			
≥150 KU/I ***	3.18	(1.8–5.4)	10.0
Unknown***	3.00	(1.4–6.4)	

17

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¹Explanatory weight is conditional change in deviance due to each term in model, divided by deviance explained by full model.

*, **, *** refer to significance of odds ratios: **P*<0.05; ***P*<0.01; ****P*<0.001.

low rates of reactions to less common allergens were found in a subset of our population who underwent quite extensive allergy skin testing (M. Olivieri, personal data).

Total IgE might also be an expression of humoral autoimmunity, since IgE antibody reactive to human proteins structurally similar to pollen proteins has been recently demonstrated (27). This IgE reactivity to a self-antigen suggests a mechanism partially independent of allergen stimulus that could maintain a high titer of IgE in type I allergy (27).

High serum IgE levels seem to be inherited as an autosomal genetic recessive trait with an additional polygenic component, whereas different factors seem to govern the specific IgE response (28). Therefore, it is tempting to speculate that each of these allergy indexes might express separate genetic traits, which, in turn, might be differently related to the pathogen-

esis of airway hyperresponsiveness. It is also possible that the relationship observed expresses the coinheritance of two genetic traits associated with atopy and bronchial responsiveness (7).

A different explanation is that total serum IgE levels are the consequence, instead of the cause, of the bronchial inflammation causing airway hyperresponsiveness. In bronchial asthma, lymphocyte infiltration of the bronchial mucosa has been reported (29), and recent studies have shown that polyclonal IgE production may be the consequence of the release of interleukin-4 by T cells, by a mechanism which is not related to the presence of the antigen (30). The fact that the relationship between total IgE levels and BHR is independent of bronchial asthma (and probably of bronchial inflammation) does not support this hypothesis.

Atopy and total IgE together accounted for 33% of the total deviance explained by all the variables studied, strongly underlining the importance of IgE synthesis in the pathogenesis of BHR.

Self-reported asthma heavily influences bronchial reactivity. In respect to asymptomatic subjects, current asthmatics showed a 9–20-fold increase in the risk of BHR. Past asthmatics had a 3–6-fold higher risk, suggesting that the effect of asthma decreases with the passing of time from the last attack, but does not disappear. This evidence supports the hypothesis that, in some asthmatics, minimal inflammation persists in symptom-free periods to a degree sufficient to increase BHR (31). The decrease in the odds ratios for asthma after controlling for atopy and IgE (15.3 vs 8.8 for current asthma; 4.9 vs 3.2 for past asthma) indicates that atopic status partially explains increased BHR in asthmatic subjects. Nevertheless, a marked effect of asthma not related to atopy still remains to be explained.

Baseline airway caliber was associated in a highly significant manner with hyperresponsiveness. In particular, FEV₁ and FEV₁/FVC were independently and negatively related to the risk of BHR. This result indicates that subjects with normal but small airways (i.e., those with a low absolute FEV₁ value) or with relative bronchial narrowing (i.e., those with a low FEV₁/FVC ratio) may be expected to have an increased response to an inhaled bronchoconstrictor.

After the adjustment for baseline airway caliber, age exerted a significant independent effect, so that higher age became associated with lower risk of BHR. Our data thus indicate, in agreement with Britton et al. (4) but in contrast to data from Rijcken et al. (32), that normal-size airways in older subjects are relatively unlikely to be hyper-reactive. However, these results must be interpreted with caution, because of the narrow age range of our sample.

The number of reports on the relationship of sex to bronchial responsiveness is limited and the results are conflicting (4, 8, 32). In our analysis, the twofold increase in risk of BHR for women vanished when we controlled for baseline FEV₁, indicating that the higher reactivity in women is almost totally due to their lower airway caliber. Hence, our results demonstrate that the level of responsiveness did not differ between men and women if the sex difference in pulmonary function was taken into account.

A family history of asthma/allergy, early respiratory infections, and allergic rhinitis did not prove to be significant when the model accounted for symptomatic and atopic status.

Our finding that smoking habits do not exert any influence on BHR is only apparently in contrast to previously reported epidemiologic evidence, and can be explained by the young age of the population studied. In fact, an increase in the risk of BHR has been reported in older subjects (5, 10, 11).

Acknowledgement

This work was partly supported by grants from the Italian Ministry for University and Scientific and Technological Research.

References

- Bakke PS, Baste V, Gulsvik A. Bronchial responsiveness in a Norwegian community. *Am Rev Respir Dis* 1991; 143:317-22.
- Burrows B, Sears MR, Flannery EM, Herbison GP, Holdaway MD. Relationships of bronchial responsiveness assessed by methacholine to serum IgE, lung function, symptoms and diagnoses in 11-year-old New Zealand children. *J Allergy Clin Immunol* 1993;90:376-85.
- Peat JK, Salome CM, Woolcock AJ. Factors associated with bronchial hyperresponsiveness in Australian adults and children. *Eur Respir J* 1992;5:921-9.
- Britton J, Pavord I, Richards K, et al. Factors influencing the occurrence of airway hyperreactivity in the general population: the importance of atopy and airway caliber. *Eur Respir J* 1994;7:881-7.
- Rode A, Shephard RJ. The ageing of lung function: cross sectional and longitudinal studies of an Inuit community. *Eur Respir J* 1994;7:1653-9.
- Sherrill DL, Lebowitz MD, Halonen M, et al. Longitudinal evaluation of the association between pulmonary function and total serum IgE. *Am J Respir Crit Care Med* 1995; 152:98-102.
- Sunyer J, Anto JM, Castellsaguè J, et al. Total serum IgE is associated with asthma independently of specific IgE levels. *Eur Respir J* 1996;9:1880-4.
- Paoletti P, Carozzi L, Viegi G, et al. Distribution of bronchial responsiveness in a general population: effect of sex, age, smoking, and level of pulmonary function. *Am J Respir Crit Care Med* 1995;151:1770-7.
- Sparrow D, O'Connor BJ, Rosner B, Segal M, Weiss ST. The influence of age and level of pulmonary function on nonspecific airway responsiveness. *Am Rev Respir Dis* 1991;143:978-82.
- Cerveri I, Bruschi C, Zoia MC, et al. Smoking habit and bronchial reactivity in normal subjects. A population-based study. *Am Rev Respir Dis* 1989;140:191-6.
- Tashkin DP, Simmons MS, Chang P, et al. Effects of smoked substance abuse on nonspecific airway hyperresponsiveness. *Am Rev Respir Dis* 1993;147:97-103.
- Dirksen A, Madsen F, Engel T, et al. Airway caliber as a confounder in interpreting bronchial responsiveness in asthma. *Thorax* 1992;47:702-5.
- Sears MR, Burrows B, Flannery EM, et al. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 1991;325:1067-71.
- Burney PGJ, Luczynska C, Chinn S, et al. European Community Respiratory Health Survey. *Eur Respir J* 1994; 7:954-60.
- De Marco R, Verlato G, Zanolin E, et al. Nonresponse bias in EC Respiratory Health Survey in Italy. *Eur Respir J* 1994;7:2139-45.
- European Community Respiratory Health Survey – Italy. Prevalence of asthma and asthma symptoms in a general population sample from northern Italy. *Allergy* 1995;50: 755-9.
- Verlato G, Cerveri I, Villani A, et al. Evaluation of methacholine dose response curves by linear and exponential mathematical models: goodness of fit and validity of extrapolation. *Eur Respir J* 1996;9:506-11.
- Burney PGJ, Laitinen LA, Perdrizet S, et al. Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. *Eur Respir J* 1989;2:940-5.
- Quanjer PH. Standardised lung function testing. *Bull Eur Physiopathol Respir* 1983;Suppl 5:1-95.
- Chinn S, Burney P, Jarvis D, Luczynska C. Variations in bronchial responsiveness in the European Community Respiratory Health Survey. *Eur Respir J* 1997;10:2495-2501.
- Clayton D, Hills M. Statistical models in epidemiology. Oxford: Oxford University Press, 1994.
- EGRET: Epidemiological Graphics, Estimation and Testing. Seattle: Epidemiological Resources, 1991.
- Miettinen OS. Theoretical epidemiology. Principles of occurrence research in medicine. Albany: Delmar, 1985.
- De Marco R, Bugiani M, Zanolin E, et al. Doses and models for risk assessment analysis for bronchial hyperresponsiveness (BHR). *J Clin Epidemiol* 1998;51:19-28.
- Tracey M, Villar A, Dow L, Coggon D, Lampe FC, Holgate ST. The influence of increased bronchial responsiveness, atopy and serum IgE on decline in FEV₁: a longitudinal study in the elderly. *Am J Respir Crit Care Med* 1995;151:856-62.
- Burrows B, Martinez FD, Halonen M, et al. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med* 1989;320:271-7.
- Valenta R, Duchêne M, Pettenburger K, et al. Identification of profilin as a novel pollen allergen; IgE autoreactivity in sensitized individuals. *Science* 1991;253: 557-9.
- Sibbad B. Genetics. In: Barnes PJ, Rodger IW, Thomson NC, editors. *Asthma: basic mechanism and clinical management*. London: Academic Press, 1992: ch. 2.
- Lundgren R, Soderberg M, Horstedt P, Stenling R. Morphological studies of bronchial mucosal biopsies from asthmatics before and after ten years of treatment with inhaled steroids. *Eur Respir J* 1988;1:883-9.

30. Del Prete G, Maggi E, Macchia D, et al. Human T clones can induce *in vitro* IgE synthesis in normal B cells regardless of alloantigen recognition or specificity for peculiar antigens. Eur J Immunol 1986;16: 1509-14.
31. Canonica GW, Ciprandi G, Buscaglia S, et al. Adhesion molecules of allergic inflammation: recent insight into their functional roles. Allergy 1994;49:135-41.
32. Rijcken B, Schouten JP, Mesinga TT, et al. Factors associated with bronchial responsiveness to histamine in a population sample of adults. Am Rev Respir Dis 1993; 147:1447-53.

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