

Review article

Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA²LEN

This update aimed to review the new evidence available to support or refute prior Allergic Rhinitis and its Impact on Asthma (ARIA) statements. A Medline search of publications between 2000 and 2005 was conducted, with articles selected by experts. New evidence supports previous ARIA statements, such as: (i) allergic rhinitis (AR) is a risk factor for asthma; (ii) patients with persistent rhinitis should be evaluated for asthma; (iii) most patients with asthma have rhinitis; (iv) a combined strategy should be used to treat the airways and (v) in low- to middle-income countries, a different strategy may be needed. The increased risk of asthma has also been found among sufferers from non-AR. Recent reports show AR is a global problem. Many studies demonstrated parallel increasing prevalence of asthma and rhinitis, but in regions of highest prevalence, it may be reaching a plateau. Factors associated with a reduced risk of asthma and AR have been identified, confirming previous findings of protection related to exposure to infections. Treatment of rhinitis with intranasal glucocorticosteroids, antihistamines, leukotriene antagonists or immunotherapy may reduce morbidity because of asthma. To take advantage of the paradigm of unified airways, there is a need to rationalize diagnosis and treatment to optimize management.

All authors have no conflicts of interests.

**A. A. Cruz¹, T. Popov², R. Pawankar³,
I. Annesi-Maesano⁴, W. Fokkens⁵,
J. Kemp⁶, K. Ohta⁷, D. Price⁸,
J. Bousquet⁹ on behalf of ARIA
Initiative Scientific Committee**

¹ProAR, Programme for Control of Asthma and Allergic Rhinitis in Bahia, Federal University of Bahia School of Medicine, and CNPq, Salvador, Brazil; ²Clinical Centre of Allergology, Medical University Sofia, Sofia, Bulgaria; ³Division of Rhinology & Allergy, Department of Otolaryngology, Nippon Medical School, Tokyo, Japan; ⁴Epidemiology of Allergic and Respiratory Diseases, INSERM, Paris, France; ⁵Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam, the Netherlands; ⁶Department of Pediatrics, University of California School of Medicine, San Diego, CA, USA; ⁷Department of Otolaryngology, Tokyo, Japan; ⁸Department of General Practice and Primary Care, University of Aberdeen, Foresterhill Health Centre, Aberdeen, UK; ⁹University Hospital, Montpellier and INSERM, France

Key words: allergy; asthma; atopy; review; rhinitis.

Alvaro A. Cruz
ProAR – Rua Carlos Gomes, 270 40060-330
Salvador, Bahia
Brazil

The links between the upper and lower airways had been clinically observed as early as in the beginning of 1800s, and these interactions were revisited by the Allergic Rhinitis and its Impact on Asthma (ARIA) Initiative Workshop (1) held in December 1999. Since then, a large number of papers on the subject have been published. The ARIA Scientific Committee prepared an update on common characteristics of upper and lower airways disease in rhinitis and asthma so as to:

- 1 add up new scientific advances;
- 2 propose recommendations using an evidence-based model;
- 3 adapt the recommendations to the needs of all countries and all populations;

4 critically review whether the major statements of the ARIA Workshop Report regarding common characteristics of upper and lower airways disease in rhinitis and asthma (2) remain valid.

- Allergic rhinitis is one of the multiple risk factors identified for asthma development.
- Patients with persistent AR should be evaluated for asthma.
- Patients with asthma should be properly evaluated for rhinitis.
- A combined strategy should be used to treat the upper and lower airways for better efficacy/safety ratio.

- In middle- to low-income countries, a specific strategy may be needed, depending on available treatments and interventions, as well as their costs.
- 5 support health policy-makers, in line with the positive impact ARIA publications have had on health management decisions in some countries (3).

Objectives

This document updates the ARIA sections on the links between rhinitis and asthma. Relevant publications between January 2000 and December 2005 were included. Complementary and alternative medicine is not evaluated in this document since it has been published separately (4). Likewise, an update on pharmacological therapy of AR was published separately (5). Therefore, in the therapeutic component of the current review we decided to focus on aspects related to concomitant rhinitis and asthma.

The aim of this review was to present new evidence related to major ARIA statements, either to support or to refute them, by bringing the most recent information in the context of the previous knowledge on this subject. Additionally, we looked for information that could potentially lead to novel statements.

Methods

Search strategy

- 1 Studies were sought from Medline (01-01-2000 to 31-12-2005). Moreover, in case some papers have not been identified by the electronic search, we also used the expert group database.
- 2 The following key words were used for the search strategy: asthma [AND] rhinitis in title or abstract. We found 1489 papers indexed.

Selection criteria

- 1 After screening by title, we had a list of 571 original papers, whose abstracts were sent to at least two different co-authors for their expert review on whether those papers should be included in this review, according to the following criteria:
- impact on the ARIA Workshop Report (confirm or modify ARIA recommendations or statements or add new relevant information) and
 - reliable methodology.

After selection of the abstracts by the reviewers, we had 236 original papers. In case of disagreement, the leading

author decided whether to include the paper, which was finally submitted to approval of all the co-authors.

Only full manuscripts published in peer-reviewed journals were considered. Abstracts or review papers were not included.

- 1 Further selection was performed by the team leader to restrict the review to the subtopics predefined by ARIA Scientific Committee as specific for this update, and to exclude papers published in 2000 and already mentioned in the previous ARIA Workshop Report.

- 2 One hundred and eighty original papers remained. The subtopics recommended were:

- prevalence of asthma in rhinitis and of rhinitis in asthma;
- rhinitis as a risk factor for asthma;
- costs and pharmaco-economics;
- links between the upper and lower airways in children;
- diagnosis of co-morbidities in patients with rhinitis or asthma in general practices and pharmacies;
- co-morbidities in the developing world;
- treatment of rhinitis improves asthma and
- treatment of asthma improves rhinitis.

A draft of the manuscript was elaborated and all the reviewers were given the chance to identify any missing relevant publication within the predefined time frame. This procedure resulted in the incorporation of comments on 17 extra papers that had been overlooked in the first draft. After this point, no further articles were included and the review work focused on interpretation, statements and style. In conclusion, a final draft was circulated among all co-authors and the ARIA Review Group*.

The funding source, i.e. the ARIA Initiative, proposed the review topic, the group of authors and the working meetings of these experts.

Prevalence of asthma in patients with rhinitis and of rhinitis in patients with asthma

Numerous publications have addressed the issue of rhinitis and asthma in various regions of the world. Many studies looked at factors associated with risk or

*Review group: Nadia Aït-Khaled, Carlos Baena-Cagnani, Jacques Bouchard, G. Walter Canonica, Yuzhi Chen, Ronald Dahl, Pascal Demoly, Elisabeth Garcia, Peter G. Gibson, Michael Kaliner, You-Y. Kim, Marek Kowalski, Youssef Mohammad, Hugo Neffen, Giovanni Passalacqua, Paul Potter, Jose Rosado-Pinto, F. Estelle Simons, Ron Tomlins, Osman Youssuf, Erkka Valovirta, Paul Van Cauwenberge, De Yun Wang, Barbara Yawn, Habib Douagui, Ali Ben Kheder, Claus Bachert, Jacques Bouchard, Regina Emuzyte, Marc Humbert, Omer Kalayci, Richard Lockey, Sandra Mavale Manuel, Robert Naclerio, Klaus Rabe.

with protection for rhinitis and asthma. However, the reports were not always unequivocal regarding the prevalence of asthma in subjects with rhinitis or the prevalence of rhinitis in subjects with asthma.

Coexistence of asthma and rhinitis

Previous ARIA publications (2) have stated that most patients with allergic and nonallergic asthma have rhinitis, that many patients with AR have increased bronchial hyper-reactivity (BHR), and that there is a temporal relationship between the onset of AR and asthma, with rhinitis often preceding the development of asthma.

- 1 Quality of life in patients with AR from 850 subjects recruited in two French centres participating in the European Community Respiratory Health Survey (ECRHS) was reported (6). Seventy-eight per cent of asthmatics had AR. Both asthma and AR, defined according to questionnaires, were associated with impairment in quality of life. As asthma was not found to further impair the quality of life in subjects with AR for the domains related to mental disability and well-being, and as subjects with asthma often suffered from AR, the authors recommended that further studies on quality of life in asthma should ensure that the impairment in quality of life attributed to asthma is not the result of concomitant AR. To evaluate quality of life in patients having both rhinitis and asthma, a questionnaire named Rhinasthma has been set up and validated (7).
- 2 In a randomly selected sample of 3000 children from 80 schools surveyed in north-east England (8) by means of the International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire, rhinitis was reported by 53% of boys and 61% of girls with asthma. The criteria for definition of AR and asthma in ECRHS and ISAAC questionnaires are not exactly the same.
- 3 Self-reported upper airway symptoms, symptoms of asthma and Chronic Obstructive Pulmonary Disease (COPD) were examined in 12 079 adults living in southern Sweden (9). The response rate was 70%, of whom 33% had significant nasal symptoms. Significant nasal symptoms were reported by 46% of subjects with asthma and 40% of those with COPD.
- 4 In a study performed in mainland China (10), 10 009 members of 2544 families were selected on the basis of doctor-diagnosed asthma in two or more siblings. Although 46.9% of the study participants were sensitized to at least one allergen, only 3.5% of study subjects reported nasal symptoms consistent with rhinitis. Among asthmatic subjects, only 6.2% reported nasal symptoms. Whereas sensitization to perennial aeroallergens was associated with asthma among families of asthmatic subjects in rural China, sensitization to silk was the strongest predictor of

rhinitis in this population. These findings suggest that AR is far less common among asthmatic subjects in rural China than in asthmatic subjects in industrialized or urban populations with a Western lifestyle.

- 5 A prospective population-based study performed in Copenhagen (11) confirmed the epidemiological interrelationship between AR and allergic asthma. Individuals who were seen in 1990 (15–69 years old) were invited to a follow-up interview. A total of 734 subjects were examined on two occasions 8 years apart. At follow-up, all subjects with allergic asthma to pollen ($n = 52$) had also AR to pollen. In the longitudinal analysis, there were 28 new cases of allergic asthma to pollen. They all had AR to pollen at baseline, or had developed AR to pollen at follow-up. Accordingly, AR to animals and mite were ubiquitous in subjects with allergic asthma to animals and mite, respectively.
- 6 In Italy (12), a survey was conducted on the prevalence of rhinitis in preschool children in randomly selected nursery schools. The ISAAC written questionnaire was distributed and filled out by parents of 1402 children 3–5 years old. The prevalence of rhinitis in the past 12 months prior to the study was 16.8%. Rhinitic children compared to nonrhinitic ones presented a significant increase in undiagnosed asthma (20.8% vs 6.2%), lifetime wheezing (43.2% vs 21.6%) and wheezing in the last 12 months (25.0% vs 9.4%).
- 7 In the Greek city of Thessaloniki, a study was performed on 2005 children 9–12 years old attending primary schools (13). The authors used questionnaires and carried out clinical evaluation complemented with provocation tests; they found that 168 (8.4%) of the subjects suffered from AR only, 84 (4.2%) from both allergic asthma and rhinitis concurrently and 38 (1.9%) from allergic asthma alone. Although the criteria used for the case definition may be a matter of debate, we can conclude that, in this region of low prevalence of asthma and rhinitis, 69% of allergic asthmatics also had rhinitis, whereas 33% of children with AR had asthma.
- 8 An Italian multicentre, cross-sectional survey on respiratory symptoms in young adults (Italian Study of Asthma in Young Adults; 14) explored the relationship between individual risk factors and asthma, AR and their coexistence. Sixty per cent of asthmatics reported AR. Subjects with AR presented an eight-fold risk of having asthma compared to subjects without AR. The risk of AR without asthma was significantly higher in the upper social classes.
- 9 Observations from the Netherlands (15) aimed to determine the prevalence and severity of AR among asthmatic patients. Based on history and clinical symptoms 92% of 164 asthmatic patients were diagnosed as having AR.

- 10 A retrospective multicentre study was conducted in Europe to characterize the clinical features of patients with seasonal allergic rhinitis (SAR) with concomitant asthma and to compare them with those in patients with persistent asthma (16). Patients with seasonal rhinitis and asthma had a significantly higher total asthma symptom score compared to those with asthma only. In particular, cough was three times more severe. Asthma and nasal symptom severity scores were correlated in patients with seasonal rhinitis and asthma.
- 11 A prospective cohort study was conducted in southern France (17) to evaluate seasonal quality of life modifications in patients with AR with or without asthma. A total of 135 subjects were included, 83 with isolated SAR and 52 with associated asthma. The authors concluded that female gender, living in the countryside, and having a lower level of education level were all independent predictors of a poorer quality of life in seasonal allergic patients.
- 12 In the ARIA classification, intermittent and persistent rhinitis were proposed to replace seasonal and perennial AR. To better understand the ARIA classification of rhinitis, a cross-sectional study was carried out in France in 591 patients consulting otolaryngologists or allergy specialists for AR and 502 control subjects (18). Ten per cent of patients had mild intermittent rhinitis, 14% mild persistent rhinitis, 17% moderate/severe intermittent rhinitis and 59% moderate/severe persistent rhinitis. Most patients with intermittent rhinitis had pollen sensitivity, but 5% were monosensitized to house dust mite. Over 50% of patients with persistent rhinitis were allergic to pollens or house dust mite. Asthma was present in 24% of patients with rhinitis and in only 2% of the control population ($P < 0.0001$). Patients with moderate/severe persistent rhinitis had the highest asthma prevalence (33%). The authors concluded that intermittent and persistent rhinitis are not synonymous to seasonal and perennial rhinitis and that asthma prevalence increases with the duration and severity of rhinitis, supporting the major recommendation of ARIA that patients with persistent rhinitis should be evaluated for asthma.
- 13 To test the new ARIA classification against the classical one used in medical practice in France, two cross-sectional surveys were conducted by Demoly et al. (19): (i) a spring survey, where 1321 general practitioners (GP) enrolled 3026 patients consulting for SAR and (ii) an autumn–winter survey, where 1346 doctors enrolled 3507 patients for perennial AR. Both doctors and patients filled out a specific questionnaire on AR. About 43.7% of the patients, classified by their doctor as seasonal, did in fact have persistent rhinitis, whereas 44.6% classified as perennial had intermittent rhinitis.
- 14 To investigate whether reactivity to aeroallergens in skin prick testing (SPT) and serum eosinophil cationic protein levels can be used to predict BHR in AR patients (20), 59 consecutive patients with AR underwent methacholine challenge tests. Bronchial hyper-reactivity was detected in 23 patients (39%). There was a significant inverse correlation between PC_{20} (concentration of inhaled methacholine that induces a 20% reduction in forced expiratory volume in 1 s, FEV_1) and the number of positive SPT responses ($r = -0.28$; $P = 0.03$). There was no correlation between serum eosinophil cationic protein levels and methacholine PC_{20} doses. The authors concluded that AR patients with SPT responses to a higher number of allergens are more likely to have BHR. Whether the number of positive SPT responses correlates with the risk of developing asthma in AR patients remains to be determined.
- 15 To evaluate the factors associated with BHR in rhinitis, 410 patients with symptomatic rhinitis had their FEV_1 and forced vital capacity (FVC) measured (21). In all subjects SPT, a determination of total serum immunoglobulin E (IgE) and blood eosinophil counts were also obtained. One hundred and sixty-one (39.3%) exhibited a methacholine PD_{20} (dose of inhaled methacholine that induces a 20% reduction in FEV_1) of 800 mg or less, whereas 249 (60.7%) had a methacholine PD_{20} more of 800 mg. Despite the matched mean values for FEV_1 and FVC, subjects that were hyper-reactive had a lower forced expiratory flow between 25% and 75% ($FEF_{25-75\%}$). A greater proportion of hyper-reactive subjects presented positive SPT (93.7% vs 67.0%, $P < 0.0001$), had higher levels of total serum IgE, higher blood eosinophil counts and reported increased nasal obstruction. Logistic regression identified nasal obstruction and the presence of positive SPT as the strongest predictors of BHR. Nasal obstruction was also directly correlated with blood eosinophil counts, $FEF_{25-75\%}$ and having an asthmatic mother.
- 16 Recent work has investigated whether patients with AR with or without asthma differed in their degree of perception of dyspnoea (22). Twenty-nine patients with SAR were investigated with methacholine challenges and 14 healthy nonreactive subjects served as controls. Eighteen patients reported AR only, without asthma symptoms. Of these, 12 (67%) were hyper-reactive to methacholine. Eleven subjects had both rhinitis and asthma symptoms. Patients with rhinitis and asthma reported significantly more dyspnoea per per cent fall in FEV_1 compared to those with rhinitis that were hyper-reactive but had no asthma. The authors speculated that the difference between rhinitis patients with or without asthma symptoms might be a matter of perception of dyspnoea.

Table 1. Prevalence of rhinitis among asthmatics

Authors	Location	Number of individuals studied	Study design	Proportion of rhinitis in asthmatics	Comments
Leynert et al. (6)	France	850 adults	Cross-sectional	78%	Quality of life impaired in rhinitis
Shamssain and Shamsian (8)	England	3000 children	Cross-sectional	53% in boys 63% in girls	Nothing remarkable
Montnemery et al. (9)	Sweden	12 079 adults	Cross-sectional by postal questionnaire	46%	'Significant nasal symptoms'
Celedon et al. (10)	China	10 009	Cross-sectional	6.2%	Within a cohort
Terreehorst et al. (15)	The Netherlands	164	Cross-sectional	92%	Nothing remarkable
Linneberg et al. (11)	Denmark	743	Longitudinal	100%	Two evaluations 8 years apart
Sichletidis et al. (13)	Greece	2005 children	Cross-sectional	69%	33% of rhinitics had asthma
Leynaert et al. (113)	Europe	90 478	Cross-sectional	74–81%	Nothing remarkable

Table 1 summarizes the most important findings on this topic of the review.

The evidence provided by these studies supports previous ARIA statements that are:

- 1 most subjects with allergic and nonallergic asthma have rhinitis;
- 2 many patients with AR have asthma or subclinical manifestations of BHR and
- 3 there is a temporal relationship between the onset of AR and asthma, with rhinitis often preceding the development of asthma.

An exception is the finding of low rhinitis prevalence among asthmatics in China, which requires further investigation to identify likely reasons for the difference. It would be important to investigate whether it is related to specific genetic or environmental factors.

Although the selection of patients and controls is crucial, clinical observations have been confirmed by population-based information.

Asthma and rhinitis – variation in prevalence

Previous ARIA publications (2) have mentioned that AR is a global health problem, that is a common disease worldwide, affecting at least 10–25% of the population and that the prevalence is increasing. Recent studies reported increasing prevalence of both asthma and rhinitis.

- 1 Estimates of intergenerational trends in the prevalence of asthma and AR in adults were undertaken in Scotland (23). Two surveys were performed 20 years apart using identical questions. About 1477 married couples aged 45–64 years participated in a general population survey in 1972–1976; and 2338 offspring aged 30–59 years participated in the 1996 survey. Among never smokers, prevalence of asthma and hay fever were 3.0% and 5.8%, respectively, in 1972–1976, and 8.2% and 19.9% in 1996. In both generations, the prevalence of asthma was higher in those who reported to be suffering from hay fever. Atopic asthma increased more than twofold while the prev-

alence of nonatopic asthma did not change. The authors concluded that the prevalence of asthma in adults has increased more than twofold in 20 years, and that this increase was largely associated with increasing trends in atopy, as measured indirectly by the prevalence of hay fever.

- 2 An Italian survey (24) evaluated 28 327 18-year-old male conscripts during a 4-year period (1999–2002) in a military navy hospital. Detailed history, clinical examination, SPT, spirometry and methacholine challenge were performed in subjects with suspected diagnosis of respiratory allergy. Allergic rhinitis was diagnosed in 2876 conscripts (10.2%), a fivefold increase when compared to a survey in the previous decade. Most of the subjects with AR (67.2%) have an association with asthma.
- 3 In a population-based study in Sweden, Braback et al. (25) evaluated records of 1 309 652 male conscripts in three successive cohorts born between 1952 and 1981. The prevalence of AR and eczema displayed a continuous increase throughout the study period, but the rise in asthma mainly occurred in conscripts born after 1961. Farming environments provided protection from AR and asthma.
- 4 In Saudi Arabia (26), the changing prevalence of asthma was evaluated in two samples of schoolchildren between the ages of 8 and 16 years using questionnaires. A total of 2123 schoolchildren were enrolled in 1986 and 1008 in 1995. The comparison of data revealed that the prevalence of asthma increased significantly from 8% in 1986 to 23% in 1995. Likewise, the prevalence of AR also increased from 20% to 25% since 1986. However, no significant change in the prevalence of eczema was noted.
- 5 A comparison of prevalence of asthma and rhinitis between East (Erfurt, $n = 1648$) and West Germany (Augsburg, $n = 1572$) populations was performed (27). The prevalence of AR, wheezing, asthma and atopic sensitization was higher in Augsburg than in Erfurt. Although the effects of globalization have reduced the environmental disparities between German cities, the observed differences in prevalence

- suggest that nonspecific causes related to western lifestyle may play a role.
- 6 The prevalence of symptoms of rhinitis and asthma according to the climate was studied in a random sample of 18 873 subjects from different regions of Italy (28). No association was found between geo-climatic variables and AR, but asthma symptoms were more common in central-southern Italy, with the Mediterranean climate, than in areas with a continental climate (northern Italy).
 - 7 A comparison of prevalence of rhinitis and asthma in two distinct ethnic populations living in the same region in the Middle East was reported recently (29). Israeli schoolchildren from two neighbouring towns, one Jewish ($n = 585$) and the other Arab ($n = 658$) were surveyed. The children (8–17 years) shared the same climate and had similar demographic characteristics. They received similar medical care and had the same general rates of hospitalization and emergency room visits. The Jewish children had a higher prevalence of asthma (13.7% vs 9.4%) and chronic rhinitis (19.7% vs 9.7%) than their Arab counterparts.
 - 8 In a UK survey (30), AR was found to be more common than asthma, hypertension, skin rashes, eczema and diabetes. In all, 2139 subjects were questioned about their medical conditions, severity and frequency of symptoms and satisfaction with treatment. A group of GPs was also invited to discuss their experiences in the management of rhinitis. The prevalence of SAR and perennial AR was 15% and 2%, respectively. Symptoms were well controlled in only 32% of patients. Allergic rhinitis affected work, home and social life in 29%, 34% and 30% of patients, respectively.
 - 9 During a Phase III ISAAC Study in Hong Kong in 2001 (31), the prevalences of asthma and AR in schoolchildren aged 6–7 years old were examined and compared to observations from 1995. There were 3618 and 4448 children participating in 1995 and 2001, respectively. The prevalence of current rhinitis (35.1 vs 37.4%) and current rhino-conjunctivitis (13.6 vs 17.2%) increased significantly. There was no significant change in the prevalence of lifetime asthma, lifetime wheeze and current wheeze in spite of a significant increase in severe asthma symptoms.
 - 10 A study conducted in Taiwan (32) has assessed the relationship between air pollution and the varying prevalence of allergic diseases in the city of Taichung and the rural town of Chu-Shan. In Taichung, the prevalence of asthma was 7.0%, of AR 27.6% and of atopic dermatitis 3.4%. In Chu-Shan, the prevalence of asthma was 5.6%, of AR 21.8% and of atopic dermatitis 3.3%. Taichung had higher air concentrations of nitric oxide (NO), carbon monoxide, nitrogen and sulphur dioxide. The prevalences of asthma and rhinitis in the urban more polluted environment are not considerably higher than in the rural community.
 - 11 A population-based survey in six West European countries (33) has demonstrated that within the population with AR, 29% of the subjects had persistent symptoms. There was no association between the intermittent/persistent and the seasonal/perennial classifications. Subjects with persistent rhinitis had more severe symptoms and higher rate of self-awareness; they were also clearly distinct in their sensitization pattern and medication use. These results support the importance of the new ARIA classification of AR, based on severity, for planning therapeutical interventions.
 - 12 To determine the prevalence of asthma and AR among children in the Province of Quebec (34), three groups of more than 1100 children were surveyed with the ISAAC questionnaire. The prevalence rates for reported history of asthma varied from 14% to 15%. The prevalence of rhinitis, rhino-conjunctivitis and reported history of hay fever increased with age, reaching 28.0%, 15.9% and 21.1%, respectively, in the 16-year-old group.
 - 13 Consecutive surveys in Finland (35) have demonstrated that the prevalence of asthma increased 12-fold from 1966 (0.29%) to 2003 (3.45%), showing a continuous rising trend during this period. The average annual increment in prevalence during this period was 0.1%. Prevalence of AR remained low ($< 0.1\%$) until 1970 but increased steadily thereafter. The rise in prevalence of AR has been particularly striking since 1991, with the peak in 2000 (8.9%), and the trend is still upwards. Prevalence of atopic eczema, however, has remained fairly constant (about 1.2%) since the early 1980s.
 - 14 In Croatia (36), an estimate of prevalence of asthma, AR and atopic dermatitis among schoolchildren in the region of Primorsko-Goranska county was conducted using ISAAC questionnaire among 1634 participating children in the age group of 6–7 and 2194 children in the age group of 13–14. Estimated 12-month prevalence rates of symptoms were: wheezing 9.7% and 8.4%, AR symptoms 16.9% and 17.5%, allergic rhino-conjunctivitis symptoms 5.6% and 6.7%, and atopic dermatitis symptoms 5.4% and 3.4%, for younger and older age group, respectively. According to the authors, the current results suggest an increase in the prevalence of atopic disease symptoms in north-west part of Croatia over the last few decades when compared to prior studies.
 - 15 A cohort study in Finland (37) has estimated the incidence rate of asthma and AR from birth to early adulthood and the prevalences of these diseases at 16, 22 and 32 years of age. The data were drawn from a follow-up survey of a Finnish urban age cohort (1967 birth cohort, $N = 2269$) from age 16 to 32 years. All

data were based on self-report. The prevalence of asthma from age 16 to 32 years changed from 3.0% to 5.0%; and that of AR from 17.5% to 26.0%, respectively. The overall incidence rate of asthma was approximately 2.1 new cases per 1000 person-years (95% CI: 1.6–2.8). The incidence rate for AR in males was 13.4 per 1000 person-years, slightly greater than in females, 11.4. Between both genders, the highest incidence rate of AR was from 17 to 22 years.

- 16 Repeated consecutive studies in Aberdeen (38), UK, by questionnaires given to the parents of children attending the same primary schools in 1994 and 1999 have found that the prevalence of asthma or wheeze and the proportion of children with respiratory symptoms reporting a diagnosis of asthma changed little, although small but significant increases in the diagnosis of both eczema and hay fever were detected.
- 17 Another study in Taiwan (39), conducted in 1999 but published later on, has evaluated 21 clusters of adults randomly. Face-to-face interviews were conducted with 2076 individuals using a questionnaire designed to assess asthma and asthma-like symptoms. The lifetime prevalence rate of asthma in adults in Taipei City was 7.8%. A multiple logistic regression model showed the odds ratio (OR) of having asthma among subjects with AR to be 3.2 (95% CI: 2.03–5.16).
- 18 Two cross-sectional surveys (1995/1996 and 2001/2002) were carried out according to the ISAAC protocol among 6- to 7- and 13- to 14-year-old schoolchildren in Antwerp, Belgium (40). No significant differences in current prevalence of asthma and asthma medication were found in 6- to 7-year olds and 13- to 14-year-old girls. Significantly less asthma and asthma medication was reported by 13- to 14-year-old boys in 2002. Symptoms of wheeze had lower occurrence in all groups in 2002, which was significant for older age groups, but they reported significantly more rhinitis.
- 19 To estimate the trends in the prevalence of asthma, eczema and AR, two surveys were conducted in 1993 and 2002 in primary schoolchildren aged 6–7 years in Melbourne, Australia (41). There was a 26% reduction in the 12-month period prevalence of reported wheeze, from 27.2% in 1993 to 20.0% in 2002. The 12-month period prevalence of reported eczema increased from 11.1% in 1993 to 17.2% in 2002, and rhinitis increased from 9.7% to 12.7%.
- 20 Time trends in the prevalence of asthma and allergic diseases in Estonian (42) children born before and after the collapse of the Soviet Union, have been studied in two identical cross-sectional studies performed as part of Phase I and Phase III of the ISAAC studies. The prevalence of respiratory symptoms was similar in the two studies. Even though, the prevalence of diagnosed asthma increased. This was considered to be due to modified diagnostic criteria and increased awareness. The prevalence of rhinitis during the pollen season increased, from 1.7% to 3.5% in 6- to 7-year olds, and from 2.6% to 5.5% in 13- to 14-year olds. The prevalence of flexural dermatitis also increased from 12.0% to 13.5% in 6- to 7-year olds, and from 7.7% to 9.4% in 13- to 14-year olds. The increase was similar in children born before and after the regaining of Estonian independence, indicating that the influence of factors related to a Western lifestyle and affecting the prevalence of allergic symptoms is not restricted to infancy, but may be operative throughout childhood.
- 21 Three cross-sectional questionnaire-based studies of asthma and allergy in schoolchildren were conducted in the counties of Troms and Finnmark, in northern Norway (43) in 1985, 1995 and 2000. Identical items of asthma and allergy were employed and the analyses comprised only children 9–11 years of age. The prevalence of asthma was 9.3%, 13.2% and 13.8% in 1985, 1995 and 2000, respectively. However, great gender differences were detected; the prevalence of asthma increased in males from 1995 to 2000 (from 14.1% to 17.0%, RR = 1.2), but decreased in females from 1995 to 2000 (from 12.3% to 10.5%, RR = 0.9). The prevalence of self-reported allergic rhino-conjunctivitis was 16.5%, 24.7% and 29.6% in 1985, 1995 and 2000.
- 22 A second ISAAC survey was carried out 7 years after the first to evaluate trends in asthma and allergies prevalence in Singapore (44). The change in the prevalence of current wheeze occurred in opposing directions in two age groups, decreasing in the 6- to 7-year age group (16.6% to 10.2%) but increasing to a small extent in the 12- to 15-year age group (9.9–11.9%). The 12-month prevalence of rhinitis did not change.
- 23 Prevalence trends for asthma and allergies were studied among adolescents living in Switzerland (45). Between 1992 and 2000, the change in the prevalence of asthma symptoms and hay fever symptoms assessed by the ISAAC questions was investigated using three cross-sectional surveys. Prevalence rates of asthma and current asthmatic symptoms remained constant (students' report of current wheeze 8.8%, 7.3% and 8.3%). Similarly, no further increase was observed for reported hay fever rates.
- 24 In 2002, a survey was repeated in Scotland (46), Wales and the islands in the same school grades, using the same questionnaire and procedures in the same period of the year and, mostly, in the same schools. In 1995, as part of the ISAAC, a questionnaire survey based upon the ISAAC protocol was administered to secondary schoolchildren aged 12–14 years. Overall, the prevalence of any wheezing or whistling in the chest in the past 12 months fell from 34% to 28% (19% relative reduction). Large relative reductions were also observed in recent symptoms of

- allergic rhino-conjunctivitis (16%) and atopic eczema (30%). However, the proportion of children reporting 'ever' having had asthma or eczema increased (26% and 15%), as did the lifetime prevalence of 'hay fever' (8%). Trends in the four regions were similar.
- 25 A Phase III survey of the ISAAC was conducted in Taipei between 2001 and 2002 (47). Of 6653 eligible children from 23 high schools, 6381 (95.9%) participated. The prevalence of symptoms of asthma, AR and atopic eczema in the past 12 months in 13- to 14-year-old children increased by 37%, 51% and 193%, respectively, on written questionnaires during a 7-year period after ISAAC Phase I. However, the severity of asthma did not change significantly.
 - 26 A second survey of schoolchildren in Khon Kaen, north-eastern Thailand (48), using the Thai version of the ISAAC questionnaire analysed 2119 6- to 7- and 2956 13- to 14-year-old children. The cumulative *vs* 12-month prevalence were: 14.3% *vs* 9.8% for wheezing, 42.6% *vs* 33.3% for rhinitis and 13.5% *vs* 11.2% for eczema, respectively. Most Phase III prevalence was significantly lower than the first survey except for the steady, 12-month prevalence of wheeze.
 - 27 In Spain (49), the Phase III of ISAAC was carried out in schoolchildren aged 6–7 years from eight areas to estimate time trends and geographic variations in the prevalence of symptoms of AR. In all centres, AR symptoms tended to increase, with a prevalence ratio of 1.61 in rhino-conjunctivitis when both phases were compared. Wide variations in the prevalence of AR were observed across centres with a higher prevalence in Asturias, Madrid, Cartagena and Bilbao. Lower prevalences were reported in Barcelona, Castellon and Pamplona.
 - 28 In Poland (50), studies have been conducted to assess the prevalence of symptoms and diagnosis of AR in schoolchildren in 1994/1995 and 2001/2002, using standardized ISAAC questionnaires in Krakow and Poznan. The prevalence of AR symptoms ever increased significantly in the 6–7 years old group, from 28.5% to 33.6% in Krakow and from 13.0% to 31.3% in Poznan. A similar rise was found in the 13- to 14-year-old group, in Krakow from 26.1% to 41.1%, in Poznan from 19.0% to 39.6%. In both age groups and both centres the number of children with established diagnosis of AR has also increased.
 - 29 An evaluation of young adults in Western Europe (51), aimed to assess the change in IgE sensitization in relation to age. Serum-specific IgE to common allergens and total IgE were measured on two occasions about 9 years apart in 6371 individuals living in 28 centres, who took part in the ECRHS II. Overall, there was no net change in the prevalence of sensitization to at least one of house dust mite, grass or cat, although there was a fall in mean total IgE. There was evidence that sensitization to at least one allergen was higher in more recent cohorts, and this was largely explained by a higher prevalence of sensitization to grass.
 - 30 An analysis of serum samples of British (52) men, taken in three occasions during routine medical examinations from 1975 to 1998, has been performed aiming to compare the proportion of specific IgE to aeroallergens over time and to correlate markers of infection and markers of atopy. Highly significant increases were detected in the proportion of men with circulating specific IgE to inhaled allergens according to birth date. The average rate of increase was equivalent to an additional 4.5% of men becoming positive each decade. In multiple regression, year of birth was associated with the prevalence of atopy ($P < 0.001$), but current age was not. No inverse association between two common enteric infections (hepatitis A and *Helicobacter pylori*) and adult atopy was found.
- In summary, most of the recent reports support previous ARIA statements. Allergic rhinitis is a global health problem; it is a common disease worldwide affecting a variable proportion of the population. The prevalence of rhinitis can be above 30%. Many studies have demonstrated parallel increases in the prevalence of asthma and rhinitis; but in regions of highest prevalence the proportion of subjects suffering from asthma or rhinitis may be reaching a plateau. Differences in environmental exposures may be associated with the observed variations in the prevalence of rhinitis.
- Asthma and rhinitis – prevalence in developing countries
- 1 In a study performed in Turkey (53), 60 children with Familial Mediterranean Fever (FMF), which results from a genetic predisposition to elevated Th₁ cytokine production, were questioned about asthma and AR using the ISAAC Study Phase II questionnaire and underwent SPTs. The ISAAC Study Phase II with skin tests was conducted in a similar ethnic sample of 3041 children. The prevalence of diagnosed asthma and AR were 3.3 and 1.7, respectively, in children with FMF, while the corresponding prevalences in the control sample were 6.9 and 8.2. However, only the prevalence of AR was significantly lower in those with FMF.
 - 2 A study in Ha-Noi, Vietnam (54), using the parent self-administered questionnaire as part of the ISAAC survey, included 969 children aged 5–11 years in two schools. The overall prevalence of 'wheezing in past 12 months' was 14.9% and 'allergic rhinitis-conjunctivitis symptoms in past 12 months' was 10.7%. Age- and gender-adjusted OR were consistently significant across wheeze and AR symptom categories, being highest (OR: 10.10) between allergic rhino-conjunctivitis and wheeze in past 12 months.

- 3 In Ethiopia (55), a survey was conducted to determine the prevalence of symptoms of asthma and allergies among 3365 13- to 14-year-old schoolchildren in Gondar using the ISAAC questionnaire. The 12-month period prevalences of wheeze (16.2%) and rhino-conjunctivitis (14.5%) were similar or higher than previous reports from other regions of this country. The authors call attention that the prevalence of diagnosed atopic diseases (8.6%) was less than a quarter of the symptom prevalence rate, which may reflect a generally poor awareness and low health service utilization, or under-diagnosis by healthcare providers.
- 4 In Nigeria (56), an ISAAC Phase I study of rhinitis and asthma was conducted among 1704 children aged 6–7 years. Both recent rhino-conjunctivitis and wheeze were reported by 5.1%. The cumulative prevalence of reported wheezing and symptoms of chronic rhinitis were 7.2% and 11.3%, respectively.
- 5 In Colombia (57), a multistage stratified random sample selection of schools with subjects aged 5–18 years in six cities was surveyed. Guardian subjects selected were contacted, and home visits were arranged. Subjects aged 1–4 years and older than 19 years were also selected randomly by systematic sampling based on the addresses of the subjects aged 5–18 years. Subjects with asthma symptoms were invited to provide a blood sample. Information was obtained from 6507 subjects. The prevalence of asthma, rhinitis and atopic dermatitis symptoms in the past 12 months was 10.4%, 22.6%, and 3.9%, respectively. Thirty-eight per cent of asthmatic subjects had visited the emergency department or have been hospitalized, and 50% reported lost school days and workdays. Seventy-six per cent of sampled asthmatic patients were considered atopic.
- 6 A study in Ankara, Turkey (58), has investigated the prevalence and determinants of asthma and allergic diseases in a cross-sectional survey of schoolchildren aged 6–14 years in 2002. This was the third of a series of cross-sectional surveys, also conducted in 1992 and 1997, in the same school. Questionnaire including information on house characteristics, dietary habits, past and current exposures and diseases were distributed to 1064 children and filled by the parents at home. Current prevalences of asthma (1992: 8.3%, 1997: 9.8%, 2002: 6.4%), wheeze (1992: 11.9%, 1997: 13.3%, 2002: 6.4%), hay fever (1992: 15.4%, 1997: 14.1%, 2002: 7.2%) and eczema (1992: 4%, 1997: 4.3%, 2002: 1.8%) were significantly lower in 2002 compared with 1992. Multiple logistic regression analysis model for current wheeze has found ingestion of cow's milk and red meat to be associated with it. Similar analysis of those with AR also found an association with the ingestion of red meat. It is not clear, however, if these nutritional factors are linked directly as a risk factor, or are merely a surrogate of other factors related to affluence and/or westernized lifestyle of the families. No satisfactory explanation is provided for the reported decrease in the prevalence of asthma and rhinitis is provided either.
- 7 In Adana (59), Turkey, a cross-sectional population-based study using the ISAAC protocol was carried out on 3164 schoolchildren aged 6–18 years between March and June 1997. The prevalence of asthma, AR and eczema was found to be 12.6%, 13.6% and 8.3%, respectively. The prevalence of asthma was highest in 6- to 10-year-old schoolchildren (14.7%), and lowest (6.0%) in 15- to 18-year-old children. The cumulative and current prevalences of wheezing were found to be 19.0% and 13.5%, respectively.
- 8 In Trinidad and Tobago (60), in a study to estimate the prevalence of symptoms of asthma and rhinitis among children of primary school age who are exposed to household environmental tobacco smoke, ISAAC questionnaires were distributed, via the children in their schools, to parents of 6611 year 2 students (typically 6 years old) or year 3 students (typically 7 years old) in 106 randomly selected schools. Two questions were added to the standard questionnaires: one on household smoking and one on the ethnicity of the children. A total of 3170 completed questionnaires were suitable for further analysis. Parental smoking was significantly associated with wheezing in the last 12 months (29.3–37.4%; OR: 1.43), exercise-induced wheezing (OR: 2.12), and symptoms of rhinitis (OR: 1.35) in the last 12 months as well as a history of hay fever/sinus problems (13–17%; OR: 1.39). The authors comment that even in such a tropical environment where more time is spent outdoors and homes have much better ventilation than in temperate climates, environmental tobacco smoke exposure is associated with an increased prevalence of symptoms of asthma and rhinitis in primary school-aged children.
- 9 In Maputo, Mozambique (61), a case-control study has been performed to evaluate risk factors associated with childhood asthma in 199 age-matched children (100 asthmatic and 99 nonasthmatic) who attended a Central Hospital between January 1999 and July 2000. Information concerning their family history of atopy, birth weight, environment and breast-feeding, as well as detailed information about morbidity and treatment was obtained for each asthmatic child. The children were aged between 18 months and 8 years. Childhood asthma was associated with urban living, parental history of asthma or rhinitis, parental smoking and early weaning.
- 10 In Bangladesh (62), a study to determine the prevalence of asthma, AR and eczema in schoolchildren was conducted in Dhaka district using the ISAAC protocol in 2000. A total of 6260 written questionnaires were eligible for the analysis (3029 from

6–7 years of class I and 3231 from 13–14 years of class VIII). The lifetime (ever) and 12-month period (recent) prevalences of three allergic conditions were as follows: wheezing 13.8% and 7.6%; AR 25.0% and 20.0%; and eczema 8.7% and 6.5%, respectively. The prevalence of wheezing was higher in the younger children than in the older children but recent rhinitis, conjunctivitis and eczema were lower in younger age group.

- 11 The prevalence of rhinitis and its related symptoms were investigated in Brazilian children and adolescents by using the ISAAC written questionnaire (63). The questionnaire was answered by the parents of 11 403 children aged 6–7 years and by 20 587 adolescents (13 14 years old) from different cities and regions. The mean prevalence of rhinitis (affirmative response to question 2) was 26.6% and 34.2% in the 6- to 7- and 13- to 14-year-old groups, respectively. Applying the criteria that evaluate the association between nasal and ocular symptoms, the mean prevalences of AR were 12.8% for the 6- to 7-year-old children and 18.0% for the adolescents.

In summary, the prevalence of rhinitis and asthma in rural communities or middle- to low-income countries, in general, is lower than that in developed westernized urban communities. However, one should be cautious when comparing prevalence between studies because asthma and rhinitis were assessed differently in various studies, even when the same questionnaires are used.

A considerable difference between the prevalence of symptoms and the prevalence of medical diagnosis, detected in underserved populations, indicates a significant proportion of under-diagnosis, which might be related to lack of awareness and limited access to health care.

Asthma and rhinitis – common risk and protection factors

Infections, parasites and vaccination

- 1 An ecological analysis (64) of the relationship between tuberculosis notification rates and the prevalence of symptoms of asthma, allergic rhino-conjunctivitis and atopic eczema in 85 centres from 23 countries having participated in ISAAC Phase I has shown tuberculosis notification rates were inversely associated with prevalence of wheeze and asthma. Symptoms of allergic rhino-conjunctivitis in the past 12 months were also inversely associated with tuberculosis notification rates.
- 2 A study conducted in Germany (65) has addressed the question of Bacillus Calmette-Guerin vaccine (BCG) protection against asthma. A survey included all preschool children from Berlin in 1994 ($n = 38\,808$). Trained medical personnel asked parents whether their child ever had a diagnosis of bronchial asthma and AR or symptoms suggestive of these conditions. Bacillus Calmette-Guerin-vaccination status was recorded from official vaccination documents. The adjusted OR and 95% confidence interval (CI) for asthma was 0.85 (0.71–1.00) for BCG-vaccinated individuals. Bacillus Calmette-Guerin vaccination was not significantly associated with AR. This study demonstrated a weak protective effect of BCG vaccination against asthma.
- 3 In Denmark (66), the occurrence of AR in nearly 2000 women participating in the Danish National Birth Cohort study, in which detailed information on age at BCG vaccination (age 0–15 years) was available from school health records, has been assessed. Atopic status was evaluated serologically by a specific response to 11 common inhalant allergens using serum samples. Information on AR and asthma was available from telephonic interviews. Age at BCG vaccination was not associated with increased risk of AR, or asthma.
- 4 In Spain (67), the relationship between immunization with BCG and the prevalence of asthma, hay fever and atopic dermatitis was studied in a homogeneous population of Spanish schoolchildren. The ISAAC core and environmental questionnaires were used in four different centres of the Spanish North Atlantic coast. Bilbao, San Sebastian and Asturias have a universal BCG immunization policy during the first days of life, whereas La Coruna discontinued this practice in 1989. Except for this centre, immunization coverage was above 90%. Children with 6 and 7 years old were surveyed. After excluding those children born outside Spain, the numbers were 6762 immunized and 2828 nonimmunized. The adjusted ORs of the BCG-immunized children suffering from asthma, hay fever and atopic dermatitis were, respectively, 0.87 (95% CI: 0.76–1.00), 0.87 (0.75–1.01) and 0.89 (0.76–1.05), leading to the conclusion that neonatal BCG immunization offers a weak but significant protection against asthma in Spanish schoolchildren.
- 5 In Salvador (68), Brazil, an estimate of the association between neonatal BCG vaccination and prevalence of asthma was obtained by a cross-sectional study of 1612 schoolchildren aged 12–16 years. The presence of a scar compatible with BCG was used as a surrogate of neonatal vaccination. A self-administered structured questionnaire was prepared based on that used by the ISAAC. The prevalence of asthma was categorized according to the report of lifetime wheeze, lifetime asthma, lifetime asthma among those referring allergy and among those referring allergy and sneezing. Neonatal BCG vaccination was not associated with the overall prevalence of reported wheezing or asthma. However, in the subgroup reporting current allergy and sneezing, in which a greater risk of asthma was detected, neonatal BCG was associated with a 37% lower prevalence of lifetime asthma.

- 6 In France (69), the relationship between childhood immunization and the development of atopic diseases (asthma, AR and eczema) was examined in a population-based sample of 718 adolescents by taking into account individual data drawn from personal paediatric records on the schedule and the type of vaccination. Atopic diseases were determined using the ISAAC questionnaire. After adjustments, adolescents having been vaccinated ($n = 694$) had a significant lower risk to suffer from asthma, AR or atopic dermatitis than nonvaccinated adolescents did ($n = 24$, OR: 0.30; 95% CI: 0.10–0.92). The relationship did not depend on the disease against which the vaccine was used as prophylaxis, the observance of the vaccination schedule or the number of inoculations. A higher protection was observed in the case of live attenuated vaccines (oral poliomyelitis and BCG; OR: 0.26; 95% CI: 0.08–0.83).
- 7 In Italy (70), an investigation on the possibility that infection by *Salmonella* in early life can protect from development of respiratory allergies later in life was conducted during 2003, by studying two groups of Sardinian children (age 6–18 years) who had been hospitalized before 4 years of age (during 1989–2001) with nontyphoid salmonellosis ($n = 148$) or acute enteritis of nonbacterial aetiology (NB-enteritis; $n = 167$). Allergic rhino-conjunctivitis and asthma were evaluated by telephonic interview with an ISAAC questionnaire; participants reporting AR and/or asthma were further examined through a complete diagnostic work-up to objectively confirm or exclude current disease. Children who had been hospitalized with salmonellosis had a lower prevalence of allergic rhino-conjunctivitis (5.4% vs 13.8%; $P = 0.019$) or asthma (3.4% vs 12.6%; $P = 0.006$) than those who had been hospitalized with NB-enteritis.
- 8 Scientists from New Zealand (71) have investigated the possibility that antibiotic and/or paracetamol use may increase the risk of asthma. The study measured the association between infections, and medication use early in life and the risk of asthma at age 6–7 years. It involved 1584 children who had been notified to public health services with serious infections at age 0–4 years, and 2539 children sampled from the general population. For both groups, parents completed postal questionnaires. There was little difference in the prevalence of current wheezing between the childhood infections group (23.5%) and the general population group (24.3%). However, in both groups, there were associations with antibiotic (OR: 1.78, 95% CI: 1.49–2.14) or paracetamol (OR: 1.38, 95% CI: 1.04–1.83) use in the first year of life or recent paracetamol use (OR: 2.10, 95% CI: 1.78–2.49) and current wheezing. The authors comment these findings are consistent with previous evidence that antibiotic and paracetamol use early in life may increase the risk of asthma.
- 9 Previous infection with hepatitis A and *H. pylori* was assessed in a community-based sample of young British (72) adults, as well as associations with serum-specific IgE to environmental allergens, asthma-like symptoms and hay fever. There was no association of previous infection with hepatitis A or *H. pylori* with wheeze or hay fever. There was no evidence of an association of infection with either agent or sensitization except for the isolated finding of a lower prevalence of sensitization to grass in those with IgG antibodies to *H. pylori* (OR: 0.65, 95% CI: 0.43–0.99).
- 10 In the Netherlands (73), aiming to examine independent effects on atopic sensitization and symptoms of daycare attendance, older siblings, pet ownership and early infancy's airway disease, a cross-sectional survey among 8- to 13-year-old schoolchildren with complete data for 1555 children was performed. Atopic sensitization occurred less frequently in children that had attended a daycare centre (OR: 0.73, 95% CI: 0.55–0.98) or had a cat or dog before 2 years of age (OR: 0.78, 95% CI: 0.61–0.99). For symptoms, there was no relation with having older siblings, daycare attendance and pet ownership.
- 11 To evaluate the role of *Chlamydia pneumoniae* respiratory tract infection on paediatric asthma, AR or atopic eczema in Germany (74), children of three age groups ($n = 1211$) were prospectively studied for a *C. pneumoniae* infection using throat swabs and polymerase chain reaction (PCR) with enzyme immunoassay (EIA) detection. Infected children were examined monthly until the agent could not be detected, quantifying persistent infection. They were compared with randomly selected, noninfected children without asthma matched for age, gender and origin regarding lung function as well as initiation of allergic diseases judged by family doctor diagnosis after, in median, 22 months. Incidence of asthma (0/55 vs 5/54, $P = 0.03$) and AR (3/53 vs 10/52, $P = 0.04$) as well as prevalence of asthma (1/56 vs 9/58, $P = 0.02$) and AR (6/56 vs 16/58, $P = 0.03$) were lower in the *Chlamydia*-infected children. There was no association with atopic eczema.
- 12 An estimate of the associations between early respiratory infections and doctor-diagnosed asthma, AR and skin prick sensitization in children at 10 years of age was obtained in the Oslo Birth Cohort (75), established in 1992–1993. A total of 2540 children were followed from birth to the age of 10 years. Experiences of respiratory infections were recorded in follow-up surveys at 6 and 12 months. At age 10, questions were asked about current symptoms of asthma and AR and about having ever received a doctor diagnosis for these diseases. A subsample ($n = 1740$) of the cohort was tested for SPT reactivity. Current asthma was related to lower respiratory tract infection (OR: 2.1; 95% CI: 1.3–3.0) and

croup (OR: 2.3; 95% CI: 1.3–4.2) in the first year. Odds ratio for AR and skin prick sensitization were smaller but mainly positive. Birth order and childcare attendance at age 1 were not significantly associated with any of the studied outcomes.

- 13 An ecologic analysis of the relationship between antibiotics sales and the prevalence of symptoms of asthma, allergic rhino-conjunctivitis and atopic eczema in 99 centres from 28 countries has been performed (76). Data for antibiotic sales for 28 countries were obtained from the Institute for Medical Statistics (IMS), Health Global Services, UK. Data on the prevalence of symptoms of asthma, rhinitis and eczema in 13- to 14-year olds were based on the responses to the written and video questionnaires from the ISAAC Study. The analysis was adjusted for gross national product (GNP) as an estimate of the level of affluence. In general, there was a positive association between per capita antibiotic sales and the prevalence of symptoms for asthma, rhinitis and eczema, but the associations generally became negative once the analyses had been adjusted for GNP. There was a statistically significant positive association with wheeze at rest as measured by the asthma video questionnaire; however, even this association was weak and would not account for more than a 1% difference in asthma prevalence between countries.
- 14 In Taiwan (77), the relationship between allergy and parasites has been studied. Data were collected from school records and questionnaires distributed to all children in four primary schools grades 1 through 6 ($n = 3107$). The prevalence of doctor-diagnosed asthma (9.3% vs 14.1%, $P = 0.007$) and AR (27.4% vs 38.3%) were lower in pinworm-positive compared to uninfected children. With logistic regression controlling for sex, parent allergy and lower respiratory infection, current asthma (OR: 0.25, 95% CI: 0.10–0.63) and rhinitis (OR: 0.61, 95% CI: 0.45–0.84) were negatively associated with pinworm current infection.
- 15 A retrospective study conducted in the USA (78) analysed the data of 33 994 residents recorded in a public database of a nationally representative cross-sectional survey (Third National Health and Nutrition Examination Survey, 1988–1994) and provides further serological evidence that acquisition of certain infections, mainly food-borne and orofecal, is associated with a lower probability of having hay fever and asthma.
- 16 Data from the European Respiratory Health Survey (79) on 18 530 subjects aged 20–44 years, regarding early life exposures, have led to the conclusions that subjects exposed to many children at home or in daycare experienced less hay fever and more asthma in adulthood.
- 17 A case-control study to investigate whether exposure to food-borne and orofecal microbes are associated with atopy and respiratory allergies comparing 240

atopic cases and 240 nonatopic controls from a population sample of 1659 Italian male cadets has been reported (80). There was a lower prevalence of *Toxoplasma gondii*, hepatitis A virus and *H. pylori* in atopic participants. The authors speculate that hygiene and a westernized, semi-sterile diet may facilitate atopy by influencing the overall pattern of commensals and pathogens that stimulate the gut-associated lymphoid tissue.

- 18 To determine the frequency of asthma and rhinitis symptoms and immediate skin reactivity to aeroallergens in Human T-cell Lymphotropic Virus Type 1 (HTLV-1)-infected individuals, compared with non-infected subjects, a cross-sectional study of 101 HTLV-1-infected and 101 control uninfected blood donors was performed in Brazil (81). The subjects were age- and sex-matched, identified as presenting allergy history by questionnaire, which was complemented by a complete clinical examination and SPT for aeroallergens. The frequency of atopy, defined by the coexistence of symptoms of rhinitis and/or asthma and a positive prick test was lower in infected than uninfected subjects, 14.9% and 29.7% ($P = 0.017$), respectively. Infection by HTLV-I was found to be a factor of protection to atopy (prevalence ratio (PR): 0.44; $P = 0.005$).

Farming

- 1 In a cross-sectional survey (82), parents of 2283 children aged 8–10 years from a rural area in Austria answered a standardized questionnaire and 1137 children underwent SPTs to seven local allergens. The prevalence of hay fever, asthma and positive SPT reactivity to at least one of the common local allergens was significantly lower in children living on a farm than in children from a nonfarming environment. In a multivariate logistic regression model, adjusting for genetic background, parent education, living and housing conditions and dietary factors did not change the OR for the association of farming and allergic sensitization. Only after including regular contact with livestock and poultry into the model did the OR change significantly indicating an association between regular contact with farm animals and reduced risk of atopic sensitization.
- 2 Similar findings were reported from Germany (83), where 10 163 children entering school (aged 5–7 years) were evaluated. Farmers' children had lower prevalence of hay fever, diagnosed asthma and wheeze than their peers not living in an agricultural environment. The reduction in risk was stronger for children whose families were running the farm on a full-time basis when compared with families with part-time farming activity. Among farmers' children, increasing exposure to livestock was related to a decreasing prevalence of atopic diseases.

- 3 Some extra evidence for the protective role of a farming environment come from the ECRHS (84). Data from 6251 randomly selected adults 20–44 years of age who had answered a detailed questionnaire and underwent specific IgE measurements to five allergens was analysed. After adjustment for potential confounders, living on a farm in childhood was associated with a reduced risk of atopic sensitization in adulthood (OR: 0.76, 95% CI: 0.60–0.97). The protective effect of farming environment in childhood observed in this population-based sample of young adults provides evidence in favour of the hypothesis that environmental factors encountered in childhood may have a lifelong protective effect against the development of allergy.
- 4 In Finland (85), to examine the association of farm environment with atopic sensitization, allergic diseases and the importance of specific sensitization against allergens for asthma and allergic diseases in children, a cross-sectional study including 344 farmers' and 366 nonfarmers' children aged 6–13 years, using a self-administered written questionnaire and SPTs has been conducted. Farmers' children had less asthma and allergic diseases and were less often sensitized against common allergens than the nonfarmers' children. Among the single allergens, sensitization against pets or pollen, or against horse or cow, had the strongest association with asthma, hay fever and atopic eczema; no such association was seen with *Dermatophagoides pteronyssinus*, mugwort, cockroach or *Lepidoglyphus destructor* sensitization.
- 5 In Australia (86), a comparison of the prevalence and risk factors for wheeze, asthma diagnosis and AR in Aboriginal and non-Aboriginal children living in rural areas was conducted by means of a cross-sectional study in two towns. Aboriginal children were less likely to be atopic and to have AR than non-Aboriginal children, but were equally likely to have had wheeze (31.0% vs 27.3%) and asthma (39.4% vs 39.3%). The authors concluded that asthma and wheeze were equally prevalent in Aboriginal and non-Aboriginal children living in the same towns, but appeared to have a different aetiology.
- 6 To examine the associations between pet contact and the occurrence of asthma and allergies in children of the rural Allergy and Endotoxin (ALEX) Population Study (87), taking farm animal contact, endotoxin and cat allergen levels in mattress dust into account, information about contact with pets and farm animals, asthma and allergy were collected for 812 children by a standardized parents' questionnaire and an interview. Current contact with dogs was inversely associated with diagnosed hay fever (OR: 0.26, 95% CI: 0.11–0.57), diagnosed asthma (OR: 0.29, 95% CI: 0.12–0.71), sensitization to cat allergen (OR: 0.48, 95% CI: 0.23–0.99) and to grass pollen (OR: 0.55, 95% CI: 0.33–0.94). Early and current contact with

cats were associated with reduced risk of wheezing (OR: 0.48, 95% CI: 0.23–1.00, and OR: 0.49, 95% CI: 0.26–0.92, respectively) and grass-pollen sensitization. Adjustment for farm animal contact but not for endotoxin and cat allergen exposure attenuated these associations and the effect of pet was stronger among farmers' children. The authors concluded that the inverse relation between current dog contact, asthma and allergy was mostly explained by simultaneously occurring exposure to stable animals or was restricted to farm children.

Ecological studies and/or environmental factors

- 1 An ecological analysis was performed by Burr et al. (88) to evaluate whether pollen exposure is associated with symptoms of allergic rhino-conjunctivitis and asthma in 28 centres within 11 countries (nine being in Europe) in 13- to 14-year olds in the frame of ISAAC. The analysis was adjusted for GNP and mean annual relative humidity. There was little relationship between pollen exposure and symptom prevalence, except for a weak but significant inverse association between grass-pollen counts and lifetime prevalence of the symptoms of AR. This finding accords with evidence suggesting that the prevalence of AR tends to be lower among people living on farms. On the other hand, exposure to allergenic pollen in early life did not appear to increase the risk of acquiring symptoms of respiratory allergy, and may even give some protection against them. Such results must be taken cautiously as mean concentrations of pollens were taken at the country level, without making any differences according to the type of climate present in it.
- 2 In Sweden (89), sensitization to different airborne allergens in relation to asthma and rhinitis has been studied. A cross-sectional study was performed among 2148 7- to 8-year-old children. Independently from other risk factors, sensitization to dog (OR: 2.4) and horse (OR: 2.2) were significant risk factors for asthma. Sensitization to birch (OR: 6.0), horse (OR: 4.1) and timothy (OR: 2.8) were significant risk factors for rhinitis. Despite a large overlapping of the diseases the pattern of sensitization was different for asthma and rhinitis. Sensitization to cat was most common among all children, but sensitization to dog and horse was associated with the highest risk for asthma, and sensitization to birch showed the highest risk for rhinitis.
- 3 The prevalence of symptoms of asthma and rhinitis was surveyed among schoolchildren living in the heavily polluted Arctic town of Nikel, Russia (90). A self-administered questionnaire was distributed to the parents of 1800 children aged 8–17 years. Atopic diseases were reported in 508 (30.2%) of the children. Eczema occurred most frequently (15.5%), followed

- by allergic rhino-conjunctivitis (13.9%) and asthma (3.9%). The authors conclude that although atopic diseases are a common health problem in Nikel, they are less prevalent than has been reported in recent studies of northern European countries. Air pollution did not seem to be a major risk factor for the development of atopic diseases.
- 4 Interesting findings came from a broad USA survey (91) in a population of 173 859 women and men in a large prepaid health plan in northern California. The study examined racial/ethnic and socioeconomic patterns in the prevalence of asthma and rhinitis. Using education as a measure of socioeconomic position, they found evidence of a positive gradient for asthma and AR with increasing level of education but an inverse gradient for asthma without rhinitis. Allergic rhinitis was also strongly associated with education. Compared with their white counterparts, black women and men were more likely to report asthma without rhinitis. Asian men were more likely to report asthma with AR, and Asian women and men were much more likely to have AR. Racial/ethnic disparities in prevalence of allergic diseases were largely independent of education.
 - 5 To evaluate the interrelationship between socioeconomic status and asthma/rhinitis in Stockholm (92), 4089 families with children born between 1994 and 1996 in predefined areas answered questionnaires on environmental factors, socioeconomic status (parental occupation) and symptoms of allergic disease at birth, 1, 2 and 4 years of age. Blood samples taken at 4 years from 2614 children were analysed for specific IgE to common airborne and food allergens. There was a decreasing risk of asthma and rhinitis with increasing socioeconomic status. The OR for asthma was 0.33 (95% CI: 0.17–0.66) and for rhinitis 0.50 (0.32–0.79) comparing the highest and the lowest socioeconomic groups, with a tendency to stronger effects in those with heredity for allergic disease. The risk of sensitization to food allergens also decreased with increasing socioeconomic status (OR: 0.65, 0.41–1.02) in the highest socioeconomic group, which was not clearly seen for airborne allergens.
 - 6 Another study in Sweden, aimed to assess whether the association with social class differed between AR and asthma and whether these associations have changed over time (93). The Swedish Military Service Conscription Register was linked to two other national registers for 1 247 038 male conscripts in successive cohorts born between 1952 and 1977. The percentage of asthma cases associated with AR was 15% in the oldest cohort and 44% in the youngest cohort. The role of social class has changed over time. The steepest increase in asthma and AR occurred in conscripts with a low socioeconomic status.
 - 7 A survey in Ethiopia (94), in urban population of Jimma, tested the hypothesis that the risk of allergy is increased by the use of nonbiomass fuels (kerosene, gas or electricity) in the home. Questionnaire data on allergic symptoms, domestic fuel use and lifestyle factors were collected from 9844 adults and children, and allergen skin sensitization measured in a subsample of 2372. Use of any nonbiomass fuel was reported by 959 individuals (10%), usually in combination with biomass fuel, and was significantly associated with an increased risk of allergic sensitization (OR: 1.78), wheeze (1.56) and rhinitis (2.06) relative to use of biomass fuel only. The effects were predominantly because of kerosene, which was significantly related to all outcomes. The authors speculated that domestic combustion of refined fossil fuels increases the risk of allergic sensitization and symptoms in a region of low prevalence of atopy. Nevertheless, other changes in habits associated with the use of nonbiomass fuels might have contributed to their findings.
 - 8 To explore the association of household gas cooking and respiratory illnesses in preschool children and their relation to outdoor air pollution in Hong Kong (95), a cross-sectional study was conducted among households that used gas stoves for cooking in two housing estates with contrasting air qualities. A structured questionnaire was administered to parents of 426 children aged 0–6 years on their exposure to gas cooking and passive smoking, and the prevalence of respiratory illnesses. A total of 111 children (26.1%) were reported to have one or more respiratory illnesses (AR, asthma, bronchitis, sinusitis and pneumonia). Hierarchical logistic regression models adjusting for socioeconomic, demographic and indoor risk factors including passive smoking showed that household gas cooking was positively associated with respiratory illnesses. There was a dose–response relation between the frequency of gas cooking and the prevalence of respiratory illnesses in the estate with lower outdoor air pollution (OR: 6.1 and 3.2, respectively, for cooking three and two meals a day, compared to one meal a day). This relation was not observed in the more polluted estate. The association between the presence of a cigarette smoker in the household and the prevalence of respiratory illnesses was not significant.
 - 9 A population-based sample of 14 578 adolescents was enrolled in an epidemiological survey on allergies in France (96), aiming to assess whether adolescents with asthma have higher rates of active smoking compared with adolescents without asthma, after controlling for environmental tobacco smoking exposure. After controlling for age, sex, geographic region, familial allergy and passive smoking, current wheezing (12.4%), current asthma (5.6%), lifetime asthma (12.3%), current rhino-conjunctivitis

(13.9%), lifetime hay fever (14.4%) and current eczema (9.3%) were all significantly related to active smoking. Passive smoking was significantly associated only with current diseases. Active smoking was also highly related to both severe asthma (OR: 4.02; 95% CI: 1.37–11.79) and severe rhino-conjunctivitis (OR: 2.95; 1.58–5.49). The highest rate of adolescents suffering from the co-morbidity of lifetime asthma and hay fever (3.6%) was also seen in active smokers compared with passive and nonsmokers (5.5% vs 3.6% and 3.1%, respectively; $P = 0.001$).

- 10 In Sweden (97), a study was performed to assess whether the association with body mass index differed between allergic rhino-conjunctivitis and asthma and if these associations have changed over time. The Swedish Military Service Conscription Register was linked to the Register of the Total Population and the Population and Housing Censuses. Asthma (with and without allergic rhino-conjunctivitis) and allergic rhino-conjunctivitis at conscription were analysed in relation to body mass index for 1 247 038 male conscripts in successive cohorts born between 1952 and 1977. Obesity was associated with asthma without allergic rhino-conjunctivitis, adjusted OR 1.53 (95% CI: 1.43–1.63), and with asthma with allergic rhino-conjunctivitis, adjusted OR 1.34 (95% CI: 1.20–1.50), but not with allergic rhino-conjunctivitis. The ORs were similar in three successive cohorts (conscripts born in 1952–1961, 1962–1971 and 1972–1977).
- 11 The association between climate and atopic diseases has been studied using worldwide data from 146 centres of the ISAAC Study (98). In Western Europe (57 centres in 12 countries), the prevalence of asthma symptoms, assessed by written questionnaire, increased by 2.7% (95% CI: 1.0–4.5%) with an increase in the estimated annual mean of indoor relative humidity of 10%.
- 12 A birth cohort analysis of 29 238 children of the West Midlands General Practice Research Database, UK (99) has confirmed previous observations that the presence of older siblings reduces the risk of developing rhinitis, atopy and asthma. There was a dose-related decrease in the incidence of rhinitis and eczema with increasing number of older siblings. For children diagnosed over the age of 2 years the presence of older siblings was protective for asthma. Birth order and multiple birth effects were independent of sex, maternal age, consulting behaviour, and parental allergy and smoking habit.
- 13 Again in the UK, a birth cohort of 1456 children was recruited over a 14-month period (1989–1990) and their risk of asthma and rhinitis attributable to atopy has been estimated (100). These children have been seen at 1 and 2 years of age. At 4 years, 1218 children were reviewed and an interview was administered or postal questionnaire was completed for the presence

of allergic diseases (asthma, rhinitis and eczema). Additionally, in 981 children, SPTs with a battery of 12 common allergens were performed. To ascertain how much of allergic disease is attributable to atopy, they estimated the population-attributable risk. The authors conclude atopy is closely associated with asthma, rhinitis and eczema at 4 years of age, with a direct and linear relationship. However, the proportion of cases of allergic disease attributable to atopy is < 50%, and propose a model for the development of allergic disorders, where 30–40% of cases of allergic disease (asthma, eczema and rhinitis) in early childhood are attributable to atopy and 60–70% of cases could be accounted for by organ-based and other factors. Despite the author's conclusions, one should not forget allergic asthma and AR do not follow sensitization immediately, and often appear later than 4 years of age. Therefore, the estimates presented by Arshad et al. considering 30–40% of cases of allergic diseases in early childhood are attributable to atopy should be followed by a question: how much would it be at the age 10 years? If we have a linear time-dependent correlation, uninfluenced by other environmental factors, it could approach 100%.

- 14 A study was undertaken to determine whether asthma and allergy were associated with irregular menstruation in a general population, and the potential role of asthma medication for this association (101). A total of 8588 women participated in an 8-year follow-up postal questionnaire study of participants of the ECRHS stage I in Denmark, Estonia, Iceland, Norway and Sweden. Only nonpregnant women not taking exogenous sex hormones were included in the analyses ($n = 6137$). Irregular menstruation was associated with asthma, asthma symptoms and asthma preceded by hay fever among women aged 26–42 years. Irregular menstruation was associated with new onset asthma in younger women but not in women aged 42–54 years.
- 15 To examine whether frequent intake of margarine is associated with allergy prevalence in adults, data on 7124 subjects aged 18–79 years were obtained from the German National Health Survey 1998 (102). Frequent intake of margarine of any kind was positively associated with current asthma during the past 12 months in young adults aged 18–29 years (OR: 2.33; 95% CI: 1.03–5.26). In subgroup analysis, the positive association was confined to frequent intake of low-fat margarine (4.51; 1.78–11.43) or the combination of low-fat margarine and low-fat butter (4.79; 1.84–12.44). Consumption of margarine of any kind was not related to hay fever, atopic dermatitis and atopic sensitization to inhalant allergens. The authors conclude that frequent intake of low-fat margarine is not consistently associated with allergic diseases in adults. Other constituents of low-fat

margarine or certain dietary habits and lifestyle factors, associated with the use of low-fat margarine, may be related to current asthma.

- 16 To investigate potential associations between persistent allergic symptoms in children and the concentration of phthalates (components of plastic products such as polyvinyl chloride – PVC) in dust collected from their homes, a case–control study nested within a cohort of 10 852 Swedish children was performed (103). From the cohort, 198 cases with persistent allergic symptoms and 202 controls without allergic symptoms were analysed. Higher median concentrations of butyl benzyl phthalate (BBzP) in dust among cases than among controls (0.15 vs 0.12 mg/g dust). Analysing the case group by symptoms showed that BBzP was associated with rhinitis ($P = 0.001$) and eczema ($P = 0.001$), whereas di(2-ethylhexyl) phthalate (DEHP) was associated with asthma ($P = 0.022$). This study shows that phthalates, within the range of what is normally found in indoor environments, are associated with allergic symptoms in children.
- 17 To explore the impact of long-term air pollution on asthma and AR, 6672 children aged 9–11 years recruited from 108 randomly selected schools in six French cities (104), and 3-year averaged concentrations of major air pollutants were calculated at children's schools. Both lifetime asthma and lifetime AR were found to be positively related to an increase in the exposure to sulphur dioxide, particulate pollution and ozone after adjustment for potential confounders. Such results are supported by experimental data.

Occupational exposures. Occupational exposures might be relevant risk factors for asthma and rhinitis, although no precise estimate of the size of the problem is currently available.

- 1 A report on the time-course of the incidence of work-related symptoms, skin reactivity, occupational rhino-conjunctivitis and asthma, in apprentices exposed to laboratory animals, in a 3–4 years programme has been published (105). Four hundred and seventeen apprentices at five institutions were assessed prospectively with questionnaire, skin testing with animal-derived allergens, spirometry and airway responsiveness ($n = 373$). At all follow-up visits, the incidence was greater for work-related rhino-conjunctivitis symptoms, followed by skin reactivity and occupational asthma. Sensitization, symptoms and diseases occurred maximally in the first 2–3 years after starting exposure to laboratory animals.
- 2 A study of occupational risk for rhinitis and asthma performed in Turkey (106), evaluated 125 grooms randomly selected among 1000 grooms working in the Hippodrome of Istanbul, compared to 92 subjects who worked in the different parts of this hippodrome. Sensitization to horsehair was found in 12.8% in grooms and 4.3% in controls. Asthma was found in 14.4% of the grooms and 5.4% of the controls, AR in 42.4% of the grooms and 18.4% of the controls. Forced expiratory volume in 1 s was significantly lower in the groom group.
- 3 In Italy (107), the features of a large group of hairdressers consecutively referred for suspected occupational asthma over an 8-year period was described. Forty-seven hairdressers (mean age, 25 years; range: 17–52) were studied. On the basis of the response to the specific inhalation challenge, 24 patients received a diagnosis of occupational asthma (51.1%), which was due to persulphate salts in 21 patients (87.5%), permanent hair dyes in two patients (8.3%) and latex in one patient (4.2%). Thirteen of these 24 patients (54.2%) also received a diagnosis of occupational rhinitis, which was due to persulphate salts in 11 patients (84.6%) and to paraphenylenediamine in two patients (15.4%). Patients with persulphate asthma had a long period of exposure to bleaching agents, a long latent period between the start of exposure and the onset of symptoms, and a prevalent eosinophilic airway inflammation in induced sputum. The SPT with ammonium persulphate performed in a subset of patients gave negative results.
- 4 A cross-sectional study of grape farmers has been performed in the Malevisi region in northern Crete, Greece (108). One hundred and twenty grape farmers and 100 control subjects were examined. The protocol comprised a questionnaire, SPTs for 16 common allergens, measurement of specific IgE antibodies against eight allergens, and spirometry. Grape farmers were found to have an excess of respiratory symptoms. In multiple logistic regression model, grape farmers were found to have increased work-related symptoms, such as sneezing (OR: 2.9; 95% CI: 1.3–6.6), rhinorrhoea (OR: 2.9; 95% CI: 1.3–6.6), cough (OR: 3.7; 95% CI: 1.2–11.4) and dyspnoea (OR: 3.8; 95% CI: 1.1–13). The prevalence of AR was 40.8% in grape farmers and 26% in control subjects (OR: 2.0; 95% CI: 1.1–3.5). Increased but statistically nonsignificant values of asthma prevalence were found in grape farmers (6.7%) compared with the control group (2.0%). The prevalence of atopy was 64.2% in grape farmers and 38.0% in the control group (OR: 2.2; 95% CI: 1.2–3.5). Mean FEV₁ was significantly lower in grape farmers than in control subjects, after adjusting for age, sex and smoking status.
- 5 To study the prevalence of respiratory symptoms and diseases among construction painters a questionnaire study was conducted on 1000 male Finnish construction painters and 1000 carpenters (mean response rate 60.5%; 109). Symptoms and diseases of the respiratory tract were studied in relation to occupation and duration of painting experience, by

logistic regression modelling. Age, atopy and smoking habits were taken into account. The painters reported more asthma-like, rhinitis, laryngeal and eye symptoms than the carpenters (OR: 1.4–1.8). The difference in the prevalence of asthma between the occupations was not statistically significant, but the painters with 1–10 years of painting experience had a threefold risk of asthma compared with the carpenters. Occupation was not associated with AR or conjunctivitis.

- 6 In Poland (110), a case-control study was conducted to evaluate the risk factors of work-related respiratory symptoms and occupational asthma and/or rhinitis in farmers. The study groups comprised 100 cases who were farmers reporting work-related asthmatic and/or rhinitis symptoms and 102 healthy controls. Respiratory allergic disease was recognized in 68 symptomatic patients, including 41 cases of occupational allergens (asthma: $n = 38$, rhinitis: $n = 41$). Stepwise logistic regression analysis confirmed the protective role of small farms against work-related symptoms (OR: 0.23; 95% CI: 0.11–0.47) as well as the risk associated with positive SPT to cereals (OR: 5.55; 95% CI: 1.6–19.21) and storage mites (OR: 3.73; 95% CI: 1.27–10.96) for the presence of these symptoms.
- 7 A prospective study describes the incidence, risk factors and natural history of occupational respiratory allergy in apprentice bakers in Poland (111). Two hundred and eighty-seven apprentice bakers were examined using a questionnaire, SPTs to common and occupational allergens, evaluation of total serum IgE level and specific antiflour and α -amylase IgE, before, 1 year and 2 years after the onset of vocational training. The incidence of work-related chest symptoms was 4.2% in the first year and 8.6% in the second year of exposure. Hypersensitivity to occupational allergens developed in 4.6% and 8.2% of subjects, respectively. The incidence of occupational AR was 8.4% after 1 year and 12.5% after 2 years, and that of occupational asthma/cough-variant asthma 6.1% and 8.7%, respectively. In 21 of 25 subjects with occupational asthma, chronic cough was the sole clinical manifestation of the disease. Stepwise logistic regression analysis revealed that positive SPT to common allergens was a significant risk factor of hypersensitivity to occupational allergens (OR: 10.6, 95% CI: 5.27–21.45), occupational rhinitis (OR: 3.9, 95% CI: 1.71–9.14) and occupational asthma (OR: 7.4, 95% CI: 3.01–18.04).

In summary, asthma, AR and atopy usually share common risk factors. The reports reviewed in this update reinforce previous publications on this matter and are compatible with the theory of asthma and rhinitis being manifestations of one disease spectrum. Nonetheless, many studies have provided evidences for some

differences in environmental or genetic risk among these related conditions, suggesting a certain degree of specificity for asthma or rhinitis. On the other hand, various recent reports have identified factors associated with reduced risk of atopy, asthma and AR, confirming previous findings of protection related to exposure to infections or close contacts with animals. The loss of these protection factors in westernized societies may be more relevant to the worldwide atopy epidemic than the risk associated with environmental exposure to allergens. According to the categories of evidence proposed by Shekelle et al. (112):

Most of asthmatics present rhinitis	Category of evidence I
Many patients with rhinitis present asthma	Category of evidence I
Allergy is associated with rhinitis and asthma	Category of evidence I
Occupational agents can cause rhinitis and asthma	Category of evidence I
Nonallergic rhinitis is associated with asthma	Category of evidence I
Allergic and nonallergic rhinitis are risk factors for asthma	Category of evidence I
Rhinitis is associated with bronchial hyper-reactivity	Category of evidence I

Rhinitis as a risk factor for asthma

Various studies around the globe and using different observational designs have looked at the question whether rhinitis is a risk factor for asthma, and if it is an independent risk factor.

- 1 Leynaert and colleagues (113) have assessed whether the coexistence of asthma and rhinitis could be explained by common risk factors through an international cross-sectional study of young adults who completed a detailed questionnaire and underwent lung function tests, bronchoprovocation, IgE measurements and SPT (ECRHS). In all countries, asthma and BHR were more frequent in subjects with rhinitis. About 74–81% of subjects with asthma reported rhinitis, depending on sensitization to specific allergens. The risk of asthma increased from 2.0% in subjects without rhinitis to 6.7% in subjects with rhinitis only when exposed to pollen, 11.9% in subjects with rhinitis when exposed to animals, and 18.8% in subjects with rhinitis either when exposed to pollen or to animals. The association between rhinitis and asthma remained significant after adjustment for total IgE, parental history of asthma, and allergen sensitization suggesting that the coexistence of asthma and rhinitis is not solely due to atopic predisposition to these two diseases. Although there were some variations in the association between asthma and rhinitis according to sensitization to individual allergens, the strong association between asthma and rhinitis was not fully explained by shared risk factors, including atopy.

- 2 Lombardi et al. (114) describe the follow-up of 99 allergic patients up to 10 years and the evolution of their disease. At baseline, 44 patients suffered from AR alone, 12 from allergic asthma alone and 43 from both AR and allergic asthma. After 10 years, 31.8% of the AR patients developed allergic asthma and 50% of the patients with allergic asthma developed AR. Sixty-five per cent of patients with a single sensitization to aeroallergens at the beginning developed new sensitizations.
- 3 Ninety-four children with atopic dermatitis were followed up to 7 years of age by Gustafsson et al. (115). During the follow-up, the eczema improved in 82 of the 94 children, but 43% developed asthma and 45% AR.
- 4 A nested case-control study of adult-onset asthma was performed in a random sample from the general population ($n = 15\,813$), aged 21–51 years, in Sweden (116). Cases for the study included subjects reporting doctor-diagnosed asthma ($n = 235$) and controls ($n = 2044$) randomly selected from the whole population sample. The case-control sample was investigated with a comprehensive respiratory questionnaire. Adult-onset doctor-diagnosed asthma was associated with occurrence of noninfectious rhinitis before the onset of asthma (OR: 5.4). This population-based study indicates that chronic rhinitis is associated with increased risk for adult-onset asthma.
- 5 Another nested case-control study (117), conducted in Arizona, USA, evaluated 173 incident patients with doctor-confirmed asthma who were compared with 2177 subjects who reported no asthma or shortness of breath with wheezing. Potential risk factors, including the presence of rhinitis, were assessed before the onset of asthma (patients) or before the last completed survey (control subjects). Rhinitis was found to be a significant risk factor for asthma (crude OR: 4.13). After adjustment for years of follow-up, age, sex, atopic status, smoking status and presence of COPD, the magnitude of the association was reduced but still highly significant (adjusted OR: 3.21). After stratification, rhinitis increased the risk of development of asthma by about three times both among atopic and nonatopic patients and by more than five times among patients in the highest IgE tertile. Patients with rhinitis with persistent and severe nasal symptoms and a personal history of doctor-confirmed sinusitis had an additional increased risk of asthma development.
- 6 To assess the risk factors for onset and remission of AR and asthma in Swedish adults (118), a random sample of 1370 subjects, aged 20–44 years was investigated by means of postal questionnaires in 1990 and 1993. Skin prick tests were conducted in 1991–1992. The association between risk factors and onset or remission of AR and asthma was estimated using multivariate logistic regression analysis. Onset of AR was associated with sensitization to birch (OR: 6.5), *Parietaria* (OR: 7.4) and pets (OR: 3.0). Onset of asthma was associated with AR (OR: 4.9), sensitization to pets (OR: 2.4) and with smoking (OR: 3.0). Onset of asthma was strongly associated with AR among atopics (OR: 5.7), but onset of asthma and rhinitis also tended to be related among nonatopics (OR: 3.5).
- 7 To evaluate the association of rhinitis and atopic eczema with asthma severity among asthmatic schoolchildren, the ISAAC Questionnaire was applied to parents of 6- to 7-year-old ($n = 3033$), and to 13- to 14-year-old ($n = 3487$) schoolchildren living in Sao Paulo, Brazil (119). Prevalence of severe asthma was higher among children and adolescents with asthma, rhinitis and eczema combined. In patients with asthma, the presence of rhinitis or eczema, each taken independently, was a risk factor for severe asthma, and the presence of concomitant rhinitis and eczema was associated with a higher risk.
- 8 A birth cohort study of 494 Brazilian children (120) born in 1993 and followed up to the age of 6 years in Pelotas has also demonstrated rhinitis is a risk factor for asthma. A standardized and validated asthma questionnaire, based on the ISAAC, was applied. The prevalence of asthma found in this study was 12.8% (95% CI: 10–15.9%). In the multivariate analysis, risk factors such as nonwhite skin colour were found to be associated with a relative risk (RR) of 1.9 (95% CI: 1.1–3.3%), family history of asthma (RR: 2.8; 95% CI: 1.5–5.1), AR (RR: 2.6; 95% CI: 1.5–4.4) and maternal smoking during pregnancy (RR: 1.7; 95% CI: 1–2.9).
- 9 In Denmark (121), a study of the clinical outcome of asymptomatic hyper-responsiveness (BHR) to histamine or exercise-induced bronchospasm has looked at data from a 12-year follow-up study of a random population sample of individuals aged 7–17 years at enrolment. Only individuals without asthma at enrolment were included in the analysis. Among the 281 nonasthmatic participants studied, 58 (22%) had BHR to histamine, 33 (12%) had exercise-induced bronchospasm (EIB) and 82 (29%) had BHR to histamine and/or EIB. At follow-up, 37.9% of individuals with BHR to histamine and 30% of individuals with EIB had developed current asthma, compared with only 5% of individuals in whom these test results were negative. In patients with BHR to histamine, parental asthma (OR: 12.6; 95% CI: 1.5–108.5), furred pet ownership (OR: 6.0; 95% CI: 1.2–19.6), and dermatitis and/or rhinitis in childhood (OR: 2.2; 95% CI: 1.1–5.1) predicted the subsequent development of asthma.
- 10 In Arizona (122), USA, in a large longitudinal cohort, a study was performed to determine whether rhinitis is significantly associated with recurrent

cough alone, wheezing alone or the combination of both symptoms during childhood. Determinants of recurrent cough, with or without wheezing, were investigated using longitudinal data from the Tucson Children's Respiratory Study. Among the 1246 subjects originally enrolled, 1024 children completed at least one questionnaire between the ages of 6 and 18 years and were included in the present study. After adjusting for sex, skin test reactivity and parental asthma, both rhinitis (OR: 2.47; CI: 1.84–3.30) and sinusitis (OR: 1.54; CI: 1.11–2.14) were associated with an increased risk of recurrent cough plus wheezing.

- 11 Another study to evaluate the interrelationship between rhinitis and cough has used data from the 'Pisa Prospective Study', a population-based longitudinal cohort study composed of a baseline and a follow-up survey taken approximately 5 years apart from each other in Pisa (123). Information on cough, rhinitis and other risk factors was collected by a standardized questionnaire. Complete information was available for 1670 subjects who were ≥ 15 years old and had no positive history of cough apart from colds at the baseline survey. Among them, 299 (18%) had rhinitis at baseline. By the follow-up survey, 16% of the subjects with rhinitis had developed any cough apart from colds, when compared with only 10% of the subjects without rhinitis (OR: 1.7, 95% CI: 1.2–2.5). After adjustment for age, gender, asthma status, smoking and occupational exposure, rhinitis remained significantly associated with an increased risk of cough.
- 12 Again in Italy (124), a 7-year follow-up of a homogeneous population of nonasthmatic children with AR has been performed to study and its role in asthma development. Twenty-eight children (6–15 years) with AR were studied. None of the children with negative methacholine test developed bronchial asthma after 7 years. Of the 13 hyper-reactive to methacholine only two reported asthma symptoms after 7 years.
- 13 A secondary analysis of a previous prospective study identified 568 pregnant women whose patient-reported asthma course during pregnancy was compared with the women's usual disease course (125). Improvement of asthma during pregnancy was noted in 33.6%, worsening was reported in 36.3%, no

change was reported in 26.4% and the course was uncertain in 3.7%. There was a significant concordance between asthma course and course of rhinitis during pregnancy. Rhinitis improved in 51.1% of patients whose asthma improved during pregnancy and worsened in 19.8% of these women. Rhinitis worsened in 55.9% of patients whose asthma worsened during pregnancy and improved in 2.1% of these women. The authors speculate the relationship of gestational asthma course to rhinitis symptoms may have clinical and mechanistic significance.

Table 2 summarizes the reports on this topic. Previous observations of increased risk of asthma among subjects suffering from rhinitis have been confirmed in many studies in different countries from three continents. Furthermore, new evidence supports the concept that the risk is not restricted to individuals with AR. The increased risk of asthma has been observed in suffers from non-AR likewise.

Rhinitis has an impact on asthma severity

This is a recent concept, neither investigated in detail previously, nor emphasized in previous ARIA Reports.

- 1 To determine the incremental effect of AR on healthcare resource use in adults with asthma, a retrospective cohort study using data from an UK general practice enrolled subjects 16–55 years of age, with asthma-related GP visits during a 12-month follow-up period (126). Concomitant AR was documented in 4611 (16.9%) of the total sample of 27 303 adults with asthma. Compared to those with asthma alone, patients with concomitant AR experienced more GP visits (5.2 vs 4.2; $P < 0.0001$) and more of them were hospitalized for asthma (0.76% vs 0.45%; $P < 0.01$) during the 12-month follow-up period. In multivariable regression analyses, AR was predictive of hospitalization for asthma (OR: 1.52, 95% CI: 1.03–2.24) and was associated with an increase in the annual number of asthma-related GP visits and annual asthma-related drug costs.
- 2 A similar study was performed to determine the incremental effect of AR on healthcare resource use in children with asthma (127). A population-based historical cohort study in a general practice database

Table 2. Rhinitis as a risk factor for asthma

Authors	Location	Number of subjects	Study design	Estimated risk	Comments
Leynaert et al. (113)	Europe (ECRHS)	90 478 adults	Cross-sectional	6.63 (OR)	Nothing remarkable
Toren et al. (116)	Sweden	15 813 adults	Nested case-control	5.4 (OR)	Nothing remarkable
Guerra et al. (117)	USA	2350	Nested case-control	3.21 (OR)	Atopic and nonatopic
Plaschke et al. (118)	Sweden	1370 adults	Cross-sectional	4.09 (OR) for allergic rhinitis	3.5 (OR) for nonallergic rhinitis
Chatkin and Menezes (120)	Brazil	494 children	Birth cohort	2.8 (RR)	Nothing remarkable

OR, odds ratio; RR, relative risk.

in the United Kingdom during 1998–2001, looking at children 6–15 years old with asthma. Of 9522 children with asthma, 1879 (19.7%) had AR recorded in the general practice (GP) medical records. Compared with children with asthma alone, children with co-morbid AR experienced more GP visits (4.4 vs 3.4) and more of them were hospitalized for asthma (1.4% vs 0.5%) during the 12-month follow-up period. In multivariable regression analyses, co-morbid AR was an independent predictor of hospitalization for asthma (OR: 2.34; 95% CI: 1.41–3.91) and was associated with increases in the number of asthma-related GP visits and asthma drug costs. The association between AR and higher costs of prescriptions for asthma drugs was independent of asthma severity, measured indirectly by the intensity of use of asthma drugs.

- 3 An assessment of asthma-related medical resource use in asthmatic patients according to coexistence of AR in a clinical trial to evaluate the addition of montelukast or salmeterol to baseline treatment with inhaled fluticasone (128). A *post hoc* analysis of a 52-week, double-blind multicentre clinical trial including 1490 adults with chronic asthma, aged 15–72 years was undertaken. A self-reported history of concomitant AR was identified in 60% of the patients ($n = 893$). Multivariate analysis adjusting for treatment group, age and baseline asthma severity indicates the presence of concomitant AR in patients with asthma increases the likelihood of emergency room visits (OR: 2.35, 95% CI: 1.12–4.80) and asthma attacks (OR: 1.35, 95% CI: 1.03–1.77). Patients with asthma alone compared with patients with both conditions did not differ in terms of unscheduled or specialist visits and hospitalizations.
- 4 Aiming to assess the effect of concomitant AR on asthma-related hospital resource utilization among children below 15 years of age with asthma in Norway (129), a population-based retrospective cohort study of children (aged 0–14 years) with asthma was conducted using data from a patient-specific public national database of hospital admissions during a 2-year period, 1998–1999. Among 2961 asthmatic children under 15 years of age with at least one asthma-related hospital admission over a 2-year period, 795 (26.8%) had a recorded history of AR. Asthmatic children with AR had a 1.72 times greater hazard of asthma-related readmissions than asthmatic children without AR. Multivariate analysis revealed that history of concomitant AR was also a significant predictor of increased number of hospital days per year.
- 5 In Canada (130), to investigate the severity of asthma among patients with and without nasal symptoms, atopic and nonatopic asthmatic patients were identified from the records of a university-based asthma clinic. A total of 178 patients were classified as having atopic asthma and 218 as having nonatopic asthma.

The atopic asthmatic patients with nasal symptoms had a higher mean FEV₁, a higher FVC, and a higher FEV₁/FVC ratio, used fewer oral steroids, and had fewer hospitalizations. The nonatopic asthmatic patients with nasal symptoms used more inhaled steroids (and they were also more likely to have nasal polyps on examination).

- 6 An interesting recent letter (131) has reported that nasal response to natural cat allergen exposure is significantly greater in patients with rhinitis and asthma than in patients with rhinitis alone, suggesting the existence of two-way phenomena in this matter and further supporting the ‘united airways’ concept.

Most reports have demonstrated an association between the presence of rhinitis and asthma severity or health resources consumption because of asthma. These observations are in accordance with the hypothesis that both asthma and rhinitis are manifestations of the same disease that affects the entire airways. In such circumstances, uncontrolled rhinitis could contribute to poor asthma control, or else, uncontrolled rhinitis could be a sign of the severity of the airway disease affecting also the lower airways.

Asthma and rhinitis – costs

Previous ARIA reports have stated both asthma and rhinitis represent a significant burden to the healthcare system, to families and to society, and rhinitis increases the cost of asthma.

- 1 Schramm and colleagues (132) evaluated the cost of illness of moderate-to-severe atopic asthma and/or SAR in Germany from the perspective of third-party payers and patients, in a cross-sectional study of 500 patients. Information was collected using a specific patient questionnaire and the abstraction of patient records. Overall, annual costs per patient increased with the severity of atopic asthma and if it was associated with AR. The average annual cost of SAR was €1089 per child/adolescent and €1543 per adult. Annual costs of severe asthma plus SAR increased to €7928 per child/adolescent and to €9287 per adult. For third party payers, the main cost drivers were medication, hospitalization and rehabilitation. The most significant costs for patients were household modifications. For children/adolescents, 60–78% of the expenditures were direct costs, while in adults, 58% of expenditures were indirect costs.
- 2 In the USA (133), a retrospective cost of illness study of AR on asthma medical care resource utilization has been undertaken, by comparing patients with asthma plus AR to patients with asthma alone. Patients with one or more claims for asthma ($n = 27\,398$) were identified from a database from a U.S. health insurance plan. A subset of 9226 patients

who had at least one visit for AR was included in the analysis. The presence of AR was associated with greater frequencies and costs of prescriptions for all asthma-related medications. Allergic rhinitis in patients with asthma nearly doubles annual medical resource utilization and costs and is associated with increased consumption of asthma-related medications. This study reinforces previous observations already registered in ARIA basic documents.

The costs of rhinitis and asthma are cumulative and the proportion of direct and indirect costs may vary depending on the age of subjects.

Genetic studies

Asthma and rhinitis have been associated with common genetic determinants of atopy. However, no genetic characterization of individuals that would have rhinitis without asthma, when compared to those with concomitant rhinitis and asthma has been established. Research work has begun to explore this matter.

- 1 An investigation performed in Poland (134) looked at HLA-DR genotyping with the sequence-specific primers method in 82 patients with symptoms of SAR and/or bronchial asthma and 52 healthy nonatopic control subjects. A significant association was found between HLA-DRB1*02, B5* haplotype and asthma phenotype in patients with grass-pollen allergy when compared to patients with rhinitis only.
- 2 Palmer et al. (135) have investigated the genetic and environmental components of variance in FEV₁ and FVC measured in adulthood in an Australian population-based sample of 468 Caucasian nuclear families. The interrelationships of the genetic determinants of these traits with asthma and atopic rhinitis were also investigated. Serial cross-sectional studies were conducted in Western Australia between 1966 and 1981 and follow-up of previous attendees was undertaken in 1995. Data from each subject included in this study were from a single survey in adulthood (25–60 years of age) when the subject was as close to age 45 years as possible. Multivariate analysis suggested that FEV₁ and FVC levels were associated with age, sex, height, tobacco smoke exposure, asthma and atopic rhinitis. After adjustment for relevant covariates, FEV₁ levels had a narrow-sense heritability (h²N) of 38.9%. Forced vital capacity levels had an h²N of 40.6%. Extended modelling demonstrated little overlap in the genetic determinants of asthma or atopic rhinitis and either FEV₁ or FVC levels. The results of this study were consistent with the existence of important genetic determinants of adult lung function that are independent of asthma or other atopic disease, cigarette smoking, height, age or sex.
- 3 In a sample of 295 French families with at least one asthmatic subject (136), a genome screen was conducted to identify potential linkage regions specific either to AR or to asthma as well as those shared by the two diseases. Two binary rhinitis phenotypes based on (i) diagnosis (ARbin1) and (ii) symptoms (ARbin2) and a categorical ordered trait (ARcat) were considered. Asthma phenotype was based on answers to a standardized questionnaire plus the presence of BHR. Linkage analyses were conducted using the maximum likelihood binomial (MLB) method. These analyses provided potential evidence for linkage to three regions in the whole sample: 1p31 for the phenotype defined by ARbin2 plus asthma ($P = 0.00016$), 2q32 for ARbin2 ($P = 0.00016$) and 3p24-p14 for ARcat ($P = 0.001$). Two other regions were detected in the subset of 185 families with at most one asthmatic sib: 9p22 and 9q22-q34 for ARbin1 ($P = 0.001$ and 0.0007 , respectively). No region showed evidence for linkage to asthma without being also linked to AR. While 1p31 may contain a genetic determinant common to asthma and AR, 2q32, 3p24-p14, 9p22 and 9q22-q34 are more likely to harbour genetic factors specific to AR.
- 4 To investigate the genetic characteristics of atopic basis of asthma, and the sensitization to mite (*D. pteronyssinus*) allergens as a pathophysiologically important intermediate phenotype, a genome-wide scan was performed based on a multiethnic European population consisting of 82 nuclear families with at least two affected siblings (137). Three novel regions appeared to be significant: the region 2p12 and the region 16q21. The most significant result was found for the region 3q21.3 with the same microsatellite marker, which showed significant linkage to atopic dermatitis in another study. The authors conclude these findings indicate that atopy, allergic asthma, AR and eczema, on one hand, are distinct traits on both the clinical and genetic basis, but on the other hand, the results also underline that these traits are closely related diseases concerning the atopic basis of the traits.

A few studies have indicated the existence of genetic determinants of predisposition for rhinitis without asthma or rhinitis with concomitant asthma. Further investigation is required to fully understand this complex matter.

Common aspects in pathogenesis

ARIA publications have stated:

- 1 asthma and rhinitis are common co-morbidities, suggesting the concept of 'one airway, one disease';
- 2 many patients with AR have nonspecific BHR;
- 3 pathophysiological studies suggest a strong relationship between rhinitis and asthma. However, only a

few studies have compared nasal and bronchial biopsies in the same subjects. In these studies the following features were demonstrated: there was a variable degree of inflammation between the nose and bronchi; airway remodelling was present in most asthmatics, but it was not obvious in rhinitis; epithelial shedding was more pronounced in the bronchi than in the nose and

- 4 there is a need for further studies to investigate common and differential pathophysiological mechanisms.

Biopsy and nasal lavage studies

- 1 Aiming to compare airway inflammation and remodelling in nasal and bronchial mucosa of subjects with AR with or without asthma, Braunstahl et al. (138) have examined four experimental groups: allergic asthma and rhinitis; AR, no asthma; atopic subjects, with no asthma, no rhinitis and nonallergic healthy control subjects. In nasal and bronchial mucosa, numbers of eosinophils were significantly higher in rhinitis patients with and without asthma than in asymptomatic atopics and controls. In bronchial mucosa, the reticular basement membrane (RBM) was significantly thickened in rhinitis patients with and without asthma compared to asymptomatic atopics and controls, while in nasal mucosa no differences were seen. This study shows that allergic inflammation, increased basement membrane thickness and epithelial desquamation are present in the lower airways of atopic subjects, even before the onset of clinical symptoms. Despite the presence of inflammatory cells, no structural changes could be assessed in nasal mucosa of allergic patients.
- 2 Braunstahl et al. (139) have also looked at the pathophysiological connections between the nose and lungs and reported a comparison on allergic inflammation and clinical findings in the upper and lower airways after segmental bronchial provocation in nonasthmatic AR patients. Eight nonasthmatic, grass pollen-sensitive patients with AR and eight healthy controls were studied. Bronchial biopsies and blood samples were taken before (T_0) and 24 h (T_{24}) after segmental bronchial provocation. Nasal biopsies were obtained at T_0 , 1 h after provocation (T_1) and T_{24} . Immunohistochemical staining was performed for eosinophils, interleukin (IL)-5 and eotaxin. The number of eosinophils increased in the challenged and unchallenged bronchial mucosa and in the blood of atopic subjects at T_{24} . An increase of eosinophils and eotaxin-positive cells in the nasal lamina propria and enhanced expression of IL-5 in the nasal epithelium of atopic subjects was observed only at T_{24} . Segmental bronchial provocation induced nasal and bronchial symptoms as well as reductions in pulmonary and nasal function in the allergic group. No significant changes could be observed in healthy controls. In summary, the study shows that segmental bronchial provocation, in nonasthmatic AR patients, results in peripheral blood eosinophilia, and can induce allergic inflammation in the nose.
- 3 Gaga et al. (140) have examined whether inflammatory cellular infiltration exists in the nasal mucosa of asthmatics even in the absence of symptoms and signs of rhinitis, by performing nasal mucosa biopsies in 27 nonatopic subjects comprising nine asthmatic rhinitis patients, eight asthmatic nonrhinitis patients and 10 healthy control subjects. Bronchial mucosa biopsies were also taken simultaneously from some of the patients ($n = 10$) to determine whether there was an association between cellular infiltration in the nose and the lungs. Eosinophil counts were higher in both asthma groups compared with control nasal biopsies (median values for asthmatics with symptoms of rhinitis = 8.3, and for asthmatics without symptoms of rhinitis = 9.2, whereas normal controls had 2.1 eosinophils per field). Furthermore, there was a significant correlation between eosinophil counts in the nose and the airways ($r = 0.851$). The authors conclude that eosinophil infiltration was present in the nasal mucosa of asthmatic patients even in the absence of symptoms of rhinitis.
- 4 Milanese et al. (141) have reported a study on the association between bronchial RBM thickness and airway responses to inhaled methacholine in perennial allergic asthma, perennial AR, SAR and COPD. Reticular basement membrane was significantly thicker in asthma ($10.1 \pm 3.7 \mu\text{m}$) and perennial rhinitis ($11.2 \pm 4.2 \mu\text{m}$) than in seasonal rhinitis ($4.7 \pm 0.7 \mu\text{m}$) and COPD ($5.2 \pm 0.7 \mu\text{m}$). The authors concluded that RBM thickening is not unique to bronchial asthma, it may also happen in subjects with perennial AR.
- 5 Crimi et al. (142) examined nine subjects with mild asthma and eight with rhinitis alone who underwent methacholine and allergen inhalation challenges, preceded and followed by bronchoalveolar lavage and bronchial biopsy. The authors have concluded that rhinitic subjects may develop similar airway inflammation and remodelling as the asthmatic subjects.
- 6 To test the hypothesis that histopathological features of asthma are also present in sino-nasal specimens from patients with chronic rhinosinusitis, Ponikau et al. (143) examined histological specimens from 22 randomly selected patients with refractory chronic rhinosinusitis undergoing endoscopic sinus surgery and four healthy control subjects. Specimens from all patients with chronic rhinosinusitis (22 of 22) revealed epithelial damage (shedding) and basement membrane thickening. Strikingly heterogeneous eosinophilic inflammation, which did not differ

between allergic and nonallergic patients, was detected in all patients with chronic rhinosinusitis and was absent in all healthy control subjects. Although the methodology utilized in this study has limitations, such as a limited number of controls that may have resulted in bias, the results suggest that histopathological findings of asthma, heterogeneous eosinophilic inflammation and features of airway remodelling, might also be present in chronic rhinosinusitis.

- 7 A comparison between the airway inflammatory response to antigen in patients with atopic asthma and AR has also been reported (144). Segmental bronchoprovocation with saline or ragweed antigen was performed in nine patients with atopic asthma and nine patients with AR without asthma. Antigen challenge led to similar patterns of cellular recruitment, mediator levels and bronchoalveolar lavage cell cytokine generation in both groups; however, the dose of antigen required to promote comparable responses in the airway was significantly less in patients with asthma, which suggests that the pattern of acute airway inflammation in response to allergen does not by itself explain antigen-induced lower airway obstruction and asthma symptoms. The authors speculate that other factors, such as increased airway sensitivity to allergen or pre-existing airway injury and remodelling, might explain why patients with asthma and rhinitis differ in their clinical and physiological response to antigen exposure.
- 8 Boulay and Boulet (145) have examined lower airway inflammatory changes following repeated inhalation of very low doses of allergen in nonasthmatic subjects with AR compared with mild allergic asthmatic subjects. The conclusion of the study is that very low doses of allergen can increase the percentage of eosinophils in induced sputum of nonasthmatic subjects with AR without associated respiratory symptoms or physiological modifications.
- 9 Riccio et al. (146) have evaluated the cytokine levels in nasal lavage fluids of asthmatic children suffering of chronic rhino-sinusitis, to compare the allergic vs nonallergic subjects. Thirty-five asthmatic children were evaluated, with an average age of 8.7 years. Twenty were allergic and 15 were nonallergic. Ten healthy children were studied as normal controls. Allergic subjects showed a significant increase of IL-4 and tumour necrosis factor (TNF)- α and a significant decrease of IL-12 and of interferon (IFN)- γ , whereas IL-1 β , IL-6 and IL-8 were not significantly increased. Nonallergic children showed a significant increase of IL-4 and a significant decrease of IFN- γ , IL-12 was not significantly decreased, and IL-1 β , IL-6 and IL-8 were not significantly increased. A significant inflammatory nasal cytological pattern was present in all asthmatic children. Significant correlations were demonstrated between IL-4 and IL-12, IL-12 and IFN- γ , IL-8 and neutrophils and TNF- α and monocytes/macrophages, in allergic asthmatics. Interleukin-4 and IL-12 were significantly correlated as well as IL-8 and neutrophils in nonallergic asthmatics. The authors conclude that allergic asthmatic children with chronic rhino-sinusitis have a typical Th2 cytokine pattern, but also nonallergic asthmatic children share a similar pattern. These findings would suggest the existence of a common pathophysiological mechanism shared by upper and lower airways and are consistent with the concept of united airways disease.
- 10 A study by Palczynski et al. (147) aimed to evaluate the changes in the nasal cytogram, and nasal lavage recovered fluids protein content, eosinophil cationic protein and mast-cell tryptase concentrations after glutaraldehyde inhalation challenge in patients with a history of glutaraldehyde-induced asthma. There was a significant increase in eosinophil number and percentage, albumin, eosinophil cationic protein and tryptase concentrations in nasal lavage recovered fluids from patients with occupational asthma and rhinitis when compared to controls. The results indicate the immunological mechanism of glutaraldehyde induced asthma as assessed by the nasal recovered fluids.
- 11 Aiming to characterize lower airway inflammation in nonasthmatic subjects with SAR, Chair et al. (148) studied bronchial biopsies from subjects with rhinitis who had no past or current history of asthma. The results showed that natural pollen exposure was associated with an increase in lymphocyte numbers, eosinophil recruitment and IL-5 expression in the bronchial mucosa of nonasthmatic subjects with AR.
- 12 Aiming to map the inflammatory process in fatal asthma (149), from the upper airways to the lung parenchyma, eosinophil, neutrophils, mast cell and lymphocyte content were determined in nasal mucosa, the trachea, intrapulmonary airways and parenchyma (per bronchiolar and distal) of 20 patients with fatal asthma and 10 controls. Eosinophil content was higher in all studied areas in fatal asthma compared with controls. Mast-cell content was higher in the outer area of larger airways, small membranous bronchioles and in per bronchiolar parenchyma of fatal compared with controls. There was a positive correlation between CD4 + cell content in nasal mucosa and larger airways in asthmatics.
- 13 A study of induced sputum and acetylcholine and capsaicin challenges were assessed in four groups of adult subjects: AR, AR with lower airway symptoms, mild stable asthma and healthy volunteers to correlate lower airway inflammatory markers with bronchial and cough reactivity. Patients with AR ($n = 13$) and AR with lower airway symptoms ($n = 11$) did not take any anti-inflammatory drugs. Those with asthma ($n = 9$) used inhaled glucocorticosteroids

and healthy volunteers ($n = 10$) were respiratory symptoms free. The patients underwent capsaicin cough challenge and sputum induction with hypertonic saline during the first visit, and acetylcholine bronchial challenge on a separate day. The percentage of eosinophils in induced sputum was significantly higher in patients with AR, AR with lower airway symptoms, and asthma than in healthy volunteers. In contrast, acetylcholine PD(20) in patients with AR, AR with lower airway symptoms and asthma was significantly lower than in healthy volunteers, leading to the conclusion that eosinophilic inflammation of lower airways and increased bronchial reactivity were present in adult patients with AR.

- 14 An assessment of nasal symptoms and flow, cytology, cytokines, pulmonary function and methacholine positivity in a large number of patients with pure pollinosis has been undertaken in Italy (150). Young men presenting at a military hospital for routine follow-up were recruited for the study. They had to suffer from rhinitis alone (without asthma) for at least 2 years and had to have a positive SPT to pollens only. During the pollen season, they underwent symptom evaluation, measurement of nasal flow, nasal scraping and lavage (cell count and assay for IL-4, IL-5, IL-8 and IFN- γ), pulmonary function tests and methacholine challenge. Fifty subjects (23.7 ± 4.9 years old) were enrolled. All patients had high clinical scores and inflammatory cells with a low nasal flow. The number of eosinophils in nasal scrapings highly correlated with all the above-mentioned parameters, including nasal flow, cytokines and spirometric values. A significant positive correlation was found between all inflammatory cells and all cytokines. Methacholine test positivity significantly correlated with the number of eosinophils in the nasal smear.

Nasal and bronchial inflammation in asthma and rhinitis share many common aspects. Remodelling, defined as 'model again or differently, reconstruct', is present in the airways of almost all asthmatic patients. The pathological extent of nasal remodelling in patients with rhinitis seems to be far less extensive than that of the lower airways, although remodelling has been demonstrated in the paranasal sinuses (151, 152). In AR, epithelial damage is only minimal, and the RBM does not appear to be thickened. Moreover, fibrogenic growth factors have been shown in the nasal mucosa of patients with AR, but have not been linked to extracellular matrix changes yet (153). The reasons why remodelling appears to be less extensive in the nasal mucosa than in the bronchial mucosa are still unclear, but two hypotheses can be put forward. On one hand, the cytokine production of smooth muscle cells that are poorly represented in the nose might partly explain differences in remodelling of the two sites of the airways.

On the other hand, the genes of the embryologic differentiation might persist in the nose and bronchi or might be re-expressed in asthma and rhinitis. Because the nose is of ectodermal origin and the bronchi of endodermal origin, these genes might also govern remodelling patterns. More studies are urgently required to better characterize nasal remodelling in patients with rhinitis. A better understanding of nasal and bronchial remodelling might help to identify new pathways and new therapeutic strategies to reduce long-term remodelling in asthma (1, 154, 155).

Indirect methods to assess inflammation

- 1 An evaluation of exhaled nitric oxide (eNO) and SPT were conducted among 53 asthmatic children without corticosteroid treatment and 96 nonasthmatics, in France (156). Atopic asthmatic children had higher eNO than nonatopic asthmatic children with a significant increase when one SPT or more were positive. Similarly, nonasthmatic, atopic subjects had higher eNO than nonatopic subjects with a significant increase when two SPTs or more are positive. In the case of equal levels of positive SPTs, asthmatic children always had higher eNO than nonasthmatic ones. Furthermore, among nonasthmatic children, the eNO level increased only in atopics who had rhinitis.
- 2 A cross-sectional study of the respiratory health of bleachers conducted in 246 nonsmoking bleachery and paper-mill workers (157), who answered a questionnaire and were examined by measurements of exhaled and nasal nitric oxide (nNO) and spirometry, outside the pollen season. Blood samples were collected and analysed for specific IgE against common aeroallergens (birch, timothy, cat and house dust mite). The atopic and the nonatopic subjects without asthma or rhinitis had similar levels of eNO. Subjects reporting asthma or rhinitis who were also sensitized to perennial allergens had higher levels of eNO, whereas those sensitized to only seasonal allergens had similar eNO levels as nonatopic subjects with asthma or rhinitis. In multiple linear regression models adjusted for nNO, eNO was associated with asthma and sensitization to perennial allergens. The results indicate that only atopic subjects who have recently been exposed to the relevant allergen have elevated levels of eNO. Atopic subjects who are not being exposed to a relevant allergen or have never experienced symptoms of asthma or rhinitis show normal eNO. These observations suggest varying inflammation in the respiratory tract of atopics related to asthma and rhinitis, which is dependant on exposure to allergen.
- 3 Aiming to investigate the relationship between eNO, total serum IgE and allergic sensitization in childhood asthma and AR, eNO levels, lung function,

SPTs and total serum IgE were determined in 109 children (mean age, 10.4 years) with mild intermittent asthma and in 41 children (mean age, 10.1 years) with AR; 25 healthy nonatopic children were recruited as controls. Exhaled nitric oxide levels (median) were significantly higher in patients with asthma (22.7 p.p.b.) and in those with AR (15.3 p.p.b.) than in healthy controls (5.9 p.p.b.). Children with allergic asthma had higher eNO levels than children with AR. A significant positive correlation was found between eNO and total serum IgE (asthma, $r = 0.42$, $P > 0.0001$; AR, $r = 0.31$, $P > 0.01$), and between eNO and the number of positive SPTs (asthma, $r = 0.31$, $P < 0.0001$; AR, $r = 0.39$, $P < 0.01$). This correlation was independent of allergic sensitization. High total serum IgE represents a specific and predictive marker of eNO increase in children with asthma or AR. This finding adds further support to the hypothesis that increased serum IgE could be itself a marker of airway inflammation in patients with allergic disease.

- 4 In a study to examine the clinical features of asthmatic patients with increased excretion levels of urinary LTE₄ (hyperleukotrienuria), Higashi et al. (158) have measured the U-LTE₄ concentrations in 137 asthmatic patients (including 64 patients with aspirin-induced asthma) who were in clinically stable condition. The basal concentration of urinary LTE₄ was significantly higher in the patients with aspirin-induced asthma than in those with aspirin-tolerant asthma. In patients with aspirin-tolerant asthma, hyperleukotrienuria was associated with severe asthma and chronic hyperplastic rhino-sinusitis with nasal polyposis.
- 5 Bavbek et al. (159) have determined the differences in airflow rates, bronchial and nasal resistance between nonasthmatic rhinitis patients with or without BHR to methacholine. A total of 66 patients with AR but not asthma were selected for the study and divided into two groups; 40 patients with AR and negative methacholine provocation test and 26 patients with AR and positive methacholine provocation test. Pulmonary function tests, methacholine tests, anterior rhino-manometry and SPTs were performed on the patients. Expiratory airflow parameters including FVC, FEV₁, peak expiratory flow (PEF) and forced expiratory flow at 25% of vital capacity (FEF25) were similar in both groups; however, FEV₁/FVC, forced expiratory flow between 25% and 75% (FEF25–75), forced expiratory flow at 50% of vital capacity (FEF50) and forced expiratory flow at 75% of vital capacity (FEF75) were significantly lower in subjects with BHR. Additionally, lower airway resistance was significantly greater in patients with BHR and negatively correlated with the expiratory airflow parameters for small airways. There was no correlation between nasal resistance and BHR to methacholine or lower airway resistance. This study

suggests that nonasthmatic rhinitis patients with BHR may have mild but significant changes in the small airways.

- 6 Nickel and co-workers (160) have tested whether BHR is present in children with history of AR, by performing pulmonary function tests and histamine challenges in a total of 654 children in Germany, who were compared to children with asthma, AR, asymptomatic allergic sensitization and nonatopic controls. Most pronounced BHR to histamine was observed in allergic asthmatics, irrespective of the presence or absence of AR. PC₂₀ values in nonasthmatic children with AR ($n = 24$) were not significantly different from those seen in asymptomatic atopic ($n = 54$) or nonatopic controls ($n = 92$). The authors conclude that in contrast to adult study populations, 7-year-old nonasthmatic children with AR do not have a higher degree of responsiveness than asymptomatic atopic or nonatopic controls.
- 7 A relationship between nonspecific nasal and bronchial responsiveness exists in perennial AR patients with asthma in 51 perennial AR patients with the definitive or suspected asthma who underwent methacholine bronchial provocation tests and nasal histamine challenge tests (161). The association between nasal and bronchial responsiveness observed supports the hypothesis that nonspecific nasal responsiveness may be related to the nonspecific bronchial responsiveness in patients with AR and asthma. This is in accordance with the viewpoint that AR and asthma represent a continuum of inflammation involving one common airway.
- 8 To investigate the type and intensity of nasal symptoms, nasal and bronchial airflow, and BHR during the pollen season, 121 polysensitized rhinitic patients with no asthma were studied (162). Sixty-five (53.7%) patients had impaired FEF25–75 values. Total nasal symptoms correlated with nasal airflow and BHR. Nasal airflow correlated with FEF25–75 values and BHR. FEF25–75 values correlated with FEV₁ levels, BHR degree and nasal obstruction symptom. Severe BHR correlated with FEV₁ and FEF25–75 values, nasal airflow and nasal symptoms. This study evidences that early bronchial impairment is frequently detectable in patients with persistent AR and BHR.
- 9 To evaluate the relationship between the levels of nNO and eNO with bronchial responses to exercise in patients with rhinitis and asthma, 24 subjects with asthma and rhinitis underwent an exercise test (163). The exercise test was positive in 17 cases. The baseline value of nNO was 1185 ± 439 p.p.b., and the value at 15 and 50 min was 1165 ± 413 and 1020 ± 368 p.p.b., the latter value being significantly lower than the baseline. The baseline value of eNO was 21 ± 19 p.p.b., with no significant differences at 15 and 50 min. There was no significant correlation

between either the decrease in FEV₁ and the nasal response, or the baseline eNO and nNO values. The authors comment that the nasal and bronchial response to exercise are completely different in rhinitis and asthma and that there is no relationship between the values of nasal or eNO and the nasal and bronchial response after exercise.

- 10 To compare cytological and biochemical changes in nasal lavage fluid induced by wheat flour inhalatory challenge in bakers with AR and with asthma accompanied by rhinitis (164), a single-blind, placebo-controlled study was conducted in bakers with AR ($n = 17$), bronchial asthma and rhinitis ($n = 24$) and without occupational allergy ($n = 23$). A significant decrease in PC₂₀ after the challenge test was observed only in patients with asthma and rhinitis. Eosinophil count and percentage, basophil count and the permeability index induced by specific provocation were significantly increased in both rhinitis patients and asthmatics.

Systemic inflammation in rhinitis and asthma

Previous ARIA documents have stated that in AR there are systemic repercussions of the local inflammation, involving upregulation of IgE production, immunological and bone marrow changes (2).

- 1 Saini and co-workers (165) have investigated the effects of local intranasal allergen challenge on circulating basophils regarding levels of FcεpsilonRIβ protein and for FcεpsilonRIβ mRNA expression, and also for spontaneous secretion of IL-4 and IL-13. Intranasal allergen challenge transiently activates circulating basophils by increasing expression of the FcεpsilonRIβ subunit and spontaneous IL-13 secretion. Because FcεpsilonRIβ is an amplifier of FcεpsilonRI-mediated responses and IL-13 is proinflammatory, these findings support a primed basophil functional state and demonstrate a systemic effect of local allergen challenge that could contribute to exacerbating allergic reactions.
- 2 Wilson and co-workers (166) failed to demonstrate an effect of a single nasal allergen challenge on peripheral blood eosinophil/basophil (Eo/B) progenitor cells and induced sputum eosinophil counts in subjects with AR. Sixteen adults entered a sequential nasal control and allergen challenge study, outside the pollen season. Blind assessment of peripheral blood Eo/B progenitor colony-forming units (CFU), induced sputum and nasal lavage cell counts was made before and 24 h after both challenges. When comparing the values 24 h after the control vs the allergen challenge, there were no significant differences in Eo/B progenitor CFU despite a significant increase in eosinophils in nasal lavage and significant worsening of nasal peak inspiratory flow and rhinitis symptoms.

- 3 Braunstahl et al. (138) compared airway inflammation and remodelling in nasal and bronchial mucosa of subjects with allergic in four experimental groups: allergic asthma and rhinitis ($n = 19$); AR, no asthma ($n = 18$); atopic subjects, no asthma, no rhinitis ($n = 8$) and nonallergic healthy control subjects ($n = 16$). Blood samples, nasal and bronchial biopsy specimens were collected during stable disease. Patients with asthma and rhinitis had increased numbers of blood eosinophils ($P = 0.05$) compared to patients with rhinitis only. No significant differences could be found between the investigated groups with respect to serum IL-5 and eotaxin levels.

Rhinosinusitis and asthma

- 1 To evaluate chronic rhinosinusitis in patients with severe steroid-dependent asthma, 35 patients with severe corticosteroid-dependent asthma were compared to 34 mild-to-moderate asthmatics by using a clinical score and coronal computerized tomography (CT) scanning (167). The proportion of patients with symptoms of rhino-sinusitis was similar in both groups of asthmatic subjects (74% in patients with severe steroid-dependent asthma and 70% in patients with mild-to-moderate asthma). All subjects with steroid-dependent asthma vs 88% of subjects with mild-to-moderate asthma had abnormal CT scan results. However, the clinical and CT scan severity scores were higher in the subjects with severe steroid-dependent asthma. In both groups the CT scan scores were correlated with the clinical scores.
- 2 To investigate the relationship between sino-nasal inflammation as assessed on CT scanning, lung function, sputum eosinophilia and eNO in exhaled air in patients with severe asthma (168), 89 nonsmoking outpatients with severe asthma were evaluated. Computerized tomographic scans were scored (0–30) by a blinded investigator using a validated method. Computerized tomographic scans showed abnormalities in 84% of patients. Extensive sinus disease (score 12–30) was found in 24% of patients. There was a significant positive correlation between CT scores and eosinophils in peripheral blood and induced sputum and level of eNO. Computerized tomographic scores were also positively related to functional residual capacity and inversely related to diffusion capacity, particularly in patients with adult-onset asthma. The results of this study showed a direct relationship between sino-nasal mucosa thickness and bronchial inflammation in severe asthma, particularly in patients with adult-onset disease. Whether sinus disease directly affects the intensity of bronchial inflammation is still an unanswered question.
- 3 A comparison of the sinus mucosal histopathologies of asthmatic patients with those of nonasthmatic

patients has been reported (169). Fifty-three rhinosinusitis patients with a diagnosis of asthma and 54 patients with rhinosinusitis but no asthma, who served as controls, were enrolled in the study. All of these patients underwent endoscopic sinus surgery. No statistically significant differences were found between the two groups in terms of the presence of allergy, the degree of preoperative polyposis or the extent of preoperative disease. Basement membrane thickening, goblet cell hyperplasia and eosinophil infiltration were more prominent in the asthmatic compared to the nonasthmatic group. These findings suggest that patients with both rhinosinusitis and asthma present the histopathological characteristic of a marked chronic inflammatory reaction, and that eosinophil infiltration may play a significant role in this inflammation of the sinus mucosa.

These studies have confirmed and reinforced previous ARIA statements regarding the concept of unity of the airway disease in asthma and rhinitis. It was also described that not only patients with AR have nonspecific BHR, but also have bronchial basal membrane thickening preceding symptoms of asthma. Conversely, nasal eosinophilic inflammation has been found in allergic asthmatics regardless of symptoms of rhinitis. Nasal allergen provocation induces bronchial inflammation as segmental allergen bronchial provocation results in nasal inflammation. Various other pathophysiological studies reinforce the idea of a strong interrelationship between rhinitis and asthma, which leads to the consolidation of the paradigm of pathophysiological identity of these two syndromes. These studies also show that there is a strong relation between chronic rhino-sinusitis and asthma and that a considerable percentage of patients with asthma have chronic rhino-sinusitis. However, the reason for some differences between nasal and bronchial inflammation and remodelling remain to be clarified. According to the categories of evidence proposed by Shekelle et al. (112):

Eosinophilic inflammation is present in nasal and bronchial mucosa of asthmatics	Category of evidence I
Remodelling is a major feature of bronchial biopsies but it is less extensive in nasal biopsies	Category of evidence II
Bronchial and nasal mucosa of asthmatic patients is similar	Category of evidence II
Endobronchial challenge in rhinitis patients induces inflammation	Category of evidence II
Bronchial challenge induces nasal inflammation	Category of evidence II
Nasal challenge induces bronchial inflammation	Category of evidence II
Allergic inflammation has a systemic component	Category of evidence II
Most asthmatics present sinusitis demonstrated by CT scans	Category of evidence II
Severe asthmatics have more severe rhinitis than mild patients	Category of evidence II

Treatment of rhinitis improves asthma?

Asthma and AR commonly occur together and the ARIA initiative has proposed that treatments for one condition may alleviate the coexisting condition. Medications for asthma and rhinitis can be administered via local intranasal, inhalatory, oral and parenteral routes.

Intranasal glucocorticosteroids

Randomized clinical trials (including meta-analyses)

- 1 To review the common pathophysiology of combined AR and asthma and to investigate the efficacy of intranasal glucocorticosteroids. A Cochrane systematic review was performed to assess the efficacy of intranasal glucocorticosteroids in subjects with concomitant AR and asthma (170). The efficacy of intranasal glucocorticosteroids on asthma outcomes was assessed in 12 randomized-controlled trials involving 425 subjects. After intranasal glucocorticosteroids there were nonsignificant trends for improvement in asthma symptom score [standardized mean difference (SMD) of 0.61; $P = 0.07$], FEV₁ (SMD of 0.31; $P = 0.08$), and morning PEF (weighted mean difference of 36.51; $P = 0.06$). There was no impact on methacholine airways responsiveness (SMD of -0.20 ; $P = 0.4$). The authors recognized trends for a benefit of intranasal glucocorticosteroids in concomitant AR and asthma, but recognizes that more research is needed.
- 2 To investigate the effect of intranasal, inhaled corticosteroid or the combination of both in patients with both pollen-induced rhinitis and asthma (171), total of 262 patients were randomized to 6 weeks' treatment with intranasal fluticasone propionate (INFP) 200 µg o.d., inhaled fluticasone propionate (IHFP) 250 µg bid, their combination, or intranasal or inhaled placebo, in a multicentre, double-blind, parallel-group study. Treatment was started 2 weeks prior to the pollen season and patients recorded their nasal and bronchial symptoms twice daily. Intranasal fluticasone propionate significantly increased the percentages of patients reporting no nasal blockage, sneezing or rhinorrhoea during the pollen season, compared with IHFP or intranasal or inhaled placebo. In contrast, only IHFP significantly improved morning PEF, FEV₁ and methacholine PD₂₀, and the seasonal increase in the sputum eosinophils and BHR.
- 3 To investigate the effect of rhinitis therapy on asthma outcomes in adult and adolescent patients with both SAR and persistent asthma (172), a total of 863 patients were randomized to receive open-label fluticasone propionate/salmeterol (FSC), 100/50 µg bid for 4 weeks, plus either blinded fluticasone propionate aqueous nasal spray (FPANS) 200 µg/days,

montelukast 10 mg/days or placebo. Patients kept daily records of PEF, asthma and rhinitis symptoms and rescue albuterol use. fluticasone propionate aqueous nasal spray added to FSC resulted in superior outcomes for daytime total nasal symptom scores (D-TNSS) and individual daytime nasal-specific symptoms (congestion, rhinorrhoea, sneezing and itching) compared with montelukast plus FSC and placebo plus FSC ($P \leq 0.001$). Montelukast plus FSC was superior to placebo plus FSC only for D-TNSS and itching and sneezing. Morning PEF, asthma symptoms and rescue albuterol use improved significantly in all treatment groups, but improvements were comparable across the treatment groups. In conclusion, patients with persistent asthma treated with FSC, the addition of montelukast or FPANS for the treatment of SAR resulted in no additional improvements in overall asthma control compared with FSC alone.

- 4 Aiming to determine the effects of inhaled or topical nasal beclomethasone dipropionate (BDP) administered separately or in combination on the control of asthma and BHR in patients with the rhinitis/asthma association (173), a double-blind, parallel, three-group study was conducted. Seventy-four patients with mild-to-moderate asthma and AR (median age, 25 years) received nasal or inhaled BDP separately or in combination for 16 weeks after a 2-week placebo run-in period. Patients in all three groups demonstrated a progressive and significant decrease in nasal and pulmonary symptoms, which started after 4 weeks ($P \leq 0.05$) and continued through the end of treatment ($P \leq 0.001$). Clinical improvement was similar and parallel in the three groups. Asthma-related morbidity, evaluated by quantifying absence from work, emergency department visits and nighttime awakenings, also decreased in the three groups ($P \leq 0.05$). The authors comment that failure to consider treatment of rhinitis as essential to asthma management might impair clinical control of asthma and their observations suggest that asthma and rhinitis, in some patients, can be controlled by the exclusive use of nasal medication.
- 5 Aiming to assess the efficacy of nasally inhaled BDP in the simultaneous treatment of rhinitis and asthma (174), a randomized-controlled trial was conducted with 78 AR and asthma patients aged 5–17 years. During 8 weeks, 38 subjects received BDP-CFC aerosol (≥ 500 $\mu\text{g/day}$) exclusively via nasal inhalation through a facemask attached to a plastic valved spacer. The control group (37 patients) received 200 $\mu\text{g/day}$ of aqueous intranasal beclomethasone plus oral inhalation of BDP-CFC (≥ 500 $\mu\text{g/day}$) through a mouthpiece connected to the same spacer. Allergic rhinitis clinical scoring and nasal inspiratory peak flow did not differ in the two groups at admission or follow-up visits. Nasal

inhalation of BDP provided AR symptom relief while maintaining control of asthma by delivering it to the lungs.

- 6 Thio et al. (175) evaluated the effect of INFP and BDP, when compared to placebo, on BHR in children and young adults with seasonal rhinitis and mild asthma during two consecutive grass-pollen seasons, and found no difference in BHR between the study groups.
- 7 Sandrini et al. (176) have evaluated the effect of treatment with a nasal corticosteroid on eNO and H_2O_2 in 23 subjects with AR. A randomized, double-blind, 4-week treatment with triamcinolone acetonide (220 $\mu\text{g/day}$) was compared to placebo. Exhaled nitric oxide levels were greater in the subjects with AR and concomitant asthma ($n = 16$) and decreased significantly with treatment. Breath condensate levels of H_2O_2 were higher in patients with AR without asthma than in those with asthma and decreased significantly with treatment in both subgroups. The authors conclude that treatment of AR with triamcinolone results in decrease of two noninvasive markers of lower airway inflammation, eNO and H_2O_2 , supporting that upper and lower airway inflammation should be seen as a continuum.

Post hoc analyses of cohorts.

- 1 Adams et al. (177) determined whether treatment with intranasal steroids or prescription antihistamines were associated with a reduced risk for emergency visits caused by asthma. They performed a retrospective cohort study of members of a managed care organization aged > 5 years who were identified during the period of October 1991 to September 1994 as having a diagnosis of asthma. The main outcome measure was an emergency visit for asthma. Of the 13 844 eligible persons, 1031 (7.4%) had an emergency department visit for asthma. The overall RR for an emergency visit among those who received intranasal glucocorticosteroids, adjusted for age, sex, frequency of orally inhaled corticosteroid and β -agonist dispensing, amount and type of ambulatory care for asthma, and diagnosis of an upper airways condition (rhinitis, sinusitis or otitis media), was 0.7 (95% CI: 0.59–0.94). For those receiving prescription antihistamines, the risk was indeterminate (RR = 0.9; 95% CI: 0.78–1.11). When different rates of dispensing for intranasal steroids were examined, a more reduced risk was seen in emergency visits in those with > 3 (RR = 0.5; 95% CI: 0.23–1.05) dispensed prescriptions per year.
- 2 Crystal-Peters et al. (178) studied subjects with both AR and asthma to test the hypothesis that treating AR reduces healthcare utilization for co-morbid asthma in a retrospective cohort study. The cohort was limited to patients aged 12–60 years, who were

continuously enrolled and had no evidence of COPD. Allergic rhinitis treatment and asthma-related events (hospitalizations and emergency department visits) were identified. The study sample population consisted of 4944 patients with allergic asthma, approximately 73% of whom were treated for their AR. Asthma-related events (emergency department visits or hospitalizations) were half as frequent for subjects receiving treatment for AR than for those who were not treated.

- 3 Corren et al. (179) have demonstrated that treatment of AR significantly reduces the frequency of asthma exacerbations resulting in emergency room visits and/or hospitalizations. In a nested, case-control study the authors have found treatment with either nasal glucocorticosteroids or second-generation antihistamines to be associated with a lower risk of asthma-related emergency room treatment and hospitalization (adjusted OR: 0.51; 95% CI: 0.34–0.77 and 0.34, 0.18–0.62, respectively). Patients who used nasal glucocorticosteroids had a significantly lower risk of both asthma-related emergency room treatment and hospitalization (adjusted OR: 0.75; 95% CI: 0.62–0.91 and 0.56, 0.42–0.76, respectively), whereas there was a trend towards lower risk of emergency room treatment and hospitalization in patients who used second-generation antihistamines (adjusted OR: 0.88; 95% CI: 0.62–1.26 and 0.68, 0.40–1.14, respectively). Combined treatment with both medications was associated with a further lowering of the risk of both emergency room treatment and hospitalization (adjusted OR: 0.37; 95% CI: 0.19–0.73 and 0.22, 0.07–0.63).

Three retrospective cohort studies from the USA have reported considerable reduction in asthma morbidity in individuals with concomitant asthma and rhinitis, when properly treated for their rhinitis with nasal glucocorticosteroids. However, the intranasal treatment of rhinitis using topical nasal glucocorticosteroids was found to improve asthma, albeit moderately at best, in some but not all controlled studies. One can speculate that patients with asthma and rhinitis that receive treatment for rhinitis are those that more rigorously consult their doctor and are more careful with their health. Consequently, it would be possible that they have a lower incidence of hospitalizations and emergency visits because of asthma which is not related to the treatment for rhinitis.

Antihistamines

- 1 Aubier et al. (180) designed a study to assess the effect of cetirizine, on nonspecific BHR in patients with AR. Twelve patients were included in a double-blind, crossover, placebo-controlled trial. All patients had positive skin tests for common allergens and

showed BHR to inhaled methacholine after specific nasal allergen challenge. After a washout period of 1 week to ensure the stability of the BHR, the patients received, by crossover randomization, cetirizine 10 mg daily or placebo for 2 weeks. After each treatment period, BHR and nasal blocking index were measured 1 and 6 h after nasal challenge. Measurements were then performed after 2 weeks of cetirizine and after 2 weeks of placebo. One hour after allergen they found no significant differences between cetirizine (methacholine PD_{20} = 0.522 mg) and placebo (methacholine PD_{20} = 0.455 mg). In contrast, 6 h after challenge, methacholine PD_{20} was 0.918 mg for cetirizine and 0.483 mg for placebo (P = 0.042). Similarly, no difference was observed in the effect on nasal obstruction between cetirizine and placebo 1 h after challenge, whereas the difference was significant 6 h after challenge. These data demonstrate a protective effect of cetirizine on BHR and nasal obstruction measured 6 h after nasal allergen challenge in patients with AR. These findings could be explained either by a direct effect of cetirizine on the lower airways, or else, indirectly, by a protection related to the control of rhinitis.

- 2 To evaluate the safety and efficacy of desloratadine 5 mg in moderate SAR (181), nasal congestion, and symptoms of seasonal allergic asthma, a 4-week, multicentre, double-blind study compared desloratadine treatment with placebo in 331 subjects with AR and mild seasonal allergic asthma. Compared with placebo, desloratadine significantly reduced mean total symptom scores, beginning with the first dose and continuing throughout days 1–29. Desloratadine significantly decreased AM/PM reflective total asthma symptom scores for days 1–15 (P = 0.02) and AM/PM reflective nasal congestion scores over days 1–29.
- 3 Safety and efficacy of desloratadine and montelukast were assessed in a double-blind, placebo-controlled trial of patients with SAR and symptoms of asthma (182), who were assigned randomly to once daily treatment with desloratadine 5 mg, montelukast 10 mg or placebo for 4 weeks. Desloratadine and montelukast each were associated with statistically significant reductions from baseline in the mean total symptom scores for asthma averaged over the 4-week period ($P \leq 0.02$ vs placebo). Individual asthma symptom scores also improved significantly for both therapies ($P \leq 0.05$). Patients treated with desloratadine or montelukast demonstrated improvement from baseline in FEV_1 vs placebo; significant improvement was seen in a subset of patients with baseline $FEV_1 < 80\%$ of predicted normal (both $P < 0.05$). Both active therapies significantly reduced $\beta(2)$ -agonist use (both $P < 0.01$). Improvements for both therapies were comparable for all efficacy parameters; they were tolerated well with adverse event profiles similar to placebo.

- 4 The effect of treatment with desloratadine on systemic inflammation and on nasal and bronchial mucosal inflammation after nasal allergen provocation in subjects with grass-pollen AR and asthma has been reported (183). Twenty-six subjects with grass-pollen AR and asthma were randomly allocated to 8 days of treatment with desloratadine or placebo outside the grass-pollen season. On day 7 they underwent nasal provocation with allergen. Nasal and bronchial biopsies were taken for immunohistochemical evaluation, and blood samples were analysed. The number of circulating eosinophils decreased during desloratadine treatment, and there was an attenuated increase in circulating eosinophils after nasal provocation in these subjects. There was also a significant reduction in early bronchial clinical response, but no significant reduction in nasal symptoms. Nasal and bronchial mucosal inflammation parameters were the same regardless of treatment.

Although antihistamines are not recommended for the treatment of asthma; when used for rhinitis they may improve concomitant asthma. On the other hand, despite not being the best option in rhinitis with prominent nasal obstruction, antihistamines have been shown consistently to have beneficial effects in reducing nasal obstruction when compared to placebo.

Leukotriene receptor antagonists

- 1 Desloratadine and montelukast (182) were shown to be associated with statistically significant reductions from baseline in the mean asthma symptoms scores averaged over a 4-week period in patients with concomitant SAR and asthma. Individual asthma symptom scores also improved significantly for both therapies. Patients treated with desloratadine or montelukast demonstrated improvement from baseline in FEV₁ vs placebo; significant improvement was seen in a subset of patients with baseline FEV₁ < 80% of predicted normal. Both active therapies significantly reduced β (2)-agonist use. Improvements for both therapies were comparable for all efficacy parameters; they were tolerated well with adverse event profiles similar to placebo. Improvements in asthma symptoms were comparable for both active-treatment groups.
- 2 To compare oral montelukast with inhaled plus intranasal budesonide in patients with SAR and asthma (184), a single-blind double-dummy placebo-controlled crossover study was performed comparing once daily 10 mg oral montelukast with 400 μ g inhaled plus 200 μ g intranasal budesonide in 12 patients with AR and asthma. Each treatment was for 2 weeks with a 1-week placebo run-in and washout. There were no significant differences between the placebos for any measurement. For adenosine

monophosphate PC₂₀, geometric mean fold differences (95% CI for difference) were 6.4 (2.2–18.6) for placebo vs budesonide, 2.9 (1.0–8.4) for placebo vs montelukast and 2.1 (1.1–4.5) for budesonide vs montelukast. For eNO (p.p.b.) there was significant ($P < 0.05$) suppression with both montelukast (10.9) and budesonide (10.1) compared with placebo (18.8). For nNO and nasal peak inspiratory flow there were only significant differences with budesonide compared with placebo.

- 3 Aiming to evaluate montelukast 10 mg daily as treatment for AR in patients with symptomatic AR and active asthma during the allergy season, a multicentre study of 831 patients with seasonal allergen sensitivity, active symptoms of SAR and active asthma was performed (185). Following a single-blind, placebo run-in period of 3–5 days, patients were randomized to oral montelukast 10 mg ($n = 415$) or placebo ($n = 416$) daily during the 2-week, double-blind, active-treatment period. Montelukast reduced the daily rhinitis symptoms score: difference between montelukast and placebo in mean change from baseline was -0.12 . In exploratory analyses, improvement in rhinitis symptoms was numerically (though not statistically) larger in patients with greater levels of asthma at study start. Montelukast provided benefit in the global evaluations of asthma by patient and by doctor: mean differences were -0.24 (-0.41 to -0.06 ; $P = 0.008$) and -0.17 (-0.33 to -0.01 ; $P = 0.037$). Similarly, as-needed β -agonist use (puffs/day) was reduced with montelukast ($P = 0.005$).
- 4 To determine the benefit of montelukast, 10 mg, for patients with concomitant asthma and AR, a randomized, crossover study-treated patients with montelukast vs placebo during two 2-week, double-blind treatment periods, separated by a 1-week washout period was conducted. After each treatment period, patients underwent a 60-min or less exposure to high levels of airborne cat allergen. Lower and upper airway responses were measured by spirometry and symptom scores. Of 52 patients with data from both treatment arms, 79% of patients taking montelukast and 67% taking placebo were exposed to the full 60-min allergen challenge. Montelukast provided significant ($P \leq 0.001$) protection against allergen challenge in the lower airway co-primary end point of area under the curve during challenge (AUC_{0-60} min) for percentage decrease in FEV₁: mean of 10.5% per hour and 14.7% per hour for montelukast and placebo, respectively. Although the effect on the overall NSS co-primary end point of AUC_{0-60} min was not statistically significance ($P = 0.12$), nasal congestion during the challenge and NSS during recovery showed statistically significant ($P = 0.048$) protection by montelukast. Additional analyses of simultaneous lower and upper airway responses

showed that more patients taking montelukast (22, 43%) *vs* placebo (13, 26%) were protected from both asthma and rhinitis ($P = 0.02$), with an OR of 2.24 (95% CI: 1.16–4.32) in favour of montelukast.

- 5 To compare the clinical efficacy of leukotriene receptor antagonists with that of placebo, antihistamines and nasal glucocorticosteroids in patients with AR or nasal polyposis, Wilson et al. (186) performed a systematic review and meta-analysis of randomized-controlled trials of the effectiveness of leukotriene receptor antagonists in patients with rhinitis. Eleven studies on SAR were used in the analysis: eight evaluating leukotriene receptor antagonists alone or in combination with other treatments *vs* placebo or other treatments ($n = 3924$) and three evaluating leukotriene receptor antagonists plus an antihistamine ($n = 80$). There were no randomized-controlled trials evaluating the effect of leukotriene receptor antagonists on perennial AR or polyposis. Leukotriene receptor antagonists are modestly better than placebo, as effective as antihistamines, but less effective than nasal glucocorticosteroids in improving symptoms and quality of life in patients with SAR.

Although leukotriene receptor antagonists have been recommended for asthma treatment for years, the evidence for their use in rhinitis is more recent. Confirming previous observations, some new studies have also demonstrated the potential usefulness of antihistamines and leukotriene receptor antagonists in patients with rhinitis and co-morbid asthma.

Specific immunotherapy

The indications of specific immunotherapy in allergic asthma and rhinitis have been separated in some guidelines. This artificial separation has led to unresolved issues possibly because the allergen-induced IgE-mediated reaction has not been considered to be a multiorgan disease. It is therefore important to consider specific immunotherapy based on the allergen sensitization rather than on the disease itself as most patients with allergic asthma also present rhinitis or rhino-conjunctivitis. A specific ARIA review in preparation is devoted to specific immunotherapy, therefore only a few selected papers have been included in the current review, chosen for providing information on outcomes related to both upper and lower airways.

- 1 Moller and co-workers (187) have investigated whether specific immunotherapy can prevent the development of asthma and reduce BHR in children with seasonal allergic rhino-conjunctivitis. From six paediatric allergy centres, 205 children aged 6–14 years (mean age, 10.7 years) with grass and/or birch pollen were randomized either to receive specific immunotherapy for 3 years or to an open control group. All subjects had moderate-to-severe hay fever symptoms,

but at inclusion none reported asthma with need of daily treatment. Among those without asthma, the actively treated children had significantly fewer asthma symptoms after 3 years as evaluated by clinical diagnosis (OR: 2.52; $P < 0.05$).

- 2 Novembre and co-workers (188) studied short-term co-seasonal sublingual immunotherapy, and have shown the actively treated children, when compared to the placebo group, used less medication in the second and third years of therapy, and their symptom scores tended to be lower. From the second year of immunotherapy, subjective evaluation of overall allergy symptoms was favourable in the actively treated children. Development of asthma after 3 years was 3.8 times more frequent (95% CI: 1.5–10.0) in the control subjects.
- 3 Similar findings have been reported by Chang et al. (189) in an open study conducted to evaluate the effect of immunotherapy on the degree of nonspecific BHR in patients with allergic bronchial asthma and/or AR. Methacholine bronchoprovocation, allergic skin test, serum IgE and peripheral blood eosinophil counts were performed before and after 12 months or more of immunotherapy. Seventy-five per cent of subjects with AR ($n = 16$) tolerated at least two extra doubling concentrations of methacholine, whereas 41.7% of patients with tranquil asthma ($n = 24$) and 53.8% of those with bronchial asthma and AR ($n = 13$) did. The geometric mean of the methacholine PC₂₀ changed from 3.40 to 14.36 mg/ml in AR. In conclusion, nonspecific BHR was improved by immunotherapy in three quarters of the AR cases and in about a half of the asthma patients.
- 4 Walker and co-workers (190) have assessed the effects of grass-pollen immunotherapy on symptoms, BHR and quality of life in seasonal rhinitis and asthma in 44 patients with severe summer hay fever (of whom 36 reported seasonal chest symptoms and 28 had seasonal BHR). In a randomized, double-blind, placebo-controlled, parallel-group study, after symptom monitoring for one summer, participants received injections of a depot grass-pollen vaccine or matched placebo injections in a rapid up dosing cluster regimen for 4 weeks, followed by monthly injections for 2 years. Significant reductions were observed in the immunotherapy group compared with the placebo group in hay fever symptoms, medication scores and seasonal chest symptoms. During the pollen season there was no change in airway methacholine PC₂₀ in the immunotherapy-treated group, compared with an almost three doubling-dose decrease in the placebo-treated group.
- 5 Another publication (191) has reported on the ability of specific immunotherapy to reduce the progression of AR to asthma and prevent the associated increase in BHR. Forty-four subjects monosensitized to *D. pteronyssinus*, with perennial rhinitis and BHR to

- methacholine, were randomly assigned to receive specific immunotherapy or placebo in a double-blind study conducted over a period of 2 years. After 1 year of treatment, a 2.88-fold increase in the methacholine PD₂₀ was recorded in the immunotherapy-treated group, with a further increase to fourfold at the end of year 2. At the end of the study, the methacholine PD₂₀ was within the normal range in 50% of treated subjects, and was significantly higher in this group than in the group receiving placebo. In contrast, no changes in methacholine PD₂₀ were found in the placebo group throughout the study. Although 9% of subjects given placebo developed asthma, none of those treated with specific immunotherapy did. The authors conclude that specific immunotherapy, when administered to carefully selected, monosensitized patients with perennial AR, reduces airway responsiveness in subjects with rhinitis, and may be an appropriate prophylactic treatment for rhinitis patients with hyper-reactive airways.
- 6 Polosa et al. (192) have examined 30 nonasthmatic patients with AR, who were monosensitized to *Parietaria judaica*, in a randomized, double-blind, placebo-controlled, parallel-group study of the effects of a *Parietaria* pollen vaccine on symptoms/medication score, response to inhaled methacholine and adenosine 5'-monophosphate (AMP), and cell counts in the sputum collected out of and during the pollen seasons for 36 months. Seasonal variation in BHR to inhaled methacholine and AMP and changes in sputum cell counts were documented. Changes were consistent for AMP, but not methacholine, and invariably associated with modifications in sputum eosinophils and epithelial cells. The clinical efficacy of *Parietaria*-specific immunotherapy was associated with a decline in the seasonal deterioration of response to AMP, whereas no significant effect was observed on the response to methacholine or sputum cell differentials. Bronchi of nonasthmatic patients with AR exhibit features of active inflammation that deteriorate during natural allergen exposure, particularly with regard to BHR to AMP. The clinical efficacy of *Parietaria*-specific immunotherapy was exclusively associated with attenuation in seasonal worsening of concentration of AMP that provokes a 15% reduction in VEF₁ (PC15 AMP), suggesting that AMP may be useful in monitoring changes in allergic inflammation of the airways.
 - 7 Lombardi and co-workers (193) have reported an open controlled trial that evaluated whether a pre-seasonal immunotherapy with grass pollen in orosoluble tablets added to pharmacotherapy, can improve nonspecific BHR. Fifty-one patients (mean age 27.4 years) suffering from rhino-conjunctivitis and/or mild-intermittent/mild-persistent asthma because of grass pollen were allocated to two groups receiving pharmacotherapy alone ($n = 25$) or pharmacotherapy plus immunotherapy in tablets ($n = 26$). A methacholine test was performed in asthmatic subjects out of the pollen seasons at baseline and after 3 years of treatment. A significant increase in the PD₂₀ was observed in the immunotherapy group, as well as a significant clinical improvement both for rhinitis and asthma. This improvement was paralleled by a clear-cut reduction of drug intake.
 - 8 A systematic review to evaluate the efficacy of sublingual immunotherapy, compared with placebo, for reductions in symptoms and medication requirements has been reported (194). Twenty-two trials, involving 979 patients, were included. There were six trials of sublingual immunotherapy for house dust mite allergy, five for grass pollen, five for *Parietaria*, two for olive and one each for, ragweed, cat, tree and cupressus. All included studies were double-blind placebo-controlled trials of parallel-group design. There was significant heterogeneity, most likely due to widely differing scoring systems between studies, for most comparisons. Overall there was a significant reduction in both symptoms (-0.42 , 95% CI: -0.69 to -0.15 ; $P = 0.002$) and medication requirements [-0.43 (-0.63 to -0.23); $P = 0.00003$] following immunotherapy. Subgroup analyses failed to identify a disproportionate benefit of treatment according to the allergen administered.
 - 9 A meta-analysis to evaluate the efficacy of sublingual allergen immunotherapy compared to placebo in paediatric patients has also been published (195). Randomized double-blind placebo-controlled clinical trials involving children ≤ 14 years old with either rhinitis or asthma of proved allergic aetiology. Two reviewers analysed independently the eligibility of studies for inclusion. The combined SMD method was used to evaluate differences. The main outcomes were clinical symptom (asthma, rhinitis and conjunctivitis) and drug requirement scores. Seven double-blind placebo-controlled trials, enrolling 256 children (129 treatment and 127 placebo recipients), were analysed. Only reductions in asthma ($P = 0.01$) and drug dosage ($P = 0.06$) scores reached statistical significance with the random effect model. Changes in rhinitis symptoms ($P = 0.27$) or conjunctival symptoms ($P = 0.19$) were not statistically significant. Safety was a constant in all the studies; neither severe nor systemic reactions were observed and, oral and gastrointestinal complains were the most common adverse effects.
 - 10 Aiming to investigate history of AR as a risk factor for asthma and the potential effect of allergen immunotherapy in attenuating the incidence of asthma, a hospital-referred nonasthmatic adult, aged 18–40 years between 1990 and 1991, were retrospectively followed up until January and April 2000 (196). At the end of follow-up, available subjects were

clinically examined for asthma diagnosis and history of allergen-specific immunotherapy, second-hand smoking and the presence of pets in the household. A total of 436 nonasthmatic adults (332 subjects with AR and 104 with no AR nor history of atopy) were available for final analyses. The highest OR associated with a diagnosis of asthma at the end of follow-up was for the diagnosis of AR at baseline (OR: 7.8; 95% CI: 3.1–20.0). Treatment with allergen immunotherapy was significantly and inversely related to the development of new onset asthma (OR: 0.53; 95% CI: 0.32–0.86). In the present study, we found that AR is an important independent risk factor for asthma. Moreover, treatment with allergen immunotherapy lowers the risk of the development of new asthma cases in adults with AR.

Various studies have provided evidence that treatment of AR with specific immunotherapy, either sublingual or subcutaneous, can reduce BHR and may prevent asthma.

Anti-IgE

A multicentre, randomized, double-blind, parallel-group, placebo-controlled trial evaluated the safety and efficacy of omalizumab in a total of 405 patients (12–74 years) with moderate-to-severe asthma (197). Fewer patients treated with omalizumab experienced asthma exacerbations (20.6%) than placebo-treated patients (30.1%, $P = 0.02$). A clinically significant improvement in both asthma quality of life questionnaire and rhinitis quality of life questionnaire occurred in 57.7% of omalizumab patients compared with 40.6% of placebo patients ($P < 0.001$). Omalizumab reduced symptom scores for asthma ($P = 0.023$), rhinitis ($P < 0.001$) and the com-

posite asthma/rhinitis scores ($P < 0.001$) compared with placebo. Omalizumab is well tolerated and effective in preventing asthma exacerbations and improving quality of life in patients with concomitant asthma and persistent AR.

The observations we have just described in this item support previous ARIA Initiative reports on the benefits of optimal management of rhinitis on asthma control. Table 3 summarizes the findings on this topic. Intranasal glucocorticosteroids for the treatment of rhinitis, may reduce morbidity in asthmatics. Antihistamines and leukotriene receptor antagonists were shown to contribute to asthma control or prevention. Specific immunotherapy of rhinitis may reduce the risk of asthma or improve asthma control. According to the strength of recommendations proposed by Shekelle et al. (112):

Oral H1-antihistamines are effective in rhinitis	Strength of recommendation A
Oral H1-antihistamines have a modest effect on asthma	Strength of recommendation A
Intranasal glucocorticosteroids are effective in asthma	Strength of recommendation B
Intranasal glucocorticosteroids reduce asthma exacerbations	Strength of recommendation B
Intra-bronchial glucocorticosteroids are effective in rhinitis	Strength of recommendation A (single study)
Oral leukotriene receptor antagonists are often effective in rhinitis	Strength of recommendation A
Allergen-specific immunotherapy is effective in both rhinitis and asthma in atopic subjects	Strength of recommendation A
Anti-IgE monoclonal antibody is effective in both rhinitis and asthma (approved for severe uncontrolled asthma)	Strength of recommendation A

Table 3. Treatment of rhinitis improves asthma?

Authors	Location	Number of subjects	Study design	Benefit	Comments
Adams et al. (177)	USA	13 844	Retrospective cohort	RR 0.7 (emergency department visits)	For subjects using nasal glucocorticosteroids
Crystal-Peters et al. (178)	USA	4944	Retrospective cohort	RR 0.5 (emergency visits/hospitalizations)	Nothing remarkable
Corren et al. (179)	USA		Nested case-control	RR 0.56 (hospitalizations)	For subjects using nasal corticosteroids
Moller et al. (187)	Europe	205	Randomized trial	RR 0.40* (of having asthma)	Three years study with immunotherapy
Grembiale et al. (191)	UK	44	Randomized trial	Reduced BHR to Mch	Two years study with immunotherapy
Polosa et al. (192)	Italy	30	Randomized trial	Reduced BHR to AMP but not to Mch	Three years study with immunotherapy
Dahl et al. (171)	Europe	262	Randomized trial	Nonsignificant trend to improvement	Treatment with intranasal fluticasone
Lombardi et al. (193)	Italy	51	Open controlled trial	Reduced BHR to Mch	Three years study with immunotherapy
Taramarcaz and Gibson (170)	Cochrane (multiple)	425	Systematic review of randomized trials	Nonsignificant trend to improvement	Assessment of 11 trials to evaluate the effect of nasal steroids

RR, relative risk; BHR, bronchial hyper-responsiveness; Mch, methacoline; AMP, adenosine 5'-monophosphate.

* Extrapolated from published information.

Discussion

Within the time period between the years 2000 and 2005 new evidence has emerged supporting the notion that the epidemiological association between asthma and rhinitis is stronger than previously thought. Patients with asthma and AR incur higher costs and disease severity than those with symptoms of asthma alone. On the other hand, asthmatics with symptoms of rhinitis have worse quality of life. Rhinitis and asthma share common genetic and environmental risk factors, but rhinitis is the most significant independent risk factor for asthma and might have some specific risk factors of its own. New convincing imaging and histopathological evidence has been provided that chronic rhinitis is closely related to chronic sinusitis, and that both of them are related to asthma. No new entries to the list of treatment options for management of rhinitis, which also improve asthma control (nasal glucocorticosteroids, antihistamines, leukotriene receptor antagonists and specific immunotherapy) could be added.

We found various publications on the topics 'prevalence of asthma in rhinitis and of rhinitis in asthma', 'rhinitis as a risk factor for asthma' and 'treatment of rhinitis improves asthma'. These reports were reviewed and grouped in specific sections of this article, some of them further divided in subtopics. However, reports on 'links between the upper and lower airways in children', 'diagnosis of co-morbidities in patients with rhinitis or asthma in general practices and pharmacies' and 'co-morbidities in the developing world', were scarce, and we have decided to switch from these proposed items to: 'common characteristics of the upper and lower airways in rhinitis and asthma' and 'co-morbidities in patients with rhinitis or asthma'.

Although some evidence of direct nose–lung interaction exists, indicating that an exacerbation of rhinitis may precipitate asthma symptoms, and therefore control of rhinitis could protect subjects from asthma, it is likely that the strong association between asthma and rhinitis results from the fact they are both manifestations of a combined allergic respiratory disease. Moreover, finding rhinitis as a risk factor for asthma does not necessarily imply causality. Being a risk factor could also be explained in the context of sequential manifestations of one systemic disease, in which symptoms of rhinitis often precede those from asthma. It might be easier to envisage rhinitis and asthma as a systemic illness if we take the vascular consequences of hypertension, diabetes or dyslipidaemia in many different organs for analogy. If

we are to fully exploit the new paradigm of unity of the airways or pathophysiological identity between rhinitis and asthma in clinical practice, the need emerges to rationalize decisions on treatment to optimize risk/benefit and cost/effectiveness ratios. Topical nasal glucocorticosteroids are the preferred choice of treatment for moderate-to-severe persistent AR. In milder forms of rhinitis, when necessary and possible, the choice of oral treatment with antihistamines or leukotriene receptor antagonists, may provide additional benefit for those having concomitant asthma. Interventions such as immunotherapy, and eventually anti-IgE, can also be incorporated to treatment, providing simultaneous effects on the upper and lower airways.

The publication available after the last ARIA papers mostly reinforces the previous statements:

- 1 allergic rhinitis is one of the multiple risk factors for asthma development;
- 2 patients with persistent AR should be evaluated for asthma;
- 3 patients with asthma should be evaluated for rhinitis;
- 4 a combined strategy should be used to treat the upper and lower airways for better efficacy/safety ratio and
- 5 in middle- to low-income countries, a specific strategy may be needed, depending on available treatments and medical resources, and the respective costs involved.

Conflict of interest statements

ARIA Initiative has received support from various pharmaceutical companies, but there was no specific funding requested or provided for the activity of preparing this update. No honorarium was received by any of the experts for writing this review.

Acknowledgments

We are grateful to Anna Bedbrook for her administrative assistance.

Source of funding: Allergic Rhinitis and its Impact on Asthma Initiative, which is a nongovernment organization member of the Global Alliance against Chronic Respiratory Diseases. Member of GA²LEN, supported by EU Framework programme for research, contract no. FOOD-CT-2004-506378.

References

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic Rhinitis and its Impact on Asthma. *J Allergy Clin Immunol* 2001;**5**(Suppl.):S147–S334.
2. Bachert C, van Cauwenberge P, Khaltaev N. Allergic Rhinitis and its Impact on Asthma (in collaboration with the World Health Organization. Executive summary of the workshop report. 7–10 December 1999, Geneva, Switzerland). *Allergy* 2002;**57**:841–855.
3. Brazil MS. Asma e Rinite, 1st edn. Brasília: Editora Ministério da Saúde, 2004.
4. Passalacqua G, Bousquet PJ, Carlsen KH, Kemp J, Lockey RF, Niggemann B et al. ARIA update: I. Systematic review of complementary and alternative medicine for rhinitis and asthma. *J Allergy Clin Immunol* 2006;**117**:1054–1062.
5. Bousquet J, van Cauwenberge P, Ait Khaled N, Bachert C, Baena-Cagnani CE, Bouchard J et al. Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update (in collaboration with GA2LEN). *Allergy* 2006;**61**:1086–1096.
6. Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma. A population-based study of young adults. *Am J Respir Crit Care Med* 2000;**1**:1391–1396.
7. Baiardini I, Pasquali M, Giardini A, Specchia C, Passalacqua G, Venturi S et al. Rhinasthma: a new specific QoL questionnaire for patients with rhinitis and asthma. *Allergy* 2003;**58**:289–294.
8. Shamsain MH, Shamsian N. Prevalence and severity of asthma, rhinitis, and atopic eczema in 13- to 14-year-old schoolchildren from the northeast of England. *Ann Allergy Asthma Immunol* 2001;**86**:428–432.
9. Montnemery P, Svensson C, Adelroth E, Lofdahl CG, Andersson M, Greiff L et al. Prevalence of nasal symptoms and their relation to self-reported asthma and chronic bronchitis/emphysema. *Eur Respir J* 2001;**17**:596–603.
10. Celedon JC, Palmer LJ, Weiss ST, Wang B, Fang Z, Xu X. Asthma, rhinitis, and skin test reactivity to aeroallergens in families of asthmatic subjects in Anqing, China. *Am J Respir Crit Care Med* 2001;**163**:1108–1112.
11. Linneberg A, Henrik Nielsen N, Frolund L, Madsen F, Dirksen A, Jorgensen T. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2002;**57**:1048–1052.
12. Peroni DG, Piacentini GL, Alfonsi L, Zerman L, Di Blasi P, Visona G et al. Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. *Clin Exp Allergy* 2003;**33**:1349–1354.
13. Sichletidis L, Chloros D, Tsiotsios I, Gioulekas D, Kyriazis G, Spyrtos D et al. The prevalence of allergic asthma and rhinitis in children of Polichni, Thessaloniki. *Allergol Immunopathol (Madr)* 2004;**32**:59–63.
14. Bugiani M, Carosso A, Migliore E, Piccioni P, Corsico A, Olivieri M et al. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. *Allergy* 2005;**60**:165–170.
15. Terreehorst I, Oosting AJ, Tempels-Pavlica Z, de Monchy JG, Bruijnzeel-Koomen CA, Hak E et al. Prevalence and severity of allergic rhinitis in house dust mite-allergic patients with bronchial asthma or atopic dermatitis. *Clin Exp Allergy* 2002;**32**:1160–1165.
16. Bousquet J, Boushey HA, Busse WW, Canonica GW, Durham SR, Irvin CG et al. Characteristics of patients with seasonal allergic rhinitis and concomitant asthma. *Clin Exp Allergy* 2004;**34**:897–903.
17. Laforest L, Bousquet J, Neukirch F, Aubier M, Pietri G, Devouassoux G et al. Influence of sociodemographic factors on quality of life during pollen season in seasonal allergic rhinitis patients. *Ann Allergy Asthma Immunol* 2005;**95**:26–32.
18. Bousquet J, Annesi-Maesano I, Carat F, Leger D, Rugina M, Pribil C et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. *Clin Exp Allergy* 2005;**35**:728–732.
19. Demoly P, Allaert FA, Lecasble M, Bousquet J. Validation of the classification of ARIA (Allergic Rhinitis and its Impact on Asthma). *Allergy* 2003;**58**:672–675.
20. Mete N, Sin A, Gulbahar O, Erdinc M, Sebik F, Kokuludag A. The determinants of bronchial hyperresponsiveness in patients with allergic rhinitis. *Ann Allergy Asthma Immunol* 2004;**93**:193–199.
21. Di Lorenzo G, Pacor ML, Mansueto P, Esposito Pellitteri M, Lo Bianco C, Ditta V et al. Determinants of bronchial hyperresponsiveness in subjects with rhinitis. *Int J Immunopathol Pharmacol* 2005;**18**:715–722.
22. Aronsson D, Tufvesson E, Bjermer L. Allergic rhinitis with or without concomitant asthma: difference in perception of dyspnoea and levels of fractional exhaled nitric oxide. *Clin Exp Allergy* 2005;**35**:1457–1461.
23. Upton MN, McConnachie A, McSharry C, Hart CL, Smith GD, Gillis CR et al. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ* 2000;**321**:88–92.
24. Cirillo I, Vizzaccaro A, Tosca MA, Milanese M, Ciprandi G. Prevalence and treatment of allergic rhinitis in Italian conscripts. *Allerg Immunol (Paris)* 2003;**35**:204–207.
25. Braback L, Hjern A, Rasmussen F. Trends in asthma, allergic rhinitis and eczema among Swedish conscripts from farming and non-farming environments. A nationwide study over three decades. *Clin Exp Allergy* 2004;**34**:38–43.
26. Al Frayh AR, Shakoor Z, Gad El Rab MO, Hasnain SM. Increased prevalence of asthma in Saudi Arabia. *Ann Allergy Asthma Immunol* 2001;**86**:292–296.
27. Filipiak B, Heinrich J, Nowak D, Wichmann HE. The distribution in specific IgE and the prevalence of allergic symptoms in 25–64-years old inhabitants of an eastern and a western German city – results from Augsburg and Erfurt. *Eur J Epidemiol* 2001;**17**:77–84.
28. Zanolin ME, Pattaro C, Corsico A, Bugiani M, Carrozzi L, Casali L et al. The role of climate on the geographic variability of asthma, allergic rhinitis and respiratory symptoms: results from the Italian Study of Asthma in Young Adults. *Allergy* 2004;**59**:306–314.
29. Kivity S, Sade K, Abu-Arisha F, Lerman Y, Kivity S. Epidemiology of bronchial asthma and chronic rhinitis in schoolchildren of different ethnic origins from two neighboring towns in Israel. *Pediatr Pulmonol* 2001;**32**:217–221.

30. Scadding GK, Richards DH, Price MJ. Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis. *Clin Otolaryngol Allied Sci* 2000;**25**:551–557.
31. Lee SL, Wong W, Lau YL. Increasing prevalence of allergic rhinitis but not asthma among children in Hong Kong from 1995 to 2001 (Phase 3 International Study of Asthma and Allergies in Childhood). *Pediatr Allergy Immunol* 2004;**15**:72–78.
32. Yu JH, Lue KH, Lu KH, Sun HL, Lin YH, Chou MC. The relationship of air pollution to the prevalence of allergic diseases in Taichung and Chu-Shan in 2002. *J Microbiol Immunol Infect* 2005;**38**:123–126.
33. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy* 2005;**60**:350–353.
34. Levesque B, Rhainds M, Ernst P, Grenier AM, Kosatsky T, Audet N et al. Asthma and allergic rhinitis in Quebec children. *Can Respir J* 2004;**11**:343–348.
35. Latvala J, von Hertzen L, Lindholm H, Haahtela T. Trends in prevalence of asthma and allergy in Finnish young men: nationwide study, 1966–2003. *BMJ* 2005;**330**:1186–1187.
36. Banac S, Tomulic KL, Ahel V, Rozmanic V, Simundic N, Zubovic S et al. Prevalence of asthma and allergic diseases in Croatian children is increasing: survey study. *Croat Med J* 2004;**45**:721–726.
37. Huurre TM, Aro HM, Jaakkola JJ. Incidence and prevalence of asthma and allergic rhinitis: a cohort study of Finnish adolescents. *J Asthma* 2004;**41**:311–317.
38. Devenny A, Wassall H, Ninan T, Omran M, Khan SD, Russell G. Respiratory symptoms and atopy in children in Aberdeen: questionnaire studies of a defined school population repeated over 35 years. *BMJ* 2004;**329**:489–490.
39. Jan IS, Chou WH, Wang JD, Kuo SH. Prevalence of and major risk factors for adult bronchial asthma in Taipei City. *J Formos Med Assoc* 2004;**103**:259–263.
40. Vellinga A, Droste JH, Vermeire PA, Desager K, De Backer WA, Nelen VJ et al. Changes in respiratory and allergic symptoms in schoolchildren from 1996 to 2002, results from the ISAAC surveys in Antwerp (Belgium). *Acta Clin Belg* 2005;**60**:219–225.
41. Robertson CF, Roberts MF, Kappers JH. Asthma prevalence in Melbourne schoolchildren: have we reached the peak? *Med J Aust* 2004;**180**:273–276.
42. Annus T, Riikjarv MA, Rahu K, Bjorksten B. Modest increase in seasonal allergic rhinitis and eczema over 8 years among Estonian schoolchildren. *Pediatr Allergy Immunol* 2005;**16**:315–320.
43. Selnes A, Nystad W, Bolle R, Lund E. Diverging prevalence trends of atopic disorders in Norwegian children. Results from three cross-sectional studies. *Allergy* 2005;**60**:894–899.
44. Wang XS, Tan TN, Shek LP, Chng SY, Hia CP, Ong NB et al. The prevalence of asthma and allergies in Singapore; data from two ISAAC surveys seven years apart. *Arch Dis Child* 2004;**89**:423–426.
45. Braun-Fahrlander C, Gassner M, Grize L, Takken-Sahli K, Neu U, Stricker T et al. No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. *Eur Respir J* 2004;**23**:407–413.
46. Anderson HR, Ruggles R, Strachan DP, Austin JB, Burr M, Jeffs D et al. Trends in prevalence of symptoms of asthma, hay fever, and eczema in 12–14 year olds in the British Isles, 1995–2002: questionnaire survey. *BMJ* 2004;**328**:1052–1053.
47. Yan DC, Ou LS, Tsai TL, Wu WF, Huang JL. Prevalence and severity of symptoms of asthma, rhinitis, and eczema in 13- to 14-year-old children in Taipei, Taiwan. *Ann Allergy Asthma Immunol* 2005;**95**:579–585.
48. Teeratakulpisarn J, Wiangnon S, Kosalaraksa P, Heng S. Surveying the prevalence of asthma, allergic rhinitis and eczema in school-children in Khon Kaen, Northeastern Thailand using the ISAAC questionnaire: phase III. *Asian Pac J Allergy Immunol* 2004;**22**:175–181.
49. Arnedo-Pena A, Garcia-Marcos L, Garcia Hernandez G, Aguinagua Ontoso I, Gonzalez Diaz C, Morales Suarez-Varela M et al. Time trends and geographical variations in the prevalence of symptoms of allergic rhinitis in 6–7-year-old children from eight areas of Spain according to the ISAAC. *An Pediatr (Barc)* 2005;**62**:229–236.
50. Lis G, Breborowicz A, Cichocka-Jarosz E, Sobkowiak P, Gazurek D, Swiatly A et al. The prevalence of allergic rhinitis and conjunctivitis in school children from Krakow and Poznan – ISAAC study (International Study of Asthma and Allergies in Childhood). *Otolaryngol Pol* 2004;**58**:1103–1109.
51. Jarvis D, Luczynska C, Chinn S, Potts J, Sunyer J, Janson C et al. Change in prevalence of IgE sensitization and mean total IgE with age and cohort. *J Allergy Clin Immunol* 2005;**116**:675–682.
52. Law M, Morris JK, Wald N, Luczynska C, Burney P. Changes in atopy over a quarter of a century, based on cross sectional data at three time periods. *BMJ* 2005;**330**:1187–1188.
53. Sackesen C, Bakkaloglu A, Sekerel BE, Ozaltin F, Besbas N, Yilmaz E et al. Decreased prevalence of atopy in paediatric patients with familial Mediterranean fever. *Ann Rheum Dis* 2004;**63**:187–190.
54. Nga NN, Chai SK, Bihn TT, Redding G, Takaro T, Checkoway H et al. ISAAC-based asthma and atopic symptoms among Ha Noi school children. *Pediatr Allergy Immunol* 2003;**14**:272–279.
55. Hailu T, Tessema T, Silverman M. Prevalence of symptoms of asthma and allergies in schoolchildren in Gondar town and its vicinity, northwest Ethiopia. *Pediatr Pulmonol* 2003;**35**:427–432.
56. Falade AG, Olawuyi JF, Osinusi K, Onadeko BO. Prevalence and severity of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema in 6- to 7-year-old Nigerian primary school children: the International Study of Asthma and Allergies in Childhood. *Med Princ Pract* 2004;**13**:20–25.
57. Dennis R, Caraballo L, Garcia E, Caballero A, Aristizabal G, Cordoba H et al. Asthma and other allergic conditions in Colombia: a study in 6 cities. *Ann Allergy Asthma Immunol* 2004;**93**:568–574.
58. Demir AU, Karakaya G, Bozkurt B, Sekerel BE, Kalyoncu AF. Asthma and allergic diseases in schoolchildren: third cross-sectional survey in the same primary school in Ankara, Turkey. *Pediatr Allergy Immunol* 2004;**15**:531–538.

59. Bayram I, Guneser-Kendirli S, Yilmaz M, Altintas DU, Alparslan N, Bingol-Karakoc G. The prevalence of asthma and allergic diseases in children of school age in Adana in southern Turkey. *Turk J Pediatr* 2004;**46**:221–225.
60. Monteil MA, Joseph G, Chang Kit C, Wheeler G, Antoine RM. Smoking at home is strongly associated with symptoms of asthma and rhinitis in children of primary school age in Trinidad and Tobago. *Rev Panam Salud Publica* 2004;**16**:193–198.
61. Mavale-Manuel S, Alexandre F, Duarte N, Albuquerque O, Scheinmann P, Poisson-Salomon AS et al. Risk factors for asthma among children in Maputo (Mozambique). *Allergy* 2004;**59**:388–393.
62. Kabir ML, Rahman F, Hassan MQ, Ahamed F, Mridha MA. Asthma, atopic eczema and allergic rhinoconjunctivitis in school children. *Mymensingh Med J* 2005;**14**:41–45.
63. Sole D, Camelo-Nunes IC, Vana AT, Yamada E, Werneck F, de Freitas LS et al. Prevalence of rhinitis and related-symptoms in schoolchildren from different cities in Brazil. *Allergol Immunopathol (Madr)* 2004;**32**:7–12.
64. von Mutius E, Pearce N, Beasley R, Cheng S, von Ehrenstein O, Bjorksten B et al. International patterns of tuberculosis and the prevalence of symptoms of asthma, rhinitis, and eczema. *Thorax* 2000;**55**:449–453.
65. Gruber C, Meinschmidt G, Bergmann R, Wahn U, Stark K. Is early BCG vaccination associated with less atopic disease? An epidemiological study in German preschool children with different ethnic backgrounds *Pediatr Allergy Immunol* 2002;**13**:177–181.
66. Bager P, Rostgaard K, Nielsen NM, Melbye M, Westergaard T. Age at bacille Calmette-Guerin vaccination and risk of allergy and asthma. *Clin Exp Allergy* 2003;**33**:1512–1517.
67. Garcia-Marcos L, Suarez-Varela MM, Canflanca IM, Garrido JB, Quiros AB, Lopez-Silvarrey Varela A et al. BCG immunization at birth and atopic diseases in a homogeneous population of Spanish schoolchildren. *Int Arch Allergy Immunol* 2005;**137**:303–309.
68. da Cunha SS, Cruz AA, Dourado I, Barreto ML, Ferreira LD, Rodrigues LC. Lower prevalence of reported asthma in adolescents with symptoms of rhinitis that received neonatal BCG. *Allergy* 2004;**59**:857–862.
69. Martignon G, Oryszczyn MP, Annesi-Maesano I. Does childhood immunization against infectious diseases protect from the development of atopic disease? *Pediatr Allergy Immunol* 2005;**16**:193–200.
70. Pelosi U, Porcedda G, Tiddia F, Tripodi S, Tozzi AE, Panetta V et al. The inverse association of salmonellosis in infancy with allergic rhinoconjunctivitis and asthma at school-age: a longitudinal study. *Allergy* 2005;**60**:626–630.
71. Cohet C, Cheng S, MacDonald C, Baker M, Foliaki S, Huntington N et al. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. *J Epidemiol Community Health* 2004;**58**:852–857.
72. Jarvis D, Luczynska C, Chinn S, Burney P. The association of hepatitis A and *Helicobacter pylori* with sensitization to common allergens, asthma and hay fever in a population of young British adults. *Allergy* 2004;**59**:1063–1067.
73. de Meer G, Janssen NA, Brunekreef B. Early childhood environment related to microbial exposure and the occurrence of atopic disease at school age. *Allergy* 2005;**60**:619–625.
74. Schmidt SM, Muller CE, Wiersbitzky SK. Inverse association between *Chlamydia pneumoniae* respiratory tract infection and initiation of asthma or allergic rhinitis in children. *Pediatr Allergy Immunol* 2005;**16**:137–144.
75. Nafstad P, Brunekreef B, Skrandal A, Nystad W. Early respiratory infections, asthma, and allergy: 10-year follow-up of the Oslo Birth Cohort. *Pediatrics* 2005;**116**:e255–e262.
76. Foliaki S, Nielsen SK, Bjorksten B, Von Mutius E, Cheng S, Pearce N. Antibiotic sales and the prevalence of symptoms of asthma, rhinitis, and eczema: The International Study of Asthma and Allergies in Childhood (ISAAC). *Int J Epidemiol* 2004;**33**:558–563.
77. Huang SL, Tsai PF, Yeh YF. Negative association of Enterobius infestation with asthma and rhinitis in primary school children in Taipei. *Clin Exp Allergy* 2002;**32**:1029–1032.
78. Matricardi PM, Rosmini F, Panetta V, Ferrigno L, Bonini S. Hay fever and asthma in relation to markers of infection in the United States. *J Allergy Clin Immunol* 2002;**110**:381–387.
79. Svanes C, Jarvis D, Chinn S, Omenaas E, Gulsvik A, Burney P. Early exposure to children in family and day care as related to adult asthma and hay fever: results from the European Community Respiratory Health Survey. *Thorax* 2002;**57**:945–950.
80. Matricardi PM, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000;**320**:412–417.
81. Souza-Machado A, Galvao TS, Porto A, Figueiredo J, Cruz AA. Skin reactivity to aeroallergens is reduced in human T-lymphotropic virus type I-infected healthy blood-donors (asymptomatic carriers). *Allergy* 2005;**60**:379–384.
82. Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin Exp Allergy* 2000;**30**:194–200.
83. Von Ehrenstein OS, Von Mutius E, Illi S, Baumann L, Bohm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy* 2000;**30**:187–193.
84. Leynaert B, Neukirch C, Jarvis D, Chinn S, Burney P, Neukirch F. Does living on a farm during childhood protect against asthma, allergic rhinitis, and atopy in adulthood? *Am J Respir Crit Care Med* 2001;**163**:1829–1834.
85. Remes ST, Koskela HO, Iivanainen K, Pekkanen J. Allergen-specific sensitization in asthma and allergic diseases in children: the study on farmers' and non-farmers' children. *Clin Exp Allergy* 2005;**35**:160–166.
86. Downs SH, Marks GB, Belosouva EG, Peat JK. Asthma and hayfever in Aboriginal and non-Aboriginal children living in non-remote rural towns. *Med J Aust* 2001;**175**:10–13.
87. Waser M, von Mutius E, Riedler J, Nowak D, Maisch S, Carr D et al. Exposure to pets, and the association with hay fever, asthma, and atopic sensitization in rural children. *Allergy* 2005;**60**:177–184.
88. Burr ML, Emberlin JC, Treu R, Cheng S, Pearce NE. Pollen counts in relation to the prevalence of allergic rhinoconjunctivitis, asthma and atopic eczema in the International Study of Asthma and Allergies in Childhood (ISAAC). *Clin Exp Allergy* 2003;**33**:1675–1680.

89. Ronmark E, Perzanowski M, Platts-Mills T, Lundback B. Different sensitization profile for asthma, rhinitis, and eczema among 7-8-year-old children: report from the Obstructive Lung Disease in Northern Sweden studies. *Pediatr Allergy Immunol* 2003;**14**: 91-99.
90. Dotterud LK, Odland JO, Falk ES. Atopic diseases among adults in the two geographically related arctic areas Nikel, Russia and Sor-Varanger, Norway: possible effects of indoor and outdoor air pollution. *J Eur Acad Dermatol Venereol* 2000;**14**:107-111.
91. Chen JT, Krieger N, Van Den Eeden SK, Quesenberry CP. Different slopes for different folks: socioeconomic and racial/ethnic disparities in asthma and hay fever among 173,859 U.S. men and women. *Environ Health Perspect* 2002;**110**(Suppl. 2):211-216.
92. Almquist C, Pershagen G, Wickman M. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. *Clin Exp Allergy* 2005;**35**:612-618.
93. Braback L, Hjern A, Rasmussen F. Social class in asthma and allergic rhinitis: a national cohort study over three decades. *Eur Respir J* 2005;**26**:1064-1068.
94. Venn AJ, Yemaneberhan H, Bekele Z, Lewis SA, Parry E, Britton J. Increased risk of allergy associated with the use of kerosene fuel in the home. *Am J Respir Crit Care Med* 2001;**164**:1660-1664.
95. Wong TW, Yu TS, Liu HJ, Wong AH. Household gas cooking: a risk factor for respiratory illnesses in preschool children. *Arch Dis Child* 2004;**89**:631-636.
96. Annesi-Maesano I, Oryszczyn MP, Raherison C, Kopferschmitt C, Pauli G, Taytard A et al. Increased prevalence of asthma and allied diseases among active adolescent tobacco smokers after controlling for passive smoking exposure. A cause for concern? *Clin Exp Allergy* 2004;**34**:1017-1023.
97. Braback L, Hjern A, Rasmussen F. Body mass index, asthma and allergic rhinoconjunctivitis in Swedish conscripts-a national cohort study over three decades. *Respir Med* 2005;**99**:1010-1014.
98. Weiland SK, Husing A, Strachan DP, Rzehak P, Pearce N. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med* 2004;**61**:609-615.
99. McKeever TM, Lewis SA, Smith C, Collins J, Heatlie H, Frischer M et al. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database. *Thorax* 2001;**56**:758-762.
100. Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics* 2001;**108**:E33.
101. Svanes C, Real FG, Gislason T, Jansson C, Jogi R, Norrman E et al. Association of asthma and hay fever with irregular menstruation. *Thorax* 2005;**60**:445-450.
102. Bolte G, Winkler G, Holscher B, Thefeld W, Weiland SK, Heinrich J. Margarine consumption, asthma, and allergy in young adults: results of the German National Health Survey 1998. *Ann Epidemiol* 2005;**15**:207-213.
103. Bornehag CG, Sundell J, Weschler CJ, Sigsgaard T, Lundgren B, Hasselgren M et al. The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. *Environ Health Perspect* 2004;**112**:1393-1397.
104. Penard-Morand C, Charpin D, Raherison C, Kopferschmitt C, Caillaud D, Lavaud F et al. Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren. *Clin Exp Allergy* 2005;**35**:1279-1287.
105. Gautrin D, Ghezzi H, Infante-Rivard C, Malo JL. Natural history of sensitization, symptoms and occupational diseases in apprentices exposed to laboratory animals. *Eur Respir J* 2001;**17**:904-908.
106. Tutluoglu B, Atis S, Anakkaya AN, Altug E, Tosun GA, Yaman M. Sensitization to horse hair, symptoms and lung function in grooms. *Clin Exp Allergy* 2002;**32**:1170-1173.
107. Moscato G, Pignatti P, Yacoub MR, Romano C, Spezia S, Perfetti L. Occupational asthma and occupational rhinitis in hairdressers. *Chest* 2005;**128**:3590-3598.
108. Chatzi L, Prokopoulos E, Tzanakis N, Alegakis A, Bizakis I, Siafakas N et al. Allergic rhinitis, asthma, and atopy among grape farmers in a rural population in Crete, Greece. *Chest* 2005;**127**:372-378.
109. Kaukiainen A, Riala R, Martikainen R, Reijula K, Riihimäki H, Tammilehto L. Respiratory symptoms and diseases among construction painters. *Int Arch Occup Environ Health* 2005;**78**:452-458.
110. Walusiak J, Krawczyk-Adamus P, Hanke W, Wittczak T, Palczynski C. Small nonspecialized farming as a protective factor against immediate-type occupational respiratory allergy? *Allergy* 2004;**59**:1294-1300.
111. Walusiak J, Hanke W, Gorski P, Palczynski C. Respiratory allergy in apprentice bakers: do occupational allergies follow the allergic march? *Allergy* 2004;**59**:442-450.
112. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ* 1999;**318**:593-596.
113. Leynaert B, Neukirch C, Kony S, Guenegou A, Bousquet J, Aubier M et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol* 2004;**113**:86-93.
114. Lombardi C, Passalacqua G, Gargioni S, Senna G, Ciprandi G, Scordamaglia A et al. The natural history of respiratory allergy: a follow-up study of 99 patients up to 10 years. *Respir Med* 2001;**95**:9-12.
115. Gustafsson D, Sjöberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis - a prospective follow-up to 7 years of age. *Allergy* 2000;**55**:240-245.
116. Toren K, Olin AC, Hellgren J, Hermansson BA. Rhinitis increase the risk for adult-onset asthma - a Swedish population-based case-control study (MAP-study). *Respir Med* 2002;**96**:635-641.
117. 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.
118. Plaschke PP, Janson C, Norrman E, Björnsson E, Ellbjär S, Jarvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. *Am J Respir Crit Care Med* 2000;**162**:920-924.
119. Sole D, Camelo-Nunes IC, Wandalsen GF, Melo KC, Nasipitz CK. Is rhinitis alone or associated with atopic eczema a risk factor for severe asthma in children? *Pediatr Allergy Immunol* 2005;**16**:121-125.

120. Chatkin MN, Menezes AM. Prevalence and risk factors for asthma in schoolchildren in southern Brazil. *J Pediatr (Rio J)* 2005;**81**:411–416.
121. Porsbjerg C, von Linstow ML, Ulrik CS, Nepper-Christensen SC, Backer V. Outcome in adulthood of asymptomatic airway hyperresponsiveness to histamine and exercise-induced bronchospasm in childhood. *Ann Allergy Asthma Immunol* 2005;**95**:137–142.
122. Sherrill DL, Guerra S, Cristina Minervini M, Wright AL, Martinez FD. The relation of rhinitis to recurrent cough and wheezing: a longitudinal study. *Respir Med* 2005;**99**:1377–1385.
123. Guerra S, Sherrill DL, Baldacci S, Carrozzi L, Pistelli F, Di Pede F et al. Rhinitis is an independent risk factor for developing cough apart from colds among adults. *Allergy* 2005;**60**:343–349.
124. Cibella F, Cuttitta G, La Grutta S, Hopps MR, Passalacqua G, Pajno GB et al. Bronchial hyperresponsiveness in children with atopic rhinitis: a 7-year follow-up. *Allergy* 2004;**59**:1074–1079.
125. Kircher S, Schatz M, Long L. Variables affecting asthma course during pregnancy. *Ann Allergy Asthma Immunol* 2002;**89**:463–466.
126. Price D, Zhang Q, Kocovar VS, Yin DD, Thomas M. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy* 2005;**35**:282–287.
127. Thomas M, Kocovar VS, Zhang Q, Yin DD, Price D. Asthma-related health care resource use among asthmatic children with and without concomitant allergic rhinitis. *Pediatrics* 2005;**115**:129–134.
128. Bousquet J, Gaugris S, Kocovar VS, Zhang Q, Yin DD, Polos PG et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the improving asthma control trial. *Clin Exp Allergy* 2005;**35**:723–727.
129. Sazonov Kocovar V, Thomas J 3rd, Jonsson L, Valovirta E, Kristensen F, Yin DD et al. Association between allergic rhinitis and hospital resource use among asthmatic children in Norway. *Allergy* 2005;**60**:338–342.
130. Kanani AS, Broder I, Greene JM, Tarlo SM. Correlation between nasal symptoms and asthma severity in patients with atopic and nonatopic asthma. *Ann Allergy Asthma Immunol* 2005;**94**:341–347.
131. Corren J, Fish H, Gumarange J. Nasal response to natural cat allergen exposure is significantly greater in patients with rhinitis and asthma than in patients with rhinitis alone. *J Allergy Clin Immunol* 2005;**115**:202–203.
132. Schramm B, Ehlken B, Smala A, Quednau K, Berger K, Nowak D. Cost of illness of atopic asthma and seasonal allergic rhinitis in Germany: 1-yr retrospective study. *Eur Respir J* 2003;**21**:116–122.
133. Halpern MT, Schmier JK, Richner R, Guo C, Togias A. Allergic rhinitis: a potential cause of increased asthma medication use, costs, and morbidity. *J Asthma* 2004;**41**:117–126.
134. Woszczek G, Kowalski ML, Borowiec M. Association of asthma and total IgE levels with human leucocyte antigen-DR in patients with grass allergy. *Eur Respir J* 2002;**20**:79–85.
135. Palmer LJ, Knuiman MW, Divitini ML, Burton PR, James AL, Bartholomew HC et al. Familial aggregation and heritability of adult lung function: results from the Busselton Health Study. *Eur Respir J* 2001;**17**:696–702.
136. Dizier MH, Bouzigon E, Guilloud-Bataille M, Betard C, Bousquet J, Charpin D et al. Genome screen in the French EGEA study: detection of linked regions shared or not shared by allergic rhinitis and asthma. *Genes Immun* 2005;**6**:95–102.
137. Kurz T, Altmueller J, Strauch K, Ruschendorf F, Heinzmann A, Moffatt MF et al. A genome-wide screen on the genetics of atopy in a multiethnic European population reveals a major atopy locus on chromosome 3q21.3. *Allergy* 2005;**60**:192–199.
138. Braunstahl GJ, Fokkens WJ, Overbeek SE, Kleinjan A, Hoogsteden HC, Prins JB. Mucosal and systemic inflammatory changes in allergic rhinitis and asthma: a comparison between upper and lower airways. *Clin Exp Allergy* 2003;**33**:579–587.
139. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000;**161**:2051–2057.
140. Gaga M, Lambrou P, Papageorgiou N, Koulouris NG, Kosmas E, Fragakis S et al. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. *Clin Exp Allergy* 2000;**30**:663–669.
141. Milanese M, Crimi E, Scordamaglia A, Riccio A, Pellegrino R, Canonica GW et al. On the functional consequences of bronchial basement membrane thickening. *J Appl Physiol* 2001;**91**:1035–1040.
142. Crimi E, Milanese M, Oddera S, Mereu C, Rossi GA, Riccio A et al. Inflammatory and mechanical factors of allergen-induced bronchoconstriction in mild asthma and rhinitis. *J Appl Physiol* 2001;**91**:1029–1034.
143. Ponikau JU, Sherris DA, Kephart GM, Kern EB, Gaffey TA, Tarara JE et al. Features of airway remodelling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma? *J Allergy Clin Immunol* 2003;**112**:877–882.
144. Becky Kelly EA, Busse WW, Jarjour NN. A comparison of the airway response to segmental antigen bronchoprovocation in atopic asthma and allergic rhinitis. *J Allergy Clin Immunol* 2003;**111**:79–86.
145. Boulay ME, Boulet LP. Lower airway inflammatory responses to repeated very-low-dose allergen challenge in allergic rhinitis and asthma. *Clin Exp Allergy* 2002;**32**:1441–1447.
146. Riccio AM, Tosca MA, Cosentino C, Pallestrini E, Ameli F, Canonica GW et al. Cytokine pattern in allergic and non-allergic chronic rhinosinusitis in asthmatic children. *Clin Exp Allergy* 2002;**32**:422–426.
147. Palczynski C, Walusiak J, Ruta U, Gorski P. Occupational asthma and rhinitis due to glutaraldehyde: changes in nasal lavage fluid after specific inhalatory challenge test. *Allergy* 2001;**56**:1186–1191.
148. Chakir J, Laviolette M, Turcotte H, Boutet M, Boulet LP. Cytokine expression in the lower airways of non asthmatic subjects with allergic rhinitis: influence of natural allergen exposure. *J Allergy Clin Immunol* 2000;**106**:904–910.
149. de Magalhaes Simoes S, dos Santos MA, da Silva Oliveira M, Fontes ES, Fernelian S, Garippo AL et al. Inflammatory cell mapping of the respiratory tract in fatal asthma. *Clin Exp Allergy* 2005;**35**:602–611.
150. Ciprandi G, Vizzaccaro A, Cirillo I, Tosca M, Massolo A, Passalacqua G. Nasal eosinophils display the best correlation with symptoms, pulmonary function and inflammation in allergic rhinitis. *Int Arch Allergy Immunol* 2005;**136**:266–272.

151. Watelet JB, Claeys C, Perez-Novo C, Gevaert P, Van Cauwenberge P, Bachert C. Transforming growth factor beta1 in nasal remodelling: differences between chronic rhinosinusitis and nasal polyposis. *Am J Rhinol* 2004;**18**:267–272.
152. Watelet JB, Bachert C, Claeys C, Van Cauwenberge P. Matrix metalloproteinases MMP-7, MMP-9 and their tissue inhibitor TIMP-1: expression in chronic sinusitis vs nasal polyposis. *Allergy* 2004;**59**:54–60.
153. Salib RJ, Kumar S, Wilson SJ, Howarth PH. Nasal mucosal immunorepression of the mast cell chemoattractants TGF-beta, eotaxin, and stem cell factor and their receptors in allergic rhinitis. *J Allergy Clin Immunol* 2004;**114**:799–806.
154. Bousquet J, Jacot W, Vignola AM, Bachert C, Van Cauwenberge P. Allergic rhinitis: a disease remodelling the upper airways? *J Allergy Clin Immunol* 2004;**113**:43–49.
155. Salib RJ, Howarth PH. Remodelling of the upper airways in allergic rhinitis: is it a feature of the disease? *Clin Exp Allergy* 2003;**33**:1629–1633.
156. Jouaville LF, Annesi-Maesano I, Nguyen LT, Bocage AS, Bedu M, Caillaud D. Interrelationships among asthma, atopy, rhinitis and exhaled nitric oxide in a population-based sample of children. *Clin Exp Allergy* 2003;**33**:1506–1511.
157. Olin AC, Alving K, Toren K. Exhaled nitric oxide: relation to sensitization and respiratory symptoms. *Clin Exp Allergy* 2004;**34**:221–226.
158. Higashi N, Taniguchi M, Mita H, Kawagishi Y, Ishii T, Higashi A et al. Clinical features of asthmatic patients with increased urinary leukotriene E4 excretion (hyperleukotrienuria): involvement of chronic hyperplastic rhinosinusitis with nasal polyposis. *J Allergy Clin Immunol* 2004;**113**:277–283.
159. Bavbek S, Saryal S, Karabiyikoglu G, Misirligil Z. Pulmonary function parameters in patients with allergic rhinitis. *J Investig Allergol Clin Immunol* 2003;**13**:252–258.
160. Nickel R, Lau S, Niggemann B, Sommerfeld C, Wahn U. Comparison of bronchial responsiveness to histamine in asthma, allergic rhinitis and allergic sensitization at the age of 7 years. *Clin Exp Allergy* 2002;**32**:1274–1277.
161. Koh YI, Choi IS. Relationship between nasal and bronchial responsiveness in perennial allergic rhinitis patients with asthma. *Int Arch Allergy Immunol* 2002;**129**:341–347.
162. Ciprandi G, Cirillo I, Vizzaccaro A, Monardo M, Tosca MA. Early bronchial airflow impairment in patients with persistent allergic rhinitis and bronchial hyperreactivity. *Respir Med* 2005;**99**:1606–1612.
163. Valero A, Serrano C, Valera JL, Barbera A, Torrego A, Mullol J et al. Nasal and bronchial response to exercise in patients with asthma and rhinitis: the role of nitric oxide. *Allergy* 2005;**60**:1126–1131.
164. Walusiak J, Wiszniewska M, Krawczyk-Adamus P, Palczynski C. Occupational allergy to wheat flour. Nasal response to specific inhalative challenge in asthma and rhinitis vs. isolated rhinitis: a comparative study. *Int J Occup Med Environ Health* 2004;**17**:433–440.
165. Saini S, Bloom DC, Bieneman A, Vasagar K, Togias A, Schroeder J. Systemic effects of allergen exposure on blood basophil IL-13 secretion and FcepsilonRIbeta. *J Allergy Clin Immunol* 2004;**114**:768–774.
166. Wilson AM, Duong M, Crawford L, Denburg J. An evaluation of peripheral blood eosinophil/basophil progenitors following nasal allergen challenge in patients with allergic rhinitis. *Clin Exp Allergy* 2005;**35**:39–44.
167. Bresciani M, Paradis L, Des Roches A, Vernhet H, Vachier I, Godard P et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001;**107**:73–80.
168. ten Brinke A, Grootendorst DC, Schmidt JT, De Bruine FT, van Buchem MA, Sterk PJ et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002;**109**:621–626.
169. Dhong HJ, Kim HY, Cho DY. Histopathologic characteristics of chronic sinusitis with bronchial asthma. *Acta Otolaryngol* 2005;**125**:169–176.
170. Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. *Cochrane Database Syst Rev* 2003;**4**:CD003570.
171. Dahl R, Nielsen LP, Kips J, Foresi A, Cauwenberge P, Tudoric N et al. Intranasal and inhaled fluticasone propionate for pollen-induced rhinitis and asthma. *Allergy* 2005;**60**:875–881.
172. Nathan RA, Yancey SW, Waitkus-Edwards K, Prillaman BA, Stauffer JL, Philpot E et al. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. *Chest* 2005;**128**:1910–1920.
173. Stelmach R, do Patrocinio TNM, Ribeiro M, Cukier A. Effect of treating allergic rhinitis with corticosteroids in patients with mild-to-moderate persistent asthma. *Chest* 2005;**128**:3140–3147.
174. Camargos PA, Rodrigues ME, Lasmar LM. Simultaneous treatment of asthma and allergic rhinitis. *Pediatr Pulmonol* 2004;**38**:186–192.
175. Thio BJ, Slingerland GL, Fredriks AM, Nagelkerke AF, Scheeren RA, Neijens HJ et al. Influence of intranasal steroids during the grass pollen season on bronchial responsiveness in children and young adults with asthma and hay fever. *Thorax* 2000;**55**:826–832.
176. Sandrini A, Ferreira IM, Jardim JR, Zamel N, Chapman KR. Effect of nasal triamcinolone acetonide on lower airway inflammatory markers in patients with allergic rhinitis. *J Allergy Clin Immunol* 2003;**111**:313–320.
177. Adams RJ, Fuhlbrigge AL, Finkelstein JA, Weiss ST. Intranasal steroids and the risk of emergency department visits for asthma. *J Allergy Clin Immunol* 2002;**109**:636–642.
178. Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol* 2002;**109**:57–62.
179. Corren J, Manning BE, Thompson SF, Hennessy S, Strom BL. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. *J Allergy Clin Immunol* 2004;**113**:415–419.
180. Aubier M, Neukirch C, Peiffer C, Melac M. Effect of cetirizine on bronchial hyperresponsiveness in patients with seasonal allergic Rhinitis and asthma. *Allergy* 2001;**56**:35–42.
181. Berger WE, Schenkel EJ, Mansfield LE. Safety and efficacy of desloratadine 5 mg in asthma patients with seasonal allergic rhinitis and nasal congestion. *Ann Allergy Asthma Immunol* 2002;**89**:485–491.

182. Baena-Cagnani CE, Berger WE, DuBuske LM, Gurne SE, Stryszak P, Lorber R et al. Comparative effects of desloratadine versus montelukast on asthma symptoms and use of beta 2-agonists in patients with seasonal allergic rhinitis and asthma. *Int Arch Allergy Immunol* 2003;**130**:307–313.
183. Reinartz SM, Overbeek SE, Kleinjan A, Drunen CM, Braunstahl GJ, Hoogsteden HC et al. Desloratadine reduces systemic allergic inflammation following nasal provocation in allergic rhinitis and asthma patients. *Allergy* 2005;**60**:1301–1307.
184. Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. A comparison of topical budesonide and oral montelukast in seasonal allergic rhinitis and asthma. *Clin Exp Allergy* 2001;**31**:616–624.
185. Philip G, Nayak AS, Berger WE, Leynadier F, Vrijens F, Dass SB et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin* 2004;**20**:1549–1558.
186. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004;**116**:338–344.
187. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;**109**:251–256.
188. Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004;**114**:851–857.
189. Chang J, Hong CS. The effect of immunotherapy on nonspecific bronchial hyperresponsiveness in bronchial asthma and allergic rhinitis. *Yonsei Med J* 2001;**42**:106–113.
190. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;**107**:87–93.
191. Grembiale RD, Camporota L, Naty S, Tranfa CM, Djukanovic R, Marsico SA. Effects of specific immunotherapy in allergic rhinitis individuals with bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 2000;**162**:2048–2052.
192. Polosa R, Li Gotti F, Mangano G, Mastruzzo C, Pistorio MP, Crimi N. Monitoring of seasonal variability in bronchial hyper-responsiveness and sputum cell counts in non-asthmatic subjects with rhinitis and effect of specific immunotherapy. *Clin Exp Allergy* 2003;**33**:873–881.
193. Lombardi C, Gargioni S, Venturi S, Zoccali P, Canonica GW, Passalacqua G. Controlled study of preseasonal immunotherapy with grass pollen extract in tablets: effect on bronchial hyperreactivity. *J Invest Allergol Clin Immunol* 2001;**11**:41–45.
194. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;**60**:4–12.
195. Olaguibel JM, Alvarez Puebla MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. *J Invest Allergol Clin Immunol* 2005;**15**:9–16.
196. 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.
197. Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedegcock S, Blogg M et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004;**59**:709–717.