

Prognostic factors of asthma severity: A 9-year international prospective cohort study

Roberto de Marco, PhD,^a Alessandro Marcon, MSc,^a Deborah Jarvis, FFPHM,^b Simone Accordini, MSc,^a Enrique Almar, MD,^c Massimiliano Bugiani, MD,^d Adriana Carolei, MSc,^e Lucia Cazzoletti, MSc,^a Angelo Corsico, PhD,^e David Gislason, MD,^f Amund Gulsvik, PhD,^g Rain Jøgi, PhD,^h Alessandra Marinoni, PhD,ⁱ Jesús Martínez-Moratalla, MD,^c Isabelle Pin, MD,^j and Christer Janson, MD,^k on behalf of the European Community Respiratory Health Survey Therapy Group Verona, Turin, and Pavia, Italy, London, United Kingdom, Albacete, Spain, Reykjavik, Iceland, Bergen, Norway, Tartu, Estonia, Grenoble, France, and Uppsala, Sweden

Background: The natural history of asthma severity is poorly known.

Objective: To investigate prognostic factors of asthma severity.

Methods: All current patients with asthma identified in 1991 to 1993 in the European Community Respiratory Health Survey were followed up, and their severity was assessed in 2002 by using the Global Initiative for Asthma categorization ($n = 856$). Asthma severity (remittent, intermittent, mild, moderate, severe) was related to potential determinants evaluated at baseline and during the follow-up by a multinomial logistic model, using the intermittent group as the reference category for relative risk ratios (RRRs).

Results: Asthma severity measured at baseline was a determinant of a patient's severity at the end of the follow-up.

At baseline, severe persistent had a poorer FEV₁% predicted, a poorer symptom control, higher IgE levels (RRR, 2.06; 95% CI, 1.38-3.06), and a higher prevalence of chronic cough/mucus hypersecretion (RRR, 4.90; 95% CI, 2.18-11.02) than patients with intermittent asthma. Moderate persistent showed the same prognostic factors as severe persistent, even if the associations were weaker. Mild persistent had a distribution of prognostic factors that was similar to patients with intermittent asthma, although the former showed a poorer symptom control than the latter. Remission mainly occurred in patients with less severe asthma and was negatively associated with a change in body mass index (RRR, 0.86; 95% CI, 0.75-0.97). Allergic rhinitis, smoking, and respiratory infections in childhood were not associated with asthma severity.

Conclusion: Patients with moderate and severe persistent asthma are characterized by early deterioration of lung function. High IgE levels and persistent cough/mucus hypersecretion are strong markers of moderate/severe asthma, which seems to be a different phenotype from mild persistent or intermittent asthma.

Clinical implications: Our results suggest that the evolution of asthma severity is to a large extent predictable. (*J Allergy Clin Immunol* 2006;117:1249-56.)

Key words: Asthma, severity, prognostic factors, prospective cohort study, IgE, body mass index, asthma remission, European Community Respiratory Health Survey, ECRHS, Global Initiative for Asthma (GINA) guidelines

From ^athe University of Verona, Department of Medicine and Public Health, Unit of Epidemiology and Medical Statistics; ^bthe Department of Respiratory Epidemiology and Public Health, National Heart and Lung Institute, Imperial College, London; ^cthe Unit of Epidemiology, Public Health Department of Castilla La Mancha, Albacete; ^dthe Unit of Pneumology, Consorzio Provinciale Antitubercolare, Azienda Sanitaria Locale 4 Piemonte, Turin; ^ethe Department of Applied Health Sciences, Faculty of Medicine, University of Pavia; ^fthe Department of Allergy, Respiratory Medicine and Sleep, Landspítali University Hospital, Reykjavik; ^gthe Department of Thoracic Medicine, Haukeland University Hospital, University of Bergen; ^hthe Foundation Tartu University Clinics, Lung Clinic, Tartu; ⁱthe Division of Respiratory Diseases, Istituto di Ricovero e Cura a Carattere Scientifico "San Matteo" Hospital, University of Pavia; ^jDépartement de Pédiatrie, Centre Hospitalier Universitaire de Grenoble; and ^kthe Department of Medical Sciences, Respiratory Medicine and Allergology, Uppsala University.

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Reprint requests: Roberto de Marco, PhD, Unit of Epidemiology and Medical Statistics, Department of Medicine and Public Health, Università degli Studi di Verona, c/o Istituti Biologici II, Strada Le Grazie 8, 37134 Verona, Italy. E-mail: roberto.demarco@univr.it.

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Asthma severity is a major determinant of morbidity, disability, and use of health care and social resources.^{1,2} However, its natural history is poorly understood, and few studies have been set up to elucidate its epidemiology. It is not known whether severity is a stable trait characterizing a patient since the onset of the disease or whether it changes over time. The most relevant prognostic factors, as well as the role of genetic and environmental factors on its occurrence and persistence, are unknown.³

One of the reasons for this limitation lies in the inherent difficulty to define the severity of asthma. In fact, a definition based purely on clinical or physiological features can be useful only for naive (never-treated) patients,

Abbreviations used

AIC:	Akaike Information Criterion
BMI:	Body mass index
ECRHS:	European Community Respiratory Health Survey
GINA:	Global Initiative for Asthma
ICS:	Inhaled corticosteroid
RRR:	Relative risk ratio

whereas for patients currently in treatment, there is also the need to take therapy into account, particularly after the introduction of high-potency inhaled corticosteroids (ICSs) and long-acting bronchodilators, which may interact with the clinical/physiological dimension.

For this reason, the Global Initiative for Asthma (GINA) guidelines⁴ suggest a method to classify asthma severity that relies on 3 dimensions: perceived symptoms, lung function, and type of antiasthmatic treatment. These dimensions also underlie 3 different perspectives about asthma severity that are not necessarily overlapping: the patient perspective (perceived symptoms), the functional limitation or objective perspective (lung function), and the doctor perspective (treatment).

Although this approach to asthma categorization has been proposed for clinical use in the frame of a stepwise approach to pharmacotherapy,⁵ it also seems an attractive approach for epidemiologic studies on asthma severity, because it overcomes the confounding that exists among disease control, disease severity, and the use of drugs.⁶

The main aim of this paper is to contribute to highlighting the natural history of asthma severity. In particular, we investigated the following:

- Whether the severity of asthma changed substantially in a cohort of patients with asthma followed for 9 years
- The most relevant prognostic factors of asthma severity

For this purpose, the asthma severity of an international cohort of current patients with asthma, identified in the frame of the European Community Respiratory Health Survey (ECRHS) I and followed since 1991, was assessed in the years 1999 to 2002 (ECRHS II) by the use of the GINA multidimensional classification.

METHODS

Study design

The ECRHS is an international multicenter study of asthma. The first survey⁷ was performed in 1991 to 1993 on random samples of adults age 20 to 44 years. Each participant was sent a brief questionnaire (stage 1), and from subjects who responded, a 20% random sample was invited to undergo a more detailed clinical examination (stage 2). In addition, a symptomatic sample consisting of subjects who reported symptoms of waking with shortness of breath, asthma attacks, or using asthma medication in stage 1 was also studied. The ECRHS II⁸ was a follow-up study of all participants in stage 2 of the ECRHS I, performed in 1999 to 2002 (the full protocol can be found at www.ecrhs.org). Subjects answered a standardised questionnaire administered by trained interviewers and underwent lung function and

blood tests. Standard operative procedures and quality control procedures were set up for all of the phases of the surveys and are fully described in the study protocols.^{7,8} In all centers, at least 1 researcher involved in the ECRHS II had also been a team member in the ECRHS I study. Local training of fieldworkers, using the local language, was conducted by using a standardized protocol. Adherence to the protocol was assessed through quality control visits.

The current study includes data from 27 centers (see this article's [Table E1](#) in the Online Repository at www.jacionline.org) that took part in the ECRHS II.

Subjects and definitions

All current patients with asthma identified in the ECRHS I were eligible for this analysis. A current patient with asthma was defined as a subject who, in the ECRHS I, reported to have had asthma confirmed by a doctor and to have had asthmatic symptoms and/or to have used asthma drugs during the last 12 months (for a detailed description of definitions and variables used, see the Online Repository at www.jacionline.org).

In the ECRHS I, 1582 subjects were classified as current patients with asthma (829 from the random and 753 from the symptomatic sample). Of these, 980 (62%) attended the second study, and the average follow-up time was 8.7 years (range, 6–11 years). One hundred twenty-four (12.6%) participants in the ECRHS II could not be classified according to the GINA severity scale because some information was missing; therefore, only 856 patients (54% of the eligible patients with asthma at baseline) were included in the analysis, 387 from the random and 469 from the symptomatic sample.

Although there were no differences in age, sex, smoking habits, FEV₁, and IgE levels at baseline (ECRHS I) in random and symptomatic patients with asthma, the former had a slightly longer duration of the disease (17.7 vs 16.5 years), a lower percentage of manual workers (27% vs 36%), and a lower prevalence of hospitalization for respiratory problems (31% vs 42%). There was no statistically significant difference at baseline between patients with asthma included in the analysis and those excluded for any reason (either not participating in the ECRHS II or not having complete information for GINA classification), except that the former were slightly older (36.7 vs 32.4 years) and had fewer smokers (30% vs 38%) and a slightly lower percentage of manual workers (31% vs 32%) than the latter.

Asthma severity at the end of the follow-up

In the ECRHS II, each subject had to give detailed information on the frequency of symptoms (diurnal and nocturnal) and on the type, brand, and dosage of the drugs used over the period of the last 3 months. Furthermore, each subject underwent a lung function test.⁸ The frequency of diurnal and nocturnal symptoms and the lung function measurement (FEV₁% predicted) were combined according to the GINA in a 4-level scale measuring the severity of the clinical dimension (see the Online Repository at www.jacionline.org). According to the daily dose of ICS, each subject was classified in a 4-level scale of treatment intensity. Finally, each patient with asthma was classified as intermittent, mild persistent, moderate persistent, or severe persistent on the basis of the 2 independent clinical and treatment classifications according to the GINA Criteria⁴ (see this article's [Fig E1](#) in the Online Repository at www.jacionline.org). Patients with asthma who reported neither asthmatic symptoms nor asthma attacks nor use of antiasthmatic medications in the last 12 months in the ECRHS II were considered in remission at the end of the follow-up.

Asthma severity at baseline

In the ECRHS I, patients with asthma could not be classified according to the GINA severity classification: although lung function

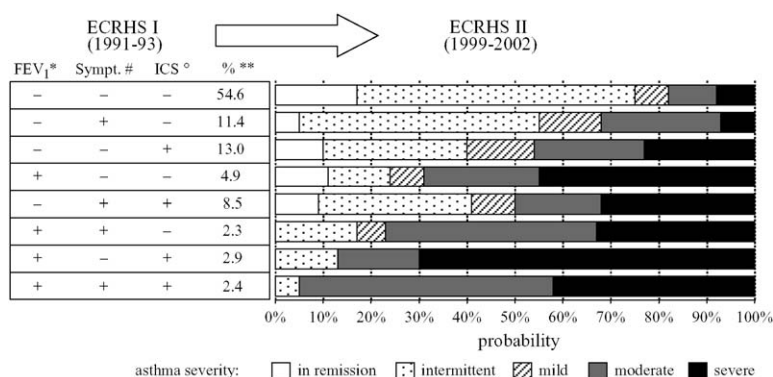


FIG 1. Probability (%) of being classified as remittent, intermittent, mild persistent, moderate persistent, or severe persistent (GINA classification) in the ECRHS II, according to the distribution of FEV₁% predicted, symptom score, and use of ICS in the ECRHS I. *FEV₁% predicted ≤80%. #symptom score ≥3rd quartile. °Use of inhaled corticosteroids in the last year. **Percentage of the subjects (777 out of 856) having available information on FEV₁% predicted, symptom score, and ICS use at baseline.

was measured both at baseline and at the end of the follow-up with the same method, detailed information on symptom frequency and treatment intensity was not available from the ECRHS I questionnaire.

The classification of severity used in the ECRHS I (ECSEV) was an 8-level combination (Fig 1) of 3 markers of severity: FEV₁% predicted, a dummy variable indicating whether a subject had a symptom score⁹ (see the Online Repository at www.jacionline.org) equal to the upper quartile or higher, and a dummy variable indicating whether a subject had used ICSs in the previous year. The correlation between the ECSEV and GINA severity score was assessed in subjects attending the ECRHS II, who were simultaneously classified according to both categorizations. The Spearman rank-order correlation coefficient was 0.73 (95% CI, 0.69-0.76). In particular, the 2 scales classified the subjects who were at the 2 extremes of the severity spectrum in a similar way (see this article's Table E2 in the Online Repository at www.jacionline.org). In fact, almost all of the subjects who had none of the markers of severity at ECSEV were classified by the GINA as mild persistent (5%) or lower (92%), whereas all of the subjects who had all of the 3 markers of severity (and all of those having FEV₁ ≤ 80% predicted) were moderate or severe persistent according to the GINA.

Determinants at baseline

Besides age and sex, the following prognostic factors were considered at baseline (ECRHS I; see the Online Repository at www.jacionline.org):

- Patient characteristics: age at onset of asthma, presence of non-seasonal asthma, coexistence with allergic rhinitis, coexistence with mucus hypersecretion and/or chronic cough, and total serum IgE in kU/L (log transformation)
- Baseline determinants: reported parental asthma, presence of respiratory infections in childhood, low educational level (having completed full-time education before the age of 16; this covariate was chosen as an indicator of socioeconomic status), smoking habits, occupational exposure, and body mass index (BMI)
- Previous hospital and/or emergency department visits for respiratory problems
- Bronchial hyperresponsiveness: at baseline, subjects performed a methacholine challenge test¹⁰; however, bronchial hyperresponsiveness was not considered in the analysis because of the existence of a strong association between the percentage of people not performing the test for any reason and the GINA severity score (test for trend: $P < .0001$)

Changes in potential determinants during the follow-up

Changes occurring between the ECRHS I and the ECRHS II in some of the baseline factors were assessed by either comparing the value of covariates on the 2 occasions or directly using the information collected in the second study. The list of variables considered is presented in Table III and fully described in the Online Repository (www.jacionline.org).

Statistics

Data were summarized as prevalence rates or means with 95% CIs, where appropriate. Univariate associations of all potential determinants with asthma severity were tested with χ^2 test for categorical variables and with Kruskal-Wallis rank test for continuous variables.

Multivariate associations of potential determinants with asthma severity were expressed by relative risk ratios (RRRs; using patients with intermittent asthma as the reference category) and their 95% CIs, obtained by fitting a multinomial logistic regression model to the data. The model used a 5-level indicator of asthma severity (remittent, intermittent, mild, moderate, severe persistent) as the dependent variable; the variables that were statistically significantly associated with severity in the univariate analysis were considered potential predictors. The model identified centers (crossed by type of sample: random/symptomatic) as the clustering factors, and length of follow-up as an independent variable.

The predictive weight of each covariate in predicting asthma severity was computed as a function of its contribution to decreasing the Akaike Information Criterion (AIC)¹¹ (see the Online Repository at www.jacionline.org).

The statistical analysis was performed by using STATA software, release 8.2 (Stata Corp, College Station, Tex).

RESULTS

Severity of asthma at the end of the follow-up (1999-2001)

At baseline (1991-1993), the mean age of the 856 patients with asthma included in the analysis was 34 years (SD, 7) and the average duration of the disease was 17 years (SD, 11). Nine years later (at the end of the follow-up),

TABLE I. Baseline (1991-1993) distribution of FEV₁% predicted, symptom score, and use of ICS in the last 12 months (%), and related 95% CIs, according to the level of severity assessed in 2002 using the GINA criteria (means/percentages that are significantly different from those of the intermittent group are reported in *bold*†)

	Severity of asthma assessed in ECRHS II (2002)				
	In remission (102)	Intermittent (388)	Persistent mild (69)	Persistent moderate (143)	Persistent severe (154)
Symptom score***	1.13 (0.79-1.46)	2.09 (1.94-2.25)	2.61 (2.25-2.97)	2.68 (2.42-2.94)	2.80 (2.58-3.03)
FEV ₁ % predicted***	103.0 (100.4-105.5)	101.2 (100.0-102.5)	101.2 (98.0-104.3)	92.0 (88.9-95.1)	86.6 (82.9-90.4)
Use of ICS*** (%)	16.3 (9.6-25.2)	15.7 (12.2-19.8)	30.4 (19.9-42.7)	37.6 (29.6-46.1)	53.3 (45.0-61.5)

****P* < .001.

†The difference was tested by using a multinomial bivariate logistic model.

TABLE II. Distribution of prognostic factors measured at baseline (1991-1993) according to the level of severity assessed in 2002 using the GINA criteria; data are presented as means (SDs) or percentages (%); means/percentages that are significantly different from those of the intermittent group are reported in *bold*†)

Covariates measured at baseline (1991-1993)	Severity of asthma assessed in ECRHS II (2002)				
	In remission (102)	Intermittent (388)	Persistent mild (69)	Persistent moderate (143)	Persistent severe (154)
Age** (y)	34.8 (6.9)	32.9 (7.3)	32.3 (7.3)	34.2 (7.3)	35.0 (7.0)
Sex* (% female)	62.8	50.8	62.3	55.2	63.6
Age at onset of asthma‡ (y)	17.8 (12.9)	15.0 (11.0)	16.0 (10.9)	18.0 (12.1)	16.8 (12.4)
Nonseasonal asthma*** (%)	37.0	43.3	52.2	57.0	64.3
Allergic rhinitis (%)	59.8	68.0	79.7	70.2	69.5
Cough§*** (%)	20.6	25.3	39.1	30.1	42.2
Total serum IgE*** (log transformation)	1.72 (0.67)	1.89 (0.68)	1.96 (0.65)	2.12 (0.70)	2.07 (0.70)
Parental asthma* (%)	20.9	27.0	22.1	31.3	37.0
Respiratory infections (%)	23.1	18.9	14.5	20.6	23.7
Low educational level* (%)	12.8	8.8	10.1	11.9	18.8
Smokers (% ex)	20.6	20.4	23.2	20.3	24.7
(% current)	29.4	32.2	23.2	25.2	30.5
Occupational exposure (%)	39.2	47.8	40.3	49.6	52.3
BMI (kg/m ²)	23.9 (4.6)	23.7 (3.8)	23.4 (5.0)	24.5 (4.9)	24.8 (4.9)
Hospitalization*** (%)	30.4	33.8	36.2	41.3	53.9

P* < .05; *P* < .01; ****P* < .001.

†The difference was tested by using a multinomial bivariate logistic model.

‡Patient age at 1st asthma attack.

§Cough = mucus hypersecretion and/or chronic cough.

102 (11.9%) were in remission (no symptoms, no exacerbations, no asthma medications in the last year), and 388 (45.3%) had intermittent, 69 (8.1%) mild persistent, 143 (16.7%) moderate persistent, and 154 (18.0%) severe persistent asthma.

Symptom control, lung function, and use of ICSs at baseline (1991-1993)

Patients with asthma in remission at the end of the follow-up (Table I) had a statistically significantly better control of symptoms at baseline (symptom score) than intermittent (the 95% CIs do not overlap), whereas all persistent groups presented a similar level of control (the CIs intervals for patients with mild, moderate and severe persistent asthma overlap), which was worse than that of patients with intermittent asthma. Moderate and severe persistent patients showed worse lung function already at baseline than the less severe groups. Furthermore,

persistent groups had a higher percentage of people using ICS at baseline.

Relationship between severity at baseline and at the end of the follow-up

At baseline, more than half of the patients with asthma (54.6%) had none of the 3 markers of severity (FEV₁% predicted >80% and no use of ICSs and symptom score below the upper quartile). Nine years later, the majority of them (75%) remitted or only had an intermittent form of asthma (Fig 1). The probability of remitting was null for subjects having all of the markers of severity at baseline, and less than 2% for those (12.5%) with FEV₁ ≤ 80% predicted at baseline (with or without other markers of severity).

The probability of being moderate to severe at the end of the follow-up was 19% for patients with asthma who had none of the markers of severity at baseline and reached

TABLE III. Distribution of changes (Δ) in some prognostic factors at the end of the follow-up (1999-2002) according to the level of severity assessed in 2002 using the GINA criteria; data are presented as means (SDs), or percentages (%; means/percentages that are significantly different from those of the intermittent group are reported in *bold*†)

Changes occurring during the follow-up	Severity of asthma assessed in ECRHS II (2002)				
	In remission (102)	Intermittent (388)	Persistent mild (69)	Persistent moderate (143)	Persistent severe (154)
Δ Allergic rhinitis (%)					
Unchanged	74.5	81.9	82.6	85.8	77.3
Worsened	11.8	9.6	10.1	8.5	9.7
Improved	13.7	8.5	7.3	5.7	13.0
Δ Cough‡*** (%)					
Unchanged	83.3	76.8	69.6	78.3	63.0
Worsened	1.0	8.5	8.7	9.1	21.4
Improved	15.7	14.7	21.7	12.6	15.6
Δ Total serum IgE (quartiles; %)					
Unchanged	61.0	54.2	53.8	63.4	57.5
Increased	22.1	26.4	15.4	21.8	22.1
Decreased	16.9	19.4	30.8	14.8	20.4
Δ Smoking habits (%)					
Unchanged	84.8	85.9	86.8	87.9	84.7
Quitters	10.1	7.6	5.8	7.1	10.0
Starters	5.1	6.5	7.4	5.0	5.3
Δ BMI‡* (kg/m ²)	1.23 (2.37)	1.87 (3.31)	2.64 (3.98)	2.32 (2.49)	1.82 (2.76)
Hospitalization*** (%)	6.9	11.9	26.1	27.3	38.6

* $P < .05$; *** $P < .001$.

†The difference was tested by using a multinomial bivariate logistic model.

‡Cough = mucus hypersecretion and/or chronic cough.

95% in patients having all of the 3 markers at baseline. The subjects who had a $FEV_1 \leq 80\%$ predicted at baseline had an 80% likelihood of being moderate to severe at the end of the follow-up.

Baseline prognostic factors of severity

Age and sex were significantly associated with severity in a nonlinear fashion. In fact, people with moderate and severe asthma at the end of the follow-up, as well as those in remission, were older at baseline than patients with intermittent asthma (Table II); moreover, there was a higher percentage of women in the persistent and remittent groups than in the intermittent one. At baseline, more patients with severe asthma had a higher prevalence of non-seasonal asthma, mucus hypersecretion or chronic cough, elevated total serum IgE, parental asthma, low educational level, and previous hospitalization. The age at asthma onset and the prevalence of allergic rhinitis were unrelated to severity.

Prognostic factors of severity measured during the follow-up

During the follow-up, patients with severe asthma had the highest increase in the prevalence of mucus hypersecretion or chronic cough. As expected, BMI increased during the follow-up because of the aging of the cohort, but patients with asthma who remitted showed the lowest increase. In general, the rate of hospitalization was higher in the persistent groups ($P < .0001$) than in the intermittent

one, whereas there was no difference in change in the other factors (Table III).

The risk profile of the GINA severity groups

When the variables significantly associated with asthma severity in the univariate analysis were considered simultaneously (Table IV), patients with intermittent and mild persistent asthma had a very similar risk profile, with the latter only having a higher rate of hospitalization during the follow-up. Patients with asthma in remission were more likely to be women (RRR, 2.40; 95% CI, 1.09-5.29), had a lower probability of having had mucus hypersecretion or chronic cough at baseline (RRR, 0.22; 95% CI, 0.05-0.39) or during the follow-up (worsening: RRR, 0.01; 95% CI, 0.00-0.02), and had a lower probability of having had a weight increase during the follow-up (change in BMI: RRR, 0.86; 95% CI, 0.75-0.97) than patients with intermittent asthma. Moderate and severe asthma were both associated with an older age, with a higher level of serum IgE at baseline, and with a higher rate of hospitalization and a lower probability of improving mucus hypersecretion or chronic cough during the follow-up. Severe asthma was positively associated with mucus hypersecretion or chronic cough at baseline (RRR, 4.90; 95% CI, 2.18-11.02) and with the probability of developing these symptoms during the follow-up (RRR, 6.88; 95% CI, 2.96-15.99).

The factors with the highest predictive weight at the multivariate analysis were the presence of chronic cough

TABLE IV. Mutually adjusted* RRRs†, with patients with intermittent asthma as the reference group, 95% CIs, conditional decrease in AIC (Δ AIC) for the association of prognostic factors with severity groups, and related predictive weights‡ (RRRs that are significantly different from the intermittent group are reported in *bold*)

Determinants	Severity of asthma assessed in the ECRHS II (2002)				Δ AIC	Predictive weight‡ (%)
	In remission (RRR)	Persistent Mild (RRR)	Persistent moderate (RRR)	Persistent severe (RRR)		
At baseline						
Age	1.04 (0.99-1.10)	1.00 (0.97-1.04)	1.04 (1.01-1.08)	1.05 (1.02-1.09)	11.6	6.2
Sex	2.40 (1.09-5.29)	1.42 (0.85-2.38)	0.93 (0.53-1.61)	1.56 (0.86-2.82)	11.2	6.0
Nonseasonal asthma	0.75 (0.37-1.49)	1.46 (0.77-2.76)	1.72 (1.01-2.93)	1.63 (0.93-2.85)	8.9	4.8
Cough§	0.22 (0.05-0.98)	1.90 (0.71-5.10)	1.54 (0.71-3.34)	4.90 (2.18-11.02)	30.9	16.6
Total serum IgE (log)	0.74 (0.44-1.23)	1.39 (0.85-2.29)	1.78 (1.18-2.70)	2.06 (1.38-3.06)	20.1	10.8
Parental asthma	0.73 (0.40-1.35)	0.66 (0.28-1.56)	1.36 (0.78-2.38)	1.52 (0.92-2.53)	5.1	2.8
Low educational level	1.19 (0.34-4.18)	1.20 (0.40-3.59)	0.80 (0.38-1.68)	1.00 (0.96-1.05)	1.6	0.8
Hospitalization	0.75 (0.37-1.54)	0.90 (0.50-1.60)	1.13 (0.61-2.09)	1.70 (1.00-2.87)	5.8	3.1
During follow-up						
Cough§ (worsened)	0.01 (0.00-0.02)	1.25 (0.29-5.41)	1.24 (0.48-3.22)	6.88 (2.96-15.99)	48.9	26.2
Cough§ (improved)	3.97 (0.91-17.28)	1.21 (0.42-3.43)	0.36 (0.13-1.01)	0.38 (0.16-0.90)		
Change in BMI	0.86 (0.75-0.97)	1.02 (0.93-1.11)	1.04 (0.94-1.16)	1.00 (0.92-1.09)	8.9	4.8
Change in hospitalization	0.30 (0.07-1.32)	2.65 (1.14-6.14)	3.53 (1.93-6.43)	3.74 (1.80-7.80)	33.6	18.0

*Also adjusted for length of follow-up.

†Obtained through a multinomial logistic regression model fitted on subjects with complete information (n = 549).

‡The predictive weight w_i of a variable x_i is the conditional change in AIC caused by the removal of x_i from the final model, divided by the total sum of predictive weights, Σw_i . The sum refers to the variables in the table.

§Cough = mucus hypersecretion and/or chronic cough.

both at baseline and during the follow-up, the occurrence of hospitalization during the follow-up, and high levels of IgE at baseline (see last 2 columns of Table IV).

DISCUSSION

Asthma severity was prospectively investigated by using the GINA classification, which consists of a 3-dimensional score based on symptoms, lung function, and medication use.

The main findings of our analysis are as follows:

- The deterioration of lung function plays a central role in predicting moderate/severe asthma, whereas the level of symptom control can help in predicting the probability of remission and whether asthma is going to be intermittent or persistent (mild, moderate, or severe)
- The presence of persistent cough and mucus hypersecretion, and of an elevated level of total serum IgE, are strong prognostic factors for moderate/severe asthma
- Asthma remission is rarely observed in people with poor lung function or a high level of symptoms at baseline and seems to be negatively associated with an increase in BMI

In agreement with other studies on patients with asthma,¹² our findings suggest that asthma severity at baseline is a determinant of the level of severity reached at the end of the follow-up. Patients with less severe asthma at baseline had a 75% likelihood of remitting or of being

classified as intermittent at the end of the follow-up. In a similar way, the subjects who had more severe disease at baseline, or who would have been classified by the GINA as moderate or severe because of their lung function ($FEV_1 \leq 80\%$ predicted), had an 80% likelihood of being moderate or severe 9 years later. This fact could reflect either that more severe asthma tends to persist over time, or that a substantial proportion of patients with more severe asthma underutilize ICS, as suggested by the relatively small percentage of patients with moderate/severe asthma under treatment at baseline. However, because of a limitation in the data collected, it was impossible to measure a patient's severity with an identical scale both at baseline and at the end of the follow-up. Therefore, a direct assessment of the stability of asthma severity could not be performed.

Symptom control, as indicated by the symptom score, is one of the most important predictors of the natural history of severity: patients with asthma who remitted had no or a minimal level of symptoms at baseline; patients with intermittent asthma had a significantly worse level of symptoms at baseline than subjects who remitted and, at the same time, a significantly better level than patients with currently persistent asthma.

However, the level of symptoms at baseline was almost the same in patients with mild, moderate, and severe asthma. Indeed, the best predictor of more severe asthma was not the level of symptoms, but poor lung function. In agreement with other studies,¹³ we found that many patients with moderate to severe asthma presented impaired

lung function already at baseline, despite their relatively young age. This strong “tracking effect of lung function” (reduced lung function entails a subsequent poor lung function) is well known,^{14,15} and has also been reported in patients with “end-stage asthma”—that is, patients repeatedly showing irreversible airways obstruction despite the use of long-term systemic and inhaled corticosteroids.¹⁶

The finding that there is a strong association between ICS use at baseline and more severe asthma 9 years later suggests that treatment, although effective on the control of the disease,^{17,18} may have limits in modifying asthma severity. This fact could reflect that patients with more severe asthma can reach and maintain an acceptable control of the disease only with an intensive and continuous use of drugs, or that there may be a subgroup of patients for whom the use of ICS is less effective,^{19,20} or that patients were using a suboptimal treatment or were not compliant.

One of the main prognostic factors of asthma severity was the occurrence of chronic cough or mucus hypersecretion, a symptom which was definitely more likely and more persistent in patients with moderate and severe asthma than in less severe ones. The presence of chronic mucus hypersecretion has already been reported as a marker of a steeper decrease in FEV₁ in patients with asthma.²¹ This association may indicate a subgroup of patients with asthma characterized by frequent exacerbations, inadequate treatment, or an inappropriate repair process of the airway epithelium, which can result in an increase in mucus production.^{22–25} Alternatively, it may be a result of the coexistence of asthma with chronic obstructive pulmonary disease, as implied by the Dutch hypothesis.²⁶

Patients with moderate and severe persistent asthma also share the presence of elevated serum IgE. Previous evidence showed that high levels of IgE are associated with an increased prevalence of asthma, an increased airway hyperresponsiveness,^{27–29} and an accelerated decrease in lung function.^{30,31} Our findings clearly document that elevated serum IgE levels are strongly associated with the more severe form of asthma, whereas the presence of allergic rhinitis is not, suggesting that the role of IgE may be independent of allergy, in agreement with previous findings.³² We cannot completely exclude that self-reporting of allergic rhinitis might lead to misclassification that weakens its association with moderate/severe asthma. However, many studies have shown the validity of self-reported allergic rhinitis.^{33,34}

Our results indicate that a weight loss or a minimal weight gain during the follow-up is significantly associated with asthma remission. In fact, despite the controversy concerning the association between severity and BMI,^{35–38} the remission of asthma after weight loss has been repeatedly reported.^{39,40}

We found that women had a higher likelihood of being severe at the end of the follow-up, as previously reported^{41–43}; sex hormones have been advocated as the reason for the worst outcome of asthma in women.⁴⁴ However, our data

have simultaneously shown that, when adjusting for the other factors, women also had a higher likelihood of remitting than men, supporting a more complex relationship between sex and asthma severity than it has been reported.

A low educational level and a parental history of asthma are prognostic factors of severity; however, their influence disappeared when the previous factors were also taken into account.

In contrast with other studies,^{3,45} our results do not confirm that early respiratory infections, active smoking, and occupational exposure are prognostic factors of asthma severity. The lack of association between moderate to severe asthma and smoking could be partially a result of the young age of our subjects and the fact that patients with more severe asthma refrain from smoking (healthy smoker effect), whereas the failure to find an association between occupational exposure and moderate to severe asthma may be a result of the low specificity of the question used to assess the presence of hazardous exposures related to the work environment.⁴⁶

Finally, in agreement with other studies,⁴⁷ we found that previous and recent hospitalization for respiratory problems is a strong predictor of more severe asthma.

This is one of the few prospective studies allowing the investigation of many prognostic factors of severe asthma in a cohort of patients with asthma from the general population. Like other epidemiological studies, asthma was defined by using the self-reported doctor diagnosis, which has been found to be highly specific⁴⁸ and reliable.⁴⁵ The rate of participation was relatively low (54%). However, the absence of differential participation in the follow-up suggests that nonresponse could have biased our estimates only to a minor extent. A limitation of the current study was the impossibility to assess the role of bronchial hyperresponsiveness in severe asthma caused by the strong differential acceptance/indication of the methacholine test.

In conclusion, our analysis has shown that patients with moderate and severe persistent asthma are characterized by an early airflow limitation. They seem to share a common pattern of prognostic factors, like the presence of chronic mucus hypersecretion, an elevated total serum IgE, and a history of hospitalization for respiratory diseases. Patients with intermittent and mild persistent asthma have a similar profile of prognostic factors, and it is likely that they are a different phenotype from patients with more severe asthma. Remission in asthma mainly occurs in patients with disease at the milder end of the spectrum, and is rarely observed among people with poor lung function or a high level of symptoms at baseline.

The knowledge of the prognostic factors and of the natural history of asthma severity could help doctors in better managing and monitoring their patients.

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