

Original article

Association between nasal and bronchial symptoms in subjects with persistent allergic rhinitis

Background: The association between nasal and bronchial symptoms, and the course of bronchial responsiveness and airway inflammation in house dust mite sensitive persistent rhinitis over a prolonged time period has not been thoroughly explored.

Objective: To determine if nasal symptoms were associated with bronchial symptoms in persistent rhinitic subjects, and to assess their bronchial responsiveness and airway inflammation in comparison to nonrhinitic, nonatopic controls. The additional impact of pollen sensitivity on the lower airways in rhinitic subjects was also addressed.

Methods: Rhinitics and controls answered telephone symptom questionnaires once every 2 weeks for 1 year. Every 3 months, exhaled nitric oxide (eNO) and bronchial responsiveness to histamine were measured.

Results: Thirty-seven rhinitics and 19 controls completed the study. High nasal symptom scores in rhinitic subjects were associated with bronchial symptoms (OR = 1.7, 95% CI 1.2–2.5). Bronchial hyper-responsiveness was present in 32.4% of rhinitic subjects on at least one clinical visit during the year. Pollen allergy caused seasonal variation in eNO ($P = 0.03$).

Conclusion: In persistent rhinitic subjects, high nasal symptom scores were associated with bronchial symptoms, and many subjects experienced bronchial hyper-responsiveness during the year. Persistent rhinitic subjects were more at risk than healthy adults of bronchial symptoms and airway inflammation, which are likely risk factors for asthma.

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Key words: bronchial hyper-responsiveness; bronchial symptoms; house dust mite; nasal symptoms; persistent rhinitis.

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Accepted for publication 10 September 2003

House dust mite (HDM) allergy is one of the most important risk factors for rhinitis and asthma, especially in Sydney (1, 2). Perennial allergic rhinitis and seasonal allergic rhinitis are now, respectively, referred to as 'persistent' and 'intermittent' allergic rhinitis (3, 4). Persistent allergic rhinitis has not been as well studied, and is less recognized by practitioners than intermittent allergic rhinitis (5). There has been ongoing debate in the literature about whether ailments of the upper and lower respiratory tract, such as rhinitis and asthma, should be treated as if they are diseases of a single organ, the respiratory tract. A naso-bronchial reflex relating upper and lower airways (6) has been described and there is evidence from asthmatic subjects that treating rhinitis can improve asthma control (7). Rhinitic subjects have slightly more airway inflammation and more occasions of wheeze than normals, but not to the same extent as

asthmatic subjects (8–10). However, it is not known if the occurrence of severe nasal symptoms leads to development of bronchial symptoms in an environment with continuous high exposure to allergen.

Since the concentration of HDM allergen in Sydney, Australia, is high [mean (95% CI): 38.9 (CI 31.8–47.5) µg/g fine dust] compared to other countries, with little seasonal variation (11), we had an opportunity to study a cohort living in an environment with continuously high allergen exposure. Little is known about the natural course of HDM-sensitive persistent rhinitic subjects regarding the relationship between nasal and bronchial symptoms, and the course of bronchial responsiveness and inflammation over a prolonged period of 1 year.

The primary aim of this study was to determine if there was an association between the occurrence of nasal and bronchial symptoms in persistent rhinitic subjects. We also wanted to assess the degree of bronchial responsiveness and inflammation in persistent rhinitic subjects at intervals during the year, compared to a control group. In addition, we assessed whether the additional allergen load of pollen had an effect on these outcomes in a subgroup

Abbreviations: DRR, dose–response ratio; eNO, exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; GEE, generalized estimating equations; HDM, house dust mite; TNSS, total nasal symptom score.

of HDM sensitive persistent rhinitic subjects who were also sensitive to pollen.

Methods

Subjects

We conducted a parallel prospective study of HDM sensitive subjects with persistent rhinitis and healthy nonallergic controls, where each individual was followed for a full calendar year. Subjects were recruited by advertisements seeking subjects with nasal symptoms who thought they were allergic to HDMs. These were displayed throughout the University of Sydney campus and in local newspapers. Written consent was obtained from all subjects and the study was approved by the Central Sydney Area Health Service Ethics Review Committee.

Inclusion criteria for persistent rhinitic subjects was on the basis of a positive (≥ 4 mm) skin test to the HDMs *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus*, and rhinitis symptoms for most of the year, for at least the previous 2 years. Subjects were not excluded if they had intermittent exacerbations of rhinitis symptoms in addition to their underlying persistent symptoms. Skin prick tests for common aeroallergens were performed at the initial visit. Exclusion criteria were current smoking, rhinitis symptoms only at one time of year, regular chest medication use, nasal polyps, major septal deviation or any chronic disease, including asthma, apart from their allergic disease. We did not modify treatment in any of the subjects. Medication management was left entirely up to the subject for the duration of the study.

Exclusion criteria for the controls were a recent history of rhinitis symptoms, chronic disease, regular medication or current smoking, and a wheal size larger or equal to 4 mm to any of the allergens on the skin prick test panel.

Study design

This was a prospective cohort study in a real-life setting. The study protocol did not inflict any modifications in treatment on any of the subjects. Medication management was left entirely up to the subject and their regular healthcare professionals for the duration of the study. Subjects were screened by a skin prick test, thorough nose and throat examination by a physician and symptom history at the initial visit to our laboratory. Every second week over the duration of 1 year, every subject from the control and persistent rhinitic groups was telephoned and asked a standard set of questions about nasal, throat and chest symptoms and medication use from the previous 1 week.

After the initial laboratory visit, subjects had four clinical visits over the following year, each 3 months apart. At every laboratory visit, including the initial one, subjects underwent a bronchial histamine challenge test and measurement of exhaled nitric oxide (eNO).

Skin prick test

At the initial visit, a skin prick test was performed by the methods of Pepys (12) to a standard set of aeroallergens, including a positive and negative control, cockroach, house dust, two HDMs – *D. farinae* and *D. pteronyssinus*, cat dander, dog dander, horse hair, feathers, ragweed, plantain, timothy grass, ryegrass, *Aspergillus* and *Alternaria*. Subjects were advised to withhold antihistamines for 48 h prior to the skin prick test. Wheal sizes of ≥ 4 mm were regarded as positive after subtracting the size of the negative control.

Telephone interview/questionnaire

This questionnaire was developed specifically for our study and answers were recorded immediately over the telephone and transferred to a computerized database.

The rhinitis symptoms of nasal obstruction, itching/sneezing and secretion/runny nose were scored separately on a severity scale between 0 and 3 (0 = absent, 1 = mild, 2 = moderate and 3 = severe). These three symptom scores were combined to produce a total nasal symptom score (TNSS) with a maximum score of 9. This composite score or TNSS was used in our analyses. The 'normal range' of the TNSS was calculated from the control group (mean + 2SD). 'High' nasal symptom scores were defined as those above the normal range.

The questions asked by phone that made up the TNSS were as follows:

Rate the following symptom for the last week:

Nasal obstruction

Was it

0 = no symptom

1 = mild – awareness but not troubled

2 = moderate – troublesome but not interfering with normal daily activities or sleep

3 = severe – interfering with normal daily activities or sleep.

The same format of questions was also asked for 'itching or sneezing' and 'secretion' (runny nose).

Bronchial symptoms were defined as present when the subject confirmed they had experienced at least one of the following symptoms in their telephone questionnaire: cough, shortness of breath, phlegm, wheezing or tightness in the chest.

Every subject was specifically asked at each telephone interview if they had experienced any health related problems in the last 2 weeks not related to their allergy, such as a respiratory tract infection. If the subject had experienced a respiratory tract infection within the last 2 weeks, then all the data from that questionnaire was excluded from our analyses.

The number of days per week that chest medications had been used was recorded. Chest medications were categorized as either inhaled bronchodilators, inhaled glucocorticosteroids, oral bronchodilators, antibiotics, alternative medicine or other. Chest medication use was classified as either intermittent or never. Regular use of chest medication was an exclusion criterion for inclusion in the study. If the subject reported medication use on one or more occasions, they were 'intermittent' users, and if they never reported medication use, they were classified as 'never' users of medication.

Bronchial histamine challenge test

Orally inhaled histamine was administered by the rapid method (13) using hand-held De Vilbiss nebulizers in doses ranging from 0.0625 to 3.9 μ mol. Subjects were advised to withhold short-acting bronchodilators for 4–6 h before the challenge. None of the subjects took long-acting β_2 agonists. Lung function was measured using the Microloop II spirometer (Micro Medical Ltd, UK), and the predicted values programmed into the spirometer were those from European Community for Coal and Steel (ECCS) (14). The challenge was stopped if the forced expiratory volume in 1 s (FEV₁) fell by 20% or more, or if the final dose of 3.9 μ mol of histamine was reached. Bronchodilator aerosol was given to aid recovery, if FEV₁ fell by 10% or more by the end of the challenge.

We calculated the dose–response ratio (DRR) of each challenge test, derived by dividing the fall in FEV₁ at the final dose by the dose of histamine in micromoles (% fall/ μ mol). Dose–response ratio

is proposed as an index of responsiveness (15–17), and we chose to use it in our analysis because the majority of our subjects were not expected to reach a PD₂₀ value. Bronchial hyper-responsiveness was defined as a fall in FEV₁ by 20% or more during the challenge test.

Orally exhaled nitric oxide

Two single breath samples of orally exhaled air were collected into reservoir bags before the bronchial histamine challenge test. These tests were repeated in the same order at every visit. Mixed expired NO was measured using a modification of the method of Massaro et al. (18), and Salome et al. (19). The measurement was performed with the subject standing, without wearing a noseclip. The patient took a deep breath and then exhaled over 5–15 s towards residual volume into an NO impermeable polyethylene bag (Scholle Industries Pty Ltd, Elizabeth West, Australia). The exhaled flow, measured by a rotameter (Dwyer Flowmeter Model VFASS-25, AMBIT Instruments Pty Ltd, Parramatta, Australia), was 10 l/min at a mouth pressure > 20 cm H₂O. This exhalation pressure forces the soft palate to close during exhalation, therefore excluding contamination of exhaled breath with the higher concentration of NO found in the nose (20). The exhaled gas from a single breath was analysed within an hour using a chemiluminescence analyser (Thermo Environmental Instruments Model 42C), which has a lower limit of detection of 1 ppb. A reference sample of ambient air from our laboratory was measured during each subject's visit.

Pollen counts

To confirm the pollen season in Sydney, pollen counts were monitored throughout periods of the study. Pollen count data were obtained from the Department of Clinical Immunology and Allergy and the Westmead Millennium Institute, Westmead Hospital, Sydney. Burkard 7-day volumetric spore traps were used between May and November to capture spore particles at a site in Homebush, a central point in the Sydney region. Details of the pollen count methods used are fully described elsewhere (21).

Statistical analysis

Data were analysed using the statistical package sas (SAS Institute, Inc, Cary, NC). Normality was tested using the Shapiro–Wilk test. Geometric means and 95% confidence intervals are reported. Two sample *t*-test was used to compare mean symptom score between rhinitis group and the control group. Chi-square test (and Fisher exact test when required) was used to compare the mean percentage of the binary outcome variables between the two groups. Generalized estimating equations (GEE) were used to examine whether there was a relationship between nasal and bronchial symptoms,

taking into account the serial correlation among repeated measures within each subject.

Results

We recruited 40 HDM sensitized persistent rhinitic subjects and 23 controls. Three of the persistent rhinitic subjects and four controls withdrew from the study because they moved out of the Sydney region (*n* = 3), moved without leaving a forwarding address (*n* = 2), or the subjects chose to withdraw due to lack of time to participate in the study (*n* = 2). A total of 37 persistent rhinitic subjects and 19 controls completed the study. All 37 persistent rhinitic subjects were sensitized to either *D. farinae* or *D. pteronyssinus*. Of these, 21 (57%) were also sensitized to one or more of the pollens of ragweed, plantain, timothy grass or ryegrass. The characteristics of the subjects at the initial visit are shown in Table 1. Persistent rhinitic subjects are divided into two groups (according to the presence or absence of pollen allergy). The three groups of subjects were similar in baseline data regarding age and percent predicted FEV₁, but eNO levels and DRR were significantly higher in the rhinitic subjects compared to controls (*P* = 0.0002 and *P* < 0.0001, respectively).

Nasal symptoms

The mean TNSS over 1 year for the control group and persistent rhinitic subjects is shown in Table 2(i). Total nasal symptom scores were reported as 'high' if they were 3 or above (above the mean for controls plus 2SD). The frequency of high nasal symptom scores reported is shown in Table 2(ii), and was consistent throughout the year among the persistent rhinitic subjects (*P* = 0.15), i.e. there was no seasonal variation in the frequency of high nasal symptom scores reported.

Medication use

Intermittent chest medication use was recorded in the fortnightly telephone questionnaires and is presented as a percentage in Table 2(iii). Chest medications used included antibiotics, cold and flu tablets, inhaled corti-

Table 1. Subject characteristics at initial visit

	Controls	Rhinitics (HDM)	Rhinitics (HDM + pollen)	<i>P</i> value*
N	19	16	21	
Mean age (range)	36.8 (18–60)	33.4 (18–51)	33.9 (18–64)	0.65
Mean% predicted FEV ₁ (SD)	104.7 (14.8)	106.2 (12.1)	102.5 (15.6)	0.74
Mean eNO (ppb) (95% CI)	9.3 (7.4–11.8)	17.1 (13.5–21.7)	20.1 (15.4–26.2)	0.0002
Mean DRR (% fall/μmol) (95% CI)	1.0 (0.5–1.5)	1.9 (0.7–3.5)	2.9 (1.8–4.3)	<0.0001

* From one-way analysis of variance (anova) between the three groups.

Table 2. Summary of results from fortnightly questionnaire, bronchial challenge tests and exhaled nitric oxide (95% CI) over the 12-month study period

	Controls	Rhinitics	P value
(i) Mean TNSS	0.7 (0.5–0.8)	3.7 (3.4–4.0)	<0.0001
(ii) Percent occurrence of 'high' nasal symptom scores in fortnightly questionnaires	9% (4–14%)	65% (59–71%)	<0.0001
(iii) Percent intermittent chest medication use	26.3% (6.5–46.1%)	37.8% (22.2–53.4%)	0.6*
(iv) Percent occurrence of bronchial symptoms	9% (4–14%)	33.8% (28.1–39.5%)	<0.0001
(v) Percent occurrence of bronchial symptoms in the presence of 'high' TNSS	5.7% (0.4–28.7%)	46.5% (38.5–54.5%)	<0.0001
(vi) Mean DRR over the year	0.7 (0.4–1.1)	2.2 (1.5–3.0)	0.004
(vii) Percent occurrence of bronchial hyper-responsiveness (BHR) on at least one clinical visit	5.3% (0.3–28.1%)	32.4% (17.3–47.5%)	0.04†
(viii) Mean eNO (ppb) over the year	9.7 (8–11.9)	17.2 (15.1–19.7)	<0.0001

* From chi-squared test.

† From Fisher exact test.

costeroids, inhaled bronchodilators, oral bronchodilators, Tilade, cough suppressants and alternative medicine.

Bronchial symptoms, dose–response ratio and exhaled nitric oxide

The percent occurrence of bronchial symptoms is shown in Table 2(iv). In the persistent rhinitic subjects, we determined if bronchial symptoms occurred more frequently when high nasal symptom scores were reported, by calculating the proportion of bronchial symptoms that were present during the periods of high nasal symptom scores from the telephone interview questionnaires (Table 2v).

The probability of persistent rhinitic subjects having bronchial symptoms was significantly increased if high nasal symptom scores were present, after adjusting for the four seasons (OR = 1.7, 95% CI 1.2–2.5). Persistent rhinitic subjects were more likely to have bronchial symptoms in the presence of high nasal symptom scores than in the presence of low nasal symptom scores (OR = 1.81, 95% CI 1.2–2.6). There was a trend for more frequent occurrence of bronchial symptoms in persistent rhinitic subjects in winter than in summer, which was of borderline significance ($P = 0.05$).

Both bronchial responsiveness to histamine (DRR) and airway inflammation (eNO) were greater in persistent rhinitic subjects than in controls (Table 2vi, viii). The incidence of bronchial hyper-responsiveness on at least one clinical visit during the year was higher in persistent rhinitic subjects than controls (Table 2vii). There was no significant seasonal variation in DRR values in either controls ($P = 0.8$) or rhinitics ($P = 0.4$). There was a significant seasonal difference in eNO levels in persistent rhinitic subjects ($P = 0.002$), but not in controls ($P = 0.88$). The highest mean eNO was 18.8 ppb in winter (95% CI 15.2–23.2), and the lowest mean eNO was 12.3 ppb in summer (95% CI 9.5–16.0). The mean eNO level in autumn was 16.4 ppb (95% CI 12.7–21.1) and in spring was 14.8 ppb (95% CI 11.4–19.0).

We classified separately those persistent rhinitis subjects who never reported bronchial symptoms to those who reported bronchial symptoms on one or more

occasions, to determine whether there was a difference in the level of eNO (inflammation) and DRR (bronchial responsiveness) between these two symptom groups. Bronchial symptoms were reported by 31 out of 37 (83.8%) persistent rhinitic subjects compared with only five of 19 (26.3%) of subjects in the control group. There were no significant differences between persistent rhinitic subjects who did and did not report bronchial symptoms in eNO (18.0 (CI 15.5–20.9) ppb vs 13.6 (CI 10.7–17.3) ppb, $P = 0.13$) or in (DRR 2.2 (CI 1.4–3.2)% fall/ μ mol vs 2.3 (CI 1.2–3.5)% fall/ μ mol, $P = 0.98$).

Pollen counts and the effect of pollen sensitivity

Pollen counts were recorded between May and November and averaged over 1998, 1999 and 2000. The peak pollen periods were September and October, with a mean weekly count of 207 grains/ m^3 and the lowest counts were in May and June, with a mean weekly count of 10 grains/ m^3 .

There were no significant differences between subjects with and without pollen allergy in the reporting of bronchial symptoms ($P = 0.1$), mean DRR to histamine ($P = 0.7$) or mean level of eNO ($P = 0.89$). There was no increased association of nasal symptoms with bronchial symptoms if the persistent rhinitic subjects also had a pollen allergy ($P = 0.15$). In subjects with pollen allergy, there was no significant seasonal variation in bronchial symptoms ($P = 0.07$) or DRR ($P = 0.8$), but eNO was higher in winter ($P = 0.03$). In subjects without pollen allergy, there was no significant seasonal variation in bronchial symptoms ($P = 0.66$), DRR ($P = 0.4$) or eNO ($P = 0.11$).

Discussion

This study has shown that in HDM allergic subjects with persistent rhinitis, living in an environment where allergen levels are known to be continually high, the occurrence of high nasal symptom scores were significantly associated with bronchial symptoms. Nasal symptom

scores were higher in persistent rhinitic subjects than in nonrhinitic controls, and persistent rhinitic subjects reported high nasal symptom scores on average for 65% of the time assessed in the study. Bronchial responsiveness and inflammation (DRR and eNO) were increased in persistent rhinitic subjects compared to our control group, but were not different between persistent rhinitic subjects with and without bronchial symptoms. In subjects with both HDM and pollen allergy, however, the additional allergen load in spring was only associated with some seasonal variation in eNO.

The presence of high nasal symptom scores was associated with bronchial symptoms. This may indicate a coexisting inflammation in the upper and lower airways. There is an intricate relationship between rhinitis and asthma which has been discussed in a number of studies (10, 22–24). Rhinitis is a significant risk factor for adult-onset asthma in both atopic and nonatopic subjects (25). The prevalence of asthma is greater in rhinitic than nonrhinitic subjects, after accounting for atopy (26), and bronchial hyper-responsiveness is a common finding in subjects with allergic rhinitis (27). Of our persistent rhinitic subjects, 32.4% had bronchial hyper-responsiveness to histamine during at least one clinical visit during the year. Our finding that the DRR to histamine was significantly higher in the persistent rhinitic subjects than nonallergic healthy controls supports the view that there may be coexisting inflammation in the upper and lower airways. However, the mean DRR of 2.2 in our persistent rhinitic subjects is within the normal range, and does not indicate bronchial hyper-responsiveness. However, it was significantly higher than the mean DRR in our control group, which may still be of clinical importance. It has also been reported that the relationship between rhinitis and asthma symptoms is stronger for animal and mite allergy than for pollen allergy (28). This is likely to be due to the smaller particle size of animal and mite allergens compared to pollen, and hence their journey deeper into the respiratory tract, in combination with the duration of exposure to persistent allergens being substantially longer than the duration of exposure to intermittent allergens.

An important finding from this study is the relationship found between bronchial and nasal symptoms in persistent allergic rhinitis, a relationship that possibly places these subjects at more of a risk of developing asthmatic symptoms. It could also be reasoned that persistent rhinitics are at a greater risk of developing bronchial symptoms than intermittent rhinitics because they are continuously exposed to the perennial allergen, rather than just for a small portion of the year as seen with seasonal allergens. It is likely that these rhinitics may have very mild undiagnosed asthma, and this mild asthma is at risk of worsening if their rhinitic inflammation and symptoms are not treated optimally.

Exhaled nitric oxide is an indirect marker of airway inflammation in atopic diseases such as asthma and rhinitis (8, 9, 29). A study by Henriksen's group (30)

looking at the effect of persistent and intermittent allergic rhinitis on eNO levels has shown that the level of eNO is 1.5-fold greater in allergic rhinitis subjects than controls ($P = 0.04$). In our study, the level of eNO was 1.8-fold greater in persistent rhinitic subjects than controls. Henriksen's study also found that baseline eNO concentration was significantly greater in subjects with both intermittent (seasonal) and persistent (perennial) sensitization than in those with intermittent sensitization only. The increase of airway inflammation as measured by eNO in persistent rhinitis compared to intermittent rhinitis is likely to be due to the constant exposure that persistent rhinitic subjects have to their allergen all year compared to the relatively short bursts of allergen exposure experienced by intermittent rhinitic subjects. Our findings of an increase in bronchial hyper-responsiveness and eNO in persistent rhinitic subjects, as measures of airway inflammation, contributes to evidence for a link between the nose and the lung. Still, in our study approximately half of all bronchial symptoms occurred when nasal symptom scores were within the normal range. This suggests that bronchial symptoms can be experienced frequently in persistent rhinitic subjects unaccompanied by high nasal symptom scores. However, high nasal symptom scores were clearly associated with bronchial symptoms (OR = 1.7). The persistent rhinitic subjects in our study with the highest frequency of bronchial symptoms also had a higher level of eNO. Although this did not reach statistical significance, it was likely to be due to the very few persistent rhinitic subjects with a low frequency of bronchial symptoms for our comparison group. The large number of persistent rhinitic subjects, who reported bronchial symptoms, although they deny having asthma, is of concern, since if they are undiagnosed they are unlikely to receive appropriate treatment.

Monitoring of pollen in our study region confirmed the peak pollen period to be in September and October, the southern hemisphere spring. In the subgroup of pollen sensitive persistent rhinitic subjects there was no difference in bronchial responsiveness, the mean level of eNO or bronchial symptoms in those with or without pollen allergy. The subgroup analysis might have had insufficient statistical power to detect other differences. In subjects with pollen allergy, there was a seasonal difference in the mean level of eNO, being highest in winter.

We excluded all data from analyses where respiratory tract infections were reported, however, it is possible that subjects could find it difficult to identify whether the cause of their sinus symptoms were from an allergy or an upper respiratory tract infection. However, the incidence of upper respiratory tract infections was similar between the rhinitic and control groups, and this finding has also been reported in a similar study (31).

In summary, we have shown that, in a real-life situation, persistent nasal symptoms over a 1-year period in persistent rhinitic subjects, high nasal symptom scores were associated with bronchial symptoms, and bronchial

responsiveness and eNO were elevated. We cannot rule out the possibility that some of these subjects may be very mild, undiagnosed asthmatics, even though we tried as best we could to exclude asthma. Additional elevation of eNO was seen in a subgroup of pollen sensitive persistent rhinitic subjects during winter but not spring. Still, the additional allergen load of pollen had only a marginal impact on the disease in the setting of high exposure to HDM.

High nasal symptom scores were strongly associated with bronchial symptoms in this group of persistent rhinitic subjects. These findings contribute to the argument that there is a link with symptoms and inflammation between the upper and lower airways. Subjects and practitioners dealing with persistent allergic rhinitis should become aware of the risks of the occurrence of bronchial symptoms, especially in the presence of

increased nasal symptoms, and will need to adjust their treatment and management of the disease accordingly.

Acknowledgments

We would like to thank Dr Tim O'Meara, Alyson Roberts and Leanne Poulos for their help with fortnightly telephone questionnaires, and Dr Greg King and Dr Conceição Maria da Costa Santos e Fonseca for their help with clinical examination of subjects. We would also like to thank Dr Connie Katelaris and Therese Burke from the Department of Clinical Immunology and the Westmead Millennium Institute, Westmead Hospital, Sydney, for their assistance in providing us with information on pollen counts. We acknowledge the financial support from the Lady Askin Trust Sydney, AstraZeneca Research and Development Sweden, Swiss National Science Foundation and the Novartis-Foundation, Switzerland.

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