Geographic variations in the effect of atopy on asthma in the European Community Respiratory Health Study

Jordi Sunyer, MD, PhD,[a] Deborah Jarvis, FFP, HM,[b] Juha Pekkanen, MD, PhD,[c] Susan Chinn, PhD,[b] Christer Janson, MD, PhD,[d] Benedicte Leynaert, MD, PhD,[e] Christina Luczynska, PhD,[b] Raquel Garcia-Esteban, MPH,[a] Peter Burney, MD, PhD,[b] Josep M. Antó, MD, PhD[a] and for the European Community Respiratory Health Survey Study Group *Barcelona, Spain, London, United Kingdom, Kuopio, Finland, Uppsala, Sweden, and Paris, France*

Background: Atopy has long been related to asthma. The prevalences of both atopy and asthma have shown substantial variation.
Objective: We sought to assess geographic variations in the fraction of asthma attributable to IgE sensitization to specific allergens in the European Community Respiratory Health Survey.
Methods: A cross-sectional study was undertaken during the years 1991 and 1992 on 13,558 individuals in 36 centers in 16 countries. Asthma was defined in several ways, variously incorporating reported symptoms, bronchial responsiveness to methacholine, and physician diagnosis. Specific IgE against house dust mite (*Dermatophagoides pteronyssinus*), cat, timothy grass, *Cladosporium herbarum*, and a local allergen (birch, *Parietaria judaica*, or ragweed) were measured.
Results: The overall attributable fraction (AF) of asthma symptoms caused by atopy was 30% but varied widely between centers, ranging from 4% to 61%. The overall AF increased to 43% when asthma was based on wheezing and bronchial responsiveness, to 45% with a physician diagnosis of asthma, and to 48% when the patient reported more than 12 attacks in the last year. Between centers, the AF for atopy was significantly correlated with the prevalence of atopy among the asthmatic patients ($r = 0.91$) and with the sensitization to house dust mite ($r = 0.64$), as well as with the prevalence of asthma among atopic individuals ($r = 0.43$) and the prevalence of asthma among nonatopic individuals ($r = -0.51$).
Conclusion: The effect of atopy on the prevalence of asthma varies widely between centers, probably because of variations in factors related to the expression of asthma and to the prevalence of sensitization, particularly to house dust mite.
(J Allergy Clin Immunol 2004;114:1033-9.)

Key words: *Atopy, asthma, attributable fraction, house dust mite, allergens*

Atopy, defined as the propensity to produce specific IgE to common allergens, has long been recognized as a characteristic of many patients with asthma. A review of the literature showed that the population-based proportion of asthma cases that are attributable to atopy is approximately one third to one half.[1] Nevertheless, this review was limited by variations in definitions of asthma and by the way atopy was measured in the different studies. In one study the fraction attributable to atopy increased in patients with more severe asthma.[2]

The European Community Respiratory Health Survey (ECRHS) is the first international multicenter study in adults using a common standard protocol measuring atopy and asthma in the same time period.[3] The study has shown that atopy varies considerably from one center to another.[4] In addition, in ECRHS the individual risk of bronchial responsiveness was associated with sensitization to specific IgE to common allergens, and the relative importance of each allergen varied between centers.[5] However, there are well-known differences between bronchial responsiveness and asthma.[6]

Our aim was to assess geographic variations in the fraction of asthma attributable to IgE sensitization to specific allergens and to investigate whether these variations were explained by the prevalence of specific atopy at the population level. This has only been assessed partially in individual countries participating in the ECRHS (Spain and Sweden),[7-9] although not at the international level.

METHODS

The ECRHS study followed a cross-sectional design and was undertaken during the years 1990 through 1994. Populations and subjects participating in the study have been described in detail elsewhere.[3] The data presented here pertain to 13,558 individuals randomly selected from the general population (age range, 20-44 years) in 36 centers in 16 countries.

Asthma was defined as used in the ECRHS, namely a positive answer to any of 3 questions referring to nocturnal attacks of shortness of breath, attacks of asthma, or taking asthma medication in the last 12 months. Other definitions of asthma used are as follows: (1) a single question on wheezing apart from colds together

From [a]Unitat de Recerca Respiratoria i Ambiental, Institut Municipal d'Investigació Mèdica, Universitat Pompeu Fabra (IMIM-UPF), Barcelona; [b]the Department of Public Health Sciences, King's College, London; [c]the Unit of Environmental Epidemiology, Nacional Public Health Institute, Kuopio; and [d]the Department of Medical Sciences: Respiratory Medicine and Allergology, University of Uppsala; and [e]Institut National de la Santé et de la Recherche Médicale, Paris.

Received for publication December 11, 2003; revised May 20, 2004; accepted for publication May 24, 2004.
Available online October 4, 2004.

Reprint requests: Jordi Sunyer, MD, PhD, Environmental Respiratory Research Unit, Institut Municipal d'Investigació Mèdica (IMIM), C. Doctor Aiguader 80, 08003 Barcelona, Spain. E-mail: jsunyer@imim.es.

0091-6749/$30.00

doi:10.1016/j.jaci.2004.05.072

TABLE I. Prevalence of asthma and specific IgE by center (range in countries with 2 or more centers) and association (odds ratio or range of odds ratios in countries) between asthma and specific IgE at the individual level by center (number of individuals = 13,558; number of centers = 36)

Countries ordered by % of atopy* (no. of centers)	Prevalence, % (95% CI)					Odds ratio (95% CI)‡			
	Asthma	House dust mite	Cat	Timothy grass	Atopy*	House dust mite	Cat	Timothy grass	Atopy*
Estonia (1)	7	9	5	9	18	1.82	8.74	3.12	1.25
Iceland (1)	3	9	7	12	23	8.91	7.02	4.59	4.21
Spain (5)	4-11	7-28	3-13	9-20	17-42	1.48-4.54	2.78-8.90	1.62-4.02	1.33-5.44
Norway (1)	7	14	7	15	26	3.17	5.46	2.76	5.16
Italy (3)	6-15	11-13	4-7	12-21	24-30	2.53-5.30	1.10-9.51	2.76-5.42	2.94-4.85
Sweden (3)	8-10	7-12	13-14	17-18	30-32	1.88-2.36	2.60-5.54	2.02-3.58	1.92-5.17
France (4)	6-13	18-35	7-10	12-20	29-43	1.79-4.64	3.43-6.48	1.37-3.98	1.53-4.60
Belgium (2)	5-9	22-27	9-9	16-17	35-36	3.65-3.65	2.78-5.03	4.17-5.10	4.24-5.28
Germany (2)	3-7	16-19	8-11	21-25	35-40	0.23-2.55	2.60-4.47	1.35-2.55	1.36-3.31
United Kingdom (4)	9-14	20-28	8-14	13-27	34-44	2.01-5.07	2.33-5.17	1.62-2.86	2.04-3.93
The Netherlands (3)	5-7	24-29	6-10	17-22	36-41	2.06-6.14	3.75-5.52	2.44-5.49	2.03-5.74
Ireland (1)	12	35	7	17	41	3.15	3.62	5.51	2.07
New Zealand (3)	11-14	31-33	6-13	23-33	40-46	1.74-6.14	0.83-8.34	2.19-3.14	1.57-4.58
United States (1)	12	19	13	34	43	1.01	2.13	2.48	2.52
Switzerland (1)	10	19	15	33	45	1.86	1.31	1.75	1.53
Australia (1)	12	32	9	29	45	2.89	3.24	2.41	3.22
All (95% CI), †*P* value for heterogeneity	9 (8-10), <.001	21 (18-23), <.001	8 (7-10) <.001	19 (17-21), <.001	34 (31-37), <.001	2.78 (2.41-3.20), .14	4.18 (3.54-4.93), .45	2.63 (2.30-3.02), .92	2.82 (2.44-3.28), .15

*Any: house dust mite, cat, timothy grass, *C herbarum*, and birch, *P judaica*, or ragweed.
†Estimated with meta-analysis.
‡Adjusting for age, sex, and smoking.

Abbreviations used
AF: Attributable fraction
ECRHS: European Community Respiratory Health Survey

with breathlessness; (2) a combination of reported asthma symptoms (ie, as above) and bronchial responsiveness (defined as a PD_{20} of <1 mg after methacholine challenge)[3]; (3) a self-reported physician diagnosis of asthma; and (4) the report of at least 12 asthma attacks during the last year.

Specific IgE levels were measured with the Pharmacia CAP System. All assay results for specific IgE were judged to be positive if they showed in excess of 0.35 kU/L of IgE to the specific allergen, the limit of detection of the assay. All centers measured specific IgE against house dust mite *(Dermatophagoides pteronyssinus)*, cat, timothy grass, *Cladosporium herbarum*, and a local allergen. The 3 regional allergens were birch in northern Europe, *Parietaria judaica* in southern Europe, and ragweed in North America and Australia. Assays were performed in a single laboratory at Pharmacia Diagnostics, Uppsala, Sweden. Atopy was defined as the presence of IgE sensitization to any allergen.

Statistical analyses were computed for each center separately to obtain estimates by center and were subsequently examined for heterogeneity (ie, if the association differed between centers with a *P* value of less than .1) and combined by using random-effects meta-analysis[10] to obtain the overall estimate. The association between specific IgE and asthma at the individual level was estimated with the odds ratio by using multiple logistic regression and adjusting for age in years, sex, and smoking.[11] The population fraction of asthma attributable to specific IgE sensitization (attributable fraction [AF]) was estimated by using maximum likelihood on the basis of logistic models as follows: $AF = Pc\,(RR - 1)/(RR)$, where Pc is defined as the prevalence of atopy among the asthmatic subjects and RR is defined as the adjusted odds ratio.[12] The AF is a measure of effect that provides the fraction of observed cases that would have been avoided if no one in the population had been exposed.[13] The analysis was repeated by using prevalence ratios rather than odds ratios, and the resulting AFs were almost the same (variations of less than 1%). Ecologic correlation between asthma prevalence and frequency of atopy was assessed, and unweighted Pearson correlation coefficients are reported. All analyses were carried out with Stata software (release 7.0; StataCorp, College Station, Tex).

RESULTS

The prevalence of specific IgE sensitization varied widely between centers, even in the same country (eg, for house dust mite, from 7% to 28% in Spain or from 18% to 35% in France; Table I). Overall, the prevalence of sensitization to house dust mite (21%) is similar to that to grass (19%), and in some of the centers, sensitization to grass is more prevalent than that to house dust mite. Mite, grass, and cat all demonstrated statistically significant heterogeneity between centers. Twenty-eight percent of atopic subjects were sensitized to house dust mite alone, 4% to cat alone, and 23% to grass alone. Sensitizations to *C herbarum* species and to birch–*P judaica*–ragweed are even less common, and they were only present alone in 1% and 4% of the atopic subjects, respectively. Because the prevalence of asthma was rather low (around 9%),

TABLE II. AF of asthma, defined on the basis of symptoms, caused by specific IgE sensitization and atopy by center

Countries ordered by % of atopy*	Center	House dust mite	Cat	Timothy grass	Atopy* (95% CI)
Estonia	Tartu	6	17	13	4 (−19.0 to 22.0)
Iceland	Reykjavik	35	28	25	40 (−2.1 to 64.5)
Spain	Albacete	3	9	7	11 (−4.8 to 24.8)
	Oviedo	10	6	15	25 (−5.9 to 46.6)
	Galdakao	40	−3	13	45 (0.0 to 70.2)
	Huelva	14	−2	10	9 (−27.3 to 35.5)
	Barcelona (bcn)	32	37	8	61 (−27.8 to 88.1)
Norway	Bergen	19	19	18	47 (26.1 to 61.3)
Italy	Pavia	24	0	24	26 (−6.1 to 47.8)
	Turin	10	17	20	37 (10.7 to 55.2)
	Verona	21	21	21	44 (6.7 to 66.8)
Sweden	Umea	6	31	26	50 (25.3 to 66.5)
	Goteborg	8	15	13	28 (5.2 to 44.7)
	Uppsala	7	16	20	20 (−5.9 to 39.2)
France	Grenoble	12	15	13	16 (−16.0 to 39.7)
	Paris	16	18	21	36 (14.4 to 51.6)
	Montpellier	15	11	5	12 (−8.8 to 28.3)
	Bordeaux	48	25	23	55 (33.1 to 69.4)
Belgium	South-Antwerp	31	11	27	46 (0.7 to 70.9)
	Antwerp city	37	22	31	55 (17.9 to 75.4)
Germany	Erfurt	−14	10	7	11 (−26.4 to 37.4)
	Hamburg	19	22	24	43 (19.5, 60.0)
United Kingdom	Cardiff	19	11	11	22 (−1.6 to 40.2)
	Ipswich	36	22	23	44 (18.1 to 61.3)
	Norwich	19	20	17	26 (−2.2 to 45.9)
	Cambridge	29	12	12	38 (−13.8 to 66.6)
The Netherlands	Groningen	54	20	23	58 (13.5 to 79.7)
	Bergen op Zoom	20	15	20	36 (2.1 to 57.7)
	Gellen	19	14	39	26 (−17.3 to 53.8)
Ireland	Dublin	35	12	31	26 (−9.7 to 50.2)
New Zealand	Hawkes-Bay	14	−1	23	14 (−29.7 to 43.0)
	Wellington	51	17	18	52 (23.7 to 70.2)
	Christchurch	51	29	30	49 (16.3 to 68.7)
United States	Portland	0	10	29	35 (3.8 to 56.2)
Switzerland	Basel	12	4	17	17 (−10.2 to 37.2)
Australia	Melbourne	32	13	25	45 (21.2 to 61.2)
ALL†		18.2 (13.7, 22.4)	14.1 (11.8, 16.3)	17.1 (14.0, 20.1)	30.4 (24.9 to 35.5)
P value for heterogeneity		<.001	.30	.91	.012

*Atopy: IgE sensitization to any of house dust mite, cat, timothy grass, *C herbarum*, and birch, *P* judaica, or ragweed.
†AF in the 36 centers estimated with meta-analysis.

the prevalence of IgE sensitization among nonasthmatic patients was only slightly lower than that shown in Table I for the entire population (18% for house dust mite or grass and 7% for cat and 32% for any allergen). The association between IgE sensitization and asthma was strong but varied substantially between centers, even in the same country (odds ratios varied from 2.8 to 8.9 in Spain for cat). However, the associations were not statistically significantly heterogeneous for any allergen. The strongest association was found for cat allergen (Table I).

The AF for house dust mite was similar to that for grass (Table II), which is coherent with a similar prevalence and similar odds ratio (Table I). The AF for cat is slightly lower to that of house dust mite or grass, although the relative risk for cat was stronger. Only the AF for house dust mite was heterogeneous between centers. Similar results were obtained when sensitization was defined as only to a single specific allergen. The AF of asthma caused by atopy was approximately 30% (Table II). The same results were obtained when atopy was defined as the joint effect of the 3

TABLE III. AF* (95% CI) of asthma caused by atopy† by using different definitions of asthma in the 36 centers

Response variable	%	House dust mite	Cat	Timothy grass	Atopy†
Symptoms of asthma‡	8.7	18.2 (13.7-22.4), $P < .001$§	14.1 (11.8-16.3), $P = .296$	17.1 (14.0-20.1), $P = .911$	30.4 (24.9-35.5), $P = .012$
Wheezing apart from cold and breathlessness	8.0	19.8 (14.5-24.8), $P < .001$	15.7 (12.3-18.9), $P = .008$	15.5 (12.3-18.6), $P = .178$	29.9 (25.2-34.2), $P = .22$
Wheezing and bronchial responsiveness	5.4	31.5 (25.8-36.8), $P = .009$	21.2 (17.0-25.1), $P = .003$	24.0 (19.9-27.9), $P = .845$	42.6 (35.0-49.3), $P = .007$
Physician diagnosis of asthma	7.7	28.7 (23.7-33.5), $P = .003$	18.4 (16.1-21.6), $P = .304$	22.9 (19.4-26.2), $P = .376$	45.3 (40.8-49.5), $P = .38$
No. of attacks of asthma in past year>12	0.5	47.8 (24.1-64.1), $P = .989$	28.0 (11.3-41.5), $P = .965$	29.4 (8.3-45.6), $P = .971$	47.6 (7.4-70.4), $P = .879$

*Adjusted for age, sex, and smoking, with data obtained by using meta-analysis.
†To any of the following allergens: house dust mite, cat, timothy grass, *C herbarum*, and birch, *P judaica*, or ragweed.
‡Nocturnal attack of shortness of breath, asthma attacks, or asthma medication.
§*P* value for test of heterogeneity.

most common allergens (ie, the addition of the 3 allergens in the same regression model). The correlation between the 2 AFs (joint and any) was very strong ($r = 0.86$). In some centers (Tartu, Estonia; Geleen, The Netherlands; and Hawkes Bay, New Zealand) the AF for atopy was lower than the AF for some of the allergens alone, which is explained by inverse associations of some of the individual allergens with asthma.

The AF for atopy could have been underestimated because of the definition of asthma used. The overall AF increased to 42.6% when the diagnosis of asthma was based on wheezing and bronchial responsiveness, to 45.3% with a physician diagnosis of asthma, and to 47.6% when patients reported more than 12 attacks within the past year (Table III). The same was observed when other definitions of severity, such as hospital admissions or treatment with steroids, were used. There was heterogeneity between centers in the AF for most of the associations with house dust mite but also with cat if the outcome was wheezing and bronchial responsiveness.

The AF of asthma caused by atopy varied in a heterogeneous way from 4% to 61% between centers, even within the same country. To understand the geographic heterogeneity in the AF, we did an ecologic analysis with center as the unit of observation, looking to the separate relationship between the AF and the 2 parameters of its function: the prevalence of atopy and the odds ratio. At the center level, variation in the AF was strongly correlated with the prevalence of atopy among the asthmatic patients ($r = .91$; $P < .01$; Fig 1). The prevalence of atopy among asthmatic patients ranged between 15% in Tartu and 78% in Barcelona (Spain), with an average of 56%.

Variation in the AF was less well correlated ($r = 0.64$; $P < .01$) with the prevalence of IgE sensitization to house dust mite among the asthmatic patients. The prevalence of IgE sensitization to house dust mite among asthmatic patients ranged between 4% in Erfurt (Germany) and 67% in Wellington (New Zealand), with an average of 37%. Correlation of AF with the prevalence of sensitization to cat ($r = 0.59$) or to grass ($r = 0.36$) was lower but statistically significant ($P < .05$).

AF was correlated with the 2 components of the odds ratio: the prevalence of symptoms of asthma among atopic subjects ($r = 0.43$) and the prevalence of symptoms of asthma among nonatopic subjects ($r = -0.51$; Fig 2). By using specific allergens, the prevalence of asthma was significantly heterogeneous only among subjects sensitized to house dust mite but not to cat or grass. Similar results were obtained when the outcome was a combination of symptoms and bronchial responsiveness. Finally, the variation in the AF to both specific allergens or to any allergen was unrelated to the prevalence of asthma ($r < .05$, irrespective of the definition of asthma used).

DISCUSSION

First, we found that between one third and one half of the prevalent cases of asthma among adults between 20 and 44 years old in the general population could be attributed to sensitization to common inhaled allergens. Second, the population AF of atopy in asthma varied widely between centers, even within the same country. Third, we found that the AF for house dust mite varied between centers, which in general did not occur for cat or grass. These findings were obtained by using the same definitions and standardized research protocol in several international centers and analyzing the effect of individual allergens.

The AF is a measure of effect that has the characteristic that wrongly misclassifying unexposed and exposed subjects does not affect the value of AF if the error is nondifferential. This is the case of using a definition of IgE sensitization with a low cutoff point to define positivity. Therefore more restrictive definitions of IgE sensitization would not change the AF. Although it is possible that some highly influential allergens were missed, it is probable that the prevalence of atopy is not greatly influenced by the selection of allergens because the prevalence of atopy to any of the 5 allergens in a multilevel model did not explain any more of the individual association of the 3 common allergens. Similarly, stratification by total IgE level (assuming that subjects with

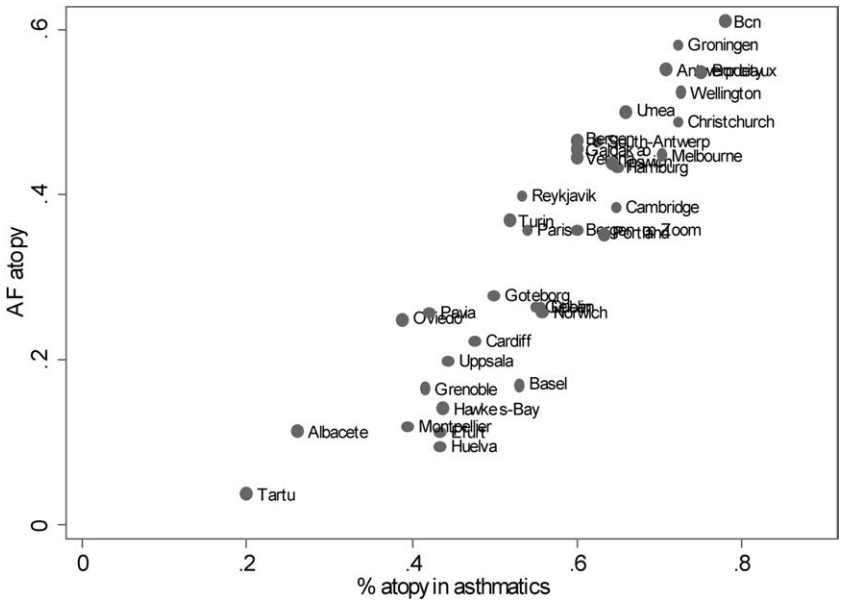

FIG 1. Distribution of centers according to the AF of asthma defined on the basis of symptoms caused by atopy and the prevalence of atopy among asthmatic subjects.

a higher total IgE level could be reactive to more specific allergens) did not modify the AFs (data not shown).

However, the AF varied with changes in the definition of the disease. The broadest definition used in the ECRHS that incorporated a combination of 3 questions referring to the last 12 months showed the highest validity in a preliminary study.[14] Nevertheless, another study within the ECRHS showed that among the self-reported symptoms used to define asthma, questions including the term *asthma* were heterogeneously correlated with the respiratory symptoms among the different countries, something that did not happen with the rest of symptoms not including the term *asthma*.[15] Therefore we used other definitions of asthma on the basis of questions not incorporating the term *asthma* to ensure comparability. Whatever the definition used, AF was never higher than 50%. Also, the AF of atopy for bronchial responsiveness per se was 32% (data not shown), suggesting that diagnostic misclassification was not a reason for an AF of less than 50%.

Interpretations of the present results in terms of causality must be undertaken with caution. First, in our study the AF refers to the prevalence of asthma. Our results are consistent with the repeated finding of an association between atopy and the prevalence of asthma.[16-20] This is in contrast with the inconsistent evidence about the association between sensitization and the development of asthma,[21,22] perhaps because sensitization to common allergens could be a more relevant factor for the prevalence of asthma than for its development. The finding that the AF was a bit higher for severe asthma might support the latter. A second aspect refers to the assessment of interactions between the different cofactors. Because we did not take into account the presence of interactions, our AF might involve some underestimation. Finally, because the theoretic upper limit of the AF is not 100% but infinity,[23] the finding that the AF of asthma for atopy was less than 50% does not allow comparison to the effect of other factors on other diseases. Our estimate of the effect of atopy on the prevalence of asthma at the population level is commensurate with a recent review of different studies.[1]

Our results might also be useful for a better understanding of causal patterns of asthma from a practical view. Asthma, like other chronic diseases, is a multifactorial disease. Although atopy is likely to be one of the relevant causal factors, its presence alone is not enough to produce asthma because only 14% of sensitized people have asthma. Thus other factors are necessary for atopy to play its role. Under the theory of component causes,[24] we assume that a certain number of asthma cases only occur when a set of factors are present (simultaneously or not), and we call this set a *sufficient cause* and each of the factors a *component cause*. Removing any component cause would prevent the corresponding case from occurring. Our data suggest that total elimination of sensitization to these allergens from a given population, an unrealistic assumption, might possibly result in a reduction of 30% of prevalent asthma cases. The other cases are those determined by other sufficient causes among which the component factor of atopy is not included. Although 56% of asthmatic patients in our study are sensitized to common allergens, the AF indicates that around 60% of them (ie, the AF among the exposed) would have been prevented by preventing sensitization in the best scenario.

Understanding the reasons for geographic variations in asthma prevalence has aroused increasing interest. The AF of asthma symptoms caused by atopy was heterogeneous,

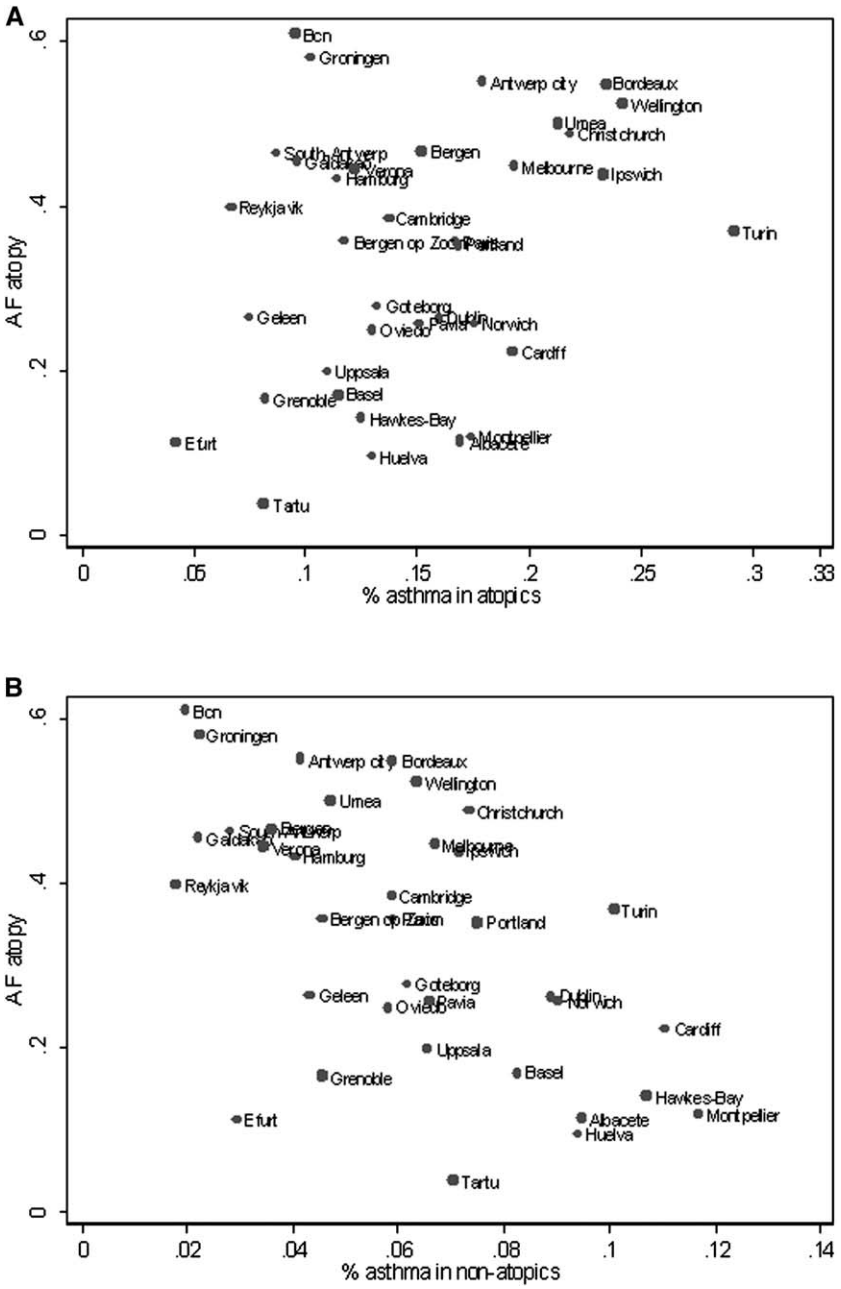

FIG 2. Distribution of centers according to the AF of asthma defined on the basis of symptoms caused by atopy and the prevalence of symptoms of asthma among atopic subjects **(A)** and the prevalence of symptoms of asthma among nonatopic subjects **(B)**.

suggesting that the potential importance of atopy in the prevalence of asthma is larger in some areas than in others. The reason for these variations should be related to either the variations in the association between atopy and asthma (ie, variations in the odds ratio) or to the variations in the prevalence of atopy among the asthmatic patients. In our study the prevalence of sensitization among asthmatic patients varies largely between centers. Although this overall pattern was also consistent for the 3 allergens included, only geographic variations in the AF for house dust mite were statistically significantly heterogeneous, suggesting that the prevalence of sensitization to house dust mite is the main determinant of geographic variations in the population fraction of asthma attributable to atopy. These geographic differences in the prevalence of atopy might be explained by differences in microenvironmental factors influencing the local levels of allergens in the indoor and outdoor environment.[25,26]

Although there were large variations in the relative risk between centers, these variations were not heterogeneous among centers in a statistically significant way. However, the 2 components of the relative risk (ie, the prevalence of

asthma in the nonatopic individuals and the prevalence of asthma in the atopic individuals) were heterogeneous between the centers and correlated with variations in the AF. Geographic variation in the prevalence of asthma among the atopic individuals is probably a result of variations in the component causes that are necessary for atopy to cause asthma, and although these factors are unknown, they are probably related to susceptibility factors. Geographic variations among the prevalence of asthma of the nonatopic individuals are due to geographic variations in the exposure to other sufficient causes of asthma that did not include atopy among its causal components, such as some occupational exposures.

Several investigations have found an association between allergy and asthma at the individual level. Cat allergen has been found to be the most strongly associated with asthma in Sweden and the Netherlands,[17,18] whereas in Belgium and the United Kingdom the strongest association was with mites.[19,20] In the present international study the strongest overall association was found with cat allergen rather than mites, although the AF was of a similar magnitude. A secondary finding of the present study is the large AF of house dust mite among the most severe asthma cases. Sensitization to house dust mite was previously found to be positively associated with severity.[27]

Overall, IgE sensitization to common allergens has an effect on asthma prevalence, which varies widely between centers. Reasons for the wide variation remain unknown, but they do not seem to be due to the strength of the association between atopy and asthma. Most important appear to be other exposures influencing the expression of asthma among atopic and nonatopic individuals. Levels of allergens in the environment, as reflected by the prevalence of atopy, particularly house dust mite, also seem to play a role. From a mechanistic point, the present results reinforce the idea that atopy is only one factor in the constellation of factors that play a role in asthma prevalence. This constellation of factors varies between centers.

REFERENCES

1. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy. Thorax 1999;54:268-72.
2. Ponsonby AL, Gatenby P, Glasgow N, Mullins R, McDonald T, Hurwitz M. Which clinical subgroups within the spectrum of child asthma are attributable to atopy. Chest 2002;121:135-42.
3. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. Eur Respir J 1994;7:954-60.
4. Burney P, Malmberg E, Chinn S, Jarvis D, Lucynska Ch, Lai E. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. J Allergy Clin Immunol 1997;99:314-22.
5. Chinn S, Burney P, Sunyer J, Jarvis D, Luczynska C. Sensitization to individual allergens and bronchial responsiveness in the ECRHS. Eur Respir J 1999;14:876-84.
6. Pekkanen J, Pearce N. Defining asthma in epidemiological studies. Eur Respir J 1999;14:951-7.
7. Janson C, Antó JM, Burney P, Chinn S, de Marco R, Jarvis D, et al. The European Community Respiratory Health Survey: what are the main results so far? Eur Respir J 2001;18:598-611.
8. Soriano J, Antó JM, Sunyer J, Tobías A, Kogevinas M, Almar E, et al. Risk of asthma in the general Spanish population attributable to specific immunoresponse. Int J Epidemiol 1999;28:728-34.
9. Plaschke P, Janson C, Norrman E, Bjornsson E, Ellbjar S, Jarvholm B. Association between atopic and asthma and bronchial hyperresponsiveness in Swedish adults: pets and not mites, are the most important allergens. J Allergy Clin Immunol 1999;104:58-65.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
11. Zocchetti C, Consonni D, Bertazzi PA. Relationship between prevalence rate ratios and odds ratios in cross-sectional studies. Int J Epidemiol 1997;26:220-3.
12. Greenland S, Drescher K. Maximum likelihood estimation of the attributable fraction from logistic models. Biometrics 1993;49:865-72.
13. Wacholder S, Benichou J, Heineman EF, Hartge P, Hoover RN. Attributable risk: advantages of a broad definition of exposure. Am J Epidemiol 1994;140:303-9.
14. Burney PG, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S, et al. Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. Eur Respir J 1989;2:940-5.
15. Sunyer J, Basagaña X, Antó JM, Burney P, on behalf of the ECRHS. International assessment of the internal consistency of respiratory symptoms. Am J Respir Crit Care Med 2000;162:930-5.
16. Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills TA. Association of asthma with serum IgE skin test reactivity to allergens among children living at high altitude: tickling the dragon's breath. Am J Respir Crit Care Med 1995;151:1388-92.
17. Plaschke P, Janson C, Norman E, Bjornsson E, Ellbjär S, Järvholm B. Association between atopic sensitization and asthma and bronchial responsiveness in Swedish adults. J Allergy Clin Immunol 1999;104:58-65.
18. Boezen HM, Postma DS, Schouten JP, Kertsjens HA, Rijcken B. PEF variability, bronchial responsiveness and their relation to allergy markers in a random population. Am J Respir Crit Care Med 1996;154:30-5.
19. Chinn S, Jarvis D, Luczynska C, Burney P. Individual allergens as risk factors for bronchial responsiveness in young adults. Thorax 1998;53:662-7.
20. Wieringa MH, Weyler JJ, van Bastelaer FJ, Nelen VJ, Van Sprudel MP, Vermiere PPA. Higher asthma occurrence in an urban than a suburban area: role of house dust mite skin allergy. Eur Respir J 1997;10:1460-6.
21. Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von Mutius E, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicenter Allergy Study Group. Lancet 2000;356:1392-7.
22. Litonjua AA, Milton DK, Celedon JC, Ryan L, Weiss ST, Gold DR. A longitudinal analysis of wheezing in young children: the independent effects of early life exposure to house dust endotoxin, allergens, and pets. J Allergy Clin Immunol 2002;110:736-42.
23. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88:15-9.
24. Rothman KJ, Greenland S. Modern epidemiology. Philadelphia: Lippincott-Raven; 1998. p. 53-5.
25. de Marco R, Poli A, Ferrari M, Accordini S, Giammanco G, Bugiani M, et al. The impact of climate and traffic-related NO2 on the prevalence of asthma and allergic rhinitis in Italy. Clin Exp Allergy 2002;32:1405-12.
26. 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.
27. Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F. European Community Respiratory Health Survey. Sensitization to airborne moulds and severity of asthma: cross sectional study from European Community Respiratory Health Survey. BMJ 2002;325:411-4.