

Allergic Rhinitis and Onset of Bronchial Hyperresponsiveness

A Population-based Study

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Rationale: Patients with allergic rhinitis have more frequent bronchial hyperresponsiveness (BHR) in cross-sectional studies.

Objectives: To estimate the changes in BHR in nonasthmatic subjects with and without allergic rhinitis during a 9-year period.

Methods: BHR onset was studied in 3,719 subjects without BHR at baseline, who participated in the follow-up of the European Community Respiratory Health Survey.

Measurements and Main Results: BHR was defined as a $\geq 20\%$ decrease in FEV₁ for a maximum dose of 1 mg of methacholine. Allergic rhinitis was defined as having a history of nasal allergy and positive specific IgE (≥ 0.35 IU/ml) to pollen, cat, mites, or *Cladosporium*. The cumulative incidence of BHR was 9.7% in subjects with allergic rhinitis and 7.0% in subjects with atopy but no rhinitis, compared with 5.5% in subjects without allergic rhinitis and atopy (respective odds ratios [OR] and their 95% confidence intervals [95% CI] for BHR onset, 2.44 [1.73–3.45]; and 1.35 [0.86–2.11], after adjustment for potential confounders including sex, smoking, body mass index and FEV₁). Subjects with rhinitis sensitized exclusively to cat or to mites were particularly at increased risk of developing BHR (ORs [95% CI], 7.90 [3.48–17.93] and 2.84 [1.36–5.93], respectively). Conversely, in subjects with BHR at baseline ($n = 372$), 35.3% of those with allergic rhinitis, compared with 51.8% of those without rhinitis had no more BHR at follow-up (OR [95% CI], 0.51 [0.33–0.78]). BHR “remission” was more frequent in patients with rhinitis treated by nasal steroids than in those not treated (OR [95% CI], 0.33 [0.14–0.75]).

Conclusions: Allergic rhinitis was associated with increased onset of BHR, and less chance for remission except in those treated for rhinitis.

Keywords: allergic rhinitis; bronchial hyperresponsiveness; ECRHS; epidemiology; longitudinal

Bronchial hyperresponsiveness (BHR), one of the hallmarks of bronchial asthma, is a risk factor for the development of asthma and chronic obstructive pulmonary diseases (1, 2), and has been used as a clinical endpoint for therapeutic intervention in asthma management. In addition, BHR has been shown to be associated

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Allergic rhinitis is strongly associated with bronchial hyperresponsiveness in cross-sectional studies, even in nonasthmatic subjects.

What This Study Adds to the Field

Allergic rhinitis was associated with increased onset of bronchial hyperresponsiveness, and less chance for remission except in those treated for rhinitis.

with an accelerated decline in lung function (3, 4) and with respiratory symptoms (5). Therefore, it has sometimes been considered as a determinant, and sometimes as an intermediary or even endpoint, variable. Because measure of bronchial responsiveness may be standardized, it is of particular interest in international epidemiologic studies (6). Several risk factors for BHR have been identified in epidemiologic studies. The most important, independent risk factors for BHR are lung function and atopy (7, 8). Smoking has been also shown to be associated with an increase in BHR in longitudinal studies (9), and cross-sectional studies have shown that BHR was increased in subjects with allergic rhinitis (10).

Allergic rhinitis is a frequent inflammatory chronic disease induced by an IgE-mediated reaction after allergen exposure in the nasal mucosa. It is now clear from a large number of cross-sectional studies that allergic rhinitis is strongly associated with asthma and BHR (11). These studies have demonstrated that dysfunction of the upper and lower airways frequently occur together and appear to share common risk factors, such as atopy. Many patients with allergic rhinitis and no clinical evidence of asthma showed increased response to methacholine or histamine (10, 12). However, the cross-sectional design of these studies precludes studying the onset of BHR in patients with allergic rhinitis. It has been suggested that longitudinal studies of patients with allergic rhinitis, including assessments of bronchial responsiveness, are critical in understanding the relationship between allergic rhinitis and lower airway diseases (13). This issue has practical implications for physicians who treat patients with chronic respiratory conditions.

Data collected as part of the large, population-based European Community Respiratory Health Survey (ECRHS) have provided valuable information on the cross-sectional association between allergic rhinitis and BHR in young adults (10). We have used the follow-up data of this international multicenter study to estimate the onset of bronchial responsiveness in patients with allergic rhinitis.

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A list of centers and participants for the European Community Respiratory Health Survey is given at the end of the article.

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METHODS

Study Design

This analysis was based on the follow-up data from the ECRHS, which is an international multicenter study involving 24 centers. The methods of ECRHS have been published elsewhere (9, 14–16). Further information is available on the online supplement. The study was approved by the appropriate ethics committee, and informed, written consent was obtained from each participant.

Baseline Study (ECRHS-I), 1991–1993

At stage 1 of ECRHS-I, 3,000 randomly selected men and women aged 20 to 44 years, completed a short, mailed questionnaire. At stage 2 of ECRHS-I, a random sample of responders were invited to a local testing center to answer a more detailed interviewer-administered questionnaire, to provide blood samples, and to perform lung function measurements and a bronchial responsiveness challenge.

Follow-up Study (ECRHS-II), 1998–2002

Participants in ECRHS-I who responded to stage 2 were eligible for ECRHS-II (Figure 1) and were invited to the testing center where, as before, they answered a more detailed interviewer-administered questionnaire, and underwent bronchial responsiveness challenge following the same method as in ECRHS-I.

Measurements

At each occasion, bronchial responsiveness to methacholine was measured in eligible subjects (those having an FEV₁ of at least 70% predicted and >1.5 L, and not suffering from heart disease or epilepsy, not pregnant or breastfeeding, and not taking a β -blocker) (9, 16). When possible, subjects who reported a respiratory tract infection in the previous 3 weeks were rescheduled for testing. Methacholine was delivered

up to a cumulative dose of 1 mg, or until a fall in FEV₁ by 20% was observed, via a Mefar dosimeter (Mefar, Bovezzo, Italy).

In ECRHS-I, total serum IgE and IgE specific to cat, house dust mite (*Dermatophagoides pteronyssinus*), *Cladosporium*, and timothy grass were measured centrally at Pharmacia Uppsala (Sweden), using the Pharmacia CAP system.

Data Analysis

BHR was defined as a decrease in FEV₁ of at least 20% of its postsaline value for a maximum dose of 1 mg of methacholine. “Onset” of BHR was defined as having BHR at the follow-up study in participants without BHR at the baseline study. “Remission” of BHR was defined as the presence of BHR at baseline and the absence of BHR at follow-up. In addition to this binary response variable, a dose–response slope used for between-center analyses in the ECRHS was used to analyze the response to methacholine as a continuous variable in a linear regression model. Change in slope (Δ slope) was expressed per year of follow-up, with a negative value indicating an increase in bronchial responsiveness.

“Atopy” was defined as having positive specific IgE (≥ 0.35 kIU/L) to at least one of the four allergens tested.

In accordance with international guidelines (11), subjects were considered to have allergic rhinitis if they reported a history of nasal allergy and had positive specific IgE (see the online supplement). Allergic rhinitis to cat was defined as a history of nasal allergy and IgE specific to cat. Allergic rhinitis to mite or pollen was defined similarly. Patients with allergic rhinitis were considered as “treated by nasal steroid” if they had used an intranasal corticoid therapy for at least 1 year since the previous study. Participants were separated into three groups: those without atopy and allergic rhinitis, those with atopy but without rhinitis, and those with allergic rhinitis.

Change in body mass index (Δ BMI) and change in FEV₁ (Δ FEV₁) were calculated as the value at follow-up minus the value at baseline divided by length of follow-up and expressed per year of follow-up.

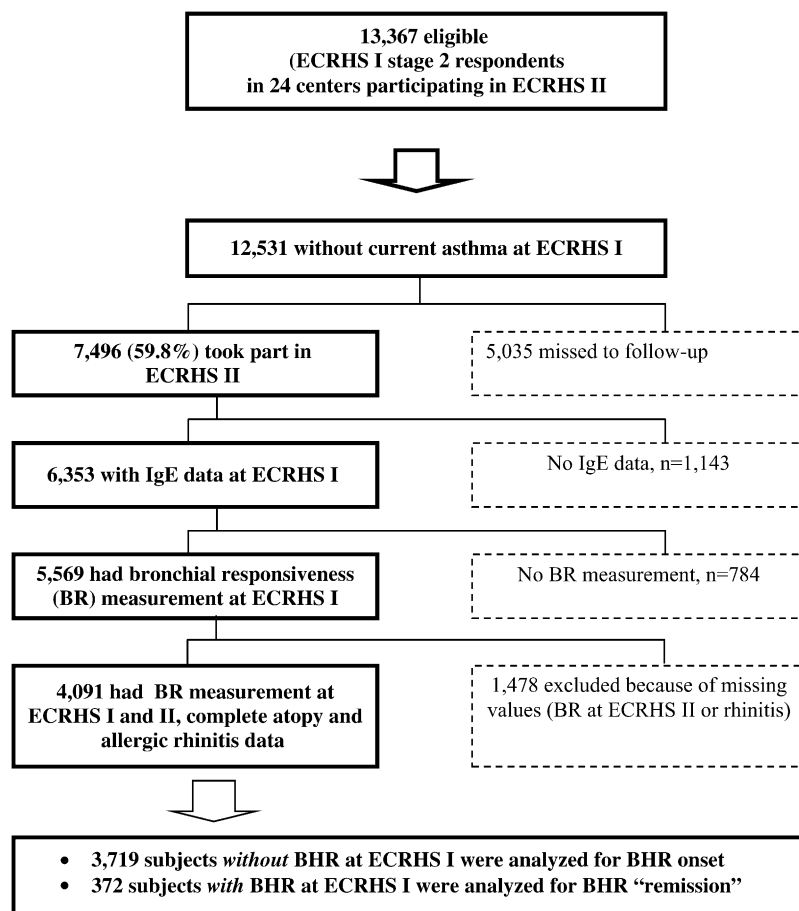


Figure 1. Subjects participating in the present analysis. BHR = bronchial hyperresponsiveness; BR = bronchial responsiveness; ECRHS = European Community Respiratory Health Survey.

Change in smoking is associated with change in BHR in the ECRHS and was included in the multivariate analysis accordingly using the following five categories: nonsmokers, ex-smokers, current smokers (at each survey), quitters (stopped between surveys), and restarters (9).

The χ^2 test was used when analyzing differences between groups. Analysis of variance was used to compare continuous variables. Logistic regression models were fitted using BHR as the dependent variable and allergic rhinitis as the independent variable. Statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC). A test for heterogeneity and combined odds ratios were determined using standard methods for meta-analysis, with country included in the model as a random effect, using the Stata version 6 package (StataCorp, College Station, TX).

RESULTS

A total of 13,367 people in the random sample in 24 centers from 11 countries (Iceland, Norway, Sweden, Germany, France, Switzerland, Spain, Italy, United States, Australia, and United Kingdom) were eligible to take part in ECRHS-II. A total of 12,531 subjects were free of current asthma in ECRHS-I, of whom 7,496 subjects were contacted and responded to the main questionnaire in ECRHS-II (participation rate = 59.8%). In total, 4,091 subjects with BHR measurements in ECRHS-I and ECRHS-II, and complete atopy and rhinitis data at baseline, were included in the analyses (Figure 1). The median length of follow-up was 8.9 years, with an interquartile range from 8.4 to 9.3 years. A comparison of baseline characteristics between followed-up and non-followed-up subjects is shown in Table 1. The groups did not differ in sex distribution or allergic rhinitis prevalence. However, followed-up subjects were slightly older than those who were not followed up, more likely to be nonsmokers, had slightly greater BMI, and had greater baseline FEV₁. In addition, asthmalike symptoms, BHR, and atopy were more frequent in subjects who were followed up. A total of 3,405 followed-up subjects were excluded from analyses because of missing values for BHR, atopy, or rhinitis for either ECRHS-I or ECRHS-II. Table 1 also shows the baseline characteristics of subjects included and excluded from analysis. No differences with regard to age, BMI, atopy, or family history of asthma or

allergic rhinitis have been found between groups. However, men were more frequent in included subjects, and included subjects had greater baseline FEV₁. A history of heavy smoking, asthmalike symptoms, and BHR were more frequent in subjects who were excluded from the analysis.

Cross-sectional Relationship between Allergic Rhinitis and BHR at Baseline

At baseline, the cross-sectional relationship between allergic rhinitis and BHR was comparable among the subjects lost to follow-up (odds ratio [OR] 95% confidence interval [95% CI], 3.07 [2.42–3.86]) and those who were followed up (OR [95% CI], 3.10 [2.58–3.74]). In the 4,091 subjects who were followed up, no heterogeneity across countries in the association was observed (Figure 2). After adjustment for the confounding factors, the combined OR and 95% CI for the association between rhinitis and BHR was 3.35 (2.57–4.38).

Onset of BHR in Subjects without BHR at Baseline

The onset of BHR between ECRHS-I and ECRHS-II was studied in the 3,719 subjects without BHR in ECRHS-I (baseline characteristics shown in Table 1). In these subjects, 6.4% (n = 238) had developed BHR at ECRHS-II. The onset of BHR was associated with sex, baseline FEV₁ and annual FEV₁ decline, baseline BMI and annual BMI change, sensitization to cat, and family history of asthma (results available from the authors).

Subjects without BHR at baseline were classified into three categories according to their atopic status and the presence of rhinitis at baseline (Table 2). There were more male subjects with allergic rhinitis than without allergic rhinitis. Subjects with allergic rhinitis at baseline were slightly younger and more frequently nonsmokers than subjects without allergic rhinitis. Family history of asthma and allergy and asthmalike symptoms were more common among subjects with allergic rhinitis (Table 2).

Table 3 shows the onset of BHR in subjects with allergic rhinitis and atopic sensitization as compared with other groups. The cumulative incidence of BHR was 9.7% in subjects with allergic rhinitis and 7.0% in subjects with atopy compared with 5.5% in subjects without allergic rhinitis and atopy ($P < 0.001$).

TABLE 1. BASELINE CHARACTERISTICS OF SUBJECTS

	12,531 Eligible, Free of Asthma at ECRHS-I		Followed-up Subjects (n = 7,496)		Included Subjects (n = 4,091)	
	Not Followed Up (n = 5,035)	Followed Up (n = 7,496)	Excluded* (n = 3,405)	Included (n = 4,091)	Without BHR at Baseline (n = 3,719)	With BHR at Baseline (n = 372)
Men, %	49.0	48.6	42.3	53.9 [†]	55.5	37.6 [†]
Age, yr, mean $\pm$ SD	33.1 $\pm$ 7.2	34.1 $\pm$ 7.1 [†]	33.9 $\pm$ 7.2	34.3 $\pm$ 7.0	34.3 $\pm$ 7.0	33.5 $\pm$ 7.1 [†]
BMI, mean $\pm$ SD	23.7 $\pm$ 3.9	23.9 $\pm$ 3.8 [†]	23.8 $\pm$ 4.0	23.9 $\pm$ 3.6	23.9 $\pm$ 3.5	24.1 $\pm$ 4.1
Smoking, %						
Nonsmokers	38.5	42.4 [†]	42.2	42.5 [†]	42.4	43.3
Ex-smokers	18.1	19.9	18.3	21.3	21.6	18.2
Moderate smokers [‡]	23.0	22.9	23.3	22.6	22.6	22.6
Heavy smokers [‡]	20.4	14.8	16.2	13.6	13.4	16.0
Atopy, %	31.4	29.2 [†]	28.7	29.5	27.4	49.7 [†]
Log total IgE, mean $\pm$ SD	3.53 $\pm$ 1.57	3.35 $\pm$ 1.57 [†]	3.36 $\pm$ 1.50	3.34 $\pm$ 1.55	3.28 $\pm$ 1.53	3.93 $\pm$ 1.59 [†]
Family history of asthma, %	10.1	11.2 [†]	11.2	11.3	10.8	16.1 [†]
Asthmalike symptoms, %	23.8	21.7 [†]	22.8	20.7 [†]	19.1	37.1 [†]
FEV ₁ , L/s, mean $\pm$ SD [§]	3.86 $\pm$ 0.49	3.90 $\pm$ 0.47 [†]	3.83 $\pm$ 0.49	3.94 $\pm$ 0.45 [†]	3.97 $\pm$ 0.44	3.69 $\pm$ 0.43 [†]
Allergic rhinitis, %	19.5	18.7	18.5	18.8	16.6	40.3 [†]
BHR, %	12.6	10.2 [†]	12.4	9.1 [†]	—	—

Definitions of abbreviations: BHR = bronchial hyperresponsiveness; BMI = body mass index; ECRHS = European Community Respiratory Health Survey.

[‡] Moderate smokers (<20 cigarettes/d) and heavy smokers ($\geq$ 20 cigarettes/d).

[†] $P < 0.05$.

* Subjects excluded because of missing value for IgE, BHR test, and/or rhinitis.

^{||} Self-reported allergic rhinitis diagnostic and/or nasal symptoms on allergen exposure with a positive allergen-specific IgE test.

[§] FEV₁ = residual FEV₁ + FEV₁ mean.

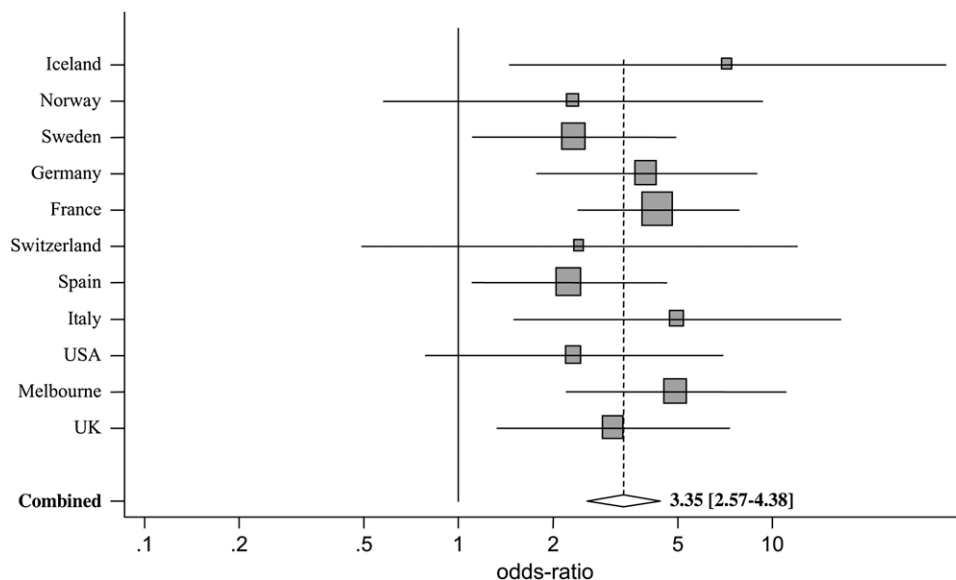


Figure 2. Multivariable-adjusted odds ratios (95% confidence interval) for the cross-sectional association between allergic rhinitis and bronchial hyperresponsiveness by country adjusted for sex, age, body mass index, smoking, respiratory symptoms, family history of asthma, and FEV₁ (current asthma excluded). The area of the squares is proportional to the reciprocal of the variance of the estimate for each country. The diamond represents the combined odds ratio, calculated using country as a random effect, with its 95% confidence interval. The dashed line, plotted vertically through the combined odds ratio, crosses the horizontal lines of all individual country results (P value for the test of heterogeneity between countries = 0.81).

A multiple logistic regression model was used to assess the independent effect of baseline allergic rhinitis on the cumulative incidence of BHR after controlling for country, sex, baseline age, BMI, FEV₁, asthmalike symptoms, family history of asthma, smoking status, and Δ BMI and Δ FEV₁. The adjusted OR (95% CI) for BHR onset in subjects with allergic rhinitis was 2.44 (1.73–3.45), whereas the corresponding OR (95% CI) for subjects with atopy alone was 1.35 (0.86–2.11) (Table 3).

There was no significant interaction between allergic rhinitis and any of the studied risk factors in determining BHR onset. Hence, a similar pattern of results was observed in men and in women, age classes, smoking categories, BMI classes, and fam-

ily history of asthma (Table 3). In addition, after excluding subjects with asthmalike symptoms at baseline or excluding subjects with current asthma at follow-up ($n = 97$), the positive association between allergic rhinitis and BHR onset remained significant (adjusted ORs [95% CI]: 2.51 [1.65–3.82] and 1.97 [1.35–2.88], respectively). Multiplicative interactions (smoking/BMI, age/sex, and age/smoking) were assessed using product terms in the fully adjusted logistic model but had no effect on the association.

Furthermore, considering the population in two classes only (i.e., those without allergic rhinitis, whatever their atopic status, vs. those with allergic rhinitis), the onset of BHR remained significantly more frequent in subjects with allergic rhinitis than

TABLE 2. RELATIONSHIP BETWEEN ATOPY AND ALLERGIC RHINITIS, AND POTENTIAL CONFOUNDING FACTORS AT BASELINE IN SUBJECTS WITHOUT BRONCHIAL HYPERRESPONSIVENESS

	No AR, No Atopy ($n = 2,699$)	Atopy, No AR ($n = 401$)	AR ($n = 619$)	P Value*
Men, %	52.3	67.8	61.6	<0.001
Age, mean (95% CI)	34.6 (34.3 to 34.9)	34.0 (33.3 to 34.6)	33.1 (32.6 to 33.6)	<0.001
BMI, mean (95% CI)	24.0 (23.9 to 24.1)	24.0 (23.7 to 24.4)	23.8 (23.5–24.0)	0.19
Δ BMI, kg/m ² /yr, mean (95% CI)	0.18 (0.17 to 0.19)	0.20 (0.18 to 0.22)	0.19 (0.17 to 0.22)	0.16
Smoking, %				<0.001
Nonsmokers	40.6	36.8	54.1	
Ex-smokers	19.5	16.2	14.7	
Smokers	26.3	32.9	21.1	
Quitters	10.0	11.3	6.8	
Restarters	3.6	2.8	3.4	
Sensitization to, %				
Cat	—	21.2	29.4	<0.001
House dust mite	—	61.1	46.5	<0.001
Cladosporium	—	16.2	7.4	<0.001
Pollen	—	45.6	73.0	<0.001
Total IgE, IU/ml, mean (95% CI)	44.5 (37.5 to 51.6)	190.8 (172.8 to 208.9)	205.7 (192.8 to 218.7)	<0.001
Log total IgE, mean (95% CI)	2.90 (2.85 to 2.95)	4.27 (4.14 to 4.40)	4.54 (4.45 to 4.63)	<0.001
Asthmalike symptoms, %				<0.001
Wheeze	14.4	15.2	22.0	<0.001
SOB at rest	3.4	2.2	4.7	0.1
Awakened by SOB	2.7	2.7	6.1	<0.001
Family history of asthma, %	10.4	8.7	13.7	0.021
Family history of allergy, %	27.0	22.0	43.9	<0.001
FEV ₁ , L/s, mean (95% CI) [†]	3.87 (3.84 to 3.91)	3.89 (3.80 to 3.98)	3.81 (3.74 to 3.87)	0.23
Δ FEV ₁ , ml/yr, mean (95% CI)	−26 (−27 to −25)	−29 (−32 to −26)	−20 (−22 to −18)	<0.001

Definitions of abbreviations: AR = allergic rhinitis; BMI = body mass index; CI = confidence interval; SOB = shortness of breath.

* For difference between groups using analysis of variance for continuous variables and χ^2 for categorical variables.

[†] FEV₁ = residual FEV₁ + FEV₁ mean.

TABLE 3. RELATIONSHIP BETWEEN ATOPY AND ALLERGIC RHINITIS AT BASELINE, AND DEVELOPMENT OF BRONCHIAL HYPERRESPONSIVENESS AT FOLLOW-UP IN SUBJECTS WITHOUT BRONCHIAL HYPERRESPONSIVENESS AT BASELINE, IN ALL SUBJECTS AND STRATIFIED BY SUBGROUPS

	No AR, No Atopy (n = 2,699)	Atopy, No AR (n = 401)	AR (n = 619)
In all subjects			
BHR, n(%)	148 (5.5)	28 (7.0)	60 (9.7)
Crude OR (95% CI)	1.00	1.29 (0.85–1.97)	1.85 (1.35–2.53)
Adjusted OR* (95% CI)	1.00	1.35 (0.86–2.11)	2.44 (1.73–3.45)
Stratified analysis by subgroups, adjusted OR†			
Men	1.00	1.96 (1.06–3.63)	3.45 (2.05–5.81)
Women	1.00	0.93 (0.46–1.87)	1.89 (1.16–3.07)
Baseline age, yr			
≤30	1.00	3.13 (1.38–7.08)	3.40 (1.72–6.72)
30–40	1.00	1.02 (0.50–2.06)	1.81 (1.06–3.11)
≥40	1.00	1.18 (0.47–2.97)	3.58 (1.80–7.12)
Smoking status at baseline			
Nonsmokers	1.00	1.36 (0.61–3.01)	2.72 (1.65–4.48)
Ex-smokers	1.00	2.27 (0.87–5.88)	2.03 (0.82–4.99)
Current smokers	1.00	1.16 (0.60–2.26)	2.66 (1.45–4.87)
BMI at baseline			
<25	1.00	1.36 (0.78–2.38)	1.98 (1.27–3.10)
25–30	1.00	1.61 (0.70–3.71)	4.09 (2.15–7.81)
≥30	1.00	0.50 (0.04–6.36)	1.60 (0.32–7.98)
Family history of asthma			
No	1.00	1.30 (0.80–2.11)	2.25 (1.54–3.30)
Yes	1.00	2.05 (0.61–6.95)	3.51 (1.50–8.24)

Definition of abbreviations: BMI = body mass index; BHR = bronchial hyperresponsiveness; CI = confidence interval; OR = odds ratio.

* Adjustment for country, sex, baseline age, BMI, FEV₁, asthmalike symptoms, family history of asthma, change in smoking, and ΔBMI and ΔFEV₁.

† Adjustment for the same variables as above, except those used to define the category for stratification.

in those without rhinitis (9.7 vs. 5.7%; adjusted OR, 2.34 [1.67–3.28]).

Effect of Number and Type of Inhaled Allergen Sensitization

The association between allergic rhinitis and BHR onset was similar in subjects with rhinitis sensitized to one allergen (n = 370; OR, 2.41 [1.62–3.60]) and in subjects with rhinitis sensitized to several type of allergens (“polysensitized”) (n = 248; OR, 2.20 [1.34–3.67]).

In contrast, different results were observed according to the type of allergen. Allergic rhinitis to cat was associated with a substantial increased risk of BHR onset during the follow-up period, as compared with subjects without allergic rhinitis to cat (adjusted OR [95% CI], 4.39 [2.75–7.00]). Allergic rhinitis to mites and allergic rhinitis to pollen were also associated with an increased risk of BHR onset, but to a somewhat lower extent (adjusted OR [95% CI], 1.73 [1.08–2.76], and OR [95% CI], 1.54 [1.02–2.32]).

Respectively, 76.0, 51.2, and 50.4% of the subjects sensitized to cat, mites, and pollen were sensitized to another type of allergen. When excluding subjects with polysensitization, and considering only subjects suffering from rhinitis and sensitized exclusively to cat, to mites, or to pollen, the adjusted ORs (95% CI) were, respectively, as follows: 7.90 (3.48–17.93), 2.84 (1.36–5.93), and 1.68 (0.94–3.00), as compared with nonatopic subjects (Table 4).

Annual Change in Level of BHR “Slope”

At baseline, the BHR slope was lower in subjects with allergic rhinitis than in nonatopic subjects without allergic rhinitis (mean [SD] BHR slope, 7.21 [2.16] vs. 8.09 [1.91]; $P < 0.001$) (i.e., the level of BHR was higher in subjects with rhinitis). The change in slope was negatively correlated to the baseline slope (correlation coefficient, -0.51 ; $P < 0.001$). Without adjusting for the baseline slope, there was no evidence for a further decrease in slope in sensitized subjects or subjects with allergic rhinitis than in nonatopic subjects without rhinitis. However, adjusting for baseline slope—that is, considering subjects with and without rhinitis starting with the same level of BHR at baseline—showed that subjects with allergic rhinitis experienced a steeper mean annual decline in slope (i.e., higher increase in BHR level) between the two surveys than subjects without allergic rhinitis, after adjustment for potential confounders ($P < 0.001$) (Figure 3). The association between the annual change in slope and rhinitis in subgroups is given in the online supplement (Table E1).

BHR Remission and Effect of Nasal Steroids for Allergic Rhinitis

Remission of BHR in the ECRHS-II was studied in the 372 subjects with BHR in the ECRHS-I (baseline characteristics shown in Table 1). Of the 372 subjects with BHR in the ECRHS-I, 45.2% had no more BHR in ECRHS-II. The likelihood of BHR “remission” was lower in subjects with allergic rhinitis (35.3%) than in those without allergic rhinitis at baseline (51.8%) (OR [95% CI], 0.51 [0.33–0.78]). BHR remission was more frequent among the patients with allergic rhinitis treated by nasal

TABLE 4. ONSET OF BRONCHIAL HYPERRESPONSIVENESS BY TYPE OF RHINITIS, IN MONOSENSITIZED SUBJECTS WITHOUT BRONCHIAL HYPERRESPONSIVENESS AT BASELINE

	No AR, No Atopy	No AR, IgE ⁺ to Cat Only	AR, IgE ⁺ to cat only
Total n	2,699	23	41
n (%)	148 (5.5)	3 (13.0)	11 (26.8)
Adjusted* OR (95% CI)	1.00	2.67 (0.69–10.32)	7.90 (3.48–17.93)
No AR, IgE ⁺ to Mites Only			
Total n	2,699	158	102
n (%)	148 (5.5)	8 (5.1)	10 (9.8)
Adjusted* OR (95% CI)	1.00	0.90 (0.40–2.05)	2.84 (1.36–5.93)
No AR, IgE ⁺ to Pollen Only			
Total n	2,699	92	223
n (%)	148 (5.5)	7 (7.5)	16 (7.1)
Adjusted* OR (95% CI)	1.00	1.69 (0.74–3.89)	1.68 (0.94–3.00)

Definition of abbreviations: AR = allergic rhinitis; CI = confidence interval; OR = odds ratio.

* Adjustment for country, sex, baseline age, BMI, FEV₁, asthmalike symptoms, family history of asthma, change in smoking, and ΔBMI and ΔFEV₁.

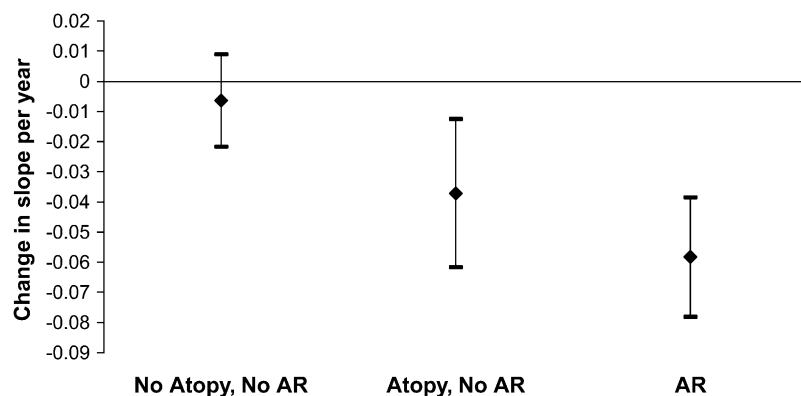


Figure 3. Mean annual change in bronchial hyperresponsiveness (BHR) expressed as Δ slope in nonatopic subjects without allergic rhinitis (AR), atopic subjects without AR, and subjects with AR, and 95% confidence interval, adjusted for country, sex, baseline slope, age, body mass index (BMI), FEV₁, asthmalike symptoms, family history of asthma, smoking, and Δ BMI and Δ FEV₁. A negative Δ slope indicates an increase in BHR.

steroids compared with those who were not treated by nasal steroids (OR [95% CI] remission, 0.33 [0.14–0.75]) (Table 5).

In contrast, in those without BHR at baseline, we were not able to find any protective effect of treatment of allergic rhinitis on BHR onset (OR onset, 1.04 [0.55–1.98]).

DISCUSSION

Results from the follow-up of more than 4,000 subjects participating in the ECRHS show that allergic rhinitis is associated with the onset of BHR. Adults with allergic rhinitis and free of BHR and asthma at baseline were at an increased risk for developing BHR over the follow-up period. It is possible that the association of allergic rhinitis with BHR is confounded by the greater burden of risk factors for BHR in individuals with allergic rhinitis. To reduce potential confounding, we excluded participants with BHR and asthma at baseline and adjusted and stratified for other risk factors (including FEV₁ decline and change in BMI and smoking during the follow-up period). In these analyses, the association remained consistent and robust.

To the best of our knowledge, this is the first study investigating the longitudinal association between allergic rhinitis and BHR. The results of this longitudinal study are in accordance with previous findings from the cross-sectional analysis of the same population (10) and from other clinical and population-based studies (12, 17), revealing a strong association between allergic rhinitis and lower airway dysfunction. The results from the present analysis extend these cross-sectional findings by showing that allergic rhinitis precedes the development of BHR. We have shown that subjects with rhinitis without BHR at baseline were more likely to have BHR at follow-up. In contrast, subjects with BHR but without allergic rhinitis at baseline survey (5.6% of the baseline sample) were not more likely to have developed allergic rhinitis at follow-up than subjects without BHR (results not shown).

The strengths of the present study are its prospective design, large size, the use of high-quality data from random samples

selected in the general population, the use of a standardized questionnaire, and the strictly standardized assessment of BHR in all participating countries. Quality controls were performed at different levels. All field workers involved in the study received identical training, quality control visits were made by ECRHS investigators, and equipment was subject to regular quality controls. According to the quality-control program, centers were requested to check dosimeter driving pressure at least once a month, and to send reports to the coordinating center. Our findings, however, should be considered in the context of the potential limitations of our study. As in any longitudinal study, there was some loss to follow-up, which might have biased the results. However, our response rate was relatively high and comparable to several recent population studies (18, 19). Those who were not followed up more often had BHR at baseline than participants, and were more likely to be smokers. The higher proportion of smokers among nonresponders could have biased the number of incident BHR toward lower values, but this difference is unlikely to have any significant effect on the reported relationship between allergic rhinitis and BHR, as the association was found in smokers as well as in nonsmokers. Furthermore, at baseline, the cross-sectional association between allergic rhinitis and BHR was comparable in followed-up and non-followed-up subjects.

In epidemiologic studies, atopic status can be defined either by skin prick tests or by measurement of specific IgE (20). In the preparation of the ECRHS-I, considerable time was spent discussing the appropriate methods and the allergens to be tested. The steering committee decided to use skin prick tests for nine allergens (*Alternaria alternata*, *Cladosporium herbarum*, *Pleum pratense* [timothy grass], birch, olive, *Parietaria judaica* [pellitory-of-the-wall], common ragweed [*Ambrosia artemisiifolia*], *D. pteronyssinus* [house dust mite], and cat) (21) and specific IgE measurements for four allergens (house dust mite, timothy grass, cat, and *Cladosporium*) (22). A recent study showed little increase in prevalence of sensitization by adding tests other than house dust mite, timothy grass, and cat (23). In our study sample, we determined that only 3.3% of the sample had positive skin tests to one of the nine allergens but would be considered as nonatopic if only the four allergens used in our analysis were taken into account (house dust mite, timothy grass, cat, and *Cladosporium*). In the present analysis, atopic sensitization was first considered to increase the specificity of the definition of allergic rhinitis. Because the purpose of our study was not to estimate the prevalence of atopy, we decided to use specific IgE measurements that were available in all countries and at both surveys. However, we checked that the prevalence of atopy was not underestimated. If we consider our study sample (asthmatics excluded) in the nine countries that performed both skin prick tests and specific IgE measurements, the prevalence of atopy

TABLE 5. STEROID NASAL EFFECT ON ONSET AND REMISSION OF BRONCHIAL HYPERRESPONSIVENESS

	Subjects with AR at ECRHS-I (n = 629)		
	Without Nasal Steroid	With Nasal Steroid	OR (95% CI)
BHR onset at follow-up	48/491 (9.8%)	13/138 (9.4%)	1.04 (0.55–1.98)
BHR remission at follow-up	36/120 (30.0%)	13/30 (56.7%)	0.33 (0.14–0.75)

Definitions of abbreviations: AR = allergic rhinitis; BHR = bronchial hyperresponsiveness; CI = confidence interval; ECRHS = European Community Respiratory Health Survey; OR = odds ratio.

considering specific IgE was 26.1%, as compared with 26.9% when atopy was defined as at least one positive skin prick test (≥ 3 mm). Moreover, it is noteworthy that possible misclassification of a few atopic subjects as “nonatopic” would more likely result in underestimating the association studied between allergic rhinitis and BHR.

There are several possible explanations for the frequent association between allergic rhinitis and BHR. On the one hand, it is possible that exposure to common risk factors for rhinitis and BHR or genetic susceptibility results in a higher risk of having both BHR and rhinitis. However, in the present analysis, we excluded participants with BHR and asthma at baseline and showed that allergic rhinitis was a risk factor for subsequent development of BHR. On the other hand, there are several possible pathophysiologic mechanisms by which allergic rhinitis may contribute to lower airway inflammation (24). First, there is a possibility of neural connections between upper and lower airways (nasobronchial reflex). Nasal exposure to cold air and application of nasal stimulus as histamine or allergen extracts onto the nasal mucosa has been found to result in an immediate bronchospasm. Second, mouth breathing caused by nasal obstruction in subjects with rhinitis does not achieve the nasal humidification, warming, and filtration of inspired air before it reaches the lower airways. Finally, the inflammation present in the upper airways of subjects with allergic rhinitis might contribute to the inflammation in the lower airways, either directly through aspiration of nasal inflammatory secretions (postnasal drip) (25) or through the absorption of inflammatory mediators in the systemic circulation (26). Most recent data point to a circulatory pathway, involving bloodstream and bone marrow, as a major mode of nasobronchial cross-talk. It has been shown that nasal provocation resulted in an increase in circulating inflammatory cells and mediators. In addition, nasal provocation caused respiratory symptoms and decreased pulmonary function in subjects with allergic rhinitis, indicating that allergic rhinitis is not a local disease but involves the entire respiratory tract (26). It also has been suggested that isolated upper airway allergen deposition initiates allergic inflammation because of activation of lymphocytes and release of cytokines as IL-4 and IL-13. IL-13, which increases in the airways after nasal challenge, has been shown to have a direct effect on bronchial epithelial and smooth muscle cells. It mediates both airway inflammation and BHR and may play a role in the communication between the upper and lower airways (27).

In the present study, the risk of developing BHR was higher for allergic rhinitis to cat and to mites (perennial allergens) than for allergic rhinitis to pollen (seasonal allergens). The reasons for these observations are not clear. One explanation could be that the period of exposure to pollens is seasonal (short exposure), whereas subjects with allergic rhinitis to mites and cat are likely to have nasal symptoms over a longer period. Also, allergic rhinitis symptoms related to exposure to mites and cat might have a stronger effect because the exposure occurs indoors rather than outdoors and people spend most of their time indoors. Sensitization to indoor allergens has been found to be associated with BHR in cross-sectional surveys of children (28) and adults (8), and with the chronicity of asthma in a longitudinal study of children (29).

Finally, we observed a lower remission rate for BHR in subjects with allergic rhinitis at baseline than in those without allergic rhinitis. Interestingly, remission of BHR occurred more frequently in subjects treated with steroid nasal sprays. The interpretation of this finding is limited by the observational design of the study. The result might be explained by uncontrolled confounding. Although limited data on rhinitis treatment were available in the ECRHS, our finding is in accordance with re-

sults of clinical studies (25, 30, 31) that demonstrated that intranasal steroids are effective in improving airway responsiveness in patients with nasal inflammation, and that this effect was principally due to improvement in nasal function.

In this longitudinal study, we found a strong association between allergic rhinitis and the onset of BHR in adults in the general population. The fact that allergic rhinitis at baseline was associated with both increased onset of BHR and less chance for remission, except in those receiving a treatment for allergic rhinitis, supports a strong relationship between allergic rhinitis and the development of lower airway inflammation.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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References

- Brutsche MH, Downs SH, Schindler C, Gerbase MW, Schwartz J, Frey M, Russi EW, Ackermann-Lieblich U, Leuenberger P. Bronchial hyperresponsiveness and the development of asthma and COPD in asymptomatic individuals: SAPALDIA cohort study. *Thorax* 2006;61:671-677.
- Xu X, Rijcken B, Schouten JP, Weiss ST. Airways responsiveness and development and remission of chronic respiratory symptoms in adults. *Lancet* 1997;350:1431-1434.
- O'Connor GT, Sparrow D, Weiss ST. A prospective longitudinal study of methacholine airway responsiveness as a predictor of pulmonary-function decline: the Normative Aging Study. *Am J Respir Crit Care Med* 1995;152:87-92.
- Laprise C, Boulet LP. Asymptomatic airway hyperresponsiveness: a three-year follow-up. *Am J Respir Crit Care Med* 1997;156:403-409.

5. Gerritsen J, Koeter GH, Postma DS, Schouten JP, Knol K. Prognosis of asthma from childhood to adulthood. *Am Rev Respir Dis* 1989;140:1325-1330.
6. Pearce N, Beasley R, Pekkanen J. Role of bronchial responsiveness testing in asthma prevalence surveys. *Thorax* 2000;55:352-354.
7. Grootendorst DC, Rabe KF. Mechanisms of bronchial hyperreactivity in asthma and chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2004;1:77-87.
8. Chinn S, Burney P, Sunyer J, Jarvis D, Luczynska C. Sensitization to individual allergens and bronchial responsiveness in the ECRHS. European Community Respiratory Health Survey. *Eur Respir J* 1999;14:876-884.
9. Chinn S, Jarvis D, Luczynska CM, Ackermann-Lieblich U, Anto JM, Cerveri I, de Marco R, Gislason T, Heinrich J, Janson C, et al. An increase in bronchial responsiveness is associated with continuing or restarting smoking. *Am J Respir Crit Care Med* 2005;172:956-961.
10. Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;104:301-304.
11. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108:S147-S334.
12. Riccioni G, Della Vecchia R, Castronuovo M, Di Pietro V, Spoltore R, De Benedictis M, Di Iorio A, Di Gioacchino M, Guagnano MT. Bronchial hyperresponsiveness in adults with seasonal and perennial rhinitis: is there a link for asthma and rhinitis? *Int J Immunopathol Pharmacol* 2002;15:69-74.
13. Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol* 1997;99:S781-S786.
14. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954-960.
15. The European Community Respiratory Health Survey II. *Eur Respir J* 2002;20:1071-1079.
16. Chinn S, Burney P, Jarvis D, Luczynska C. Variation in bronchial responsiveness in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1997;10:2495-2501.
17. Settipane RJ, Hagy GW, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc* 1994;15:21-25.
18. Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med* 2004;170:78-85.
19. James AL, Palmer LJ, Kicic E, Maxwell PS, Lagan SE, Ryan GF, Musk AW. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. *Am J Respir Crit Care Med* 2005;171:109-114.
20. Woolcock AJ, Peat J. What is the relationship between airway hyperresponsiveness and atopy? *Am J Respir Crit Care Med* 2000;161:S215-S217.
21. Chinn S, Jarvis D, Luczynska CM, Lai E, Burney PG. Measuring atopy in a multi-centre epidemiological study. *Eur J Epidemiol* 1996;12:155-162.
22. Burney P, Malmberg E, Chinn S, Jarvis D, Luczynska C, Lai E. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1997;99:314-322.
23. Bousquet PJ, Hooper R, Kogevinas M, Jarvis D, Burney P. Number of allergens to be tested to assess allergenic sensitization in epidemiologic studies: results of the European Community Respiratory Health Survey I. *Clin Exp Allergy* 2007;37:780-787.
24. Corren J. The impact of allergic rhinitis on bronchial asthma. *J Allergy Clin Immunol* 1998;101:S352-S356.
25. Aubier M, Levy J, Clerici C, Neukirch F, Herman D. Different effects of nasal and bronchial glucocorticosteroid administration on bronchial hyperresponsiveness in patients with allergic rhinitis. *Am Rev Respir Dis* 1992;146:122-126.
26. Braunstahl GJ, Fokkens W. Nasal involvement in allergic asthma. *Allergy* 2003;58:1235-1243.
27. Wang Y, McCusker CT. Interleukin-13-dependent bronchial hyperresponsiveness following isolated upper-airway allergen challenge in a murine model of allergic rhinitis and asthma. *Clin Exp Allergy* 2005;35:1104-1111.
28. Tepas EC, Litonjua AA, Celedon JC, Sredl D, Gold DR. Sensitization to aeroallergens and airway hyperresponsiveness at 7 years of age. *Chest* 2006;129:1500-1508.
29. Illi S, von Mutius E, Lau S, Niggemann B, Gruber C, Wahn U. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006;368:763-770.
30. Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992;90:250-256.
31. Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol* 1993;91:97-101.

Online data supplement

Allergic rhinitis and onset of bronchial hyperresponsiveness: A population-based study

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Methods

Study design:

This analysis was based on the follow-up data from the ECRHS, which is an international multi-center study involving 24 centers (22 were in western Europe, one in the United States and one in Australia). The methods of ECRHS have been published elsewhere (E1-E4), and further information is available from the study web site (<http://www.ecrhs.org>). The study was approved for each center by the appropriate institutional or regional ethics committee, and informed written consent was obtained from each participant

Baseline study (ECRHS I):

Participating centers were each selected as an area defined by pre-existing administrative boundaries with a population of at least 150,000 people. A community-based sampling frame was used to select randomly at least 1500 men and 1500 women aged 20 to 44 years, who were sent a short postal questionnaire (stage 1). A random sample of responders was selected to take part in stage 2, during which the responders were invited to visit a local testing center in order to answer a more detailed administered questionnaire that included questions on allergic rhinitis, to provide blood sample for total and specific IgE measurements, to perform lung function measurement by spirometry, and bronchial responsiveness challenge with methacholine. In most centers, a further sample of symptomatic subjects was also invited to participate. These subjects are not included in the present report. ECRHS I took place in 1991-1993.

Follow-up study (ECRHS II):

Participants in ECRHS I who responded to stage 2 were eligible for ECRHS II (Figure 1). From 1998 to 2002 (depending on center), eligible subjects in the 24 participating centers completed the short symptom questionnaire and were then invited to a local testing center where, as before, they answered a more detailed administered questionnaire, and underwent bronchial responsiveness challenge following the same method as ECRHS I.

Lung function testing:

The maximum forced expiratory volume in one second (FEV1) of up to five technically acceptable blows was determined in accordance with the American Thoracic Society criteria for reproducibility. Changes in FEV1 (Δ FEV1) was expressed per year of follow-up ([ECRHS II value minus ECRHS I value]/length of follow-up).

Methacholine challenge:

Details of methacholine challenge have been described elsewhere (E1, E4) . At each occasion, bronchial responsiveness to methacholine was measured in eligible subjects for test (those having an FEV1 of at least 70% predicted and >1.5 L, and not suffering from heart disease or epilepsy, not pregnant or breastfeeding, and not taking a beta blocker). Subjects were advised to avoid smoking for 1 h, using a β 2-agonist or anticholinergic inhaler for 4 h or oral medication (β 2-agonist, theophylline or antimuscarinic) for 8 h before the test. When possible, subjects who reported a respiratory tract infection in the previous 3 weeks were rescheduled. Methacholine was delivered via a Mefar dosimeter (Mefar, Bovezzo, Italy). The test started with inhalation of saline diluent, with the maximum post-diluent FEV1 being recorded as the control value. FEV1 was measured two minutes after each inhalation of methacholine. The test was stopped either when FEV1 fell by 20% or when a maximum cumulative dose of 1 mg had been given.

Total and specific Immunoglobulin E (IgE):

Blood samples were collected and total serum IgE and IgE specific to cat, house-dust mite (*D pteronyssinus*), *Cladosporium* and timothy grass were measured centrally at Pharmacia Uppsala at ECRHS I, using the Pharmacia CAP system. The measurement range was from 2 to 2000 kU/L for total IgE, and from 0.35 to 100 kU/L for specific IgE.

Data analysis:

BHR was defined as a decrease in FEV1 of at least 20% of its post-saline value for a maximum dose of 1 mg of methacholine. “Onset” of BHR was defined as having BHR at the follow-up study in participants without BHR at the baseline study. “Remission” of BHR was defined as the presence of BHR at baseline and the absence of BHR at follow-up. As well as this binary response variable, a dose-response slope used for between-center analyses in the ECRHS was used to analyze the response to methacholine as a continuous variable in a linear

regression model. This allows the data from all subjects to be interpreted regardless of whether FEV₁ declined by 20% during the test or not. Change in slope (Δ slope) was expressed per year of follow-up ([ECRHS II value minus ECRHS I value]/length of follow-up), a negative value indicating an increase in bronchial responsiveness.

“Atopy” was defined as having positive specific IgE (≥ 0.35 kIU/L) to at least one of the four allergens tested.

The definition of allergic rhinitis was based on a positive allergen-specific IgE test and a history of nasal allergies as recommended elsewhere (E5). Subjects were considered to have allergic rhinitis if they had positive IgE antibodies (≥ 0.35 kIU/L) to at least one of house-dust mite, timothy grass, cat and/or cladosporium and answered positively to either question “Do you have any nasal allergies including hay fever?” or “Do you get runny or stuffy nose or start to sneeze when you are near grass, trees, flowers, or near animals, or in a dusty part of the house?”. Allergic rhinitis to cat was defined as having a history of nasal allergy and IgE specific to cat. Allergic rhinitis to mite or pollen was defined similarly. Patients with allergic rhinitis were considered as “treated by nasal steroid sprays” if they received an intranasal corticoid therapy for at least one year since the previous study. Participants were separated into three groups: without atopy and allergic rhinitis, with atopy but without rhinitis, and with allergic rhinitis.

BMI was calculated at each occasion as weight in kilograms divided by the square of height in meters. Change in BMI was expressed per year of follow-up (Δ BMI).

Information on smoking history was obtained by questionnaire at each occasion. The subjects were categorized into four groups according to smoking habits: non-smokers, ex-smokers, moderate smokers (< 20 cigarettes per day) and heavy smokers (≥ 20 cigarettes per day). Change in smoking during the follow-up period has been shown to be associated with change in BHR in the ECRHS and was included in the multivariate analysis accordingly (E1). Participants were divided into five categories: non-smokers, ex-smokers, current smokers (at each survey), quitters (stopped between surveys), and restarters.

“Current asthma” was defined as reporting asthma attacks during the previous 12 months or as currently using asthma medication. “Asthma-like symptoms” were defined as having wheeze, shortness of breath at rest and/or nocturnal shortness of breath at rest during the last 12 months. A parental history of asthma was defined as a report of asthma ever in the subject’s father or mother.

The chi-square test was used when analyzing differences between groups. ANOVA was used to compare continuous variables. Logistic regression models were fitted using BHR as the dependent variable and allergic rhinitis as independent variable. The models were adjusted for country, sex, baseline age, BMI, observed FEV1, asthma-like symptoms, family history of asthma, change in smoking status, and Δ BMI and Δ FEV1.

Statistical analysis was carried out using SAS version 8.2 (SAS Institute Inc., Cary, USA). We carried out sensitivity analysis to test the consistency of the association between BHR and allergic rhinitis in men and in women, classes of age, smoking categories, BMI classes, and in subjects with and without family history of asthma. Test for heterogeneity and combined odd ratios were determined using standard methods for meta-analysis, with country included in the model as a random effect, using the STATA package (STATA Corporation, College Station, Tex). Values of $p < 0.05$ (two-tailed test) and odds-ratios (OR) with the 95% confidence intervals (95%CI) excluding 1.0 were regarded as statistically significant.

- E1. Chinn, S., D. Jarvis, C. M. Luczynska, U. Ackermann-Liebrich, J. M. Anto, I. Cerveri, R. de Marco, T. Gislason, J. Heinrich, C. Janson, N. Kunzli, B. Leynaert, F. Neukirch, J. P. Schouten, J. Sunyer, C. Svanes, M. Wjst, and P. G. Burney. 2005. An increase in bronchial responsiveness is associated with continuing or restarting smoking. *Am J Respir Crit Care Med* 172(8):956-61.
- E2. Burney, P. G., C. Luczynska, S. Chinn, and D. Jarvis. 1994. The European Community Respiratory Health Survey. *Eur Respir J* 7(5):954-60.
- E3. 2002. The European Community Respiratory Health Survey II. *Eur Respir J* 20(5):1071-9.
- E4. Chinn, S., P. Burney, D. Jarvis, and C. Luczynska. 1997. Variation in bronchial responsiveness in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 10(11):2495-501.
- E5. Bousquet, J., P. Van Cauwenberge, and N. Khaltaev. 2001. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 108(5 Suppl):S147-334.

Table E1. The relationship between baseline allergic rhinitis (AR), atopy and annual change in BHR “Δ slope”* by multivariate[†] linear regression

	No AR, No atopy	Atopy, No AR	AR
Δ slope coefficient, [95%CI], <i>p</i> value [‡]	0.00	-0.025 [-0.046 to -0.003], <i>p</i> =0.029	-0.042 [-0.066 to -0.030], <i>p</i> <0.001
In Men	0.00	-0.036 [-0.062 to -0.010], <i>p</i> =0.007	-0.056 [-0.078 to -0.033], <i>p</i> <0.001
In Women	0.00	-0.006 [-0.045 to 0.033], <i>p</i> =0.76	-0.038 [-0.067 to -0.009], <i>p</i> =0.011
Baseline age			
≤30 yr	0.00	-0.048 [-0.084 to -0.011], <i>p</i> =0.011	-0.052 [-0.081 to -0.024], <i>p</i> <0.001
30-40 yr	0.00	0.005 [-0.029 to 0.039], <i>p</i> =0.76	-0.042 [-0.069 to -0.044], <i>p</i> =0.003
≥40 yr	0.00	-0.038 [-0.084 to 0.009], <i>p</i> =0.11	-0.055 [-0.095 to -0.014], <i>p</i> =0.009
Smoking status at baseline			
<i>Non smokers</i>	0.00	-0.032 [-0.069 to 0.005], <i>p</i> =0.09	-0.056 [-0.082 to -0.029], <i>p</i> <0.001
<i>Ex- smokers</i>	0.00	-0.024 [-0.077 to 0.028], <i>p</i> =0.37	-0.067 [-0.111 to -0.024], <i>p</i> =0.003
<i>Current smokers</i>	0.00	-0.030 [-0.062 to 0.001], <i>p</i> =0.06	-0.036 [-0.067 to -0.006], <i>p</i> =0.021
BMI at baseline			
<25	0.00	-0.010 [-0.036 to 0.016], <i>p</i> =0.45	-0.047 [-0.069 to -0.026], <i>p</i> <0.001
25-30	0.00	-0.057 [-0.098 to -0.017], <i>p</i> =0.006	-0.050 [-0.085 to -0.015], <i>p</i> =0.005
≥30	0.00	0.011 [-0.114 to 0.136], <i>p</i> =0.87	-0.040 [-0.135 to 0.054], <i>p</i> =0.40
Family history of asthma			
<i>No</i>	0.00	-0.025 [-0.048 to -0.002], <i>p</i> =0.034	-0.046 [-0.065 to -0.026], <i>p</i> <0.001
<i>Yes</i>	0.00	-0.010 [-0.089 to -0.069], <i>p</i> =0.81	-0.058 [-0.112 to -0.004], <i>p</i> =0.034

* Increasing 'slope' indicates decreasing BHR

[†] Adjustment for country, sex, baseline slope, age, BMI, FEV1, asthma-like symptoms, family history of asthma, smoking status, and Δ BMI and Δ FEV1.

[‡] for regression coefficient