Rhinitis and onset of asthma: a longitudinal population-based study

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Summary

Background **A close relation between asthma and allergic rhinitis has been reported by several epidemiological and clinical studies. However, the nature of this relation remains unclear. We used the follow-up data from the European Community Respiratory Health Survey to investigate the onset of asthma in patients with allergic and non-allergic rhinitis during an 8·8-year period.**

Methods **We did a longitudinal population-based study, which included 29 centres (14 countries) mostly in western Europe. Frequency of asthma was studied in 6461 participants, aged 20–44 years, without asthma at baseline. Incident asthma was defined as reporting ever having had asthma confirmed by a physician between the two surveys. Atopy was defined as a positive skin-prick test to mites, cat, *Alternaria*, *Cladosporium*, grass, birch, *Parietaria*, olive, or ragweed. Participants were classified into four groups at baseline: controls (no atopy, no rhinitis; n=3163), atopy only (atopy, no rhinitis; n=704), non-allergic rhinitis (rhinitis, no atopy; n=1377), and allergic rhinitis (atopy+rhinitis; n=1217). Cox proportional hazards models were used to study asthma onset in the four groups.**

Findings **The 8·8-year cumulative incidence of asthma was 2·2% (140 events), and was different in the four groups (1·1% (36), 1·9% (13), 3·1% (42), and 4·0% (49), respectively; p<0·0001). After controlling for country, sex, baseline age, body-mass index, forced expiratory volume in 1 s (FEV_1), log total IgE, family history of asthma, and smoking, the adjusted relative risk for asthma was 1·63 (95% CI 0·82–3·24) for atopy only, 2·71 (1·64–4·46) for non-allergic rhinitis, and 3·53 (2·11–5·91) for allergic rhinitis. Only allergic rhinitis with sensitisation to mite was associated with increased risk of asthma independently of other allergens (2·79 [1·57–4·96]).**

Interpretation **Rhinitis, even in the absence of atopy, is a powerful predictor of adult-onset asthma.**

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For further information on the **methods for ECRS I and ECRS II** see http://www.ecrhs.org

Introduction

The prevalence of asthma has increased during the second half of the 20th century in children and adults in most countries.[1] Although in the past 10 years the prevalence of asthma seems to have reached a plateau or even decreased slightly in some areas, it is still rising in many populations and remains high in developed countries.[1,2] Despite therapeutic progress, the morbidity and mortality of this chronic disease are substantial. Therefore, prevention of asthma through identification and management of risk factors and preclinical phases of the disease is a priority.[1]

Allergic rhinitis, a common chronic condition, has also become increasingly prevalent.[2,3] A close relation between asthma and allergic rhinitis has been reported by several epidemiological and clinical studies.[4] According to cross-sectional studies,[4] asthma and rhinitis often coexist and share common risk factors, including atopy, and might even be manifestations of the same disease.[5] The few longitudinal studies that have addressed the temporal relation between rhinitis and asthma report that rhinitis often precedes the development of asthma, suggesting that it might be a risk factor for asthma.[3,6–8] However, comparison of the results of these studies is difficult because they did not use standardised methods, especially for the definitions of asthma and rhinitis.

Cross-sectional data from the European Community Respiratory Health Survey (ECRHS) have shown a positive association between rhinitis and asthma in both atopic and non-atopic adults.[9] We used the follow-up data from this international population-based study to investigate the onset of asthma in patients with allergic and non-allergic rhinitis.

Methods

Study design

This analysis was based on the follow-up data from the ECRHS, which included 29 centres (14 countries) mostly in western European countries. The methods for ECRHS I and ECRHS II have been published elsewhere,[10,11] and further information is available from the study website. The study was approved by the appropriate ethics committee, and informed written consent was obtained from every participant.

Baseline study (ECRHS I) 1991–93

In ECRHS I, participating centres selected an area defined by pre-existing administrative boundaries with a population of at least 150 000 people. A community-based sampling frame was used to randomly select at least 1500 men and 1500 women aged

20–44 years in each centre, who were sent a short postal questionnaire. A random sample of responders was selected to take part in stage II, during which the responders were invited to visit a local testing centre, answer a more detailed administered questionnaire, provide a blood sample for measurement of specific IgE and total IgE, and undergo skin-prick tests, lung function assessment, and bronchial responsiveness challenge tests.

Follow-up study (ECRHS II) 1998–2002

Participants in ECRHS I who responded to stage II were eligible for ECRHS II and were invited to the testing centre where, as before, they answered a detailed administered questionnaire, and underwent lung function assessment by the same method as for ECRHS I.

Measurements

The maximum forced expiratory volume in 1 s (FEV_1) was calculated from up to five technically acceptable blows in accordance with the American Thoracic Society criteria for reproducibility.[12] Because FEV_1 in healthy participants is dependent on sex, age, and height, observed values can not be analysed without adjustment for these factors.[13–15] We used linear regression to calculate the internally derived predicted value of FEV_1 on the basis of age and height for men and women.[16] Differences between measured and predicted values (residual FEV_1) were used in analyses. In table 1 and table 2, results were presented using a reconstituted FEV_1—ie, residual FEV_1+mean value of the group. Bronchial responsiveness to methacholine was also measured[17] and bronchial hyper-responsiveness (BHR) was defined as a decrease in FEV_1 of at least 20% of its post-saline value for a maximum cumulative dose of 1 mg of methacholine.

Skin-prick tests were done with Phazets (Pharmacia Diagnostics, Uppsala, Sweden), which are lancets coated with standardised lyophilised allergens extracts.[18] The allergens selected in all centres were *Dermatophagoides pteronyssinus* (house dust mite), cat, *Alternaria alternata*, *Cladosporium herbarum*, timothy grass, birch, *Parietaria judaica*, olive, and common ragweed. A negative control and a histamine positive control were also tested. Results were regarded as positive if the mean weal diameter was

	Total (N=6461)	Control (n=3163)	Atopy, no rhinitis (n=704)	Non allergic rhinitis (n=1377)	Allergic rhinitis (n=1217)
Women, n (%)	3263 (50·3)	1544 (44·9)	316 (44·9)	825 (59·9)	578 (47·5)
Age, year, mean (SD)	34·2 (7·1)	34·3 (7·1)	33·5 (7·5)	34·9 (7·1)	33·4 (7·0)
Body-mass index, kg/m^2, mean (SD)	23·9 (3·8)	24·1 (3·7)	24·0 (3·7)	23·8 (4·0)	23·6 (3·5)
Smoking, n (%)					
Non-smokers	2732 (43·2)	1274 (41·2)	285 (40·1)	570 (42·4)	603 (50·8)
Ex-smokers	1266 (20·0)	621 (20·1)	122 (17·6)	296 (22·0)	227 (19·1)
Moderate smokers	1422 (22·5)	721 (23·3)	172 (24·8)	303 (22·5)	226 (19·0)
Heavy smokers	901 (14·3)	479 (15·5)	114 (16·5)	176 (13·1)	132 (11·1)
Skin-prick test, n (%)					
Dermatophagoides pteronyssinus	971 (15·0)	..	405 (57·5)	..	566 (46·51)
Cat	497 (7·9)	..	143 (20·3)	..	354 (29·1)
Cladosporium	86 (1·3)	..	31 (4·4)	..	55 (4·5)
Timothy grass	875 (13·5)	..	183 (26·0)	..	692 (56·9)
Birch	459 (7·1)	..	100 (19·2)	..	359 (29·5)
Olive	215 (3·3)	..	70 (9·9)	..	145 (11·9)
Alternaria	207 (3·2)	..	51 (7·2)	..	156 (12·8)
Parietaria	78 (1·2)	..	25 (3·6)	..	53 (4·4)
Ragweed	72 (1·2)	..	16 (2·4)	..	56 (5·1)
Total IgE, mg, mean (SD)	82·89 (194·1)	53·4 (134·8)	128·1 (265·3)	58·0 (159·4)	161·6 (269·9)
Asthma-like symptoms, n (%)	1356 (21·0)	550 (17·4)	135 (19·2)	348 (25·3)	323 (26·5)
Wheeze	1130 (17·5)	456 (14·4)	116 (16·5)	282 (20·5)	276 (22·7)
Shortness of breath at rest	244 (3·8)	90 (2·9)	23 (3·3)	81 (5·9)	50 (4·1)
Woken by shortness of breath	222 (3·4)	74 (2·3)	19 (2·7)	70 (5·1)	59 (4·9)
Family history of asthma, n (%)	687 (10·6)	292 (9·2)	60 (8·5)	176 (12·8)	159 (13·1)
Respiratory infection in childhood, n (%)	558 (8·7)	231 (7·3)	61 (6·7)	156 (11·4)	108 (8·9)
Bronchial hyper-responsiveness, n (%)	441 (8·1)	162 (6·0)	47 (7·8)	90 (7·8)	142 (13·8)
FEV_1, L/s†, mean (SD)	3·78 (0·47)	3·79 (0·47)	3·78 (0·46)	3·76 (0·45)	3·79 (0·47)

FEV_1= forced expiratory volume in 1 s. †FEV_1= residual FEV_1+FEV_1 mean.

Table 1: **Baseline characteristics of participants included in the analysis, according to category of rhinitis**

over 0 mm.[19] Participants with a negative control (>0 mm) were excluded (n=110). Individuals with at least one positive skin-prick test were considered to be atopic.

Total serum IgE and IgE specific to house dust mite, timothy grass, cat, and *Cladosporium* were measured centrally at Pharmacia Uppsala for ECRHS I and Kings College London for ECRHS II, using the Phamacia CAP system (Uppsala, Sweden). Specific IgE values 0·35 kIU/L or more were considered positive.

Asthma-like symptoms were defined as having wheeze, shortness of breath at rest, or nocturnal shortness of breath during the past 12 months. A parental history of asthma was recorded if the participant reported that their father or mother ever had asthma.

Procedures

Allergic rhinitis was defined as being atopic and reporting a history of nasal allergies, as recommended elsewhere.[4,20] Participants were considered to have allergic rhinitis if they answered positively to either of the questions "Do you have any nasal allergies including hay fever?" or "Do you get runny or stuffy nose or start to sneeze when you are near grass, trees, flowers, or near animals, or in a dusty part of the house?" and were positive for at least one skin-prick test. Individuals giving a positive answer to either of the above questions but who had negative skin-prick tests were considered as having non-allergic rhinitis. Participants with a positive skin-prick test but with negative response to both rhinitis questions were referred to as atopic without rhinitis (atopy, no rhinitis). The fourth group was made up of all other participants, those without atopy and without rhinitis (controls).

Allergic rhinitis to cat was recorded if the participant had a history of nasal allergy and had a skin-prick test positive to cat. Allergic rhinitis to house dust mite, birch, and grass was defined in the same way.

Asthma was defined as a positive answer to both questions "Have you ever had asthma?" and "Was this confirmed by a doctor?" Incident cases of asthma were defined as those at risk (free of asthma) at baseline who answered positively to the questions about asthma at follow-up.

Statistical analysis

The χ^2 test was used to analyse differences between groups. ANOVA was used to compare continuous variables. Cumulative incidence was estimated using Kaplan-Meier survival probabilities. We used the Cox proportional-hazards regression method to study the relation between rhinitis and the occurrence of asthma. The timescale was number of years from the baseline to reported age at first asthma attack, and for those without incident asthma, between baseline and follow-up. Models were adjusted for country, sex, baseline age, body-mass index, FEV_1, log total IgE, family history of asthma, respiratory infection in childhood, and smoking. Smoking was included in the multivariable analysis using four categories: non-smokers, ex-smokers (stopped for ≥1 year), moderate smokers (<20 cigarettes a day), heavy smokers (≥20 cigarettes a day). All possible interactions between the explanatory variables were tested and were not significant. Proportional hazard assumption was checked using the Grambsh and Therneau test[21] and diagnostic plots based on Schoenfeld residual. Results showed that the assumption was not violated.

The population attributable risk was calculated using the population prevalence of the exposure (p) and the adjusted relative risk associated with the exposure (RR) as p(RR–1)/(1+p[RR–1]). The 95% CI for population attributable risk was estimated using a substitution method described by Daly.[22] SAS version 9.1 (SAS Institute, Cary, USA) was used for all statistical analyses.

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 10 827 participants with complete data for atopy, rhinitis, and asthma at baseline, 7326 (67·4%) participated in the follow-up. 6461 were free of asthma at baseline and supplied full data for baseline atopy and rhinitis and for asthma at follow-up (figure 1). The mean follow-up time was 8·8 [SD 1·0] years. A comparison of baseline characteristics between participants and non-participants of the follow-up showed small but significant differences: non-participants were slightly younger (32·8 [7·1] years *vs* 34·1 [7·1] years, p<0·0001),

	No asthma onset (n=6321)	Asthma onset (n=140)	p†	Crude RR (95% CI)
Women, n (%)	3263 (50·2)	91 (65·0)	0·0005	1·84 (1·30-2·66)
Age, mean (SD)	34·2 (7·3)	34·5 (8·7)	0·591	1·06* (0·90-1·25)
Body-mass index, kg/m², mean (SD)	23·8 (3·8)	25·0(5·9)	0·017	1·28* (1·12-1·47)
Smoking, n (%)			0·607	
Non-smokers	2669 (43·2)	63 (45·7)		1·00 (reference)
Ex-smokers	1235 (20·0)	31 (22·5)		1·17 (0·75-1·83)
Moderate smokers	1397 (22·6)	25 (18·1)		0·86 (0·56-1·30)
Heavy smokers	882 (14·3)	19 (13·8)		0·85 (0·45-1·60)
Total IgE, mean (SD)	81·7(195·8)	135·5 (300·7)	0·017	1·33* (1·11-1·60)
Atopy, n (%)	1859 (29·4)	62 (44·3)	0·0001	1·91 (1·37-2·66)
Asthma-like symptoms, n (%)	1307 (20·7)	51 (36·4)	<0·0001	2·20 (1·56-3·10)
Family history of asthma, n (%)	657 (10·4)	30 (21·4)	<0·0001	2·35 (1·57-3·52)
Respiratory infection in childhood, n (%)	539 (9·0)	17 (13·4)	0·085	1·57 (0·94-2·61)
FEV_1, L/s ‡, mean (SD)	3·78(0·47)	3·57 (0·54)	<0·0001	0·64* (0·55-0·76)
Bronchial hyper-responsiveness, n (%)	414 (7·7)	27 (25·2)	<0·0001	4·06 (2·63-6·28)

FEV_1=forced expiratory volume in 1 s· *Relative risk per roughly 1 SD increase (7·1 year for age, 3·8 kg/m² for body-mass index, 1·58 for log total IgE, and 0·47 L for FEV_1)· †For difference between groups using *t* test for continuous variables and χ^2 for categorical variables· ‡FEV_1=residual FEV_1+ mean FEV_1.

Table 2: **Baseline characteristics of participants with and without asthma onset**

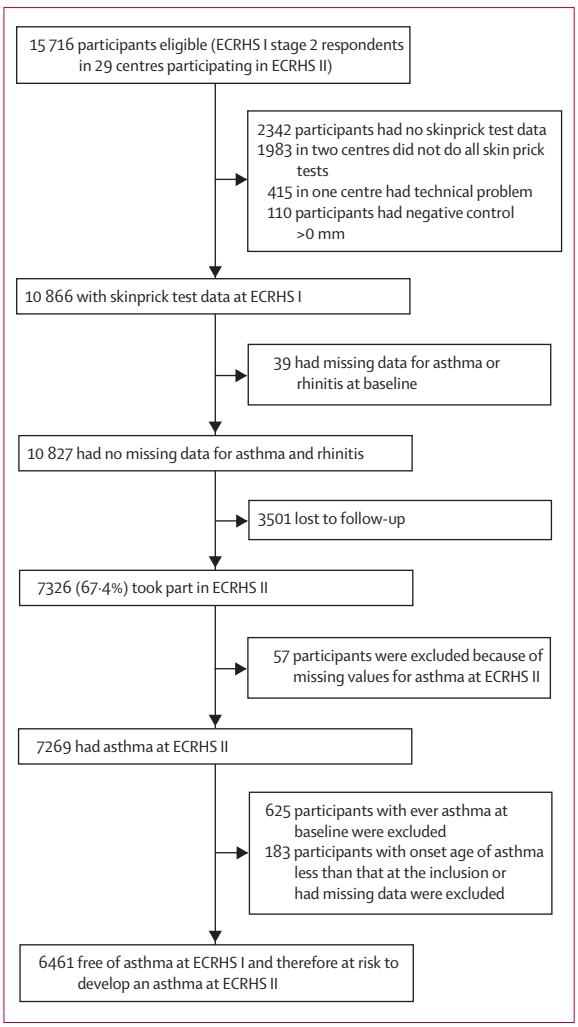


Figure 1: **Trial profile**

more likely to be smokers (42·6% *vs* 36·5%, p<0·0001), and had a higher prevalence of BHR (14·6% *vs* 12·0%, p=0·0006), asthma (9·9% *vs* 7·6%, p<0·0001), and allergic rhinitis (25·6% *vs* 23·5%, p=0·0002) than participants at baseline. By contrast, sex ratio, body-mass index, and the prevalence of atopy were not significantly different. Additionally, there were strong cross-sectional associations of asthma with rhinitis in both those who were and were not followed-up: asthma frequency in participants not followed-up was 24·6% in those with allergic rhinitis, and 6·8% in those with non-allergic rhinitis compared with 3·5% in control group (p<0·0001). In those who were followed-up the prevalence was 20·2% in those with allergic rhinitis and 7·0% in those with non-allergic rhinitis, compared with 1·8% in those without rhinitis (p<0·0001).

The baseline characteristics of the 6461 participants analysed are shown in table 1. 29·7% of participants were sensitised to at least one of the nine skin-prick tests. Sensitisation to *Dermatophagoides pteronyssinus* was the most frequent (15·0%), followed by sensitisation to timothy grass (13·5%).

During follow-up, there were 140 (91 women and 49 men) new cases of asthma, corresponding to a total cumulative incidence of 2·2%. The onset of asthma was more frequent in women, and it was positively associated with baseline total IgE, atopy, family history of asthma, asthma-like symptoms, and BHR, and negatively associated with baseline FEV_1 (table 2).

Figure 2 shows the cumulative incidence of asthma in the four groups. The probability of having asthma at the end of follow-up (mean 8·8 years) was 4·0% in patients with allergic rhinitis, 3·1% in those with non-allergic rhinitis, 1·9% in those with atopy without rhinitis, and 1·1% in controls. Relative to the control group, participants with non-allergic rhinitis had a 2·75 fold (95% CI 1·76–4·29) greater risk of asthma onset, and those with allergic rhinitis had 3·65 (95% CI 2·37–5·61) greater risk of asthma onset (table 3). By contrast, atopic patients without rhinitis had no significantly higher risk than the controls of developing asthma. After controlling for country, sex, baseline age, body-mass index, FEV_1, log total IgE, family history of asthma, respiratory infection in childhood, and smoking, the adjusted risk ratio (RR) of asthma was 2·71 (95% CI 1·64–4·46) for patients with non-allergic rhinitis and 3·53 (95% CI 2·11–5·91) for those with allergic rhinitis.

Findings were similar in men and women (table 3). Stratification of the population by baseline age (≤35 years and >35 years), baseline smoking status, baseline body-mass index classes (<25 kg/m², 25–30 kg/m², and >30 kg/m²), or the existence of a family history of asthma did not change the pattern of association of rhinitis with asthma (data available from authors); the interaction terms for these variables were not significant (p>0·05). Additionally, excluding the patients with asthma-like symptoms or BHR at baseline did not have any large effect on the results for allergic rhinitis (table 3).

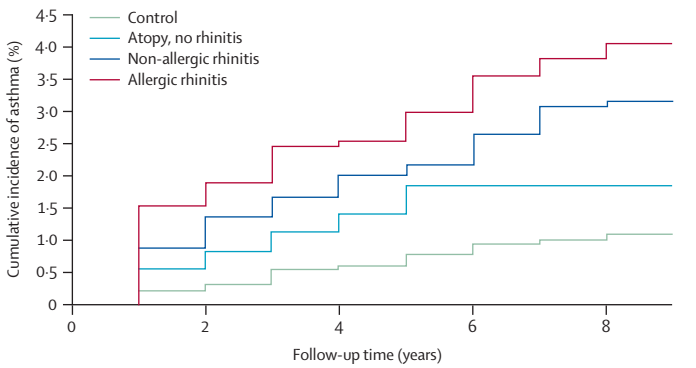
To assess whether BHR in participants with allergic rhinitis was an intermediate factor for asthma, we studied the association of rhinitis with asthma after adjusting for BHR. We found that by controlling for baseline BHR, the adjusted RR of asthma decreased from 3·53 (95% CI 2·11–5·91) to 3·05 (1·71–5·44) for participants with allergic rhinitis. However, when we controlled for baseline and follow-up BHR, the RR for the association between allergic rhinitis and asthma further decreased to 1·90 (0·91–3·95). Similarly, adjustment for BHR slightly reduced the RR for the association between non-allergic rhinitis and asthma onset (from 2·54 [1·46–4·41] to 2·11 [1·09–4·08]).

Overall, the population attributable risk of asthma onset due to allergic rhinitis was 32% (95% CI 17–48): 48% (21–71) in men and 23% (7–43) in women. The corresponding population attributable risk due to non-allergic rhinitis was 27% (12–42): 35% (10–61) in men, and 23% (5–43) in women.

The association between allergic rhinitis and incidence of asthma was stronger in patients with rhinitis sensitised to several allergens (≥three inhaled allergens, n=143; RR 5·82 [95% CI 2·58–13·14]) than in those with rhinitis sensitised to less than three allergens (n=1074; 3·19 [1·8–5·42]).

Table 4 shows the relation between allergic rhinitis and asthma onset according to the type of sensitisation. Allergic rhinitis with sensitisation to mites, cat, birch, timothy grass, or other allergens were associated with asthma risk. However, when these allergens were introduced simultaneously in the model, only allergic rhinitis sensitised to mites was associated with an increased risk of asthma, independently of the other allergens (table 4). Although sensitisation to mite was the only significant association, being also sensitised to cat increased the risk of asthma onset from 4·6% (26 of 566) to 6·4% (11 of 171) and this was further increased to 7·6% (nine of 119) by being sensitised to grass. When sensitisation to birch was also added, the risk of asthma onset increased from 7·6% to 9·1% (four of 44). None of these small increases in asthma risk were significant, probably because of the small number of patients.

Of the 6461 participants included in the present analysis, 5854 had specific IgE data. When atopy was defined as the presence of specific IgE to either house dust mite, timothy grass, cat, or *Cladosporium* the association (values ≥0·35 kIU/L) of allergic rhinitis and asthma incidence were consistent with those seen when atopy was defined by skin-prick tests (table 5).



Number at risk					
Control	3163	3158	3153	3064	2967
Atopy, no rhinitis	704	701	698	669	642
Non-allergic rhinitis	1377	1396	1358	1268	1199
Allergic rhinitis	1217	1208	1194	1093	1038

Probability of developing asthma, % (95% CI)					
Control	0	0·2 (0·1–0·5)	0·5 (0·3–0·9)	0·8 (0·5–1·2)	1·0 (0·7–1·5)
Atopy, no rhinitis	0	0·6 (0·2–1·5)	1·1 (0·6–2·3)	1·9 (1·1–3·2)	1·9 (1·1–3·2)
Non-allergic rhinitis	0	0·9 (0·5–1·5)	1·7 (1·1–2·5)	2·2 (1·5–3·1)	3·1 (2·3–4·1)
Allergic rhinitis	0	1·6 (1·0–2·4)	2·5 (1·7–3·5)	3·0 (2·2–4·1)	3·8 (2·9–5·1)

Figure 2: **Cumulative incidence rate of asthma**
Cumulative incidence of asthma by year of follow-up in 3161 individuals in the control group, 704 who had atopy alone, 1377 who had non-allergic rhinitis, and 1217 who had allergic rhinitis.

Discussion

In this study, adults were more likely to develop asthma if they had rhinitis at baseline. This association was seen for both non-allergic and allergic rhinitis and was present after accounting for country, sex, baseline age, body-mass index, FEV_1, log total IgE, family history of asthma, respiratory infection in childhood, and smoking. The positive associations between rhinitis and asthma were seen in both men and women.

Asthma-like symptoms or BHR in patients with rhinitis could be indicative of undiagnosed asthma, but even when we excluded patients with such symptoms, the association of rhinitis with asthma onset remained significant.

Previous prospective studies, often based on smaller numbers of participants, have reported a positive association between rhinitis and asthma in adults.[3,6,23,24] Of 1021 college students,[23] those with allergic rhinitis were reported to be three times more likely to develop asthma than controls during a 23-year follow-up. A similar study of people aged 18–45 years in Finland[3] showed that allergic rhinitis was a strong predictor of asthma during a 15-year follow-up. A longitudinal study[24] of 7-year-old children followed-up at age 44 years reported that childhood allergic rhinitis increased the risk of incident asthma after childhood. However, in these studies, the associations were not adjusted for atopic status. In a nested case-control study, Guerra and colleagues[6] showed an independent association between rhinitis and incident asthma in atopic and non-atopic adults. Although these studies did not report findings that disagree with a relation between rhinitis and asthma, comparison of the various results is difficult because of the heterogeneous methods used and the inadequacy of control for atopic status.

BHR is likely to be an intermediate factor in the process leading from allergic rhinitis to asthma. Two arguments support this idea. First, we have shown that allergic rhinitis is a risk factor for BHR in non-asthmatic adults.[25] Results from the follow-up of more than 4000 people participating in the ECRHS showed that adults with allergic rhinitis and free of BHR and asthma at baseline were at increased risk for developing BHR over the follow-up period. The results were in accordance with previous findings from the cross-sectional analysis of the same population[9] and from other clinical and population-based studies.[23,26] Second, there is now substantial evidence that asymptomatic BHR often precedes the development of symptomatic asthma and can be considered a risk factor for the disease. Indeed, 14–58% of participants with asymptomatic BHR could develop symptomatic asthma.[27–29] A study of 7126 participants from the general population followed-up for more than 10 years (SAPALDIA Cohort Study)[30] showed that participants with asymptomatic BHR at baseline were three times more likely to develop physician-diagnosed asthma than those without. There is good evidence of an interaction between BHR and

airway inflammation derived from cross-sectional and longitudinal studies as well as from pharmacological intervention trials.[30]

	Controls	Atopy, no rhinitis	Non-allergic rhinitis	Allergic rhinitis
All patients				
Number of patients	3163	704	1377	1217
Asthma incidence, n (%)	36 (1·1)	13 (1·9)	42 (3·1)	49 (4·0)
Crude RR (95% CI)	1·00	1·63 (0·87–3·08)	2·75 (1·76–4·29)	3·65 (2·37–5·61)
Adjusted RR* (95% CI)	1·00	1·63 (0·82–3·24)	2·71 (1·64–4·46)	3·53 (2·11–5·91)
Men				
Number of participants	1619	388	552	639
Asthma occurrence, n (%)	11 (0·7)	5 (1·3)	12 (2·2)	21 (3·3)
Adjusted RR* (95% CI)	1·00	1·75 (0·52–5·86)	3·10 (1·67–10·07)	5·64 (2·35–13·54)
Women				
Number of participants	1544	316	825	578
Asthma occurrence, n (%)	25 (1·6)	8 (2·5)	30 (3·6)	28 (4·8)
Adjusted RR* (95% CI)	1·00	1·54 (0·66–3·59)	2·21 (1·22–4·03)	2·72 (1·42–5·19)
Without baseline asthma-like symptoms				
Number of participants	2613	569	1029	894
Asthma occurrence, n (%)	25 (1·0)	8 (1·4)	28 (2·7)	28 (3·1)
Adjusted RR* (95% CI)	1·00	1·78 (0·77–4·12)	3·06 (1·67–5·60)	3·49 (1·81–6·72)
Without baseline bronchial hyper-responsiveness				
Number of participants	2542	554	1058	884
Asthma occurrence, n (%)	24(0·9)	8 (1·4)	21 (2·0)	27 (3·1)
Adjusted RR* (95% CI)	1·00	1·67 (0·70–4·03)	2·16 (1·15–4·09)	3·90 (2·03–7·50)

*Adjustment for country, sex, baseline age, body–mass index, log total IgE, family history of asthma, respiratory infection in childhood, smoking, and FEV_1.

Table 3: **Univariate and multivariable analysis (Cox regression) of the effect of rhinitis on the cumulative incidence of asthma**

	n	Asthma, n (%)	RR* (95% CI)	Adjusted† RR (95% CI)
Allergic rhinitis attributable to *Dermatophagoides pteronyssinus*	566	26 (4·6)	3·25 (1·91–5·55)	2·79 (1·57–4·96)
Cat	354	17 (4·8)	2·21 (1·19–4·08)	1·39 (0·70–2·77)
Birch	359	15 (4·2)	1·98 (1·06–3·70)	1·47 (0·73–2·99)
Timothy grass	692	25 (3·6)	1·85 (1·07–3·19)	1·16 (0·61–2·21)
Other allergens	140	13 (3·6)	1·87 (1·07–3·55)	1·15 (0·58–2·30)

*Adjustment for country, sex, baseline age, body-mass index, log total IgE, family history of asthma, respiratory infection in childhood, smoking, and FEV_1. †Adjustment for the same variables as above, with allergens included simultaneously in the model.

Table 4: **Asthma onset according to sensitisation in patients with allergic rhinitis**

	Controls	Atopy, no rhinitis	Non-allergic rhinitis	Allergic rhinitis
N	2909	590	1392	963
Asthma, n (%)	32 (1·1)	9 (1·5)	42 (3·0)	39 (4·1)
Crude RR (95% CI)	1·00	1·08 (0·53–2·19)	2·19 (1·46–3·31)	2·96 (1·95–4·51)
Adjusted RR* (95% CI)	1·00	1·20 (0·56–2·58)	2·36 (1·46–3·81)	3·35 (1·98–5·67)

*Adjustment for country, sex, baseline age, body-mass index, log total IgE, family history of asthma, respiratory infection in childhood, smoking, and FEV_1.

Table 5: **Univariate and multivariable analysis (Cox regression) of the effect of allergic and non-allergic rhinitis defined by specific IgE on the cumulative incidence of asthma**

In the present study, the association between asthma and allergic rhinitis decreased substantially by controlling for BHR, suggesting that part of the allergic rhinitis effect might be mediated through the development of BHR. This observation is important because BHR is thought to be a dynamic process and can be decreased by anti-inflammatory therapy.[25,31]

We have shown that only allergic rhinitis with sensitisation to mites was associated with an increased risk of asthma onset independently of other allergen. One possible explanation is that patients with allergic rhinitis to mites are likely to have nasal symptoms over a longer period since mites are a perennial indoor allergen. Our findings are consistent with a study that reported that early exposure to dust-mite allergen was associated with increased risk of asthma in children.[32] Sensitisation to indoor allergens (mite and cat) is strongly associated with BHR,[25] and, in a longitudinal study of children, with the chronicity of asthma.[33] There are too few incident asthma cases to draw any further conclusions on the risk of asthma in relation to each individual allergen.

Several mechanisms might be responsible for the interaction between the upper and lower airways. Two main pathways could be involved in the nasobronchial cross-talk: respiratory and systemic pathways.[34] For the respiratory pathway, the simplest explanation is the loss of protective functions of the nose. The inhalation of cold and dry air is associated with a decreased FEV_1 value in asthmatic patients[35] and cold air can be used as a provocative agent in bronchoconstriction tests. However, the role of preferential mouth breathing in the development of asthma still remains unclear. Another possible explanation is the aspiration of nasal secretions towards the lower airways (post-nasal drip), which is related to cough,[36] although no direct contact of nasal secretions and bronchial mucosa has been proved. Although aspiration might have a role in patients with impaired cough reflex, this mechanism seems to have only a poor effect on a nasobronchial cross-talk.[37] Also possible is that a nasal bronchial reflex, involving the trigeminal and vagal nerves, accounts for the interaction between nose and lungs.[38,39]

Of the possible respiratory mechanisms, alteration of nasal nitric oxide (NO) production might be important. Several chronic inflammatory conditions of the nose have been associated with reduced or absent nasal NO production.[40] Because nasal NO exerts bronchodilatory effects and modulates lower airways responsiveness,[41] reduced NO in nasal air in patients with rhinitis might contribute to lower airways dysfunction. However, the systemic pathway is now the most widely accepted explanation for nasal-lower airway interaction. Allergen provocation studies have shown an increase in circulating inflammatory cells and mediators after allergen inhalation.[42] Presumably, absorption of inflammatory mediators (eg, IL-5 and eotaxin) from sites of inflammation into the systemic circulation results in the release of eosinophils, basophils, and

their progenitor cells from the bone marrow.[43,44] Thus, there is evidence that allergic rhinitis is not a local disease but that the entire respiratory tract is involved, even in the absence of clinical asthma. On the assumption that that inflammation is present also in non-allergic rhinitis, the systemic propagation of inflammation from the nasal to the bronchial mucosa is a likely explanation for the association of rhinitis and asthma onset. However, further studies are needed to identify the possible mechanisms underlying the association between non-allergic rhinitis and asthma.

The strengths of our study include the use of nearly 6500 participants randomly drawn from the general population, the prospective design, the collection of high quality data, the standardised questionnaires, specific IgE measurements, and the ability to compare asthma onset in patients with allergic and non-allergic rhinitis simultaneously. Quality controls were done at various levels: all fieldworkers received identical training, ECRHS investigators did quality control visits, and equipment underwent regular quality controls. Nonetheless, our study had several limitations. First, as in any longitudinal study, there was some loss to follow-up. However, the response rate was high and similar to several other population studies.[45,46] Participants who were analysed were less than 2 years older than non-participants. Such a small difference is unlikely to have biased the results, due to the young age of the study population. Non-participants in the follow-up were more likely to be smokers. Since smoking has been shown to be associated with a greater risk of incident asthma in allergic rhinitis,[47] the self-selection of non-smokers is unlikely to have overestimated the association of rhinitis with asthma. Second, we used asthma confirmed by a physician as the outcome in this study, which could have led to an underestimate of true occurrence, since the condition could have remained undiagnosed in those with mild asthma or asthma like-symptoms. As in all epidemiological studies, misclassification due to the outcome relying on the participant's recall might have biased the results. However, we also investigated the association between allergic rhinitis and the development of bronchial hyper-responsiveness, which is an objective measure of lower airway disorders. Allergic rhinitis was found to predict the development of BHR, even when the analysis was restricted to those without asthma.[25]

Although, a recent study showed little increase in prevalence of sensitisation by adding tests other than house dust mite, timothy grass, and cat,[18] we assessed all nine allergens to maximise sensitivity and avoid misclassification of atopic individuals as participants with non-allergic rhinitis. For the same reason, tests were regarded as positive if the wheal was greater than 0 mm. Within the ECRHS a cutoff of more than 0 mm for a positive result gave a more consistent relation with the corresponding specific IgE value between fieldworkers than either a cutoff of 3 mm or more or the use of the mean wheal diameter, and this cutoff has been recommended.[19] Nevertheless, we repeated the analysis using the 3 mm cutoff and results were unchanged.

Longitudinal studies of children followed-up from infancy to adulthood have shown variability in the clinical course of asthma, and suggest that early pathological features might affect the disease persistence into adulthood, progression, or relapse.[48] In the present study, although we have adjusted for respiratory infection in childhood, we had no data for possible asthma-like symptoms during childhood. In a previous study, 22·4% of patients with new asthma reported "respiratory trouble before age 16 years", which might affect asthma-like symptoms that began during childhood, but which were not sufficiently severe to lead to an asthma diagnosis until adulthood. Similarly, for some of our patients, rhinitis might have predicted relapse of asthma rather than the onset of asthma. However, the association between rhinitis and asthma remained significant after excluding those participants with asthma-like symptoms at baseline. Longitudinal studies have also shown that symptoms of hay fever usually began after the onset of wheezing in asthmatic children.[49] Therefore, our findings cannot be extrapolated to the development of asthma in childhood. However, allergic rhinitis in childhood has also been shown to predict rate of asthma in pre-adolescence, adolescence, and adult life.[24]

In conclusion, this large prospective study provides strong evidence for an increased risk of asthma in adults with allergic rhinitis, and to a lesser extent non-allergic rhinitis. Some of the effect of allergic rhinitis might be mediated through the development of bronchial hyper-responsiveness. In a previous paper,[50] we have reviewed the criteria proposed by Hill to assess the extent to which evidence supports the hypothesis of a causal relation between rhinitis and asthma. Our study shows that rhinitis is predictive of the development of asthma and further supports this hypothesis. Several clinical trials in asthmatic patients with allergic rhinitis[51,52] have shown that the treatment of allergic rhinitis was associated with a reduction in asthma symptoms. However, only interventional studies could be used to conclude that the treatment of allergic rhinitis is effective in reducing the incidence of asthma.

Contributors

RS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. RS, MZ, FN, and BL were responsible for the study concept and design and the drafting of the manuscript. BL, JH, JS, MW, CN, IC, IP, JB, DJ, PB, and FN were responsible for data collection in local centres. RS, MZ, DS, CN, FN, and BL did the analysis and interpretation of the data. All authors were responsible for the interpretation and presentation of results.

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Conflict of interest statement
We declare that we have no conflict of interest.

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