

# Epidemiologic evidence for asthma and rhinitis comorbidity

Bénédicte Leynaert, PhD,<sup>a</sup> Françoise Neukirch, MD,<sup>a</sup> Pascal Demoly, MD,<sup>b</sup> and Jean Bousquet, MD<sup>b</sup> Paris and Montpellier, France

Asthma and rhinitis are often comorbid conditions, and the overall characteristics of the diseases and the treatment options for the disorders are similar. Several recent epidemiologic studies in the general population have provided evidence to strongly associate the development of asthma with a previous history of either allergic or perennial rhinitis. Additional links between asthma and rhinitis include a description of increased aspirin intolerance in both disorders and the observation that most subjects with occupational asthma experience rhinitis. Further, the likelihood of the development of asthma is much higher in individuals with both perennial and seasonal rhinitis than for individuals with either condition alone. Asthma and rhinitis were found to be comorbidities regardless of atopic state, and perennial rhinitis has been associated with an increase in nonspecific bronchial hyperresponsiveness. Several studies have identified rhinitis as a risk factor for asthma, with the prevalence of allergic rhinitis in asthmatic patients being 80% to 90%. These studies and others demonstrate that the coexistence of asthma and allergic rhinitis is frequent, that allergic rhinitis usually precedes asthma, and that allergic rhinitis is a risk factor for asthma. Finally, studies that have examined the age of onset of atopy as a confounding factor for the development of asthma and allergic rhinitis have suggested that early age atopy may be an important predictive factor for respiratory symptoms that continue into late childhood. In conclusion, rhinitis and asthma are strongly associated, and rhinitis has been identified as a risk factor for asthma. (*J Allergy Clin Immunol* 2000;106:S201-5.)

**Key words:** Atopy, epidemiology, IgE, perennial, risk factor, sensitization

Asthma and rhinitis commonly occur as comorbidities. The concept of “1 airway, 1 disease”<sup>1</sup> is supported by several factors, which include common epidemiologic, pathologic, and physiologic characteristics and a common therapeutic approach for both rhinitis and asthma.<sup>2-5</sup> Although this concept is not yet universally accepted,<sup>6</sup> the term *allergic rhinobronchitis* has been recently proposed to link allergic asthma and rhinitis.<sup>7</sup>

Despite recent studies that have attempted to shed more light on the epidemiologic factors of these 2 conditions, many questions remain to be answered. These

## Abbreviations used

CI: Confidence interval

ECRHS: European Community Respiratory Health Survey

OR: Odds ratio

include: (1) the frequency of concurrent allergic asthma and rhinitis; (2) whether the association between rhinitis and asthma is restricted to allergic patients; (3) whether asthma is more frequently associated with seasonal or perennial rhinitis; (4) whether respiratory symptoms depend on patient age during allergen sensitization; (5) whether rhinitis is associated with nonspecific bronchial hyperresponsiveness; and (6) whether rhinitis could be considered a risk factor for asthma.

## ASSOCIATION BETWEEN RHINITIS AND ASTHMA

Although several recently published epidemiologic studies have demonstrated the association between allergic rhinitis and asthma, nonallergic rhinitis was also found to be associated with asthma (Table I). In a study performed in France, a total of 20,000 households were screened for symptoms of perennial rhinitis (ie, intermittent symptoms lasting for at least 6 months or 2 continuous symptoms including rhinorrhea, sneezing, or nasal obstruction).<sup>8</sup> Of 16,786 responding households (response rate, 84%), 35,615 patients were over 15 years of age. A predetermined algorithm was used to select 1367 patients with probable perennial rhinitis for a cross-sectional collection of data on history and concurrent disease. The estimated point prevalence of perennial rhinitis was 4.1% (95% confidence interval [CI], 3.9%-4.3%). This estimated figure may be lower than actual rates because of the variability of the symptoms of perennial rhinitis, which lead to the exclusion of many patients. In this study, patients with perennial rhinitis had a significantly higher association with a history of asthma (13.4%) than those patients with no perennial rhinitis (3.8%; odds ratio [OR] = 3.26;  $P \leq .001$ ).

The European Community Respiratory Health Survey (ECRHS),<sup>9</sup> a population study, was conducted to assess the prevalence and risk factors of asthma and asthma-like symptoms. A standardized protocol was used to evaluate a random sample of 20- to 44-year-old individual subjects in several countries. In the first of 2 stages, a postal questionnaire was sent to representative samples of the population. In the second stage, a full-length questionnaire was used to examine subsamples of responders from the first stage.<sup>10</sup> In addition, the following param-

From <sup>a</sup>the Epidémiologie des Maladies Respiratoires, Faculté de Médecine Xavier Bichat, Paris, and <sup>b</sup>the Service des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, Montpellier.

No disclosure information provided.

Reprint requests: Professeur Jean Bousquet, Clinique des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, 34295 Montpellier, Cedex 5, France. Copyright © 2000 by Mosby, Inc.

0091-6749/2000 \$12.00 + 0 1/0/110151

doi:10.1067/mai.2000.110151

**TABLE I.** Recent epidemiologic studies of asthma associated with rhinitis

| Study                          | Setting                          | Subjects         | No. of subjects with rhinitis | Prevalence of asthma (%)                                                   |
|--------------------------------|----------------------------------|------------------|-------------------------------|----------------------------------------------------------------------------|
| Pariente et al <sup>8</sup>    | France                           | Adults           | 1367                          | Rhinitis: 13.4<br>No rhinitis: 3.8                                         |
| Leynaert et al <sup>11</sup>   | ECRHS; Montpellier/Paris, France | Adults           | 262                           | Rhinitis: 22.5<br>No rhinitis: 4.0                                         |
| Wright et al <sup>29</sup>     | Tucson, Ariz                     | Children         | 129                           | Rhinitis: 32.0<br>No rhinitis: 5.0                                         |
| Settipane et al <sup>30</sup>  | Providence, RI                   | College students | 162                           | Rhinitis: 10.5<br>No rhinitis: 3.6                                         |
| Sibbald and Rink <sup>20</sup> | London, England                  | Adults           | 319                           | Seasonal rhinitis: 23.0<br>Perennial rhinitis: 26.0<br>Both rhinitis: 43.0 |

ters were measured: (1) total and allergen-specific IgE in serum, (2) skin prick tests with 9 allergens, (3) FEV<sub>1</sub>, and (4) methacholine challenge. The prevalence of current asthma was assessed with the question, "Do you have any nasal allergies including hay fever?" Among the 765 subjects who were studied in the ECRHS centers of Montpellier and Paris, France, current asthma was reported in 22.5% of subjects with rhinitis and 4% of subjects with no rhinitis ( $P < .01$ ).<sup>11</sup>

Commonly, rhinitis and asthma are induced by exposure to aspirin and nonsteroidal anti-inflammatory drugs. Aspirin intolerance was studied in a population-based random sample and was found to be more frequent among subjects with allergic rhinitis (2.6%) than those without (0.3%;  $P < .01$ ).<sup>12</sup>

Another example of association between rhinitis and asthma is occupational rhinitis, which is not as well documented as occupational asthma. However, symptoms of rhinitis are commonly associated with occupational asthma. In fact, in 1 study, 92% of subjects with occupational asthma experienced rhinitis symptoms.<sup>13</sup> Bakers often have symptoms of allergic rhinitis and asthma.<sup>14-16</sup> Wood dust can also induce rhinitis and asthma; however, the mechanisms are still unclear.<sup>17-19</sup>

In conclusion, several studies have demonstrated that rhinitis is associated with asthma (Table I). Comorbidities are common in patients who are sensitized to aeroallergens and intolerant to aspirin and in patients with occupational disease. However, it seems that rhinitis per se is strongly associated with asthma.

## DIFFERENCES BETWEEN SEASONAL AND PERENNIAL RHINITIS

A study performed in the United Kingdom compared the symptoms, atopic state, and medical history in individuals with seasonal and perennial rhinitis.<sup>20</sup> Of 7702 adults who were registered with a London general practice and who were aged 16 to 65 years, 2969 (30%) were screened by postal questionnaire. Interviews were conducted with 113 subjects without rhinitis, 51 subjects with seasonal symp-

toms alone, 128 subjects with both perennial symptoms and seasonal exacerbations. Atopic and nonatopic subjects were distinguished by skin prick testing with 5 common allergens. Sneezing, itching, and a high prevalence of diurnal variation in symptoms characterized seasonal rhinitis. The estimated minimum prevalence of rhinitis was 24%. Three percent of the subjects had seasonal symptoms only, and most of those patients (78%) were atopic. In addition, 3% of patients with rhinitis had perennial symptoms; one half of them were atopic. Last, 8% of the subjects had perennial symptoms with seasonal exacerbations, 68% of whom were atopic. Subjects with perennial rhinitis were more likely to be wheezy or labeled asthmatic than controls or subjects with seasonal allergic rhinitis. Subjects with both seasonal and perennial symptoms had an intermediate clinical picture. Furthermore, subjects with seasonal and perennial rhinitis differed in their atopic state, clinical presentation, and medical history.

Leynaert et al<sup>21</sup> used data on patients 18 to 44 years of age from 34 ECRHS centers to study the associations between asthma and rhinitis. Asthma was present in 0.8% of subjects without rhinitis, in 6% of subjects with seasonal rhinitis only, in 9% of subjects with perennial rhinitis only, and in 18% of subjects with both seasonal and perennial rhinitis. A special analysis was performed to assess the impact of different factors, including atopy, on the association between asthma and rhinitis. After adjustment for sex, age, smoking habit, family history of asthma, geographic location, and season at the time of examination, asthma was found to be strongly associated with rhinitis in both atopic subjects (OR, 8.1; 95% CI, 5.4%-12.1%) and nonatopic subjects (OR, 11.6; 95% CI, 6.2%-21.9%). Moreover, the association remained strong when the analysis was restricted to nonatopic subjects with IgE levels of 80 KU/L or less (OR, 13.3; 95% CI, 6.7%-26.5%).

These studies suggest that patients with perennial and seasonal rhinitis are more likely to have asthma than those patients with either seasonal or perennial rhinitis alone and that asthma and rhinitis are associated comorbidities in both allergic and nonallergic subjects.

## RHINITIS AND NONSPECIFIC BRONCHIAL HYPERRESPONSIVENESS

Many patients with allergic rhinitis have unique physiologic features that differentiate them from asthmatic patients and normal subjects, including an increased bronchial sensitivity to methacholine or histamine.<sup>22,23</sup>

Patients with seasonal allergic rhinitis experience the development of seasonal bronchoconstriction that is not associated with clinical bronchospasm.<sup>24</sup> Moreover, bronchial hyperresponsiveness and exercise-induced bronchoconstriction were commonly observed in patients who are allergic to grass or birch pollen, seasonal increases of carbachol, histamine, or methacholine.<sup>25-27</sup>

In the ECRHS epidemiologic study, nonspecific bronchial hyperresponsiveness was increased in patients with rhinitis in comparison with nonrhinitis subjects, but to a lesser extent than in asthmatic patients. In the samples from Montpellier and Paris, 31.5% of subjects with rhinitis had a provocative dose that induced a 20% fall in FEV<sub>1</sub> to methacholine less than 4 mg versus 17.4% of the nonrhinitis subjects ( $P < .01$ ).<sup>11</sup> The analysis of the data from the 34 ECRHS centers showed that nonspecific bronchial hyperresponsiveness was significantly more frequent in subjects with perennial rhinitis than in subjects with seasonal rhinitis or without rhinitis.<sup>28</sup> Moreover, this difference was observed even in subjects with low total serum IgE levels (80 KU/L; OR, 1.7, 95% CI, 1.2%-2.6%).

These studies indicate that perennial rhinitis is associated with an increase in nonspecific bronchial hyperresponsiveness.

## RHINITIS IS A RISK FACTOR FOR ASTHMA

A study performed in Tucson, Ariz, investigated the natural history of and risk factors for allergic rhinitis in the first 6 years of life.<sup>29</sup> Parents of 747 healthy children followed from birth completed a questionnaire when the child was 6 years old. Data were obtained regarding physician-diagnosed allergic rhinitis, comorbidities, and age at onset. Risk-factor data were taken from earlier questionnaires, and data regarding IgE and skin-test reactivity were obtained at age 6 years. By the age of 6 years, 42% of children had physician-diagnosed allergic rhinitis. Children whose rhinitis began in the first year of life had more respiratory symptoms at age 6 years and were more likely to have a diagnosis of asthma. Risk factors for physician-diagnosed allergic rhinitis that remained significant in a multivariate model included maternal history of physician-diagnosed allergy (OR, 2.2; 95% CI, 1.35%-3.54%), asthma in the child (OR, 4.06; 95% CI, 2.06%-7.99%), and IgE greater than 100 KU/L at age 6 years (OR, 1.93; 95% CI, 1.18%-3.17%). This study suggested that rhinitis that develops in the first years of life is an early manifestation of an atopic predisposition and a risk factor for asthma.

A study examined the coexistence of asthma and allergic rhinitis among former college students who were diagnosed with these diseases either before or after their

freshman year.<sup>30,31</sup> A total of 738 former Brown University (Providence, RI) students (male, 69%; female, 31%) who were evaluated and who underwent skin testing during their freshman year completed a 23-year follow-up questionnaire that inquired about their history of allergies and asthma. The mean age of the participants at the time of the follow-up study was 40 years. In this group, the cumulative incidence of asthma was 11.3%, of seasonal allergic rhinitis was 41.5%, and of nonseasonal allergic rhinitis was 14.0%. The cumulative incidence of allergic rhinitis was 45.8%. Among the 84 individuals with a cumulative incidence of asthma, 85.7% had a history of allergic rhinitis. Among the 306 participants with a cumulative incidence of seasonal allergic rhinitis, 20.6% had a history of asthma. Twenty-seven percent of the 103 individuals with a history of nonseasonal allergic rhinitis had a cumulative incidence of asthma. Among the participants with a history of both asthma and seasonal allergic rhinitis, 44.8% experienced the development of seasonal allergic rhinitis first; 34.5% experienced the development of asthma first, and 20.7% experienced the development of both diseases at the same time. Among the individuals with a history of asthma and nonseasonal allergic rhinitis, 38.5% experienced the development of nonseasonal allergic rhinitis first; 30.8% experienced the development of asthma first, and 30.8% experienced the development of both diseases at the same time. This study further demonstrates the frequent coexistence of asthma and allergic rhinitis. Allergic rhinitis therefore often precedes or occurs at the same time as asthma.

A study performed in Finland examined prospectively the prevalence of asthma and seasonal allergic rhinitis and the incidence and temporal relationships of asthma, seasonal allergic rhinitis, and chronic bronchitis among adult twins during a 15-year period.<sup>32</sup> The study population included 11,540 Finnish adult men and women (initially 18 to 45 years of age) who returned a health questionnaire in 1975, 1981, and 1990 as part of the Finnish Twin Cohort study. Age-standardized prevalences and cumulative incidences among individuals were calculated for asthma, seasonal allergic rhinitis, and chronic bronchitis. The incidence of asthma among subjects with and without seasonal allergic rhinitis or chronic bronchitis was analyzed in the entire cohort and in twin pairs discordant for incident asthma. The prevalence of asthma increased slightly from 1975 (men, 2.0%; women, 2.2%) to 1990 (men, 2.9%; women, 3.1%). The prevalence of seasonal allergic rhinitis showed a larger increase in men and women (from 6.8% and 9.8% to 11.8% and 15.3%, respectively). Seasonal allergic rhinitis was usually diagnosed before asthma and increased the risk of asthma significantly on the basis of analyses of all individuals and of discordant twin pairs.

The prognosis of allergic rhinitis was studied in 154 children aged 3 to 17 years at diagnosis by means of a detailed questionnaire administered 8 to 11 years later.<sup>33</sup> Asthma or wheezing had developed in 19% of subjects and was more common ( $P < .01$ ) among those children with perennial allergic rhinitis (34%) than among those

children with seasonal allergic rhinitis (12.7%). No significant association was found between age at onset of symptoms, family history of atopic disease, type of treatment for allergic rhinitis and allergic rhinitis still present at follow-up, or development of asthma during the observation period.

These studies combine to indicate that allergic rhinitis is a risk factor for the development of asthma.

## AGE OF OCCURRENCE OF ALLERGIC SENSITIZATION

The age of onset of atopy may be an important confounding factor for the development of asthma and rhinitis or rhinitis alone.

A total of 380 schoolchildren living in Belmont, New South Wales, Australia (a coastal town where the predominant aeroallergens are house dust mites), were studied on 3 occasions at 2-year intervals.<sup>34</sup> At each study, atopy was measured by skin prick tests to 13 allergens. In the sample, 24% of the children were atopic at 8 to 10 years (early-onset atopy), and an additional 15% of the children became atopic during the study (late-onset atopy). Both early- and late-onset atopy had a close association with seasonal allergic rhinitis. Early-onset atopy was an important risk factor for asthma and continuing symptoms of wheeze in late childhood years. Late-onset atopy was strongly associated with inconsistent reporting of respiratory symptoms. The authors concluded that atopy acquired at an early age is an important predictive factor for respiratory symptoms that occur with bronchial hyperresponsiveness and continue into late childhood.

Several surveys in children and adults have shown a significantly lower prevalence of asthma and allergic diseases in eastern Europe than in western countries.<sup>35-37</sup> In the former East Germany, tremendous changes towards western lifestyle have occurred since unification. A survey investigated time trends in the prevalence of asthma and allergic diseases among children living in the eastern part of Germany.<sup>38</sup> In 1995 to 1996, 2334 school children (87.5%) in Leipzig, Germany, participated in a cross-sectional study that used the same methods as a previous survey performed shortly after the fall of Communism in 1991 to 1992. A self-administered questionnaire was distributed to the parents. Children underwent cold-air challenge and skin-prick tests to 6 common aeroallergens. The prevalence of seasonal allergic rhinitis (2.3% vs 5.1%;  $P < .0001$ ) and atopic sensitization (19.3% vs 26.7%;  $P < .0001$ ) increased significantly between 1991 to 1992 and 1995 to 1996. However, there was no significant change in the prevalence of asthma, asthma-related symptoms, or bronchial hyperresponsiveness.

These findings suggest important differences in the development of atopic disorders. Factors operating very early in life may be particularly important for the acquisition of childhood asthma (and rhinitis), whereas the development of atopic sensitization and seasonal allergic rhinitis may also be affected by environmental factors that occur beyond infancy.

## CONCLUSIONS

Recent epidemiologic studies in the general population have provided evidence that asthma and rhinitis are strongly associated with each other. Although atopic subjects commonly have asthma and rhinitis, rhinitis alone appears to be a risk factor for asthma. However, the nature of the association is still a matter of debate, and studies that will examine the relationship between these 2 diseases in groups with different allergic sensitizations and longitudinal studies will provide important insights into this comorbidity.

## REFERENCES

- Grossman J. One airway, one disease. *Chest* 1997;111(suppl 2):11S-6S.
- Rowe-Jones JM. The link between the nose and lung, perennial rhinitis and asthma: Is it the same disease? *Allergy* 1997;52:20-8.
- Vignola AM, Chanez P, Godard P, Bousquet J. Relationships between rhinitis and asthma. *Allergy* 1998;53:833-9.
- Corren J. The impact of allergic rhinitis on bronchial asthma. *J Allergy Clin Immunol* 1998;101:S352-6.
- Townley RG, Kiboneka A. Allergic rhinitis: relationship to asthma: similarities, differences, and interactions [editorial]. *Ann Allergy Asthma Immunol* 1998;80:137-9.
- American Thoracic Society Workshop. Immunobiology of asthma and rhinitis. Pathogenic factors and therapeutic options. *Am J Respir Crit Care Med* 1999;160:1778-87.
- Simons FE. Allergic rhinobronchitis: the asthma-allergic rhinitis link. *J Allergy Clin Immunol* 1999;104:534-40.
- Pariante PD, LePen C, Los F, Bousquet J. Quality-of-life outcomes and the use of antihistamines in a French national population-based sample of patients with perennial rhinitis. *Pharmacoeconomics* 1997;12:585-95.
- The European Community Respiratory Health Survey. Medicine and Health. European Commission, Directorate General XIII. L-2920 Luxembourg: Office for Official Publications; 1994.
- Burney PG, Luczynska C, Chinn S, Jarvis D. The European community respiratory health survey. *Eur Respir J* 1994;7:954-60.
- Leynaert B, Liard R, Bousquet J, Pin I, Soussan D, Neukirch F. Lessons from the French part of the European community respiratory health survey (ECRHS). *Allergy Clin Immunol Int* 1999;11:218-25.
- Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999;28:717-22.
- Malo JL, Lemiere C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. *Eur Respir J* 1997;10:1513-5.
- Baur X. Baker's asthma: causes and prevention. *Int Arch Occup Environ Health* 1999;72:292-6.
- Musk AW, Venables KM, Crook B, Nunn AJ, Hawkins R, Crook GD, et al. Respiratory symptoms, lung function, and sensitisation to flour in a British bakery. *Br J Ind Med* 1989;46:636-42.
- Brisman J, Jarvholm B. Bakery work, atopy and the incidence of self-reported hay fever and rhinitis. *Eur Respir J* 1999;13:502-7.
- Wilhelmsson B, Jernudd Y, Ripe E, Holmberg K. Nasal hypersensitivity in wood furniture workers: an allergological and immunological investigation with special reference to mold and wood. *Allergy* 1984;39:586-95.
- Kanerva L, Vaheri E. Occupational allergic rhinitis in Finland. *Int Arch Occup Environ Health* 1993;64:565-8.
- Fernandez-Rivas M, Perez-Carral C, Senent CJ. Occupational asthma and rhinitis caused by ash (*Fraxinus excelsior*) wood dust. *Allergy* 1997;52:196-9.
- Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. *Thorax* 1991;46:895-901.
- 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;104:301-4.
- Townley RG, Ryo UY, Kolotkin BM, Kang B. Bronchial sensitivity to

- methacholine in current and former asthmatic and allergic rhinitis patients and control subjects. *J Allergy Clin Immunol* 1975;56:429-42.
23. Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Bronchial responsiveness to methacholine in chronic bronchitis: relationship to air-flow obstruction and cold air responsiveness. *Thorax* 1984;39:912-8.
24. Gerblich AA, Schwartz HJ, Chester EH. Seasonal variation of airway function in allergic rhinitis. *J Allergy Clin Immunol* 1986;77:676-81.
25. Madonini E, Briatico-Vangosa G, Pappacoda A, Maccagni G, Cardani A, Saporiti F. Seasonal increase of bronchial reactivity in allergic rhinitis. *J Allergy Clin Immunol* 1987;79:358-63.
26. Karjalainen J, Lindqvist A, Laitinen LA. Seasonal variability of exercise-induced asthma especially outdoors: effect of birch pollen allergy. *Clin Exp Allergy* 1989;19:273-8.
27. Prieto L, Lopez M, Berto JM, Peris A. Modification of concentration-response curves to inhaled methacholine after the pollen season in subjects with pollen induced rhinitis. *Thorax* 1994;49:711-3.
28. Leynaert B, Bousquet J, Henry C, Liard R, Neukirch F. Is bronchial hyperresponsiveness more frequent in women than in men? A population-based study. *Am J Respir Crit Care Med* 1997;156:1413-20.
29. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994;94:895-901.
30. 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;15:21-5.
31. Greisner WA 3rd, Settipane RJ, Settipane GA. Co-existence of asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Asthma Proc* 1998;19:185-8.
32. Huovinen E, Kaprio J, Laitinen LA, Koskenvuo M. Incidence and prevalence of asthma among adult Finnish men and women of the Finnish Twin Cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. *Chest* 1999;115:928-36.
33. Linna O, Kokkonen J, Lukin M. A 10-year prognosis for childhood allergic rhinitis. *Acta Paediatr* 1992;81:100-2.
34. Peat JK, Salome CM, Woolcock AJ. Longitudinal changes in atopy during a 4-year period: relation to bronchial hyperresponsiveness and respiratory symptoms in a population sample of Australian schoolchildren. *J Allergy Clin Immunol* 1990;85:65-74.
35. von Mutius E, Fritzsche C, Weiland SK, Roll G, Magnussen H. Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. *Br Med J* 1992;305:1395-9.
36. von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;149:358-64.
37. Braback L, Breborowicz A, Dreborg S, Knutsson A, Pieklik H, Bjorksten B. Atopic sensitization and respiratory symptoms among Polish and Swedish school children. *Clin Exp Allergy* 1994;24:826-35.
38. von Mutius E, Weiland SK, Fritzsche C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998;351:862-6.