

Role of gender and hormone-related events on IgE, atopy, and eosinophils in the Epidemiological Study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy

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Background: The pattern of asthma over the lifespan is different in male and female patients, but etiologic differences according to gender are only partially understood. In women, information regarding factors explaining perimenstrual asthma and the role of hormone-related aspects on asthma-related phenotypes is scanty.

Objective: To assess the relationships of eosinophils, IgE, and atopy with (1) asthma according to gender and age of onset and (2) hormone-related events.

Methods: Using data from the Epidemiological study on the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness and Atopy, adults and children with asthma recruited in chest clinics ($n = 313$) and first-degree relatives of patients with asthma ($n = 214$) were compared with nonasthmatic controls ($n = 334$) and first-degree relatives without asthma ($n = 595$).

Results: Among asthmatic women, eosinophilia was significantly associated with perimenstrual asthma independently from age, smoking, and asthma severity (eosinophils/mm³ 330 vs 194; $P = .01$). In nonasthmatic women, IgE level was significantly decreased (by half) and atopy decreased with menopause, and IgE increased with oral contraceptive use, independently from age and smoking. Considering both genders, the increase of eosinophil counts with asthma was significantly greater in women with childhood-onset asthma than in women with adulthood-onset or in men in general. No interaction between gender and asthma was observed for eosinophils in children and for IgE level and atopy in children and adults.

Conclusion: Results suggest a role of hormone-related events on asthma-related traits and support the hypothesis of the role of eosinophils in the persistence and severity of asthma. (*J Allergy Clin Immunol* 2004;114:491-8.)

Key words: Asthma, gender, hormone, eosinophils, IgE

Abbreviations used

EGEA: Epidemiological Study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy

GM: Geometric mean

SPTQ: Skin prick test quantitative score

Despite the well known greater asthma incidence in boys in childhood and in girls from adolescence,¹ gender differences in hospital admissions,^{2,3} and the unexplained occurrence of perimenstrual asthma,⁴ few studies have addressed sex-related and gender-related issues in asthma epidemiology.⁵⁻⁸ Some risk factors for asthma may be specifically related to adult-onset asthma in women, either gender-related, such as cleaning agents,⁹ or possibly sex-related, such as increased body weight since menarche¹⁰ or postmenopausal estrogen therapy.¹¹ The immune system interacts with the endocrine system, and they communicate bidirectionally.¹² Sex differences in immune parameters vary over the lifespan in relation to hormonal pattern, such as the accumulation of T-helper lymphocytes at menopause, but the importance of changes in hormone levels on asthma and allergy-related conditions is poorly understood.^{13,14}

Phenotypic or etiologic differences between genders may relate to differences in perception, report of symptoms, and diagnosis, and may represent sex-related biological differences, directly or not in relation with sex hormones.⁵⁻⁸ It is therefore of interest to study the associations of asthma with quantitative objective asthma-related traits (IgE, atopy, and eosinophils) by gender and to assess the potential associations of hormone-related events on these phenotypes. It is well established that total IgE is greater in male than in female subjects and is increased with asthma.^{15,16} Despite the growing interest in the role of eosinophilia in the etiology of asthma,^{17,18} few epidemiologic studies have focused on the relationships of asthma and eosinophils,¹⁹⁻²¹ and the relevance of eosinophils in the etiology of asthma is a matter of debate.²² Whether gender modulates the relationships

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TABLE I. Population characteristics

	Children			Adults		
	Boys (n = 256)	Girls (n = 194)	P	Men (n = 493)	Women (n = 513)	P
Asthmatic patients, n	90	41		94	88	
Asthmatic relatives, n	43	30		68	73	
Nonasthmatic relatives, n	81	79		209	226	
Nonasthmatic controls, n	42	44		122	126	
Age, y, mean $\pm$ SD	11.0 $\pm$ 2.9	11.3 $\pm$ 2.9	.33	40.8 $\pm$ 12.1	38.0 $\pm$ 12.1	<.001
Eosinophils, IgE and atopy						
Eosinophils, %, GM (95% CI)	4.7 (1.0-22.0)	3.5 (0.8-15.9)	.0001	2.3 (0.5-11.2)	2.1 (0.4-10.0)	.02
Eosinophils, nb/mm ³ , GM (95% CI)	309 (60-1583)	242 (50-1182)	.0008	153 (31-748)	139 (28-680)	.04
IgE, IU/mL, GM (95% CI)	149 (4-5019)	92 (3-2910)	.003	77 (3-2263)	49 (2-1453)	<.0001
Atopy, skin prick test+, %	66.5	53.9	.007	53.0	42.3	.0007
Atopy, SPTQ, mean $\pm$ SD	1.47 $\pm$ 0.09	1.07 $\pm$ 0.10	.002	1.22 $\pm$ 0.07	0.97 $\pm$ 0.07	.01
Asthma, n	133	71		162	161	
Childhood asthma onset (<16 y), %				51.3	45.5	.32
Severe clinical asthma (score $\geq$ 2), %	32.5	27.0	.44	49.2	41.5	.20
Inhaled steroids (last 12 months), %	46.5	39.4	.34	54.0	53.4	.90
FEV ₁ % predicted, mean $\pm$ SD	92.9 $\pm$ 17.9	91.1 $\pm$ 20.3	.29	89.6 $\pm$ 36.7	94.7 $\pm$ 37.8	.02
Smoking habits						
Never smokers, %				36.9	57.1	<.0001
Exsmokers, %				32.1	19.5	
Current smokers, %				31.0	23.4	
Hormone-related data						
Age at first menstrues, y, mean $\pm$ SD					12.8 $\pm$ 1.4	
Early menarche (<12 y old), %					18.5	
Duration of menstrual cycle, days, mean $\pm$ SD					28.0 $\pm$ 3.6	
Menopausal women, %					13.5	
Current oral contraceptive use, %*					29.7	
Perimenstrual asthma, %*					15.7	

*In nonmenopausal women (n = 371).

of IgE and eosinophils to asthma remained unknown. In women, it has been shown that hormone-related events may modify the T_H1/T_H2 profile,^{13,23} but epidemiologic information on the role of hormone-related events in asthma related traits, such as eosinophils and IgE, is scanty.²⁴

By using the data collected in the Epidemiological Study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA), this article aims (1) to assess in children and in adults the relationships of eosinophils, atopy, and IgE to asthma according to gender, taking into account the age of asthma onset, and (2) to assess in women the relationships of eosinophils, atopy, and IgE with hormone-related events, such as menopause and oral contraceptive use, and in asthmatic subjects, perimenstrual asthma.

METHODS

Population

The design of EGEA combines a case-control study and a family study of asthmatic cases. The protocol and descriptive characteristics have been described elsewhere.²⁵⁻²⁸ Briefly, children ($\leq$ 16 years) and adult ($\geq$ 18 years) asthmatic patients were recruited in chest clinics of 6 clinical centers, and controls were population-based. The current analyses are based on 1006 adults (493 men) and 450 children (256 boys; Table I).

Asthma and asthma severity

Subjects answered a detailed questionnaire regarding respiratory symptoms, environment, and treatment based on international standardized questionnaires.²⁹ For both adult and pediatric relatives, asthma status was based on a positive answer to either, "Have you ever had attacks of breathlessness at rest with wheezing?" or "Have you ever had asthma attacks?" For all asthmatic subjects, the severity was assessed on the basis of international guidelines,³⁰ as in the study of the familial resemblance of asthma severity already performed.³¹ The clinical severity score varied between 0 and 7 and was based on the frequency of asthma attacks (from 0 for less than once a month to 3 for at least once a day), persisting symptoms between attacks (from 0 for none to 3 for limiting activities), and hospitalization in the past 12 months (0 for none, 1 for more than 0). Clinically severe asthma was based on a score equal to or greater than 2. Therapy and, in particular, inhaled steroids in the last 12 months were recorded.

Hormone-related events

Perimenstrual asthma was defined by more frequent asthma attacks before or during the menstrual period and *early menarche* by menarche at 11 years or earlier. Oral contraceptive use, age of menopause when relevant, and duration of cycle (in absence of oral contraceptive use) were recorded.

Eosinophils, IgE, and atopy

Total IgE and skin prick tests to 11 allergens (including molds and indoor and outdoor allergens) were determined as previously described.^{28,32} Total and differential white blood cell counts were obtained by standard methods.

TABLE II. Relationships of asthma to age, eosinophils, and IgE in male and female subjects

	Male subjects			Female subjects		
	Asthmatic subjects	Nonasthmatic subjects	P	Asthmatic subjects	Nonasthmatic subjects	P
Children						
Age (y), mean	11.1	10.9	.60	11.1	11.4	.43
Eosinophils, %, GM	6.2	3.5	<.0001	5.2	2.9	<.0001
Eosinophils, n/mm ³ , GM	426	230	<.0001	358	195	<.0001
IgE, IU/mL, GM	344	67	<.0001	330	46	<.0001
SPTQ, mean	2.11	0.82	<.0001	1.84	0.64	<.0001
Adults						
Age (y), mean	39.7	41.3	.17	36.6	38.6	.07
Eosinophils, %, GM	2.9	2.1	<.0001	3.1	1.8	<.0001
Eosinophils, n/mm ³ , GM	198	137	<.0001	219	117	<.0001
IgE, IU/mL, GM	199	50	<.0001	116	34	<.0001
SPTQ, mean	1.96	0.86	<.0001	1.63	0.69	<.0001

Statistical methods

Analyses were performed on log-transformed eosinophil percentage and count and IgE level, and results were expressed in geometric means (GMs). Analyses for atopy were performed for both a dichotomous response (Skin prick test+, any positive test) and skin prick test quantitative score (SPTQ; number of positive test results), quantitative score recently validated regarding its biometric properties.²⁸ Results are presented for SPTQ unless otherwise stated. The familial dependence between observations was taken into account by using the Generalized Estimated Equations (Genmod and Mixed procedures in the statistical software SAS; SAS Institute, Cary, NC).³³

RESULTS

Association of asthma and gender on eosinophil percentage and count, atopy, and IgE level

In children, eosinophil percentage and count, IgE level, and SPTQ were significantly higher in boys than in girls (Table I). In asthmatic subjects, clinical asthma severity, inhaled steroid treatment, and FEV₁ did not differ between genders. As expected, asthma was positively related to eosinophils, IgE level, and SPTQ for both genders (Table II), with associations still highly significant after adjustment on age.

In adults, male subjects exhibited higher eosinophil percentage and count, SPTQ, and IgE level than female subjects (Table I). After adjustment for age and smoking habits, all associations remained significant except eosinophil count (GMs were 154 in men and 141 in women; $P = .08$). The proportion of subjects with childhood-onset asthma was slightly higher in men than in women, but not significantly. Neither clinical severity nor inhaled steroid treatment significantly differed between genders. FEV₁ was significantly higher in women than in men, and after adjustment for age and smoking habits, the difference was of borderline significance (90.5 in men vs 94.6 in women; $P = .06$). Asthma was related to higher eosinophil percentage and count, IgE level, and SPTQ for both genders (Table II). Adjustment for age and active smoking did not change these results.

The strength of the association of allergy markers with asthma according to gender was then studied. In children, the association of asthma with eosinophils, SPTQ, and IgE level was similar in boys and girls (Table III). Strong correlations between eosinophils and IgE were observed, whatever the gender and asthma status (r varied from 0.31 in asthmatic boys to 0.49 in asthmatic girls).

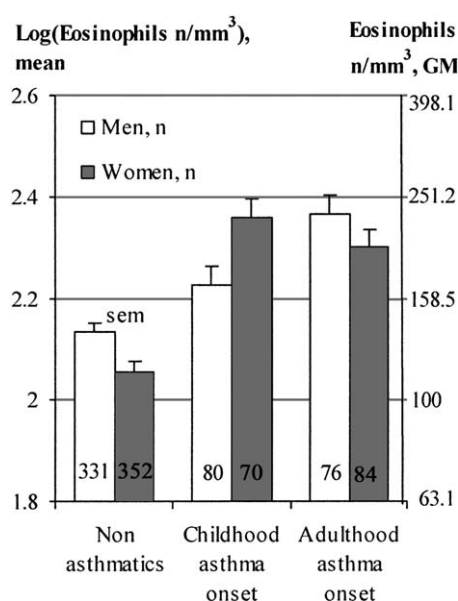
In adults, the association between asthma and eosinophils was significantly stronger in women than in men (Table III). The ratios of eosinophil geometric means in asthmatic subjects versus nonasthmatic subjects were higher in women than in men (1.8, 1.9 in women and 1.4, 1.4 in men for eosinophil percentage and count, respectively). By contrast, the increase in SPTQ and in IgE level associated with asthma was of the same magnitude in men and women, with ratios of IgE geometric means in asthmatic subjects versus nonasthmatic subjects of 3.4 in women and 3.9 in men. Taking into account that inhaled steroids were significantly more often prescribed in the last 12 months to subjects with stronger eosinophilia ($P < .0001$) did not change the findings, and the interaction of asthma and gender on eosinophilia remained significant.

Because childhood-onset asthma occurs more often in boys than in girls, asthma status was further analyzed by using a 3-class variable: nonasthmatic subjects, asthmatic subjects with childhood asthma onset (<16 years), and asthmatic subjects with adulthood asthma onset (≥ 16 years). In asthmatic subjects with adulthood asthma onset, the increased eosinophil count related to asthma was of the same magnitude in men and women (Fig 1). However, in asthmatic subjects with childhood asthma onset, eosinophilia related to asthma was significantly stronger in women than in men (P value of the interaction between asthma and gender = .0003). Adjustment for age and smoking habits did not change the results. In the analysis restricted to asthmatic subjects, the interaction between age of asthma onset and gender on eosinophilia was significant ($P = .02$) and remained significant after adjustment for potential confounders (age, smoking habits, asthma severity, or inhaled steroid treatment in the last 12 months). Correlation coefficients between

TABLE III. Interactions of gender in the relationship of asthma to eosinophils and IgE

	Male subjects		Female subjects		P interaction Gender-asthma
	Asthma+	Asthma–	Asthma+	Asthma–	
Children					
n	133	123	71	123	
Eosinophils, %, GM	6.4	3.4	5.4	2.9	.84
Eosinophils, n/mm ³ , GM	428	224	377	196	.96
IgE, IU/mL, GM	329	67	345	47	.16
SPTQ, mean	2.11	0.81	1.85	0.64	.71
Adults					
n	162	331	161	352	
Eosinophils, %, GM	2.9	2.1	3.1	1.7	.01
Eosinophils, n/mm ³ , GM	198	137	219	116	.01
IgE, IU/mL, GM	204	52	117	34	.50
SPTQ, mean	1.97	0.91	1.55	0.67	.38

In children, models included age; in adults, models included age and smoking. All models took into account the dependence of subjects from the same family (mixed models).

**FIG 1.** Eosinophil counts according to age of asthma onset and gender in adults.

eosinophils and IgE according to gender and asthma were lower than in children, with all *r* values lower than 0.22, except for asthmatic women with childhood onset, for whom *r* = 0.35.

Association of hormone-related events with eosinophils, atopy, and IgE level

Fourteen percent of women were menopausal, and 30% of the nonmenopausal women took oral contraceptives. In nonasthmatic subjects, oral contraceptive use was significantly related to higher IgE level, and inversely, menopausal status was related to lower IgE level (Table IV). After adjustment for age and smoking, the relationships remained significant. IgE level in nonasthmatic menopausal women was half of that in nonmenopausal women. Body mass index was unrelated to oral contraceptive use

and did not modify the relation with IgE. In asthmatic women, IgE level was also halved in subjects who were menopausal compared with the other asthmatic subjects, but the relationship was not statistically significant. In asthmatic and nonasthmatic women, menopause was related to a lower SPTQ, and after adjustment for age, the relationship remained significant in nonasthmatic subjects despite an overadjustment (Table IV). In asthmatic subjects only, early menarche was related to less atopy. In nonasthmatic and asthmatic women, eosinophils were not associated with menopause, oral contraceptive use, and early menarche.

Perimenstrual asthma was reported by 16% of nonmenopausal asthmatic women, independently from age or age of asthma onset. Perimenstrual asthma was less reported, although not significantly, by women taking oral contraceptive pills (odds ratio, 0.30; 95% CI, 0.06-1.39). Asthma was slightly more severe in those with perimenstrual asthma (severe clinical score, 53% vs 41%; low FEV₁, 19% vs 15%; inhaled steroids, 63% vs 50%), but the differences were not statistically significant.

Perimenstrual asthma was significantly associated with higher eosinophil percentage and count but was unrelated to IgE level and SPTQ (Table IV). Results remained basically unchanged after adjustment for age, smoking, and inhaled steroids in the last year. After adjustment for clinical asthma severity score or FEV₁, eosinophils remained significantly increased with perimenstrual asthma (*P* = .02 and .03, respectively), and the association remained statistically significant in the multivariate model including age, smoking, and all markers of asthma severity. Taking into account oral contraceptive use or body mass index did not modify the results.

DISCUSSION

In the EGEA study, IgE significantly decreased with menopause and increased with oral contraceptive use in nonasthmatic women, and atopy significantly decreased

TABLE IV. Association of hormone-related events with eosinophils, atopy, and IgE level

		Crude analysis			Adjusted analysis‡		
	n	Eosinophils, n/mm ³ , GM	IgE, IU/mL, GM	SPTQ, mean†	Eosinophils, n/mm ³ , GM	IgE, IU/mL, GM	SPTQ, mean
In nonasthmatic subjects							
Oral contraceptive use							
No	175	115	31	0.70	117	32	0.70
Yes	77	117	51	0.95	120	51	1.04
P		.87	.03	.19	.85	.04	.10
Menopause							
No	252	115	36	0.77	116	35	0.82
Yes	43	107	14	0.18	109	16	0.09
P		.59	.0006	.006	.74	.03	.009
Early menarche							
No	289	115	34	0.71	117	35	0.73
Yes	58	112	32	0.66	113	31	0.67
P		.81	.75	.82	.78	.53	.77
In asthmatic subjects							
Oral contraceptive use							
No	86	208	110	1.61	211	119	1.58
Yes	33	224	173	1.85	218	134	1.65
P		.63	.18	.49	.84	.72	.85
Menopause :							
No	120	213	126	1.66	214	115	1.49
Yes	15	230	56	0.51	210	65	1.06
P		.72	.06	.01	.95	.28	.44
Early menarche							
No	124	226	118	1.82	231	113	1.78
Yes	36	185	110	0.98	180	95	0.94
P		.20	.81	.01	.10	.53	.009
Perimenstrual asthma :							
No	86	200	135	1.76	194	128	1.65
Yes	16	339	158	1.58	330	154	1.86
P		.02	.73	.73	.01	.68	.65

*All models took into account the dependence of subjects from the same family (mixed models).

†Nonparametric tests led to similar results, with *P* values of .09 for contraceptive use, .004 for menopause, and .62 for early menarche in nonasthmatic subjects and of .71, .02, .02, respectively, in asthmatic subjects.

‡Models adjusted for age and smoking (never smokers, exsmokers, and current smokers) in nonasthmatic subjects and for age, smoking, and inhaled steroids in the past 12 months (yes/no) in asthmatic subjects.

with menopause in both asthmatic and nonasthmatic women. In nonmenopausal asthmatic subjects, eosinophilia was significantly associated with perimenstrual asthma, independently from age, smoking, or asthma severity. Considering both genders, the association between eosinophilia and asthma was significantly stronger in women than in men, particularly in women with childhood-onset asthma. No such interaction was observed for children or for IgE or SPTQ, other asthma-related traits, in adults and children. Overall, results showed different patterns of association of IgE, atopy, and eosinophils with hormone-related events in women and with asthma according to gender and supported the hypothesis of the role of eosinophils in the persistence and severity of asthma.

In women of the EGEA study, IgE and atopy decreased with menopause, and IgE increased with oral contraceptive use. No association was observed for eosinophils. To our knowledge, these relationships with IgE and atopy have not been published and need to be confirmed.

Significantly lower IgE level have been reported in women in periovulatory phase than in others.²⁴ It has been shown that healthy women have a perimenstrual shift toward a type 2 cytokine profile, a shift which occurs throughout the menstrual cycle for women taking oral contraceptive pills.²³ Current results support the role of hormone-related events in total IgE and atopy. The lack of association of eosinophils with oral contraceptive use is consistent with observations from the general population in which oral contraceptive use was unrelated to increased asthma-like symptoms.³⁴ Data available regarding changes in cytokine profile in relation to menopause³⁵ suggest a complex pattern, because no effect was reported on IL-4, but there was an increase in both IL-6, favoring a T_H1 profile, and IL-18, a proinflammatory cytokine that may favor a T_H1 profile in synergy with IL-12, but also a T_H2 profile.³⁶ The lack of statistical significance for IgE in asthmatic subjects may relate to the smaller sample size, especially for the effect of menopause, which showed a similar pattern, with IgE halved in the menopausal

asthmatic women. However, it is also possible that factors modifying the IgE level depend on the overall immunologic pattern of the subjects, which is different in asthmatic subjects and nonasthmatic subjects, as already noted for the effect of smoking.³² The effect of hormones may be difficult to show in subjects already upregulated toward a T_H2 pattern, as in asthmatic subjects. An increase in IgE at puberty in relation to hormones could explain the increased incidence of asthma after menarche and decreased incidence after menopause, but longitudinal studies are needed to understand whether changes in IgE antedate or are concomitant with the changes in asthma incidence. The limitations of our study were the lack of information on last menstrues and the lack of measures of hormone levels, which would provide complementary information on hormonal impregnation. More research is needed to understand the relation of sex hormones with immune response according to sex, age, and health conditions, a topic of interest for both allergic and autoimmune diseases.³⁷

Higher eosinophil counts were observed in women with a history of perimenstrual asthma than in other asthmatic women, an association that remained after adjustment for asthma severity. No association was observed with IgE and atopy. A limitation of our study was the lack of information about the period of cycle at the time eosinophils were counted. Perimenstrual asthma is still poorly understood,^{4,38} and to our knowledge, no study has reported an association of eosinophils with a history of perimenstrual asthma. Eosinophils have glucocorticoid receptors that can bind in a competitive fashion to cortisol, estrogen, and progesterone.³⁹ Animal models show that progesterone increases airway eosinophilia but not allergen-specific IgE.⁴⁰ The combination of estradiol and progesterone increases eosinophil degranulation.⁴¹ Results suggest the role of hormone-related events in the relationship of eosinophils with asthmatic symptoms.

Whereas gender differences in asthma and asthma-related traits have been studied, no study has looked at the gender-specific strengths of association of asthma to markers of allergy, such as IgE, atopy, and eosinophils. It is well known that asthma is more prevalent in childhood in boys,¹ that girls have a greater incidence at puberty than boys and likely a decrease at menopause,¹¹ that allergy markers such as IgE are higher in male subjects, and that bronchial hyperresponsiveness is higher in female subjects,⁴² although the reasons of such differences are poorly understood. The current study included a substantial number of asthmatic subjects with disease of moderate severity with variable age of onset, but the subjects were not representative of the general population because cases were recruited in chest clinics. Burrows et al¹⁹ already reported that eosinophilia in the general population identified a predominantly female group of elderly nonsmokers with markedly impaired ventilatory function, categorized as asthmatic bronchitis. A limitation of our study was the lack of longitudinal data to validate the age of onset of asthma in adults and conduct detailed analyses according to asthma severity.

Interaction between eosinophils and gender in asthma could be the result of bias. It is possible that men and women did not seek treatment at the hospital for the same level of severity, but we could not assess that aspect. Complex interrelations between the underlying severity, treatment, and gender could also explain the findings, because steroid treatment modifies eosinophil counts. However, considering indices of asthma severity at the time of examination and inhaled steroids in the last year in the analysis did not explain the findings.

The Carter effect could explain the findings.⁴³ It corresponds to the fact that it may be easier to evidence a risk factor common to both genders in the least affected gender. More generally, in multifactorial diseases, some factors may be more easily evidenced in subjects lacking 1 important risk factor. Numerous studies have been designed on that principle for assessing the effect of a secondary risk factor, such as studies selecting only nonsmokers to assess the role of occupation or air pollution in chronic obstructive pulmonary disease. Such a rationale implies that the factor under study has no major interaction with the missing risk factor. It is generally considered that girls are protected from asthma in childhood due to lower allergen positivity and more adequate airway/parenchyma relative dimensional characteristics.¹ Under the hypothesis of the Carter effect, the current results support the hypothesis of an important role of eosinophils in persistent asthma. Results further suggest that eosinophils should be considered differently than IgE in their relation to asthma, which has already been underlined on the basis of their respective associations,⁴⁴ their familial correlations,⁴⁵ and their relations with genetic factors.⁴⁶ The multidimensional character of asthma severity^{47,48} may partly explain that the relationships remained after adjustment for other severity markers. Our current findings combined with previous results showing the lack of a cross-sectional relationship between eosinophils and asthma severity in children⁴⁹ are consistent with a role of eosinophils in the persistence of asthma, 1 particular aspect of severe asthma.

The lack of interaction between gender and asthma in eosinophil level in children may reflect that childhood asthma concerns a different asthma phenotype. In childhood, there is more concordance between skin prick test positivity, high IgE, and eosinophilia than in adulthood, and intrinsic asthma is rare.⁴⁴ Childhood-onset asthma persisting until adulthood constitutes a severe subgroup of childhood asthma. Longitudinal studies on asthmatic children followed until adulthood are needed to assess whether a higher eosinophil count increases the susceptibility to persistent asthma or, on the contrary, is a consequence of the pathologic process of the asthmatic disease. Longitudinal observations showed that children with persistent wheeze did not exhibit the normal pattern of age-related eosinophil decrease.⁵⁰ Following asthmatic children until adulthood, Roorda et al⁵¹ showed that eosinophil counts in childhood were higher in 58 subjects

with symptoms in adulthood than in the 201 without, but the difference did not reach significance. Analyses were not performed separately by gender.

In conclusion, gender differences may be partly explained by hormone-related events, such as menopause and contraceptive use. Furthermore, the pattern of a stronger eosinophilia observed in adult asthmatic women with childhood onset and in those with perimenstrual asthma is consistent with the hypothesis of an important role of eosinophils in the persistence and severity of asthma. More generally, studying in detail each asthma-related trait could help in the understanding of the etiology of this complex disease.

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