

Relationships of Active and Passive Smoking to Total IgE in Adults of the Epidemiological Study of the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness, and Atopy (EGEA)

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The increase of total IgE in relation to active smoking has been shown in the general population, but little is known about subjects with a personal or family history of asthma. The objective of this report is to analyze the relationships of active and passive smoking to total IgE in the Epidemiological Study of the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness, and Atopy (EGEA). The sample studied includes 122 asthmatic probands, 430 first-degree relatives, and 190 control subjects, age 25 to 54 yr. As expected, first-degree relatives had total IgE intermediate between cases and control subjects and men had higher values than women. Current smokers had significantly higher IgE than never smokers. The relationship was statistically significant restricting the analysis in asthmatic probands. In a model taking into account gender, personal and familial history of asthma, socio-occupational class, and the nonindependence of subjects from the same family, IgE were in current smokers, ex-smokers, and never smokers 128, 61, and 76 IU/ml and 77, 41, and 55 IU/ml in men ($p = 0.01$) and women ($p = 0.05$), respectively. The relation was independent of skin test response. Some increase in IgE was observed in both men and women first-degree relatives in relation to passive smoking. That relation was statistically significant in women only (adjusted for asthma values: 103 IU/ml versus 48 IU/ml, $p = 0.02$). Results show that an increase in total IgE in relation to active smoking may be evidenced even in asthmatics despite the healthy smoker effect. Susceptible subjects, such as women who are first-degree relatives of asthmatics, may increase total IgE in relation to passive smoking.

The increase of total IgE in relation to active smoking has been demonstrated by studies conducted in general and occupational cohorts (1–7). The potential role of passive smoking on IgE is supported by some studies conducted in children (8), but there has been no epidemiologic study in adult never smokers. IgE plays a central role in the pathophysiology of asthma (9). Whether smoking increases IgE in asthmatics, who already have high IgE levels, has not been studied in large samples of asthmatics.

The aim of the present analysis was to assess the relationships of active and passive smoking during adulthood to total IgE in asthmatics, first-degree relatives of asthmatics, and control subjects age 25 to 54 yr drawn from the Epidemiological Study of the Genetics and Environment of Asthma

(EGEA) (10), and to examine whether atopy modifies these relationships.

METHODS

The EGEA combines both a case-control study and a family study (10). The population examined includes 348 nuclear families (213 adult and 135 pediatric probands) ascertained by one asthmatic and 416 control subjects, totaling 1,847 subjects. Of the 1,332 adult (≥ 16 yr) subjects examined, 213 were asthmatic probands, 310 control subjects, 690 first-degree relatives, and 123 spouses. Asthmatic probands were recruited in chest clinics from six clinical centers. Inclusion criteria were place of birth, area of residence, age, familial structure, and for proband cases positive answers to four standardized questions: Have you ever had attacks of breathlessness at rest with wheezing? Have you ever had asthma attacks? Was this diagnosis confirmed by a physician? Have you ever had an asthma attack in the last 12 mo?. Some subjects who answered positively only to three (or two) questions were also included after an examination of the medical records and a decision by consensus (10). Adult control subjects were mostly population-based (208 were recruited through electoral rolls, 26 through surgery departments, and 76 from a check-up center). Although no matching was performed, comparability between cases and control subjects was controlled in the recruitment phase to avoid disparities in each center (both for environmental and genetic characteristics), season (because of pollen season), sex, and 10-yr age class. The protocol was approved by the ethical committee and subjects signed informed consent forms.

Subjects answered a detailed questionnaire on upper and lower airways symptoms, allergic symptoms, childhood events including infections, medical history, and potential risk factors, based on British Medical Research Council/European Coal and Steel Community, American Thoracic Society, and European Community Respiratory Health Survey (ECRHS) questionnaires with additional questions when needed.

Active and Passive Smoking

As part of the questionnaire, all subjects answered detailed questions on smoking habits administered by a trained interviewer. Smoking was considering in three classes: current smokers, ex-smokers, and nonsmokers. Smokers were defined as subjects who reported currently smoking cigarettes, pipes, cigarillos, or cigars at the time of the survey. Ex-smokers were subjects who had smoked daily and given up since at least 1 mo before the survey. Nonsmokers were those who never smoked. The daily consumption of tobacco was evaluated considering one cigarette, one cigarillo, and one cigar equal to 1, 2, and 5 g, respectively. Current smokers smoked ≥ 1 g per day and heavy smokers were those who smoked 15 g or more per day. Passive smoking was defined as nonsmokers who reported currently living at home with one or more smokers. The amount of tobacco consumption by the spouse was recorded in three classes (less than 10, 10 to 20, and 20 cigarettes per day). Passive smoking at work was recorded (except for parents of pediatric asthmatic probands) in four classes (never, occasionally, often, always) and the analysis performed by pooling often/always and never/occasionally.

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Socio-occupational Class

Based on their last occupation, subjects were classified in four categories: no occupation, professionals, technicians, manual workers.

IgE

Total IgE was measured by radioimmunoassay (Phadebas PRIST technique; Pharmacia Diagnostics, AB, France). The sensitivity was 1 international unit (IU)/ml. All determinations were performed in one central laboratory (Lyon Pasteur Institute) in duplicate in seven series. Intra-assay intraclass correlation coefficient was 0.996 (IgE range = 1 to 10,186) and the coefficient of variation 8.8%. Samples with either low values (less than 50, and especially less than 20 IU/ml) or high values (greater than 200 IU/ml) were redone. A maximum of three duplicate measures was performed. For 171 subjects, measurements were redone as the reproducibility was not considered sufficient and the coefficient of variation became 6.6%. At the end, 79% of all measurements had a difference of 10% at most, and 94% a difference of 15% at most. Subjects with IgE values below 50 or greater than 200 represented two-thirds of those with a difference between 10 and 15% and 92% of those with a difference greater than 15%. Analyses have been performed on log10 (IgE) and results expressed in geometric means (GM).

Skin Prick Tests (SPT)

Allergens studied were all those considered in all areas of the ECRHS, i.e., cat, *Dermatophagoides pteronyssinus*, *Cladosporium herbarum*, *Alternaria tenuis*, timothy grass, olive, birch, *Parietaria judaica*, ragweed, *Aspergillus*, and *Blatta germanica* were also included in the tests. Negative (uncoated) and positive (histamine) controls were used. Prevalence of positive results was expressed by using a cutoff of mean weal diameter greater by ≥ 3 mm than the negative control.

Analysis

The present study concerns the 801 adults ages 25 to 54 yr, as in this age range, IgE is independent of age (11, 12). We excluded 59 subjects without IgE measurements or data on smoking habits. The analyses concern 742 subjects (122 cases, 190 control subjects, and 430 first-degree relatives). Among the control subjects 26 were asthmatic and were excluded in part of the analysis. All analyses were done in each gender separately. Statistical methods used include chi-square, analysis of variance, and multiple regression. The dependence of subjects from the same family has been taken into account. When few families (< 10) in a given analysis included more than one subject, one individ-

ual was chosen at random and the analysis was redone with standard test. In the other cases, mixed models have been used (13).

RESULTS

The mean age of the sample studied including cases, relatives of cases, and control subjects was 41 yr. Men were significantly older ($p \leq 0.001$), more often active smokers than women ($p \leq 0.001$). These relationships held for each group (cases, relatives, and control subjects) (Table 1). Women were more often passive smokers than men, but the difference was not significant. Overall, men had significantly higher IgE levels ($p \leq 0.001$) and were significantly more often skin prick test positive than women ($p \leq 0.01$), relationships which were statistically significant among cases ($p \leq 0.05$), but not in relatives and control subjects. Socio-occupational class significantly related to IgE, with higher values in manual workers. As expected, asthma was more prevalent in relatives than in control subjects and IgE levels were intermediate in relatives between cases and control subjects. In the age range studied, 25 to 54 yr, there was no change in IgE level according to age, considering age either as continuous or categorical variable.

IgE level was independently related to sex, the type of subjects (cases, relatives of cases, control subjects) and asthma, associations which remained statistically significant after taking into account the dependence of subjects from the same families. The analysis of the relationship of smoking to IgE was then performed by considering the four main categories of asthma, namely cases, asthmatic relatives, nonasthmatic relatives, and nonasthmatic control subjects.

In men, for all categories, active smokers had higher IgE levels than nonsmokers, with ex-smokers in an intermediate position but not among asthmatic relatives (Figure 1). The difference was statistically significant among the cases (GM IgE were 491, 210, and 144 IU/ml; $p = 0.005$, for smokers, ex-smokers, and nonsmokers, respectively) and in the largest group of nonasthmatic relatives (84, 49, and 39 IU/ml respectively; $p = 0.04$). Similar results were observed in women. In general, the difference in IgE between never and current smokers was larger in asthmatics than in the other categories (Figure 1). Among women the pattern was clearer when considering cur-

TABLE 1
DESCRIPTIVE CHARACTERISTICS OF THE SAMPLE

	Men			Women		
	Cases (n = 60)	Relatives (n = 206)	Controls (n = 89)	Cases (n = 62)	Relatives (n = 224)	Controls (n = 101)
Age, yr, mean $\pm$ SD	42.2 $\pm$ 7.9	41.4 $\pm$ 6.9	42.4 $\pm$ 8.5	39.1 $\pm$ 7.7	39.7 $\pm$ 7.1	40.3 $\pm$ 8.2
Asthma, %	100	24.3	16.9	100	22.3	10.9
Smoking habits						
Never smokers, %	28.3	33.0	36.0	54.9	52.7	55.4
Ex-smokers, %	48.3	32.5	28.0	29.0	24.5	17.8
Current smokers, %	23.3	34.5	36.0	16.1	22.8	26.7
Never smokers, n	17	68	32	34	118	56
Passive smokers (home exposure), %	17.6	22.1	12.5	23.5	26.3	23.2
Passive smokers (work exposure), %	18.8	14.8*	22.6	11.8	14.0*	23.6
Ex-smokers, n	29	66	24	18	55	18
Ex-smokers ≥ 5 yr, %	69.0	81.8	58.3	66.7	72.7	77.8
Current smokers, n	14	71	32	10	51	27
Tobacco consumption, g/day, mean $\pm$ SD	9.3 $\pm$ 7.2	17.6 $\pm$ 10.8	15.5 $\pm$ 11.2	8.2 $\pm$ 4.1	11.1 $\pm$ 9.9	12.9 $\pm$ 10.0
Heavy smokers, ≥ 15 g/day, %	21.4	60.6	53.1	10.0	35.3	40.7
Atopy, wheal ≥ 3 mm, 11 allergens, %	77.2	48.3	41.2	60.3	41.4	32.6
IgE, GM (95% CI), IU/ml	231 (27–1,998)	69 (3–1,281)	35 (1–849)	120 (5–3,242)	42 (2–1,148)	27 (1–673)

Definition of abbreviations: 95% CI = 95% confidence interval; GM = geometric mean.

* Information available for 27 men and 57 women (see METHODS).

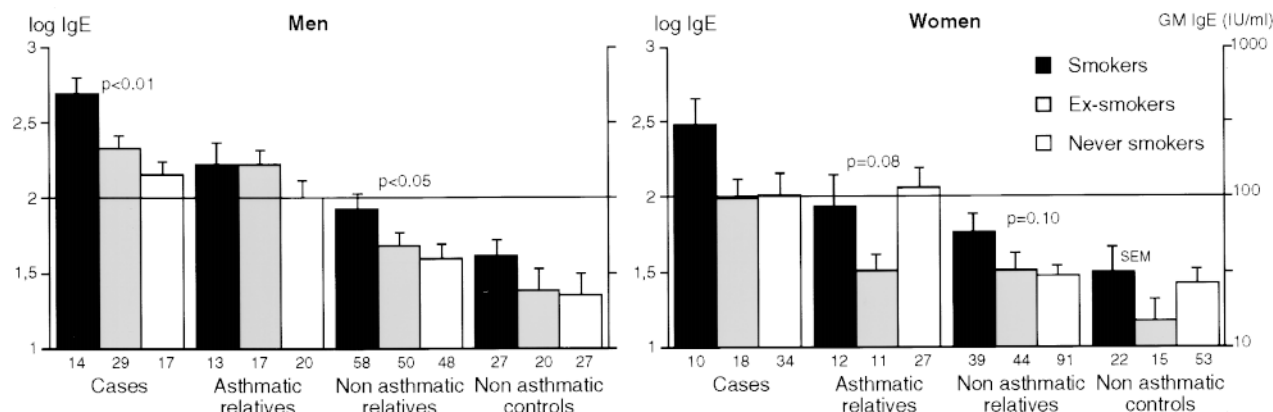


Figure 1. IgE level according to smoking habits in cases, relatives of cases, and nonasthmatic control subjects. Association of IgE with smoking habits: $p = 0.004$ in men and $p = 0.03$ in women after adjustment for personal and familial history of asthma and taking into account the nonindependence of subjects from the same family.

rent smokers versus others, than when considering the three classes of current smokers, ex-smokers and nonsmokers. A model run in cases and control subjects taking current smoking versus never smoking and sex into account showed that the increase in IgE according to smoking was higher in cases than in control subjects. A model with log IgE as the independent variable and sex, smoking (current versus never smokers), and case control status without interaction term smoking*case control status gave beta coefficients (95% confidence interval [CI]) of 0.66 (0.13; 0.26) for sex, 0.28 (0.09; 0.48) for smoking, and 0.79 (0.59; 0.98) for case control status. The IgE in current smoker versus never smokers was 3.5 and 1.5 times greater in asthmatics and nonasthmatics respectively. Testing formally the interaction by running a model with an interaction term gave a beta coefficient for smoker cases versus others of 0.38 (−0.02; 0.78); $p = 0.07$. The number of subjects necessary to reach statistical significance for an interaction of the observed magnitude would have been 215 subjects instead of 204.

After adjustment on the four-category variable (cases, asthmatic relatives, nonasthmatic relatives, and nonasthmatic con-

trol subjects) and socio-occupational class in a model taking into account the dependence between subjects of the same family, IgE values in ex-smokers were similar to those of non-smokers. In men adjusted IgE were 128, 76, 56 IU/ml in current smokers, ex-smokers, and nonsmokers, respectively; $p = 0.01$; and in women 77, 41, and 55 IU/ml; $p = 0.05$, respectively. Analysis of duration of ex-smoking (< 1 yr, 5 yr, or 10 yr) did not show any trend in decreasing IgE according to duration.

Skin prick test (SPT) positivity was significantly related to IgE ($p < 0.001$) and IgE was higher in positive SPT compared with negative SPT in 22 of the 24 strata obtained according to status (cases, asthmatic relatives, nonasthmatic relatives, nonasthmatic control subjects), sex, and smoking. Taking into account atopy in the analysis of the relations of IgE to smoking did not change the results (Table 2). In a model including sex, status, atopy, smoking (current versus never), and the interaction atopy*smoking, the interaction term was not significant ($p = 0.22$). There was a consistent pattern of increased IgE in current smokers compared with never smokers, with higher

TABLE 2
IgE LEVEL ACCORDING TO SMOKING AND ATOPY*

			Asthmatic Cases Atopy		Asthmatic Relatives Atopy		Nonasthmatic Relatives Atopy		Nonasthmatic Controls Atopy	
	Asthmatics (all)	Nonasthmatics (all)	No	Yes	No	Yes	No	Yes	No	Yes
Men										
Never smokers	118 (37)	33 (73)	159 (2)	142 (15)	14 (4)	164 (16)	31 (30)	62 (17)	8 (14)	75 (12)
Ex-smokers	195 (44)	40 (70)	209 (8)	219 (19)	237 (1)	163 (16)	35 (31)	90 (17)	13 (13)	60 (6)
Current smokers	284 [†] (25)	68 [†] (84)	439 (3)	480 (10)	82 (3)	207 (9)	52 (35)	189 (22)	34 (17)	60 (10)
Women										
Never smokers	109 (59)	29 (141)	28 (11)	201 (22)	27 (9)	250 (17)	21 (67)	79 (23)	16 (34)	76 (17)
Ex-smokers	56 (21)	27 (58)	53 (8)	146 (7)	20 (4)	42 (7)	23 (26)	51 (18)	11 (11)	42 (3)
Current smokers	153.0 (22)	47 [‡] (61)	234 (4)	366 (6)	28 (3)	125 (9)	31 (21)	121 (18)	20 (16)	107 (6)

* Values are IgE geometric means (n).

[†] $p \leq 0.01$ versus never smokers.

[‡] $p \leq 0.05$ versus never smokers.

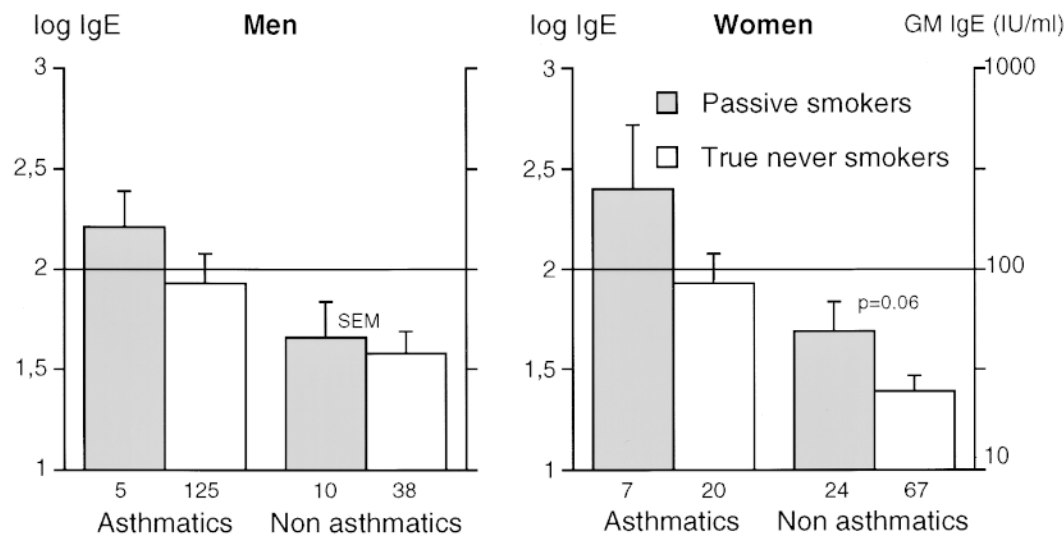


Figure 2. IgE concentration according to passive smoking in relatives. Multiple regression models for each gender with asthma and passive smoking gave p values for passive smoking of 0.20 in men and 0.02 in women.

IgE values in 14 of 16 comparisons, and all significant associations of smoking to IgE remained after adjustment for positive skin prick response. Taking into account atopy in a more detailed way, by considering mono- and polysensitized subjects, did not change the association of smoking to IgE.

Analysis of the amount smoked in current smokers was performed in nonasthmatic relatives and control subjects, as the proportion of heavy smokers was too small in asthmatics (Table 1). In control men and women, heavy smokers (15 men and eight women) did not show statistically higher IgE levels than moderate smokers (12 men and 14 women) (44 versus 39 IU/ml, in men and 49 versus 25 IU/ml in women, respectively, not significant [NS]). In nonasthmatic relatives, opposite differences were observed in men and women. In men, heavy smokers ($n = 36$) had higher IgE levels than moderate smokers ($n = 22$) (122 versus 46 IU/ml $p = 0.04$), whereas in women, heavy smokers ($n = 14$) had lower IgE values than moderate smokers ($n = 25$) (27 versus 89 IU/ml; $p = 0.04$). Results were unchanged when taking into account at random one subject per family. The proportion of atopy in heavy smokers in men (37.1%) and women (35.7%) was similar to that in moderate smokers (40.9% and 52.0% for men and women, respectively).

The analysis of passive smoking was performed in the largest subgroup of never smokers, represented by the relatives. The sample size was also large enough for the study to be performed in control women. In both men and women, either asthmatics or nonasthmatics, a consistent pattern was observed with passive smokers with higher IgE than true never smokers in relatives, but the differences did not reach statistical significance (Figure 2). For each gender, multiple regression analysis of IgE level on asthma and passive smoking was performed. In women asthma-adjusted IgE levels were significantly higher in passive smokers than in true never-smoker relatives (103 versus 48 IU/ml; $p = 0.02$). Results were unchanged when taking at random one subject per family. In women, considering the amount of tobacco smoked by their husband, a nonsignificant trend was observed with the highest IgE for those with the heaviest smoking husbands (asthma-adjusted IgE were 46, 61, and 129 IU/ml for nonsmokers, < 20 , and ≥ 20 cigarettes/d). Considering simultaneously domestic and work exposure in women relatives showed that women exposed at either domestic or work exposure had higher IgE than those exposed to none, but there were too few subjects for a detailed analysis. Asthma-adjusted IgE were in

those not exposed, and exposed at home or at work 43 ($n = 35$) and 112 IU/ml ($n = 26$); $p = 0.01$.

DISCUSSION

The analysis of factors related to IgE level in this population of 25 to 54-yr-old asthmatic cases, relatives of asthmatics, and control subjects shows that active smoking was significantly related to higher total IgE level independently of gender, socio-occupational class, personal or familial asthma, and positive skin tests. Active smoking increased IgE levels even in asthmatics. In the *a priori* susceptible group of relatives of asthmatics, passive smoking increased IgE in women.

Results confirm the higher IgE level already described in men compared with women (5, 11, 12, 14) and in asthmatics (cases or relatives of cases) compared with nonasthmatics (9, 15). As previously described, IgE level was stable in the age range of 25 to 54 yr (11, 12). Furthermore, asthmatic cases had higher IgE levels than relatives who also reported asthma; the fact that IgE levels were higher in the cases than in other asthmatics from their families may correspond to the greater severity of asthma in those recruited in chest clinics.

Besides genetic factors, environmental factors play a major role in the etiology of asthma (16). Therefore, delineating the environmental factors associated with the intermediate phenotypes of asthma, such as IgE, is important.

Results extend previous observations on higher IgE levels in smokers than in nonsmokers (4, 6, 7) both in men and women. The relation of smoking to IgE was evidenced in the present study in well-defined asthmatics, in relatives of asthmatics, and was independent of atopy. In 14 of 16 subgroups stratified by personal asthma, familial asthma, and atopy, smokers had higher IgE levels than never smokers. Atopy did not modify the relationship of smoking to IgE. In general, the pattern was more marked in men than in women. However, the lack of statistical significance in some of the subgroups of women may correspond to the lower proportion of smokers in women, as the difference for IgE level was similar in magnitude in both genders. Gender-related difference in smoking pattern (inhalation habits, filter use) would be worthwhile to study but such information was not available in our data.

IgE level in current smoker asthmatics was 3.5 times greater than the level in never smoker asthmatics whereas the increase was only 1.5 times greater in control subjects. The nonasthmatic relatives of asthmatics were in an intermediate posi-

tion with an increase of approximately twofold. Formal testing of the interaction only led to borderline statistical significance, and a marginally larger group would have been necessary to reach statistical significance. The difference, however, is worth noting as the healthy smoker effect *a priori* decreased in asthmatics the association of smoking to IgE. The "healthy smoker effect," like the "healthy worker effect" corresponds to the fact that subjects self-select toward lower levels of hazards when they are diseased. The issue of healthy smoker effect is difficult to assess regarding allergy (2) as both atopy and asthma relate to quitting smoking whereas smoking positively relates to IgE and asthma severity, as already observed in the EGEA (17). Only longitudinal design could allow one to address the whole sequence of events. The mechanisms involved in smoking-associated IgE increase may be different or enhanced in asthmatics.

Immunological changes in relation to smoking are well known (18) and two hypotheses have been proposed to explain the relation of smoking to IgE: a direct effect on IgE regulation at the cellular level and an indirect action which may lead to an increased permeability of airways to allergens (19). Both aspects are also modified in asthmatics. IgE is controlled by the T helper cell, type 2 (Th2) interleukin-4 (IL-4) cytokine (19) and smoking modifies the CD4/CD8 ratio (20). Smoking, through an increase of IL-4 without change in interferon gamma (IFN- γ) leads to an increase of IL-4/IFN- γ ratio (21). An increase of that ratio in relation to asthma (22, 23) or asthma severity (24) through a decrease in IFN- γ (23, 24) or an increase in IL-4 (22) has also been reported. Therefore, immunological changes (in particular regarding the Th1/Th2 imbalance) occurring in smokers may be enhanced in asthmatic smokers.

The permeability of bronchial epithelium is increased in smokers (25). This could enhance the already increased sensitization to allergens in asthmatics compared with control subjects. In the general population, it is difficult to show such increase of sensitization in smokers as atopy is less often smokers, in relation to the healthy smoker effect (26). However, in the quasi-experimental situation of occupational asthma, it has been shown that smoking could modify sensitization to various occupational agents (27–29).

The effect of passive smoking on IgE among adults has been scarcely studied. The role of *in utero* exposure on cord blood IgE is not established (8, 30), but environmental exposure to tobacco smoke seems to relate to IgE in childhood (8, 31, 32). In the single study conducted in an adult general population (14), some increase in IgE was associated with passive smoking but the analysis did not present data on passive smokers who were nonactive smokers, but only pooled with ex-smokers. We previously reported a significant increase in total IgE in a group of pregnant mothers in relations to their husband smoking, but results cannot be generalized from this particular group (30). In the current study, an increase in IgE in relation to spouse smoking was found in asthmatic relatives but not in control subjects. The results of the analysis of the amount smoked by husbands and of consideration of both home and work exposure are consistent with the hypothesis of an influence of passive smoking on IgE, but owing to small numbers, only trends have been observed and confirmation is needed. There were insufficient asthmatic cases exposed to passive smoking to allow an analysis. A recent analysis in EGEA showed a good validity ($\kappa > 0.70$) of passive smoking resulting from family members smoking, as direct interviews on smoking habits of other members of the family were available in a subsample. Asthma did not modify that validity (33). The inclusion of relatives of asthmatics was chosen by design for various reasons. The first one was to study familial resem-

blance and analyze genetic factors. The second reason was that this group was *a priori* susceptible to environmental factors, owing to genetic or shared environmental risk factors with asthmatics. The effect of passive smoking on IgE found in this group but not in control subjects, may relate to this increased susceptibility. Further studies are needed to confirm this finding. Various elements suggest that the mechanisms involved might be similar to active smoking (32). The consequences of passive smoking on asthma severity may be similar to those of active smoking (17, 34).

The study suffers from several limitations. First, the cases come from chest clinics and are therefore nonrepresentative of asthma in the general population regarding severity; they are more severe than those in the general population. Second, information on passive smoking was only partial and no biological marker of passive smoking was used. Third, the sample sizes were small in some subgroups. However, one strength of the present study is the large number of well defined asthmatics (probands or relatives).

The strength of the association of current smoking to IgE in asthmatic patients recruited in chest clinics should further attract attention to antismoking campaigns in patients with respiratory diseases. Further studies are needed to confirm the role of passive smoking in subjects with a personal or familial history of asthma.

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APPENDIX

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