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 ≥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], 3.48 [1.73–6.90] and 1.35 [0.86–2.11], 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 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.

(B)een d'épistemsie; longitudinaal

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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 (Δslope) 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 (ΔBMI) and change in FEV1 (ΔFEV1) 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.

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**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 $\chi^2$ 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

<table>
<thead>
<tr>
<th></th>
<th>Not Followed Up (n = 5,035)</th>
<th>Followed Up (n = 7,496)</th>
<th>Excluded* (n = 3,405)</th>
<th>Included (n = 4,091)</th>
<th>Without BHR at Baseline (n = 3,719)</th>
<th>With BHR at Baseline (n = 372)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men, %</strong></td>
<td>49.0</td>
<td>48.6</td>
<td>42.3</td>
<td>53.9$^*$</td>
<td>55.5</td>
<td>37.6$^*$</td>
</tr>
<tr>
<td><strong>Age, yr, mean ± SD</strong></td>
<td>33.1 ± 7.2</td>
<td>34.1 ± 7.1$^*$</td>
<td>33.9 ± 7.2</td>
<td>34.3 ± 7.0</td>
<td>34.3 ± 7.0</td>
<td>33.5 ± 7.1$^*$</td>
</tr>
<tr>
<td><strong>BMI, mean ± SD</strong></td>
<td>23.7 ± 3.9</td>
<td>23.9 ± 3.8$^*$</td>
<td>23.8 ± 4.0</td>
<td>23.9 ± 3.6</td>
<td>23.9 ± 3.5</td>
<td>24.1 ± 4.1</td>
</tr>
<tr>
<td><strong>Smoking, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>38.5</td>
<td>42.4$^*$</td>
<td>42.2</td>
<td>42.5$^*$</td>
<td>42.4</td>
<td>43.3</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>18.1</td>
<td>19.9</td>
<td>18.3</td>
<td>21.3</td>
<td>21.6</td>
<td>18.2</td>
</tr>
<tr>
<td>Moderate smokers$^*$</td>
<td>23.0</td>
<td>22.9</td>
<td>23.3</td>
<td>22.6</td>
<td>22.6</td>
<td>22.6</td>
</tr>
<tr>
<td>Heavy smokers$^*$</td>
<td>20.4</td>
<td>14.8</td>
<td>16.2</td>
<td>13.6</td>
<td>13.4</td>
<td>16.0</td>
</tr>
<tr>
<td><strong>Atopy, %</strong></td>
<td>31.4</td>
<td>29.2$^*$</td>
<td>28.7</td>
<td>29.3</td>
<td>27.4</td>
<td>49.7$^*$</td>
</tr>
<tr>
<td><strong>Log total IgE, mean ± SD</strong></td>
<td>3.53 ± 1.57</td>
<td>3.35 ± 1.57$^*$</td>
<td>3.36 ± 1.50</td>
<td>3.34 ± 1.55</td>
<td>3.28 ± 1.53</td>
<td>3.93 ± 1.59$^*$</td>
</tr>
<tr>
<td><strong>Family history of asthma, %</strong></td>
<td>10.1</td>
<td>11.2$^*$</td>
<td>11.2</td>
<td>11.3</td>
<td>10.8</td>
<td>16.1$^*$</td>
</tr>
<tr>
<td><strong>Asthmalike symptoms, %</strong></td>
<td>23.8</td>
<td>21.7$^*$</td>
<td>22.8</td>
<td>20.7$^*$</td>
<td>19.1</td>
<td>37.1$^*$</td>
</tr>
<tr>
<td><strong>FEV1, L/s, mean ± SD</strong></td>
<td>3.86 ± 0.49</td>
<td>3.90 ± 0.47</td>
<td>3.85 ± 0.49</td>
<td>3.94 ± 0.45$^*$</td>
<td>3.97 ± 0.44</td>
<td>3.69 ± 0.43$^*$</td>
</tr>
<tr>
<td>**Allergic rhinitis, %$^*$</td>
<td>19.5</td>
<td>18.7</td>
<td>18.5</td>
<td>18.8</td>
<td>16.6</td>
<td>40.3$^*$</td>
</tr>
<tr>
<td><strong>BHR, %</strong></td>
<td>12.6</td>
<td>10.2$^*$</td>
<td>12.4</td>
<td>9.1$^*$</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

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

† P < 0.05.

DEFINITIONS OF ABBREVIATIONS: BHR = bronchial hyperresponsiveness; BMI = body mass index; ECRHS = European Community Respiratory Health Survey.

Moderate smokers (<20 cigarettes/d) and heavy smokers (>20 cigarettes/d).

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

FEV1 = residual FEV1 + FEV1 mean.
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, and BMI and 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 family 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

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

<table>
<thead>
<tr>
<th></th>
<th>No AR, No Atopy (n = 2,699)</th>
<th>Atopy, No AR (n = 401)</th>
<th>AR (n = 619)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, %</td>
<td>52.3</td>
<td>67.8</td>
<td>61.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, mean (95% CI)</td>
<td>34.6 (34.3 to 34.9)</td>
<td>34.0 (33.3 to 34.6)</td>
<td>33.1 (32.6 to 33.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, mean (95% CI)</td>
<td>24.0 (23.9 to 24.1)</td>
<td>24.0 (23.7 to 24.4)</td>
<td>23.8 (23.3-24.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>ΔBMI kg/m²/yr, mean (95% CI)</td>
<td>0.18 (0.17 to 0.19)</td>
<td>0.20 (0.18 to 0.22)</td>
<td>0.19 (0.17 to 0.22)</td>
<td>0.16</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>40.6</td>
<td>36.8</td>
<td>54.1</td>
<td></td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>19.5</td>
<td>16.2</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>26.3</td>
<td>32.9</td>
<td>21.1</td>
<td></td>
</tr>
<tr>
<td>Quitters</td>
<td>10.0</td>
<td>11.3</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>Restarters</td>
<td>3.6</td>
<td>2.8</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Sensitization to, %</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cat</td>
<td>—</td>
<td>21.2</td>
<td>29.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>House dust mite</td>
<td>—</td>
<td>61.1</td>
<td>46.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cladosporium</td>
<td>—</td>
<td>16.2</td>
<td>7.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pollen</td>
<td>—</td>
<td>45.6</td>
<td>73.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total IgE, IU/ml, mean (95% CI)</td>
<td>44.5 (37.5 to 51.6)</td>
<td>190.8 (172.8 to 208.9)</td>
<td>205.7 (192.8 to 218.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log total IgE, mean (95% CI)</td>
<td>2.90 (2.85 to 2.95)</td>
<td>4.27 (4.14 to 4.40)</td>
<td>4.54 (4.45 to 4.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthmalike symptoms, %</td>
<td>17.6</td>
<td>17.7</td>
<td>26.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wheeze</td>
<td>14.4</td>
<td>15.2</td>
<td>22.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SOB at rest</td>
<td>3.4</td>
<td>2.2</td>
<td>4.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Awakened by SOB</td>
<td>2.7</td>
<td>2.7</td>
<td>6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of asthma, %</td>
<td>10.4</td>
<td>8.7</td>
<td>13.7</td>
<td>0.021</td>
</tr>
<tr>
<td>Family history of allergy, %</td>
<td>27.0</td>
<td>22.0</td>
<td>43.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁, L/s, mean (95% CI)</td>
<td>3.87 (3.84 to 3.91)</td>
<td>3.89 (3.80 to 3.98)</td>
<td>3.81 (3.74 to 3.87)</td>
<td>0.23</td>
</tr>
<tr>
<td>ΔFEV₁, ml/yr, mean (95% CI)</td>
<td>−26 (−27 to −25)</td>
<td>−29 (−32 to −26)</td>
<td>−20 (−22 to −18)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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 χ² for categorical variables.

1. 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

<table>
<thead>
<tr>
<th></th>
<th>No Atopy, No AR (n = 2,699)</th>
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<th>AR (n = 619)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHR, n(%)</td>
<td>148 (5.5)</td>
<td>28 (7.0)</td>
<td>60 (9.7)</td>
</tr>
<tr>
<td>Crude OR (95% CI)</td>
<td>1.00 (0.85–1.97)</td>
<td>1.85 (1.35–2.53)</td>
<td></td>
</tr>
<tr>
<td>Adjusted OR* (95% CI)</td>
<td>1.00 (0.86–2.11)</td>
<td>2.44 (1.73–3.45)</td>
<td></td>
</tr>
</tbody>
</table>

Stratified analysis by subgroups, adjusted OR†

- Men: 1.00 (1.06–3.63) 3.45 (2.05–5.81)
- Women: 0.93 (0.46–1.87) 1.89 (1.16–3.07)
- Baseline age, yr
  - <30: 1.00 (1.38–7.08) 3.40 (1.72–6.72)
  - 30–40: 1.02 (0.50–2.06) 1.81 (1.06–3.11)
  - >40: 1.18 (0.47–2.97) 3.58 (1.80–7.12)
- Smoking status
  - Nonsmokers: 1.00 (0.63–1.31) 2.72 (1.65–4.48)
  - Ex-smokers: 1.00 (0.87–5.88) 2.03 (0.82–4.99)
  - Current smokers: 1.16 (0.60–2.26) 2.66 (1.45–4.87)
- BMI at baseline
  - <25: 1.00 (0.78–2.38) 1.98 (1.27–3.10)
  - 25–30: 1.00 (0.70–3.71) 4.09 (2.15–7.81)
  - >30: 1.00 (0.46–1.04) 1.60 (0.32–7.98)
- Family history of asthma
  - No: 1.00 (0.88–1.21) 2.25 (1.54–3.30)
  - Yes: 1.00 (0.61–3.01) 2.72 (1.65–4.48)

<table>
<thead>
<tr>
<th></th>
<th>No AR, AR (n = 2,699)</th>
<th>No AR, IgE+ to cat Only (n = 401)</th>
<th>AR, IgE+ to cat only (n = 619)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n</td>
<td>2,699</td>
<td>23</td>
<td>41</td>
</tr>
<tr>
<td>n (%)</td>
<td>148 (5.5)</td>
<td>148 (5.5)</td>
<td>248 (1.24)</td>
</tr>
<tr>
<td>Adjusted* OR (95% CI)</td>
<td>1.00</td>
<td>1.00 (0.69–1.032)</td>
<td>1.00 (3.48–17.93)</td>
</tr>
</tbody>
</table>

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 (mean 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], 1.54 [1.02–2.32]).

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]).

**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.

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]).

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

<table>
<thead>
<tr>
<th></th>
<th>No AR, No Atopy (n = 2,699)</th>
<th>No AR, IgE+ to cat Only (n = 401)</th>
<th>AR, IgE+ to cat only (n = 619)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n</td>
<td>2,699</td>
<td>23</td>
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<tr>
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<td>Adjusted* OR (95% CI)</td>
<td>1.00</td>
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</tr>
</tbody>
</table>

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 (mean 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], 1.54 [1.02–2.32]).
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 (Alerrian artemis, Cladosporium herbarum, Phleum pratense [timothy grass], birch, olive, Parietaria judaica [pellitory-of-the-wall], common ragweed [Ambrosia artemisifolia], 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**

<table>
<thead>
<tr>
<th>Subjects with AR at ECRHS-I (n = 629)</th>
<th>Without Nasal Steroid</th>
<th>With Nasal Steroid</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHR onset at follow-up</td>
<td>48/491 (9.8%)</td>
<td>13/138 (9.4%)</td>
<td>1.04 (0.55–1.98)</td>
</tr>
<tr>
<td>BHR remission at follow-up</td>
<td>36/120 (30.0%)</td>
<td>33/30 (56.7%)</td>
<td>0.33 (0.14–0.75)</td>
</tr>
</tbody>
</table>

*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 allergens 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 for 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 results 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.

Centers and personnel participating in the European Community Respiratory Health Survey (ECRHS) are as follows:

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**Steering Committee for the ECRHS-I:** U. Ackermann-Liebrich (University of Basel, Basel, Switzerland); J. M. Antó (Instituto Municipal d’Investigació Mèdica [IMIM-IMAS] and Universitat Pompeu Fabra [UPF], Barcelona, Spain); P. Burney (Imperial College, London, UK); I. Cerveri (University of Pavia, Pavia, Italy); S. Chinn (King’s College London, London, UK); R. de Marco (University of Verona, Verona, Italy); T. Gislason (Iceland University Hospital, Reykjavik, Iceland); J. Heinrich (GSF-Institute of Epidemiology, Munich, Germany); C. Janson (Uppsala University, Uppsala, Sweden); D. Jarvis (Imperial College); J. Knox (King’s College London); N. Künzli (University of Southern California, Los Angeles, CA); B. Leynaert (Institut National de la Santé et de la Recherche Médicale [INSERM], Paris, France); C. Luczynska (King’s College London); F. Neukirch (INSERM); J. Schouten (University of Groningen, Groningen, The Netherlands); J. Sunyer (IMIM-IMAS and UPF); C. Swanes (University of Bergen, Bergen, Norway); P. Vermeire (University of Antwerp, Antwerp, Belgium); M. Wist (GSF-Institute of Epidemiology).


**Centers taking part at their own expense:** Australia: Melbourne (M. Abramson, R. Woods, E. H. Walters, F. Thien); France: Bordeaux (A. Taytard, C. Raherson), Montpellier (A. Bouquelet, P. Demoly); Germany: Hamburg (K. Richter); United States: Portland (M. Osborne, S. Buist, W. Vollmer, L. Johnson).

**References**


