

Slowing Progression Along the Allergic Disease Continuum: Quo Vadit Immunotherapy?

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There is emerging evidence that rhinitis frequently precedes the onset of asthmatic symptoms. The frequent association of rhinitis and asthma has led to the concept that these conditions are likely manifestations of the same disease. This hypothesis has important implications for both the diagnosis and the management of these common conditions. Unfortunately, there is little known regarding the risk factors responsible for the progression of rhinitis to asthma. The current treatment options can control symptoms but do not prevent or cure the disease. However, there is recent data supporting the notion that it is possible to prevent new asthma cases by modifying the immune response and clinical outcome with allergen immunotherapy. This review article evaluates the impact of rhinitis on the development of asthma, examines putative predictors for the progression of rhinitis to asthma, and reviews recent, promising literature suggesting that early treatment of allergic individuals with immunotherapy may aid in asthma prevention.

Introduction

THE CLOSE ANATOMICAL, FUNCTIONAL, pathogenic, immunological, and clinical relationship between the upper and lower respiratory tract has been repeatedly confirmed in recent years (reviewed in Ref.¹⁻³). Furthermore, a strong association between rhinitis and asthma has been well documented in epidemiological studies. There is also convincing evidence that rhinitis frequently precedes the onset of asthmatic symptoms and may be an important risk factor for the development of asthma (reviewed in Ref.⁴). Thus, it appears reasonable to consider asthma and rhinitis as different manifestations of a common syndromic entity. Recently, this idea has been accepted by many researchers and new nomenclature has been introduced, such as united airways disease, allergic rhinobronchitis, and combined allergic rhinitis and asthma syndrome (CARAS).⁵⁻⁷

The notion that upper and lower respiratory airways behave as a single entity supports the hypothesis that, by modulating the immune and clinical response in high-risk patients, it is possible to prevent new cases of asthma. This assumption has been recently tested in a number of environmental intervention studies, where individuals with a strong family history of asthma strictly avoid one or more environmental exposures (such as indoor aeroallergens and environmental tobacco smoke) beginning early in their

life.⁸⁻¹⁰ Unfortunately, results from these studies indicate that this approach, alone, is not very successful in preventing the development of asthma. Perhaps, considering the well-known ability of allergen immunotherapy to induce immune tolerance,¹¹ it is logical to consider early immunotherapy as a way to reduce the incidence of progression to asthma in allergic individuals.^{12,13}

The purpose of this article is to evaluate the impact of rhinitis on the development of asthma, to examine the putative predictors for the progression of rhinitis to asthma, and to review current research related to the use of allergen immunotherapy for the prevention of asthma in allergic individuals.

Progression to Asthma Along the Allergic Disease Continuum

A clinical, functional, pathogenic, and immunological association between upper and lower respiratory-airway disorders has been repeatedly documented.¹⁻³ The existence of the so-called united airways disease was first suggested by epidemiological studies, which indicated a close association between rhinitis and asthma.^{14,15} As many as 40% of the patients studied with rhinitis also had asthma, and nasal allergy symptoms occurred in up to 80% of patients with

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asthma.^{14,15} Several studies have demonstrated that allergic rhinitis usually precedes asthma and that rhinitis may be an important risk factor for the development of asthma. In a proportion of allergic rhinitic individuals, bronchial challenge with histamine or methacholine resulted in bronchial hyperresponsiveness (BHR), even in the absence of any asthmatic symptoms.^{16,17} This may be a reflection of subclinical inflammatory changes in the lower airways.^{18–20} Notably, rhinitic subjects with documented BHR are known to be at-risk for progression to asthma.^{21–23} Additionally, a number of epidemiological studies have suggested that allergic rhinitis may be a precursor to the airway symptoms related to asthma.^{24–28} However, in a recent longitudinal population-based study by Shaaban et al., the overall population attributable risk of developing asthma from rhinitis was about 30%.²⁸ Though, this was in contrast to the magnitude of the observed effect in previously reported epidemiological studies^{24–27} where the risk appeared to be much higher and more clinically relevant. For example, in the large population-based study by Leynaert et al.,²⁶ rhinitis was highly predictive of the development of new-onset asthma (OR = 7.03). Likewise, Huovinen et al.²⁷ reported that, during a 15-year follow-up period, allergic rhinitis increased the risk of asthma development by 4-fold in men and 6-fold in women. This may be significantly relevant given that allergen immunotherapy for the treatment of allergic rhinitis has the potential to modify the natural course of the disease by preventing new-onset asthma.

Unfortunately, these epidemiological studies mostly relied on written questionnaires for the diagnosis of allergic rhinitis and asthma. Additionally, there is the possibility that some medications for allergic rhinitis may prevent asthmatic symptoms, especially regular topical corticosteroids, thus reducing the accuracy of diagnosis. The impact of these factors on the outcome of epidemiological studies related to asthma and rhinitis cannot be ignored. However, in these population-based studies, the observation that a high proportion of adults with rhinitis who also develop new-onset asthma has been substantiated by data obtained from large clinical-based studies of children and adults with allergic rhinitis.^{29,30}

In a prospective pediatric study of 205 children with a clinical history of grass- or birch-induced rhinoconjunctivitis, who were randomized to receive allergen immunotherapy for 3 years or to be included in an open control group,²⁹ diagnosis of allergic rhinitis at the start of the study was predictive of new-onset asthma by the final visit; 44.4% of the subjects in the control group developed asthmatic symptoms by the end of the follow-up period, while the actively treated children developed significantly fewer asthma symptoms. This preventive effect of immunotherapy has been confirmed at later follow-up visits (5 and 10 years after IT) by the same investigators.^{31,32} In our retrospective cohort study of 332 allergic individuals, a medical diagnosis of allergic rhinitis at the start of the study was highly and independently predictive of the development of new-onset asthma by the 10-year follow-up; 46.1% of those with rhinitis at the start of the study developed asthmatic symptoms by the end of the follow-up (OR = 7.8).³⁰ It is important to note that the usage of topical corticosteroids was similar in the allergic rhinitic subjects with new-onset asthma (52.3%) compared to those who had no symptoms of asthma (47.5%).

Predictors for Progression From Rhinitis to Asthma

Recurrent exposure to inhaled antigens with strong allergenic properties may eventually dictate progression of the “allergic march” toward asthma in individuals with an atopic predisposition.³³ Of all known common allergens, the house dust mite is strongly implicated as a potential cause of asthma.^{34,35} In the multicenter study by Moller et al.,²⁹ where 205 children allergic to either grass- or birch-pollen were evaluated, specific information regarding the most prevalent type of inhaled allergen associated with patients from each center was unavailable. This would have been important for understanding the substantial variation in clinical outcomes observed between centers. In our study,³⁰ linear regression analyses demonstrated that house dust mite sensitization was not significantly predictive of new-onset asthma. Instead, a positive sensitization to *Parietaria judaica* was markedly associated with an increased risk of developing asthma. The reasons for this discrepancy are not known, but may reflect the peculiar characteristics of the type of inhaled allergen, which is strongly allergenic and often reaches very high levels in Sicily,^{36,37} where the study was conducted. As one would expect, the presence of pets in the home and a positive family history of allergic diseases were all predictive of new-onset asthma in our study population.³⁰ However, their overall population attributable risk was substantially lower than the diagnosis of allergic rhinitis. Surprisingly, the duration of rhinitis was not predictive of asthma development in this cohort. Rhinitic subjects with documented BHR are known to be at-risk for the development of new-onset asthma,^{21–23} but this was not adequately addressed in the previously mentioned studies.

The well-known gender-dependent reduction in asthma prevalence that occurs around the onset of puberty, which is due to hormonal modifications,³⁸ may have had important effects on the measured outcomes reported in the multicenter study by Moller et al.²⁹ Although specific information regarding the gender and age distribution of the children from each participating center was not specified in their article,²⁹ the proportion of the preventive effect of immunotherapy remained unchanged at later follow-up visits (5 and 10 years after IT).^{31,32}

In our study of adults, being female was a predictive factor for new-onset asthma.³⁰ Exposure to cigarette smoke has also been shown to be a powerful determinant of asthma development. In particular, an increased risk of childhood asthma and wheezing in association with maternal and household smoking has been widely reported.^{39–42} In a cohort of clinical-referred non-asthmatic subjects with established allergic rhinitis, we found a sound positive association between cigarette smoking and the development of new-onset asthma (OR = 2.98).⁴³ There was a clear dose-response effect of smoking exposure, assessed as pack-years, and the intensity of smoking appears to be associated with the strength of the association in our study population.⁴³ Multivariate analyses demonstrated that, compared to never smokers, those with 1–10 pack-years had an OR of 2.14, those with 11–20 pack-years had an OR of 3.81, and those with >20 pack-years had an OR of 5.87. This underscores the notion that the number of cigarettes smoked may be important in dictating the evolution of distinct disease phenotypes.

It is unclear why a large proportion of individuals with atopy and rhinitis eventually progress to bronchial asthma. Irrespective of the putative role of smoking, inflammatory changes are known to be present in the lower airways of subjects with allergic rhinitis, even in the absence of asthma symptoms,²⁰ and these may ultimately lead to the development of asthma. It is likely that persistent exposure of the airway to airborne allergens in combination with cigarette smoke may have an additive or synergistic effect on the progression of the inflammatory responses. Tobacco smoke is a complex mixture of gases and vapors and the particulate phase promotes an adjuvant effect that may favor the development of allergen-specific IgE antibodies and IgE-mediated allergic airway diseases. Laboratory studies in humans and animals have shown that the polyaromatic hydrocarbons (eg, anthracene, fluoranthene, pyrene, phenanthrene) present in the particulate phase of cigarette smoke and diesel fumes have the ability to induce T helper 2 (Th2) immune responses and enhance allergic inflammation.^{44,45} The formation of allergen-specific IgE antibodies is a key event in the development of allergic airway responses. In sensitized individuals, IgE increases the risk of developing allergic rhinitis and asthma.⁴⁶ Therefore, in individuals with allergic rhinitis, progression to bronchial asthma may be more common in those who smoke regularly. Given that BHR is a well-described determinant of the incidence of asthma in rhinitic subjects,^{21–23} another possible explanation for a higher incidence of new-onset asthma among rhinitics who smoke is that smoking is strongly associated with more severe BHR.⁴⁷

Preventive Role of Allergen-Specific Immunotherapy

To date, little progress has been made in the development of therapies that prevent the progression of rhinitis to asthma in at-risk individuals. For smokers with allergic rhinitis, one straightforward strategy for preventing the progression to asthma would be to counsel the patients to stop smoking and offer assistance in quitting.⁴⁸ Although cessation of smoking confers clear health benefits beyond long-term prevention of asthma, large prospective trials examining the impact of quitting smoking on the risk of incident asthma are needed to establish the true influence of cigarette use on disease progression.

Currently, allergen-specific immunotherapy (IT) is the only immune-modifying treatment for allergic disease. It has been suggested that IT should be administered early to at-risk individuals to prevent the progression to a more advanced and irreversible type of allergic disease, such as asthma.⁴⁹ Although our understanding of the immune-modifying properties of effective IT has greatly increased over the past century, the exact mechanism(s) responsible for the clinical efficacy of IT are still unclear. Several modifications of the cellular and humoral immune responses to the allergen occur throughout the course of IT (reviewed in Ref. 11) (Fig. 1). The ratio of T helper 1 (Th1) cytokines to Th2 cytokines is increased after IT, and functional regulatory T (TReg) cells are induced. Additionally, the production of interleukin-10 (IL-10) by monocytes, macrophages, B cells, and T cells is increased. The production of transforming growth factor beta (TGF- β) is also increased and, together

with IL-10, TGF- β might contribute to TReg cell function and immunoglobulin class-switching to IgG1, IgG4, and IgA. These immunoglobulins compete with IgE for allergen binding, thereby decreasing the allergen capture and presentation facilitated by IgE in complex with the high-affinity receptor (Fc ϵ RI) or low-affinity receptor for IgE (Fc ϵ RII, CD23). In addition, IT decreases the number of mast cells and their ability to release mediators. The recruitment of eosinophils and neutrophils to sites of allergen exposure is also decreased.

Given these characteristics, it is not unrealistic to believe that IT may hinder the progression of allergic diseases. The recent observation that IT prevents the development of new allergen sensitization and lowers the risk of incident asthma cases in adults and children suffering from rhinitis is, perhaps, one of the most exciting findings in the study of IT. Indeed, it can be hypothesized that, in susceptible individuals, this form of treatment could interfere with the immune responses mediating asthmatic evolution rather than reversing the immune response once the disease has been established.¹³

Initial studies have demonstrated a significantly lower rate of new allergen sensitizations in monosensitized individuals who received IT compared with untreated controls. Specifically, 45.5%–75.4% of subjects on IT did not develop a new allergen sensitization during the study period, in contrast with only 0%–33.3% of untreated controls.^{50–52}

A few studies have also suggested that IT prevents the progression of rhinoconjunctivitis to more advanced and irreversible types of allergic disease, such as asthma (Table 1). In our clinical-based study of 332 subjects with allergic rhinitis, those who were treated with IT had a significant reduction in the prevalence of physician-diagnosed asthma compared to untreated patients.³⁰ In our population, 53.1% of the subjects with allergic rhinitis who were not treated with IT developed asthma, whereas only 41.6% of those treated with IT were diagnosed with asthma by the end of the study (OR = 0.53) (Fig. 2). The observed IT-mediated reduction in the number of new asthma cases is of clinical importance with a number needed to treat (NNT) of 8.7. To the our knowledge, no other published study on asthma prevention has reported a greater protective effect. Furthermore, we have also previously shown that IT for allergic rhinitis can even decrease the risk of asthma among smokers.⁴³

The observed effect of IT in reducing the onset of asthma is in agreement with the results of an open prospective multicenter study of 205 children with a clinical history of grass- or birch-induced rhinoconjunctivitis randomized to receive IT for 3 years.²⁹ This study found a statistically significant reduction in the risk for developing incident asthma in the participants that received IT (OR = 2.52) compared to the untreated control group. At the 5-year follow-up, 2 years after IT was discontinued, the preventive effect of IT was still evident. Among 142 children without asthma before the start of the study, those receiving IT had significantly less asthma than those in the control group: 16/48 with asthma in the IT group compared with 24/29 in the untreated control group (OR = 2.68).³¹ A similar preventive effect of IT (OR = 2.5) was also confirmed at the 10-year follow-up.³² Evidence of the effect of IT in reducing the onset of asthma from placebo-controlled trials is limited. In a small randomized, placebo-controlled 3-year study of allergen immunotherapy in

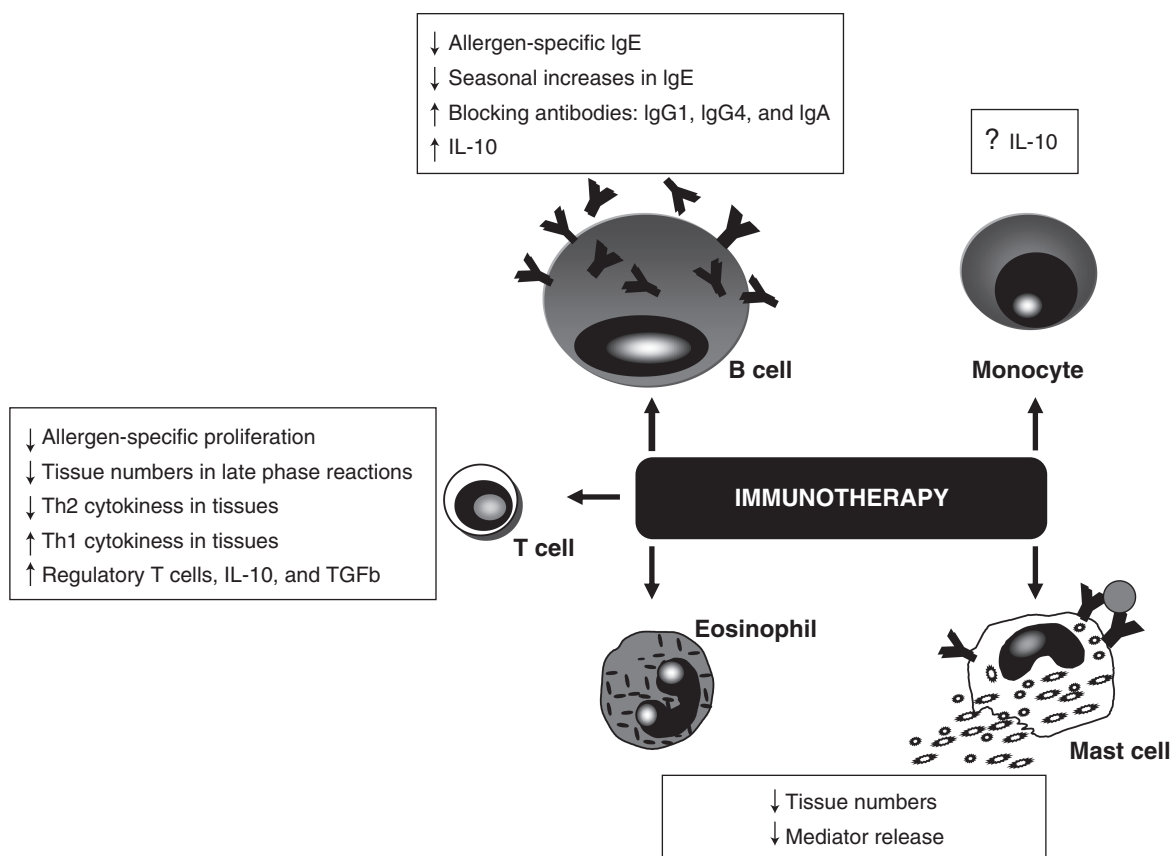


FIG. 1. Specific immunotherapy modifies cellular and humoral immune responses to allergen.

non-asthmatic, rhinitic subjects monosensitized to *Parietaria* pollen, we found that 47% of patients in the placebo group compared to 14% of the IT group developed asthma symptoms by the end of the study.⁵³

The finding that IT resulted in a significant reduction of number of new asthma cases was confirmed in studies

evaluating sublingual immunotherapy (SLIT). Two large studies have demonstrated a statistically significantly lower rate of new-onset asthma in children with allergic rhinitis randomized to a study group treated with SLIT for 3 years compared to the control population.^{54,55} In the study by Marogna et al.,⁵⁵ it was also reported that a substantially

TABLE 1. STUDIES SHOWING PREVENTION OF NEW ASTHMA CASES BY ALLERGEN IMMUNOTHERAPY

Study	Age range (years)	Follow-up (years)	Number of patients in each group	Immunotherapy (% of patients with new-onset asthma)	Control (% of patients with new-onset asthma)	P value
Moller et al ²⁹	6–15 (mean 10.7)	3	SCIT: 97 CTRL: 94	24	44	<0.05
Polosa et al ³⁰	18–40	9–10	SCIT: 202 CTRL: 130	42	53	<0.05
Niggemann et al ³¹	6–15	5	SCIT: 95 CTRL: 88	20	43	<0.01
Jacobsen et al ³²	6–14	10	SCIT: 64 CTRL: 53	25	45	<0.01
Polosa et al ⁵³	20–54 (mean 33.1)	3	SCIT: 15 PLA: 15	14	47	0.056
Novembre et al ⁵⁴	4–16 (mean 8.4)	3	SLIT: 54 CTRL: 59	18	41	<0.05
Marogna et al ⁵⁵	5–17 (mean 10.4)	3	SLIT: 130 CTRL: 66	2	29	<0.001
Milani et al ⁵⁶	(mean 22.5)	2	SLIT: 154 CTRL: 151	9	20	<0.01

Abbreviations: CTRL, control; PLA, placebo; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

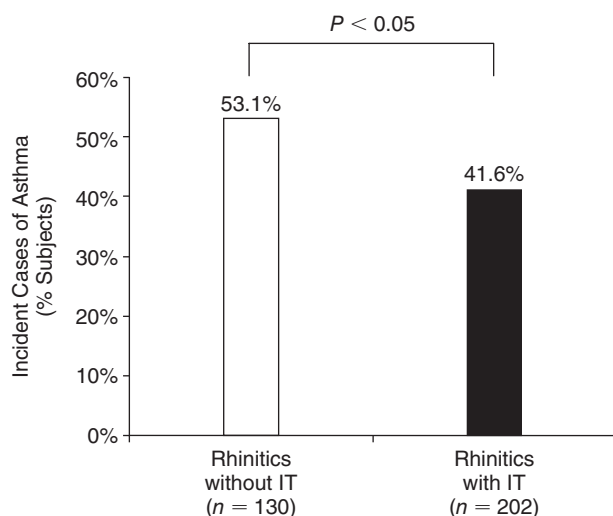


FIG. 2. Percentage of new-onset asthma by the end of the 10-year follow-up in immunotherapy (IT)-treated (closed bar) and untreated (open bar) subjects with allergic rhinitis.

lower percent of new allergen sensitizations developed in patients who received SLIT compared to untreated matched controls, 3.1% versus 34.8%, respectively (OR = 16.85). These findings with SLIT have also been confirmed in a “real-life” setting.⁵⁶ In a recent efficacia nella rinite allergica di SlitOne (EFESO) trial, a multicenter case-control observational study to evaluate the effectiveness of SLIT in a mixed adult-pediatric population with allergic rhinitis, asthma-related symptoms were present in 8.5% of SLIT-treated subjects versus 20% of the control participants.⁵⁶

Closing Remarks: Quo Vadit Immunotherapy?

Allergen immunotherapy was first utilized in the treatment of allergic diseases nearly 100 years ago. Although there have been great advances in our understanding of immunotherapy mechanisms, there has been little change in the clinical application of immunotherapy. Now, there is considerable optimism regarding the use of this therapy for controlling the allergy epidemic due to improvements in systemic and mucosal allergen-specific immunotherapy.⁵⁷ The decisive evidence that in preschool children at high risk for asthma, early anti-inflammatory therapy with inhaled corticosteroids (ICS) fails to modify the natural course of the disease,^{58–60} together with the notion that early treatment of allergic individuals with allergen IT may prevent the development of allergic manifestations, indicates that treatment of at-risk individuals could be an innovative and valuable application for IT. Considering that the studies described in the above section are observational in nature, or used an uncontrolled design, large randomized, double-blind, controlled trials are needed to confirm the beneficial effects of treating allergic subjects with IT and to define the characteristics of patients who would benefit most from this type of therapy.

The Global Prevention of Asthma in Children (GPAC) study is a Phase II multicenter, placebo-controlled, double-blind study using immunoprophylaxis for the primary prevention of allergic disease.⁶¹ The purpose of this study is to determine whether early treatment with SLIT for 1 year can

prevent the development of asthma and decrease the rate of allergic sensitization in high-risk children. The GPAC study has enrolled 200 children between the ages of 18 and 30 months from 5 international study sites. Children will be assessed for allergy/asthma symptoms over the next 3 years. The results of the GPAC study are expected by 2013 and are eagerly awaited.

Acknowledgment

Riccardo Polosa is full Professor of Internal Medicine and he is supported by the University of Catania, Italy.

References

1. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group of the World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108(5 Suppl):S147–S334.
2. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003; 111:1171–1183.
3. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy* 2003; 58:691–706.
4. Blaiss MS. Rhinitis-asthma connection: epidemiologic and pathophysiologic basis. *Allergy Asthma Proc* 2005; 26:35–40.
5. Passalacqua G, Ciprandi G, Canonica GW. The nose-lung interaction: united airways disease. *Curr Opin Allergy Clin Immunol* 2001; 1:7–14.
6. Simons FE. Allergic rhinobronchitis: the asthma-allergic rhinitis link. *J Allergy Clin Immunol* 1999; 104(3 Pt 1):534–540.
7. World Allergy Organization. Combined allergic rhinitis and asthma syndrome. http://www.worldallergy.org/professional/allergic_diseases_center/caras/airwayssynopsis.php.
8. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A; for the NAC Manchester Asthma and Allergy Study Group. Effect of environmental manipulation in pregnancy and early life respiratory symptoms and atopy during first year of life: a randomized trial. *Lancet* 2001; 358:188–193.
9. Peat JK, Mhrshahi S, Kemp A, Marks GB, Tovey ER, Webb K, Mellis CM, Leeder SR. Three year outcomes of dietary fatty acid modification and house dust mite avoidance in the childhood asthma prevention study (CAPS). *J Allergy Clin Immunol* 2004; 114:807–813.
10. Horak F, Matthews S, Ihorst G, Arshad SH, Frischer T, Kuehr J, Schwieger A, Forster J; SPACE study group. Effect of mite-impermeable encasings and an educational package on the development of allergies in a multinational randomized, controlled birth cohort study—24 months results of the Study of Prevention of Allergy in children in Europe. *Clin Exp Allergy* 2004; 34:1220–1225.
11. Till SJ, Francis JN, Nouri-Aria K, Durham SR. Mechanisms of immunotherapy. *J Allergy Clin Immunol* 2004; 113:1025–1034.
12. Demoly P, Bousquet J, Michel FB. Immunotherapy in allergic rhinitis: a prevention for asthma? *Curr Probl Dermatol* 1999; 28:119–123.
13. Polosa R. Can immunotherapy prevent progression to asthma in allergic individuals? *J Allergy Clin Immunol* 2002; 110:672–673.
14. Pedersen PA, Weeke ER. Asthma and allergic rhinitis in the same patients. *Allergy* 1983; 38:25–29.
15. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 2000; 106:S201–S205.
16. Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Asymptomatic bronchial hyperresponsiveness in rhinitis. *J Allergy Clin Immunol* 1985; 75:573–577.
17. Crimi N, Palermo F, Oliveri R, Vancheri C, Distefano SM, Palermo B, Polosa R, Mistretta A. Influence of asthmatic and

- rhinitic symptomatology and duration on bronchial responsiveness to histamine. *Int J Tiss React* 1987; IX(6):515–520.
18. Bradley BL, Azzawi M, Jacobson M, Assoufi B, Collins JV, Irani AM, Schwartz LB, Durham SR, Jeffery PK, Kay AB. Eosinophils, T lymphocytes, mast cells, neutrophils and macrophages in bronchial biopsy specimens from atopic subjects with asthma: comparisons with biopsy specimens from atopic subjects without asthma and normal control subjects and relationship to bronchial hyperresponsiveness. *J Allergy Clin Immunol* 1991; 88:661–674.
 19. Djukanovic R, Lai CKW, Wilson JW, Britten KM, Wilson SJ, Roche WR, Howarth PH, Holgate ST. Bronchial mucosal manifestation of atopy: a comparison of markers of inflammation between atopic asthmatics, atopic non-asthmatics and healthy controls. *Eur Respir J* 1992; 5:538–544.
 20. Polosa R, Ciamarra I, Mangano G, Prosperini G, Pistorio MP, Vancheri C, Crimi N. Bronchial hyperresponsiveness and airway inflammation markers in nonasthmatics with allergic rhinitis. *Eur Respir J* 2000; 15:30–35.
 21. Braman SS, Barrows AA, DeCotiis BA. Airway hyperresponsiveness in allergic rhinitis: a risk factor for asthma. *Chest* 1987; 91:671–674.
 22. Sparrow D, O'Connor G, Colton T, Barry CL, Weiss ST. The relationship of nonspecific bronchial responsiveness to the occurrence of respiratory symptoms and decreased levels of pulmonary function: the Normative Aging Study. *Am Rev Respir Dis* 1987; 135:1255–1260.
 23. Hopp RJ, Townley RG, Biven RE, Bewtra AK, Nair NM. The presence of airway reactivity before the development of asthma. *Am Rev Respir Dis* 1990; 141:2–8.
 24. 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.
 25. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002; 109:419–425.
 26. Leynaert B, Neukirch C, Kony S, Guénégou A, Bousquet J, Aubier M, Neukirch F. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol* 2004; 113:86–93.
 27. 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; 115:928–936.
 28. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, Wjst M, Cerveri I, Pin I, Bousquet J, Jarvis D, Burney PG, Neukirch F, Leynaert B. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet* 2008; 372:1049–1057.
 29. Moller C, Dreborg S, Ferdousi HA, Halken S, Høst A, Jacobsen L, Koivikko A, Koller DY, Niggemann B, Norberg LA, Urbanek R, Valovirta E, Wahn U. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002; 109:251–256.
 30. Polosa R, Al-Delaimy WK, Russo C, Piccillo G, Sarva M. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective cohort study. *Respir Res* 2005; 6:153–162.
 31. Niggemann B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Høst A, Koivikko A, Koller D, Norberg LA, Urbanek R, Valovirta E, Wahn U, Möller C; PAT Investigator Group. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy* 2006; 61:853–857.
 32. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, Koivikko A, Norberg LA, Valovirta E, Wahn U, Möller C (The PAT Investigator Group). Specific Immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT Study. *Allergy* 2007; 62:943–948.
 33. Platts-Mills TAE, Wheatley L. The role of allergy and atopy in asthma. *Curr Opin Pulm Med* 1996; 2:29–34.
 34. Platts-Mills TAE, de Weck AL. Dust mite allergens and asthma: a worldwide problem. *J Allergy Clin Immunol* 1989; 83:416–427.
 35. Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood. *N Engl J Med* 1990; 323:502–507.
 36. D'Amato G, Spiekma M, Liccardi G, Jäger S, Russo M, Kontou-Fili K, Nikkels H, Wüthrich B, Bonini S. Pollen-related allergy in Europe. *Allergy* 1998; 53:567–578.
 37. Sallusto F, Corinti S, Pini C, Biocca MM, Bruno G, Di Felice G. *Parietaria judaica*-specific T-cell clones from atopic patients: heterogeneity in restriction, Vb usage, and cytokine profile. *J Allergy Clin Immunol* 1996; 97:627–637.
 38. Venn A, Lewis S, Cooper M, Hill J, Britton J. Questionnaire study of effect of sex and age on the prevalence of wheeze and asthma in adolescence. *BMJ* 1998; 316:1945–1946.
 39. Martinez FD, Cline M, Burrows B. Increased incidence of asthma in children of smoking mothers. *Pediatrics* 1992; 89:21–26.
 40. Ehrlich RI, Du Toit D, Jordaan E, Zwarenstein M, Potter P, Volmink JA, Weinberg E. Risk factors for childhood asthma and wheezing. Importance of maternal and household smoking. *Am J Respir Crit Care Med* 1996; 154:681–688.
 41. Lux AL, Henderson AJ, Pocock SJ. Wheeze associated with prenatal tobacco smoke exposure: a prospective, longitudinal study. ALSPAC Study Team. *Arch Dis Child* 2000; 83:307–312.
 42. Mannino DM, Moorman JE, Kingsley B, Rose D, Repace J. Health effects related to environmental tobacco smoke exposure in children in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Pediatr Adolesc Med* 2001; 155:36–41.
 43. Polosa R, Knoke JD, Russo C, Piccillo G, Caponnetto P, Sarva M, Proietti L, Al-Delaimy WK. Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis. *J Allergy Clin Immunol* 2008; 121:1428–1434.
 44. Polosa R, Salvi S, Di Maria GU. Allergic susceptibility associated with diesel exhaust particle exposure: clear as mud. *Arch Environ Health* 2002; 57:188–193.
 45. Diaz-Sanchez D, Rumold R, Gong H, Jr. Challenge with environmental tobacco smoke exacerbates allergic airway disease in human beings. *J Allergy Clin Immunol* 2006; 118:441–446.
 46. Platts-Mills TA. The role of immunoglobulin E in allergy and asthma. *Am J Respir Crit Care Med* 2001; 164(8 Pt 2):S1–S5.
 47. Piccillo G, Caponnetto P, Barton S, Russo C, Origlio A, Bonaccorsi A, Di Maria A, Oliveri C, Polosa R. Changes in airway hyperresponsiveness following smoking cessation: comparisons between Mch and AMP. *Respir Med* 2008; 102:256–265.
 48. Caponnetto P, Polosa R, Best D. Tobacco use cessation counseling of parents. *Curr Opin Pediatr* 2008; 20:729–733.
 49. Polosa R. New frontiers in allergen immunotherapy for asthma. In: Polosa R, Holgate ST, eds. *Therapeutic strategies in asthma: current treatments*. Oxford: Clinical Publishing, 2007, pp. 105–110.
 50. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997; 99:450–453.
 51. Purrello-D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S, Ricciardi L. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy* 2001; 31:1295–1302.
 52. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001; 31:1392–1397.
 53. Polosa R, Li Gotti F, Mangano G, Paolino G, Mastruzzo C, Vancheri C, Lisitano N, Crimi N. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. *Allergy* 2004; 59:1224–1228.

54. Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E, Burastero SE, Calori G, Benetti L, Bonazza P, Puccinelli P, Parmiani S, Bernardini R, Vierucci A. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; 114:851–857.
55. Marogna M, Tomassetti D, Bernasconi A, Colombo F, Massolo A, Businco AD, Canonica GW, Passalacqua G, Tripodi S. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008; 101:206–211.
56. Milani M, Pecora S, Burastero S; EFESO Investigators Study Group. Observational study of sublingual specific immunotherapy in persistent and intermittent allergic rhinitis: the EFESO trial. *Curr Med Res Opin* 2008; 24:2719–2724.
57. Holgate ST, Polosa R. Treatment strategies for allergy and asthma. *Nat Rev Immunol* 2008; 8:218–230.
58. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefer SJ, Bacharier LB, Lemanske RF Jr., Strunk RC, Allen DB, Bloomberg GR, Heldt G, Krawiec M, Larsen G, Liu AH, Chinchilli VM, Sorkness CA, Taussig LM, Martinez FD. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; 354:1985–1997.
59. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006; 354:1998–2005.
60. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A; IFWIN study team. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy Infants (IFWIN): double-blind, randomised, controlled study. *Lancet* 2006; 368:754–762.
61. Promoting tolerance to common allergens in high-risk children: Global Prevention of Asthma in Children (GPAC) Study. *ClinicalTrials.gov*. <http://clinicaltrials.gov/ct2/show/NCT00346398>.

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Received for publication August 31, 2009; accepted
after revision October 13, 2009.

