

Phenotypic determinants of uncontrolled asthma

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Background: Although uncontrolled asthma remains frequent, determinants of asthma control are poorly studied.

Objectives: The aim was to estimate the distribution and the phenotypic characteristics of asthma control in 2 groups of subjects defined by the use of inhaled corticosteroids (ICS) in the past 12 months, in the Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA).

Methods: Five hundred one adult current patients with asthma who participated in the follow-up of the EGEA study were included. Asthma control was assessed from survey questions reflecting asthma control, as defined in the 2006 Global Initiative for Asthma guidelines. The factors analyzed were age, sex, educational level, body mass index, active and passive smoking, sensitization to aeroallergens, total IgE, rhinitis, chronic cough/phlegm, and age at asthma onset. Analyses were stratified according to ICS use.

Results: Uncontrolled asthma was more frequent in ICS users (27.6%, 35.0%, and 37.4% with controlled, partly-controlled, and uncontrolled asthma respectively) compared with non-ICS users (60.0%, 23.9%, and 16.1%, respectively). In ICS users, chronic cough or phlegm and female sex were independently and significantly related to uncontrolled asthma. In non-ICS users, high total IgE and sensitization to molds were associated

with uncontrolled asthma. Smoking and rhinitis were not associated with asthma control.

Conclusion: Optimal asthma control remained unachieved in the majority of patients with asthma in this study. Factors associated with uncontrolled asthma were different in ICS users (chronic cough/phlegm, female sex) and non-ICS users (high total IgE and sensitization to molds). (J Allergy Clin Immunol 2009;123:123-133.)

Key words: Asthma control, risk factor

Achieving and maintaining optimal asthma control is a major goal of asthma management.^{1,2} Uncontrolled asthma has major consequences on morbidity, quality of life, and economic burden.³ Several surveys in the general population showed that many patients with asthma have poorly controlled disease.^{4,5} The updated international guidelines for asthma management (Global Initiative for Asthma [GINA] 2006) propose a 3-level classification for asthma control—controlled, partly controlled, and uncontrolled—on the basis of the clinical features of the patients (symptoms and lung function), activity limitation, hospitalization for asthma, and the requirement of short-acting β_2 -agonist or oral corticosteroids.¹ In the European Community Respiratory Health Survey (ECRHS) II, only 15% of the subjects who had used inhaled corticosteroids (ICSs) in the past year had a controlled disease following the GINA classification.⁶

A better understanding of asthma control determinants may help to achieve disease control for a larger part of the population. However, besides the obvious impact of adequacy and adherence to the treatment, and poor perception of their own asthma control by patients,⁷ the other determinants for asthma control remain understudied. Rhinitis,⁸ active and passive smoking,^{9,10} and body mass index (BMI)^{6,11-13} have been suggested to play a role in asthma control. In the The Gaining Optimal Asthma Control (GOAL) clinical trial, optimal asthma control was achieved less frequently in patients with more severe asthma assessed by the level of daily treatment before the study.¹⁴ In a community-based study, determinants for asthma control were different according to the use of ICS in the past year.⁶

The aim of this study was to test, in the frame of the EGEA2 study, the follow-up of the Epidemiological study on the Genetics and Environment of Asthma (EGEA1), a French case-control and family study on asthma, the 2 following hypotheses: (1) controlled asthma remained unachieved in the majority of patients with asthma, and (2) the phenotypic characteristics of uncontrolled asthma are different between ICS users and non-ICS users.

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Supported by grants from Merck Sharp & Dohme (MSD); Hospital program of clinical research (PHRC)-Paris; National Research Agency - Health environment, health-work program; National Research Agency (ANR)- Biological collections for health program; French Agency of health safety, environment and work (AFSSET) and the Isere committee against respiratory diseases (COMARES).

Disclosure of potential conflict of interest: C. Pison has served as a consultant for GlaxoSmithKline, Boehringer Ingelheim France, AstraZeneca, Nutricia, Numico, and Actéllion and has received research support from AB Science. The rest of the authors have declared that they have no conflict of interest.

Received for publication January 5, 2009; revised May 11, 2009; accepted for publication June 1, 2009.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2009.06.010

Abbreviations used

BMI: Body mass index
 ECRHS: European Community Respiratory Health Survey
 EGEA: Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy
 GINA: Global Initiative for Asthma
 ICS: Inhaled corticosteroid
 OR: Odds ratio

METHODS**Population**

This is a cross-sectional study using data from the case control and family-based EGEA2 study, the 12-year follow-up of the EGEA1 study. Protocol and descriptive characteristics of the EGEA1 study have been previously published.^{15,16} Briefly, 2047 subjects were enrolled at baseline, including 388 children (<16 years) and adult patients with asthma from chest clinics, their 1244 first-degree relatives, and 415 population-based controls. Approximately 10 years later, this population was contacted (EGEA2, step 1). This self-completed questionnaire was returned by 1921 subjects (92.2% of the alive cohort + 73 new family members not examined at the first survey or born later; see this article's Fig E1 in the Online Repository at www.jacionline.org). Responders to the self-completed questionnaire were invited for a complete examination (EGEA2, step 2), and detailed information was available for 1601 subjects (77.1% of the alive cohort + 58 new family members; see the Online Repository population and protocol section and Figure E1). The examination included detailed questionnaires, total serum IgE, lung function tests (spirometry and methacholine challenge test), and skin prick tests to 11 aero-allergens (see the Online Repository population and protocol section).

For the present cross-sectional analysis, the target population included subjects with current asthma at EGEA2 (steps 1 and 2; n = 558). Finally, after selection of patients with asthma with all data available to assess asthma control and ICS use in the past 12 months, the population under study was composed of 501 adults with asthma. This population was not different from the population of patients with asthma not included (n = 57) regarding the main personal and sociodemographic characteristics and clinical characteristics (data not shown).

Written consent was obtained from all participants at both surveys. Ethical approval to carry out the study was obtained for both surveys from the relevant committees (Cochin Royal Hospital, Paris, for EGEA1; Necker-Enfants Malades Hospital, Paris, for EGEA2).

Definition of current asthma

Subjects reporting to have ever had attacks of shortness of breath at rest with wheezing in the chest or asthma attacks, and to have respiratory symptoms in the past 12 months (wheeze, nocturnal chest tightness, attacks of breathlessness following activity, at rest or at night time, asthma attacks) or to have used inhaled and/or oral medicines in the previous 12 months because of breathing problems, were defined as patients with current asthma. This definition of current asthma has already been used in ECRHS II.⁶

Asthma control classification

Four asthma control phenotypes were considered. Firstly, a multidimensional approach was used, in which responses to EGEA2 survey questions were combined to approximate as closely as possible the control definitions in the GINA 2006 guidelines, as previously published.⁶ Subjects were defined with (1) controlled asthma if all the following features were present: no more than 1 instance per week of trouble breathing (defined by the answer to, "How often have you had trouble with your breathing because of your asthma in the past 3 months?") and no asthma attack in the last 3 months (defined by the answer to, "How many asthma attacks have you had in the past 3 months?"), no nocturnal symptoms (woken up because of asthma or by an attack of shortness of breath) in the last 3 months, use of short-acting

β_2 -agonist inhalers ≤ 2 /wk in the last 3 months, no use of oral corticosteroids in the past year, $FEV_1 \geq 80\%$ predicted; (2) partly controlled asthma if 1 or 2 of these features were absent; and (3) uncontrolled asthma if ≥ 3 of these features were absent or if respiratory problems had caused hospital or emergency admissions in the past year or use of oral corticosteroids in the past year or ≥ 12 asthma attacks in the past 3 months.

Because the combination of asthma control dimensions in the GINA guidelines have not been fully validated, 3 one-dimensional aspects of control were also studied: (1) frequent daytime or nighttime symptoms in the 3 months, defined by trouble breathing ≤ 1 /wk or >1 nocturnal symptoms in the past 3 months; (2) exacerbations in the past 12 months defined by hospital or emergency admission or use of oral corticosteroids in the past year; and (3) low ventilatory function ($FEV_1 < 80\%$).

Asthma treatment level classification

On the basis of the 2006 GINA guidelines,¹ 4 levels of asthma controller medications were defined among subjects who reported to have used ICS in the past 12 months: (1) no treatment in the past 3 months, (2) no daily treatment in the past 3 months, (3) daily low/medium asthma treatment (GINA steps 2 and 3), and (4) daily high asthma treatment (GINA steps 4 and 5; see the Online Repository level of asthma controller medication section).

Determinants for asthma control considered

Potential determinants were selected from the literature, and with available data in EGEA2, and included age, sex, educational level (primary, secondary, university), BMI, active and passive smoking, sensitization to indoor allergens (cat, *Dermatophagoides pteronyssinus*, *Blattella germanica*), sensitization to outdoor allergens (olive, birch, *Parietaria judaica*, timothy grass, ragweed pollen) sensitization to molds (*Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*), total IgE, rhinitis, chronic cough or phlegm, and age at asthma onset (see the Online Repository phenotype definition section).

Attitude toward compliance to treatment was assessed by response to the following question: "If you are prescribed medicines for your breathing, do you normally take: (1) all the medicine, (2) most of the medicine, (3) some of the medicine, (4) none of the medicine?" Patients with asthma who gave answers 2 to 4 were considered as noncompliant as previously defined.¹⁷

Analysis strategy

Inhaled corticosteroid use could be considered as a severity marker.⁶ We hypothesized that determinants for uncontrolled asthma might be different in ICS users (ICS+) and non-ICS users (ICS-) in the past 12 months. Using the 3-level asthma control classification, the analysis was conducted separately in these 2 populations. For the 1-dimensional aspects of asthma control, because of the small numbers of asthmatics with uncontrolled asthma in non-ICS users, the analysis was conducted among ICS users only.

Statistical methods used for the univariate analyses include the χ^2 test for the categorical variables and the ANOVA for continuous variable. Multivariate analysis were conducted by using the polytomous logistic regression, allowing assessment simultaneously for each factor the risk for patients with uncontrolled asthma and partly controlled asthma compared with controlled asthma. The center was a potential confounder and was included in the multivariate analysis. There was no collinearity of the predictors (see the Online Repository statistics section).

RESULTS**Description of the population**

Main personal, sociodemographic, and clinical characteristics of the population with asthma are presented in Table I. The mean age of the population was 39 years, and half of the subjects were nonsmokers and not exposed to tobacco smoke at the time of the survey. Regarding allergic phenotypes, 60.2% reported allergic rhinitis, 61.3% had total IgE ≥ 100 IU/mL, and 80.8% were

TABLE I. Description of the population

	All n = 501	ICS+ n = 246	ICS- n = 255	P value (ICS+ vs ICS-)
Sex (% men)	50.9	49.6	52.2	.57
Age (y), mean $\pm$ SD	39.2 $\pm$ 16.4	43.2 $\pm$ 17.7	35.4 $\pm$ 14.0	<.0001
BMI (%)				
<20	12.4	10.1	14.5	.51
20-25	50.9	51.5	50.4	
25-30	24.7	25.7	23.8	
≥ 30	12.0	12.7	11.3	
Status at inclusion (%)				
Cases	50.5	63.8	37.6	<.0001
Relatives	40.9	30.1	51.4	
Spouses	1.6	1.6	1.6	
Controls	7.0	4.5	9.4	
Educational level (%)				
Primary	21.8	27.3	16.6	.01
Secondary	28.9	25.6	32.0	
University	49.3	47.1	51.4	
Active/passive smoking status (%)				
Non smoker and ETS-	54.7	60.6	49.0	.03
Non smoker and ETS+	19.0	16.0	22.0	
Current smoker	26.3	23.4	29.0	
Age at asthma onset (n)	472	232	240	
Age at asthma onset (y), mean $\pm$ SD	15.2 $\pm$ 14.9	17.3 $\pm$ 16.0	13.1 $\pm$ 13.2	.002
Age at asthma onset (%)				
≤ 4 y	31.1	31.3	31.0	.0047
4-16 y	34.5	28.3	41.0	
>16 y	34.3	40.4	28.0	
Chronic cough or phlegm (%)	16.1	19.7	12.6	.03
Rhinitis (%)	60.2	62.5	57.9	.30
FEV ₁ % predicted, mean $\pm$ SD	94.9 $\pm$ 18.9	89.2 $\pm$ 21.3	100.4 $\pm$ 14.1	<.0001
Total IgE ≥ 100 IU/mL (%)	61.3	62.4	60.2	.63
Sensitization to any allergens (%)	80.8	79.4	82.2	.45
Sensitization to indoor allergen (%)	65.8	67.3	64.3	.51
Sensitization to outdoor allergen (%)	57.2	54.7	59.6	.30
Sensitization to molds (%)	23.2	26.5	20.0	.10

ICS+, Report of ICS use in the past year; ICS-, report of non-ICS use in the past year.

sensitized to any of the 11 allergens. Chronic cough or phlegm was reported by 16% of the subjects. Patients with asthma treated with ICS in the past 12 months were significantly older, were more often recruited as asthmatic cases at inclusion, were more often nonsmokers and not exposed to passive smoking, and more often reported chronic cough or phlegm than subjects who did not use ICS in the past 12 months.

Distribution of asthma control

The distribution of the 3-level asthma control classification and each of the 1-dimensional criteria of asthma control are presented according to ICS use in Table II. For each of the 1-dimensional aspects of asthma control, ICS users systematically presented uncontrolled asthma more often (Table II). Regarding the 3-level composite asthma control classification, only one fourth of the ICS users had controlled asthma, compared with 60% of non-ICS users. Inversely, the frequency of uncontrolled asthma was 2-fold higher in ICS users than non-ICS users.

Asthma control and level of treatment

Among patients with asthma who reported having used ICS in the past 12 months, the level of asthma treatment of the past 3 months was studied in relation to the level of asthma control.

Among the patients with asthma with controlled asthma, 23.9% had used a daily high treatment level in the past 3 months, compared with 39.8% and 51.2% among the patients with partly controlled asthma and uncontrolled asthma, respectively (the P value assessed by the χ^2 test was <.0001; Fig 1). The level of treatment in the past 3 months was inversely related with the level of asthma control.

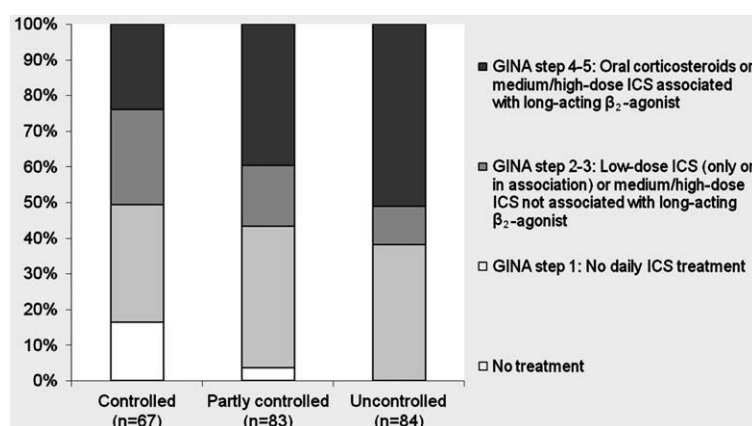
Determinants of the lack of asthma control

Each of the personal and phenotypic characteristics was studied in relation to the 3-level asthma control composite classification. These univariate analyses conducted in ICS users showed that only chronic cough or phlegm was related to a greater risk for partly controlled and uncontrolled asthma ($P = .02$) compared with controlled subjects (Table III); all the other criteria studied were not significantly associated with the level of asthma control. In non-ICS users, high total IgE level and sensitization to indoor and to outdoor allergens were significantly associated with the lack of asthma control (P values were .01, .01, and .005, respectively).

In the multivariate analysis in ICS users, female sex and chronic cough or phlegm were associated with a greater risk for partly controlled and uncontrolled asthma compared with controlled asthma, although significant results were observed only

TABLE II. Description of the 1-dimensional asthma control criteria and the 3-level asthma control level according to the use of ICS in the past year

	All n = 501	ICS+ n = 246	ICS– n = 255	P value ICS+ vs ICS–
One-dimensional asthma control aspects (%)				
Symptoms in the past 3 mo	37.5	47.6	27.8	<.0001
Exacerbations in the past 12 mo	16.8	24.5	9.4	<.0001
FEV ₁ <80% predicted	17.2	28.8	6.1	<.0001
Three-level asthma control (GINA 2006) (%)				
Controlled	44.1	27.6	60.0	<.0001
Partly controlled	29.3	35.0	23.9	
Uncontrolled	26.6	37.4	16.1	

**FIG 1.** Level of asthma treatment in the past 3 months following the GINA 2006 guidelines according to asthma control among ICS users in the past year.

with uncontrolled asthma (Fig 2). The risk for uncontrolled asthma was 4-fold greater among patients with asthma who reported chronic cough or phlegm ($P = .01$). Also, high BMI (≥ 25 kg/m²) and high total IgE increased the risk for partly controlled and uncontrolled asthma. However, although the odds ratios (ORs) were greater than 2 for partly controlled asthma, the associations were only borderline significant ($P = .06$). In the multivariate analysis conducted in non-ICS users, high total IgE was related to an increased risk for partly controlled and uncontrolled asthma with ORs of 3, but the association with partly controlled asthma was borderline significant ($P = .06$; Fig 2). Sensitization to molds was significantly associated with an increased risk for uncontrolled asthma, with an OR greater than 3 (OR, 3.15; 95% CI, 1.02-9.78; $P = .047$), but not for partly controlled asthma. Smoking status and rhinitis were not related to asthma control in both ICS users and non-ICS users.

Among patients with asthma treated by ICS, reported attitude toward compliance to the treatment was not associated with the control of the disease (37.3%, 29.3%, and 38.4% among patients with controlled, partly controlled, and uncontrolled asthma were noncompliant, respectively). A further adjustment on this variable did not change the conclusion of the multivariate analyses conducted in ICS users.

Multivariate analyses were also conducted for each of the 1-dimensional aspects of asthma control in ICS users and show that independent factors associated with these 3 criteria of asthma control were different (see this article's Table E1 in the Online

Repository at www.jacionline.org). A lower age, rhinitis, and sensitization to outdoor allergens were associated with a lower risk for a FEV₁ <80% predicted. Men were at a lower risk for severe exacerbation than women (association borderline significant), but none of the phenotypic factors were associated with the exacerbations dimension. Female sex, BMI ≥ 25 kg/m², and chronic cough or phlegm were independently associated with higher asthma symptom frequency in the past 3 months.

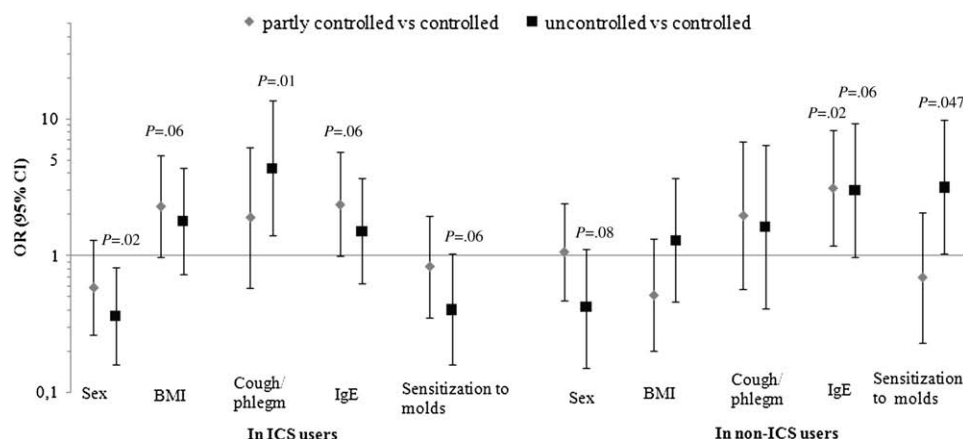
DISCUSSION

Less than half (44%) of this population of patients with asthma participating in the phase 2 of the EGEA study had a controlled asthma, on the basis of characteristics of asthma control as defined in the current GINA guidelines. The proportion of controlled asthma was lower in ICS users, in whom only one fourth of the asthmatics had a controlled asthma. The determinants for uncontrolled asthma were different in ICS users and non-ICS users. In ICS users, chronic cough or phlegm and female sex were independently related to uncontrolled asthma. Associations borderline to the significant level were also observed between the lack of asthma control and high BMI and high total IgE in ICS users. In non-ICS users, high total IgE and sensitization to molds were associated with uncontrolled asthma.

The analysis was conducted on a well characterized and large population of patients with current asthma, with detailed phenotypic data that allow to assess all asthma characteristics, except

TABLE III. Association between asthma control and sociodemographic and clinical characteristics, according to ICS use in the past 12 months

	ICS+ (n = 246)				ICS- (n = 255)			
	Controlled (n = 68)	Partly controlled (n = 86)	Uncontrolled (n = 92)	P value	Controlled (n = 153)	Partly controlled (n = 61)	Uncontrolled (n = 41)	P value
Sex (% men)	52.9	55.8	41.3	.12	53.6	54.1	43.9	.51
Age (y), mean $\pm$ SD	39.8 $\pm$ 17.4	44.0 $\pm$ 18.6	45.1 $\pm$ 17.0	.16	35.3 $\pm$ 14.4	36.2 $\pm$ 13.6	34.7 $\pm$ 13.5	.85
BMI $\geq$ 25 kg/m ² (%)	30.9	42.2	40.7	.31	34.6	32.2	41.7	.63
Educational level (%): primary	22.1	31.3	27.6	.64	18.3	11.7	17.5	.31
Secondary	26.5	21.7	28.7		33.3	25.0	37.5	
University	51.5	47.0	43.7		48.4	63.3	45.0	
Smoking (%): nonsmoker and ETS-	58.8	60.0	62.6	.78	50.3	52.5	39.0	.21
Nonsmoker and ETS+	19.1	17.6	12.1		18.3	27.9	26.8	
Current smoker	22.1	22.3	25.3		31.4	19.7	34.1	
Age at asthma onset (y), mean $\pm$ SD	15.2 $\pm$ 15.6	17.0 $\pm$ 15.9	19.2 $\pm$ 16.5	.30	13.2 $\pm$ 12.9	13.6 $\pm$ 13.7	11.7 $\pm$ 14.2	.78
Rhinitis (%)	64.2	56.1	67.0	.31	52.6	65.0	67.5	.11
Chronic cough or phlegm (%)	11.8	16.7	28.3	.02	11.1	14.7	15.0	.68
Total IgE $\geq$ 100 IU/mL (%)	56.1	66.3	63.5	.43	52.6	71.2	73.7	.01
Sensitization to indoor allergens (%)	67.7	65.8	68.3	.94	57.2	75.9	77.4	.01
Sensitization to outdoor allergens (%)	64.6	50.6	50.6	.16	53.8	66.7	74.2	.05
Sensitization to molds (%)	32.3	30.4	17.7	.09	19.3	16.7	29.0	.37

Boldface indicates *P* value < .05.**FIG 2.** Adjusted risks between asthma control and sociodemographic and clinical characteristics, according to ICS use in the past 12 months. OR estimated by multivariate logistic regression with further adjustment on age, educational level, smoking, age at asthma onset, rhinitis, sensitization to indoor allergens, sensitization to outdoor allergens, and center. None of these factors were significantly related to asthma control in ICS users or non-ICS users in the multivariate models.

activity limitations, used in the GINA guidelines to assess asthma control. Although this asthma control classification has not been fully validated, it is expected to be widely used in clinical practice to guide treatment; moreover, this multidimensional approach, with more than 1 parameter, should provide a more comprehensive picture of the disease status.¹⁸ Nevertheless, the analysis has also been conducted separately for different asthma control dimensions. Because of the ascertainment mode of the EGEA population, the asthmatic sample was large enough to study around 500 patients with current asthma. The analysis was conducted taking into account simultaneously a large number of potential determinants of asthma control. However, other potential determinants, such as psychological factors or level of exposure to

aeroallergens, were not assessed in the EGEA study. The attitude toward treatment adherence was reported by the subjects themselves and thus may be underreported. However, these questions have been used previously in population studies, and reported poor compliance has been shown to be associated with increased emergency health care use.¹⁷

The analysis was separately conducted in ICS users and non-ICS users because it is expected that in such a population, ICS use may be considered as a proxy for asthma severity. This approach has already been used.⁶ In accordance with this hypothesis, asthma was controlled in less than one third of the ICS users compared with 60% of non-ICS users. In line with recent analyses in a representative general population sample of patients with asthma,

this article underlines the high prevalence of uncontrolled asthma, specifically in patients for whom ICS have been prescribed. In a European community-based sample, ECRHS II, using an identical approach to assess asthma control, 15%, 36%, and 49% of the ICS users had controlled, partly controlled, and uncontrolled asthma, respectively.⁶ In a US representative sample of 1823 patients with moderate to severe asthma using standard asthma medication, controlled asthma, assessed with an Asthma Control Test score between 20 and 25, was achieved in less than half of the patients with asthma (45%).¹⁹ In the current analysis, among ICS users in the past 12 months, half of the subjects with uncontrolled asthma had a high daily asthma treatment level in the past 3 months (GINA treatment step 4 or 5) compared with only one third in the ECRHS study,⁶ suggesting that the EGEA population with asthma has more severe disease than the ECRHS population with asthma. The reproducibility of the factors related to poor asthma control in ECRHS, using the EGEA data, provides complementary results in the field.

In the EGEA2 population, the multivariate analysis shows a trend for overweight patients being at an increased risk for partly controlled asthma among ICS users (OR, 2.29; 95% CI, 0.97-5.40). High BMI was significantly associated with the symptoms dimension. Interestingly, in ECRHS II, the BMI-asthma control association was also restricted to ICS users.⁶ There is growing evidence for a role of obesity in asthma control and asthma severity.^{11,12,20-22} The mechanisms of this association are not yet understood, but it may be explained in part by decreased responses to ICS in overweight patients.^{23,24} This might explain why the association of high BMI with uncontrolled asthma was restricted to ICS users in EGEA and ECRHS.

Similarly to another French study,²¹ our results indicate that women with asthma are at increased risk for uncontrolled asthma compared with men, using the 3-level composite classification, the exacerbation and symptoms dimensions. This association has not been reported in ECRHS.

In ICS users, chronic cough or phlegm was significantly associated with a greater risk for uncontrolled asthma, independently of smoking. The association follows a dose-effect relationship, with ORs for partly controlled asthma (OR, 1.9; nonsignificant) being intermediate between controlled (reference) and uncontrolled asthma (OR, 4.3). Chronic cough or phlegm was not associated with asthma control in non-ICS users; however, the ORs were greater than 1.5. Chronic cough or phlegm was significantly related to the symptoms dimension but not to the ventilatory function and exacerbation dimension. In ECRHS, chronic cough and phlegm were associated with asthma control, and persistent cough and mucus hypersecretion were strong prognostic factors for moderate/severe asthma.^{6,25} Chronic cough or phlegm are more widely defined as chronic obstructive pulmonary disease-like symptoms than asthmalike symptoms and are not explicitly included in the GINA guidelines. We recently showed that nonsmoking patients with asthma with chronic phlegm exhibit a neutrophilic inflammatory pattern.²⁶ Our results showing a high level of association with uncontrolled asthma and an association restricted to the symptoms dimension suggest that chronic cough or phlegm may be considered asthma symptoms when assessing asthma control.

In the current analysis, high total IgE was significantly associated with the lack of asthma control in non-ICS users, with ORs of 3 for partly controlled and uncontrolled asthma compared with controlled asthma. A similar trend was observed

in ICS users, but the association was only borderline significant for partly controlled asthma. High total IgE has already been reported to be associated with poor asthma control in nontreated patients with asthma in ECRHS II,⁶ with lower lung function baseline and more severe asthma,²⁷ and with persistent moderate/severe asthma in the follow-up of the ECRHS study.²⁵ Interestingly, an anti-IgE treatment, omalizumab, has recently become available in clinical practice and has been shown to be efficacious in patients with moderate-to-severe persistent allergic (IgE-mediated) asthma inadequately controlled despite treatment with high-dose ICSs.²⁸

Sensitization to indoor and outdoor allergens was not associated with the 3-level asthma control classification in the EGEA2 study. Exposure to indoor allergens has been reported to increase asthma morbidity in sensitized children with asthma.^{29,30} This association has been less studied in adults, and studies have produced conflicting results.^{31,32} Conflicting results may be explained by the different phenotypes used. Although sensitization to outdoor allergens was not associated with the current level of symptoms and the exacerbation in the past year, it was associated with a lower risk for a FEV₁ <80% predicted, which is consistent with previous results showing that more allergic asthma is less severe.³³ In contrast, sensitization to molds was associated with a greater risk for uncontrolled asthma in patients with asthma not treated with ICS, although no relationship was observed for partly controlled asthma. In adults, sensitization to molds was related to asthma severity and control in ECRHS.^{6,34} Furthermore, there is current evidence to support an association between fungal sensitization and asthma severity.³⁵ Compared with other allergens, fungi are living micro-organisms with the ability to trigger host defenses against pathogens and produce nonallergen toxins and enzymes that play an accessory role in triggering allergy.³⁵ Possibly, the size of fungal spores allows them to reach the lower airways.

Previous articles have shown that smoking was related to poor asthma control,^{9,21} which may partly be explained by the impaired therapeutic response to corticosteroids in smokers.³⁶ Smoking was not associated with asthma control in this analysis. Nevertheless, the ORs associated with current smoking in ICS users were greater than 1 for both partly controlled and uncontrolled asthma compared with controlled asthma (ORs were 1.7 and 1.3, respectively). Rhinitis has been shown to be associated with the lack of asthma control.^{8,37} This association was not significant with the multidimensional asthma control classification, and heterogeneous results were observed for the 1-dimensional aspects.

In conclusion, optimal asthma control remained unachieved for the majority of patients with asthma in this study, and particularly among ICS users, despite that 39% of the patients with asthma were treated with a daily high treatment level. Our results underline the association of chronic cough or phlegm with uncontrolled asthma. A better knowledge of the determinants of uncontrolled asthma may help in the identification of patients at increased risk for uncontrolled asthma.

We thank all those who participated in the setting of the study and in the various aspects of the examinations involved: interviewers; technicians for lung function testing, skin prick tests, and IgE determinations; coders; those involved in quality control and data and sample management; and all those who supervised the study in all centers. We are indebted to all the individuals who participated, without whom the study would not have been possible.

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Clinical implications: A better knowledge of the phenotypic characteristics of uncontrolled asthma should help in the identification of patients at increased risk for uncontrolled asthma.

REFERENCES

- Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda (MD): National Heart, Lung, and Blood Institute, National Institutes of Health; 1995 (updated 2006). NIH publication no. 95-3659. Available at: <http://www.ginasthma.org>. Accessed December 15, 2009.
- National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. July 1997 (Updated August 2007). NIH publication no. 07-4051. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>. Accessed December 15, 2009.
- Van Ganse E, Laforest L, Pietri G, Boissel JP, Gormand F, Ben-Joseph R, et al. Persistent asthma: disease control, resource utilisation and direct costs. *Eur Respir J* 2002;20:260-7.
- Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, et al. World-wide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;114:40-7.
- de Marco R, Bugiani M, Cazzoletti L, Carosso A, Accordini S, Buriani O, et al. The control of asthma in Italy: a multicentre descriptive study on young adults with doctor diagnosed current asthma. *Allergy* 2003;58:221-8.
- Cazzoletti L, Marcon A, Janson C, Corsico A, Jarvis D, Pin I, et al. Asthma control in Europe: a real-world evaluation based on an international population-based study. *J Allergy Clin Immunol* 2007;120:1360-7.
- Vermeire PA, Rabe KF, Soriano JB, Maier WC. Asthma control and differences in management practices across seven European countries. *Respir Med* 2002;96:142-9.
- Ponte EV, Franco R, Nascimento HF, Souza-Machado A, Cunha S, Barreto ML, et al. Lack of control of severe asthma is associated with co-existence of moderate-to-severe rhinitis. *Allergy* 2008;63:564-9.
- Chaudhuri R, McSharry C, McCoard A, Livingston E, Hothersall E, Spears M, et al. Role of symptoms and lung function in determining asthma control in smokers with asthma. *Allergy* 2008;63:132-5.
- Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the Genetics and Environment of Asthma. *Eur Respir J* 2000;15:470-7.
- Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med* 2006;100:648-57.
- Mosen DM, Schatz M, Magid DJ, Camargo CA Jr. The relationship between obesity and asthma severity and control in adults. *J Allergy Clin Immunol* 2008;122:507-11.
- Schatz M, Mosen DM, Kosinski M, Vollmer WM, Magid DJ, O'Connor E, et al. Predictors of asthma control in a random sample of asthmatic patients. *J Asthma* 2007;44:341-5.
- Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170:836-44.
- Kauffmann F, Dizier MH, Pin I, Paty E, Gormand F, Vervloet D, et al. Epidemiological study of the genetics and environment of asthma, bronchial hyperresponsiveness, and atopy: phenotype issues. *Am J Respir Crit Care Med* 1997;156:S123-9.
- Kauffmann F, Dizier MH, Annesi-Maesano I, Bousquet J, Charpin D, Demenais F, et al. EGEA (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy)—descriptive characteristics. *Clin Exp Allergy* 1999;29(suppl 4):17-21.
- Cerveri I, Locatelli F, Zoia MC, Corsico A, Accordini S, de Marco R. International variations in asthma treatment compliance: the results of the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1999;14:288-94.
- Frey U, Suki B. Complexity of chronic asthma and chronic obstructive pulmonary disease: implications for risk assessment, and disease progression and control. *Lancet* 2008;372:1088-99.
- Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST. Real-world Evaluation of Asthma Control and Treatment (REACT): findings from a national Web-based survey. *J Allergy Clin Immunol* 2007;119:1454-61.
- Taylor B, Mannino D, Brown C, Crocker D, Twum-Baah N, Holguin F. Body mass index and asthma severity in the National Asthma Survey. *Thorax* 2008;63:14-20.
- Laforest L, Van Ganse E, Devouassoux G, Bousquet J, Chretien S, Bauguil G, et al. Influence of patients' characteristics and disease management on asthma control. *J Allergy Clin Immunol* 2006;117:1404-10.
- Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005;171:334-9.
- Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. *Eur Respir J* 2006;27:495-503.
- Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir Med* 2007;101:2240-7.
- de Marco R, Marcon A, Jarvis D, Accordini S, Almar E, Bugiani M, et al. Prognostic factors of asthma severity: a 9-year international prospective cohort study. *J Allergy Clin Immunol* 2006;117:1249-56.
- Nadif R, Siroux V, Oryszczyn MP, Ravault C, Pison C, Pin I, et al. Heterogeneity of asthma according to blood inflammatory patterns. *Thorax* 2009;64:374-80.
- Naqvi M, Choudhry S, Tsai HJ, Thyne S, Navarro D, Nazario S, et al. Association between IgE levels and asthma severity among African American, Mexican, and Puerto Rican patients with asthma. *J Allergy Clin Immunol* 2007;120:137-43.
- Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60:309-16.
- Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997;336:1356-63.
- Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL, Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. *BMJ* 2002;324:763.
- Lewis SA, Weiss ST, Platts-Mills TA, Burge H, Gold DR. The role of indoor allergen sensitization and exposure in causing morbidity in women with asthma. *Am J Respir Crit Care Med* 2002;165:961-6.
- Wisnivesky JP, Sampson H, Berns S, Kattan M, Halm EA. Lack of association between indoor allergen sensitization and asthma morbidity in inner-city adults. *J Allergy Clin Immunol* 2007;120:113-20.
- The ENFUMOSA study group. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur Respir J* 2003;22:470-7.
- Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F. Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. *BMJ* 2002;325:411-4.
- Denning DW, O'Driscoll BR, Hogaboam CM, Bowyer P, Niven RM. The link between fungi and severe asthma: a summary of the evidence. *Eur Respir J* 2006;27:615-26.
- Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax* 2005;60:282-7.
- Bousquet J, Gaugris S, Kocevar VS, Zhang Q, Yin DD, Polos PG, et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the improving asthma control trial. *Clin Exp Allergy* 2005;35:723-7.

METHODS

Population and protocol

The EGEA combines a case-control and family study of adult and childhood asthma (<http://iffr69.vjf.inserm.fr/~egeanet/>). The first EGEA survey (EGEA1) was conducted from 1991 to 1995, and the protocol and descriptive characteristics have been described elsewhere.^{E1,E2} Briefly, 388 asthmatic cases, recruited in 5 chest clinics, 1244 first-degree relatives of cases, and 415 population-based controls were recruited (total, $n = 2047$). A 12-year follow-up of this population was conducted from 2003 to 2007 (EGEA2) in 5 centers in France (Grenoble, Paris, Lyon, Marseille, Montpellier). Subjects were contacted by postal questionnaire, and non-responders were further contacted by telephone (step 1). Among the alive cohort ($n = 2002$), 92% ($n = 1845$) completed the short self-questionnaire. Responders were invited to participate in the second phase of the study (step 2). The complete examination was mostly performed in clinical centers ($n = 1316$; 85.3%). However, to improve the follow-up rate, some subjects were examined at home ($n = 72$; 4.7%) or answered questionnaires by phone ($n = 78$; 5.0%) or mail ($n = 77$; 5.0%). Finally, 77% of the alive cohort ($n = 1543$) completed at least a detailed questionnaire. In addition, 58 new family members were included in the study at the second survey. Written consent was obtained from all participants at both surveys. Ethical approval to carry out the study was obtained for both surveys from the relevant committees (Cochin Royal Hospital, Paris, for EGEA1, and Necker-Enfants Malades Hospital, Paris, for EGEA2).

Examination procedures included a detailed questionnaire, with questions on asthma and respiratory symptoms, treatment, allergic rhinitis, active smoking, and exposure to environmental tobacco smoke. Subjects had blood samples that allowed to measure total IgE in a centralized laboratory ($n = 1421$; 88.8%). Spirometry was performed by using a standardized protocol with similar equipment across centers according to the American Thoracic Society / European Respiratory Society guidelines^{E3} to measure FEV₁ ($n = 1414$; 88.3%). Skin prick tests to 11 aeroallergens (cat, *Dermatophagoides pteronyssinus*, *Blattella germanica*, olive, birch, *Parietaria judaica*, timothy grass, ragweed pollen, *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*) were performed in 1326 subjects (82.8%). Sensitization was defined by the presence of at least 1 positive skin test (mean wheal diameter ≥ 3 mm).

Strong efforts were made to standardize all the examination procedures across centers and to minimize missing data. A quality management approach was followed for the implementation of the EGEA2 data collection, and an International Organization for Standardization (ISO) 9001:2000 certification was obtained (<http://www.afaq.org/certification=262711141114>).^{E4}

Phenotype definitions

Chronic cough was defined by a positive answer to the question, "Do you usually cough during the day, or at night, in the winter, on most days for as much as 3 months each year?" Chronic phlegm was defined by a positive answer to the question, "Do you usually bring up any phlegm from your chest during the day, or at night, in the winter, on most days for as much as 3 months each year?"

Inhaled corticosteroid use was defined by a positive answer to the question, "Have you used inhaled corticosteroids to help your breathing at any time in the past year?" with an exhaustive list of medications available in France at the time of the study.

Hospitalization and emergency visits for asthma in the past year were defined by a positive answer to the questions, "Have you visited a hospital casualty department or emergency room because of breathing problems in the

last 12 months?" and "Have you spent a night in hospital because of breathing problems in the last 12 months?"

Rhinitis was defined by the report of allergic rhinitis or hay fever associated with sneezing problems or a runny or blocked nose in the past 12 months.

Level of asthma controller treatment

According to the average daily dose of ICSs and other asthma treatments during the last 3 months, the current treatment was classified for each subject following the GINA 2006 guidelines^{E5}:

- Step 5: Oral corticosteroids (daily)
- Step 4: Medium-dose/high-dose ICS (beclomethasone dipropionate [BDP] >500 mg or an equipotent dose of other ICS) plus long-acting β_2 -agonist (daily)
- Step 3: Low-dose ICS (<500 mg BDP or equivalent) plus long-acting β_2 -agonist (daily) or plus methylxanthines (daily) or plus leukotriene modifiers (daily) or medium-dose/high-dose ICS (>500 mg BDP or equivalent; daily)
- Step 2: Low-dose ICS (<500 mg BDP or equivalent; daily) or oral methylxanthines (daily) or cromones (daily) or leukotriene modifiers (daily)
- Step 1: no daily treatment in the past 3 months
- Step 0: no treatment in the past 3 months

The equipotent doses of other ICSs (budesonide and fluticasone) were the ones reported in the GINA guidelines.

Statistics

The multicollinearity of the predictors has been assessed in estimating the tolerance in the equivalent model by using a linear regression (option TOL VIF in the proc REG in the SAS 9.1 statistical software; SAS Institute, Cary, NC). The tolerance is computing by regressing each variable on all the other explanatory variables, calculating the R² and then subtracting that from 1. Low tolerance corresponds to high multi collinearity, and although there is not strict cutoff, a cutoff of 0.40 has been proposed. Using this method, none of the tolerance statistics observed was below 0.48, suggesting that there was no collinearity of the predictors. To assess to what degree the potential collinearity between the allergic predictors would have affected the results, we conducted stepwise regression model for the inclusion of the 4 allergy-related variables in the rest of the model. The model obtained by stepwise regression model and the full model presented in the article have the same results.

All analyses were performed by using the SAS 9.1 statistical software.

REFERENCES

- E1. Kauffmann F, Dizier MH, Pin I, Paty E, Gormand F, Vervloet D, et al. Epidemiological study of the genetics and environment of asthma, bronchial hyperresponsiveness, and atopy: phenotype issues. *Am J Respir Crit Care Med* 1997;156: S123-9.
- E2. Kauffmann F, Dizier MH, Annesi-Maesano I, Bousquet J, Charpin D, Demenais F, et al. EGEA (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy)—descriptive characteristics. *Clin Exp Allergy* 1999;29(suppl 4):17-21.
- E3. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
- E4. Ravault C, Pin I, Mekong Adiego E, Le Moual N, Ferran J, Matran R, et al. Quality management in epidemiology: a pilot survey in the EGEA study. *Eur Respir J* 2006;28(suppl 50):680.
- E5. Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda (MD): National Heart, Lung, and Blood Institute, National Institutes of Health; 1995 (updated 2006). NIH publication no. 95-3659. Available at: <http://www.ginasthma.org>. Accessed December 15, 2009.

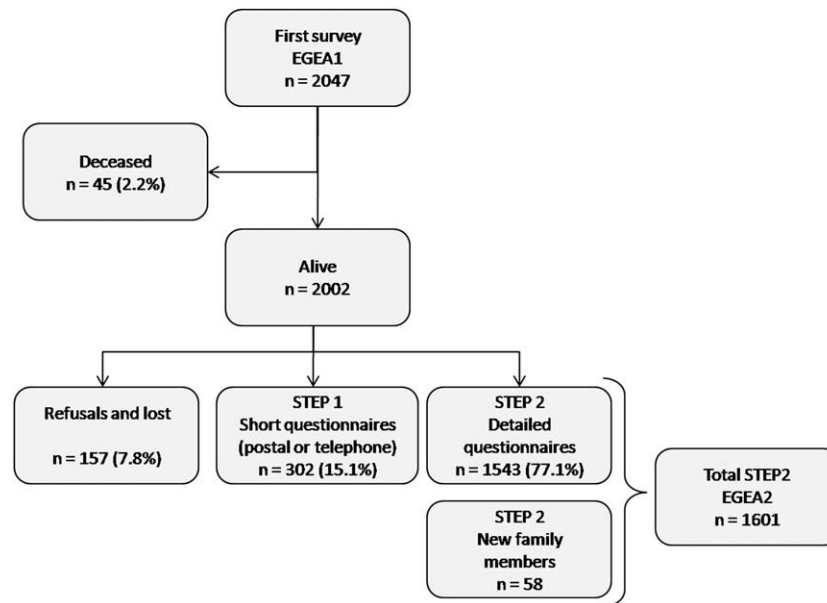
**FIG E1.** Flow chart of the EGEA population.

TABLE E1. Adjusted risk between personal and phenotypic characteristics and asthma control for each of the 3 one-dimensional aspects of asthma control among ICS users in the past 12 months

	FEV ₁ <80% predicted (n = 208)		Severe exacerbation, last 12 mo (n = 208)		Symptoms frequency, last 3 mo (n = 209)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex (men vs women)	1.66 (0.79-3.49)	.18	0.48 (0.23-1.01)	.05	0.30 (0.15-0.59)	.0005
Age (5 y increased)	1.21 (1.05-1.39)	.006	1.00 (0.87-1.14)	.96	0.98 (0.86-1.11)	.71
BMI (≥ 25 kg/m ² vs <25 kg/m ²)	0.91 (0.42-1.98)	.82	1.13 (0.51-2.48)	.76	2.52 (1.21-5.26)	.01
Educational level University	1.0	.09	1.0	.71	1.0	.37
Primary	2.60 (1.07-6.30)		1.27 (0.51-3.12)		1.67 (0.72-3.91)	
Secondary	1.92 (0.78-4.74)		0.84 (0.35-2.00)		0.90 (0.42-1.93)	
Smoking: Nonsmoker and	1.0	.83	1.0	.24	1.0	.67
ETS-Nonsmoker and	0.98 (0.35-2.72)		0.57 (0.20-1.62)		0.68 (0.28-1.68)	
ETS+Current smoker	1.33 (0.50-3.53)		0.46 (0.17-1.25)		1.03 (0.44-2.43)	
Age at asthma onset (1 y increase)	0.99 (0.96-1.02)	.56	1.00 (0.97-1.03)	.90	1.00 (0.97-1.03)	.94
Rhinitis (yes vs no)	0.41 (0.20-0.85)	.02	1.66 (0.75-3.66)	.21	1.33 (0.68-2.62)	.40
Chronic cough or phlegm (yes vs no)	1.49 (0.61-3.69)	.38	1.52 (0.59-3.89)	.38	4.22 (1.70-10.45)	.002
Total IgE (≥ 100 IU/mL vs <100 IU/mL)	1.92 (0.85-4.30)	.11	1.03 (0.47-2.25)	.94	1.14 (0.56-2.32)	.72
Sensitization to indoor allergens (yes vs no)	1.63 (0.69-3.83)	.26	1.68 (0.66-4.27)	.28	1.56 (0.69-3.54)	.29
Sensitization to outdoor allergens (yes vs no)	0.42 (0.19-0.94)	.04	0.88 (0.38-2.03)	.77	1.32 (0.62-2.83)	.47
Sensitization to molds (yes vs no)	0.83 (0.35-1.95)	.66	0.48 (0.19-1.21)	.12	0.82 (0.39-1.73)	.60

ORs were also adjusted on center. Boldface indicates *P* value < .05.