

The association of smoking with sensitization to common environmental allergens: Results from the European Community Respiratory Health Survey

Deborah Jarvis, MRCP, MFPHM, Susan Chinn, MA, Christina Luczynska, PhD, and Peter Burney, MD, for the European Community Respiratory Health Survey*

London, United Kingdom

Background: Smoking is a risk factor for sensitization to some occupational allergens, but its association with sensitization to common environmental allergens remains unclear.

Objective: We sought to determine the association of smoking with total IgE levels and with sensitization to 3 common environmental allergens in data from the European Community Respiratory Health Survey.

Methods: A detailed smoking history and blood sample for determination of serum total IgE and specific IgE levels to house dust mite, grass, and cat allergens was obtained from 13,002 randomly selected young adults living in the areas served by 34 centers in 14 countries. Associations with smoking status and amount smoked were determined. Because there was evidence of heterogeneity between centers in the association of age, sex, and smoking with sensitization, odds ratios

Abbreviations used

CI: Confidence interval
ECRHS: European Community Respiratory Health Survey
OR: Odds ratio

(ORs) were determined for each center and combined by using random-effects meta-analysis.

Results: Compared with lifetime nonsmokers, current smokers were at an increased risk of sensitization to house dust mite allergen (OR, 1.13; 95% confidence interval [CI], 1.02-1.26) but a decreased risk of sensitization to grass (OR, 0.76; 95% CI, 0.67-0.88) and cat allergens (OR, 0.69; 95% CI, 0.59-0.80). Exclusion of those with symptoms suggestive of current asthma strengthened the association of smoking with sensitization to house dust mite allergen (OR, 1.29; 95% CI, 1.11-1.50). The geometric mean total IgE level was higher in smokers and was higher among those who currently smoked the most compared with those who smoked less than 5 cigarettes per day.

Conclusion: The association between smoking and sensitization to common environmental allergens is different for different allergens. (*J Allergy Clin Immunol* 1999;104:934-40.)

Key words: Smoking, specific IgE, total IgE, European Community Respiratory Health Survey

Smoking is a risk factor for sensitization to some occupational allergens, such as platinum salts,^{1,2} coffee and castor beans (encountered by coffee workers),^{3,4} and reactive dyes,⁵ but this association has not been confirmed for all occupational allergens.⁶ Potential explanations for these discrepant results include inadequate adjustment for age and sex within the study groups, differences in the populations studied, and differences in the mechanism of sensitization for each allergen. However, a negative association between smoking and sensitization to common environmental allergens has been reported.⁷ In cross-sectional studies the observed lower levels of atopy (sensitization to one or more common allergens) in smokers may be explained by the *healthy-smoker* bias⁸ (the tendency for those with allergic symptoms not to smoke), but even from longitudinal studies there is little evidence that those who smoke are at an increased risk of sensitization.⁹⁻¹¹ Notwithstanding, there is overwhelming evidence that total IgE levels are increased in smokers,¹²⁻¹⁴ even after adjustment for age and sex.

The European Community Respiratory Health Survey

From the Department of Public Health Sciences, Guy's King's and St Thomas' School of Medicine, Kings College, Guy's Hospital, London.

*The names and location of participants in the European Community Respiratory Health Survey can be found in the appendix.

Supported by the European Commission and the following grants for local studies: *Australia:* Allen and Hanbury's, Australia; *Belgium:* Belgian Science Policy Office, National Fund for Scientific Research; *France:* Ministère de la Santé, Glaxo France, Institut Pneumologique d'Aquitaine, Contrat de Plan Etat-Région Languedoc-Rousillon, CNMATS, CNMRT (90MR/10, 91AF/6), Ministre délégué de la santé, RNSP; *Germany:* GSF, and the Bundesminister für Forschung und Technologie, Bonn; *Greece:* The Greek Secretary General of Research and Technology, Fisons, Astra and Boehringer-Ingelheim; *India:* Bombay Hospital Trust; *Italy:* Ministero dell'Università e della Ricerca Scientifica e Tecnologica, CNR, Regione Veneto grant RSF n. 381/05.93; *New Zealand:* Asthma Foundation of New Zealand, Lotteries Grant Board, Health Research Council of New Zealand; *Norway:* Norwegian Research Council project no. 101422/310; *Portugal:* Glaxo Farmacêutica Lda, Sandoz Portuguesa; *Spain:* Ministerio Sanidad y Consumo FIS grants #91/0016060/00E-05E and #93/0393, and grants from Hospital General de Albacete, Hospital General Juan Ramón Jiménez, Consejería de Sanidad Principado de Asturias; *Sweden:* The Swedish Medical Research Council, the Swedish Heart Lung Foundation, the Swedish Association against Asthma and Allergy; *Switzerland:* Swiss national Science Foundation grant 4026-28099; *United Kingdom:* National Asthma Campaign, British Lung Foundation, Department of Health, South Thames Regional Health Authority; *USA:* United States Department of Health, Education and Welfare Public Health Service Grant #2 S07 RR05521-28.

Received for publication Dec 21, 1998; revised July 8, 1999; accepted for publication July 8, 1999.

Reprint requests: Deborah Jarvis, MRCP, MFPHM, Department of Public Health Medicine, 5th Floor, Capital House, 42 Weston St, London SE1 3QD.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/1/101516

(ECRHS) is a large, collaborative epidemiologic study of risk factors for asthma and allergy. Study populations have been selected and surveyed by using a standardized protocol.¹⁵ Information on smoking was collected from participating subjects as were blood samples for determination of total IgE and specific IgE levels to common allergens. The project management group agreed to a 2-stage plan for analysis. First, data from individual centers within a country would be aggregated and analyzed to examine potential risk factors for disease within the country. Assuming the analysis was accepted by the wider research community (eg, by publication in a peer-reviewed journal), the analysis could then be repeated by using the combined ECRHS data from all centers. This approach was developed to clarify the analysis plan and prevent false associations arising from multiple-hypothesis testing on the large combined ECRHS data set. Analyses of data from 3 centers in East Anglia, England, that took part in the ECRHS represented the first stage of this process and showed that after controlling for age and sex, smokers compared with nonsmokers had higher total IgE levels, an increased risk of sensitization to house dust mite allergen, and a decreased risk of sensitization to grass and cat allergens.¹⁴ In this report these analyses have been extended to determine the association of age, sex, and smoking with specific and total IgE levels in more than 13,000 individuals living in areas served by the 34 centers that provided data for this component of the ECRHS.

METHODS

The methods used in the ECRHS have been described in detail elsewhere.^{15,16} Briefly, participating centers selected areas for study that were predefined by existing administrative boundaries, had populations of at least 150,000 people, and had up to date sampling frames of 20 to 44 year old subjects where possible. In the first stage of the study, at least 1500 people of each sex were sent questionnaires enquiring about respiratory symptoms and attacks of asthma in the previous 12 months and current use of asthma medication and current hay fever or nasal allergies, together with questions on age and sex. In the second stage of the study, a random sample of those responding to the postal questionnaire were invited for an interview during which detailed information on personal smoking history, maternal smoking history, and family size was obtained.

Blood samples were taken for the measurement of total IgE and specific IgE levels to *Dermatophagoides pteronyssinus* (house dust mite), timothy grass, cat, and *Cladosporium* species allergens. Samples were left to coagulate for either 3 to 6 hours at room temperature or overnight at 4°C. The blood was centrifuged at 2500 to 3000 rpm for 10 to 15 minutes, and the serum was pipetted off and placed in aliquots in 2-mL polypropylene microtubes with screw tops (Sarstedt, Numbrecht, Germany). Aliquots were stored at -20°C, packed in Styrofoam boxes (Sarstedt, Numbrecht, Germany), and sent on dry ice to a central laboratory at Pharmacia and Upjohn Diagnostics AB (Uppsala, Sweden) for analysis. Specific and total IgE levels were measured by using the Pharmacia CAP System (Pharmacia and Upjohn, Uppsala, Sweden). The only exception to this practice was in Melbourne, where specimens were assayed locally.

The working range for the assay of total IgE was 2 to 2000 kU/L. Subjects with no detectable IgE were ascribed a value of 1 kU/L,

and those with values above 2000 kU/L were ascribed a value of 2050 kU/L. All assays for specific IgE were judged to be positive if they had in excess of 0.35 kU/L to the specific allergen, which was the limit of detection of the assay.

Analysis

The analysis was similar to that used to examine the relationship of age, sex, and smoking history with total IgE levels and sensitization to common allergens in the 3 English centers in East Anglia.¹⁴ Only those subjects who took part in the second stage of the study who provided information on smoking history and agreed to have blood tests are included in this analysis.

The association of age and sex with specific IgE and total IgE levels in lifetime nonsmokers (defined as all those who denied ever having smoked as much as 1 cigarette per day for a year) was examined. In addition, the association of current smoking status (lifetime nonsmoker, exsmoker, and current smoker) and amount smoked (current and pack-years of smoking) with specific and total IgE levels in the entire sample was also tested. To mitigate the effects of a healthy-smoker bias, the effect of excluding all those who reported an attack of asthma before the age of 14 years and excluding those with current symptoms was examined.

Sensitization to house dust mite, grass, and cat allergens was analyzed by using logistic regression while controlling for age group, sex, and center, and tests for interaction were conducted to examine whether the effect of age group, sex, and smoking history varied between centers. Because there was strong evidence that for some allergens the effects of age, sex, and smoking history did vary, the odds ratios (ORs) were estimated separately (controlling for age group, sex, smoking history, reported maternal smoking history, and family size) in each center, and the average ORs were derived by using standard methods for meta-analysis.¹⁷ For some analyses, some centers had insufficient data to be analyzed separately while adjusting for age and sex. These were excluded from the analyses. In addition, the prevalence of sensitization to *Cladosporium* species was too low in the majority of centers to permit any meaningful analyses. The association of sensitization with the amount smoked was determined by combining all data from all centers in a single analysis while controlling for age, sex, and center.

Total IgE follows a log-normal distribution, and all analyses were performed by using the log of the total IgE values. The association of age, sex, and smoking history with total IgE in each center was determined by using multiple regression, and the average association was determined by combining effects across centers by using standard methods for meta-analysis. Because some values for total IgE were above or below the limit of detection of the assay, analyses were repeated, allowing for censoring of these high and low values.

All analyses were conducted by using the statistical software program STATA (Stata Corp).

RESULTS

Subjects from 34 centers in 14 different countries were included in the analysis.

Total and specific IgE levels were available from 13,002 (76.1%) of the 17,096 subjects who took part in the second stage of the survey. There was variation in the response to blood testing between centers (43.3% in Portland, USA, to 98.2% in Erfurt, Germany). In the sample there were 5526 lifetime nonsmokers, 2766 exsmokers (2433 with full and consistent information on pack-years of smoking), and 4710 current smokers (4336 with full and consistent information on pack-years of smoking). Substantial variation in the prevalence of sen-

TABLE I. OR* (95% CI) of sensitization to house dust mite and grass allergens by age group and sex in lifetime non-smokers

	House dust mite (n = 5526)		Test for heterogeneity†	Grass (n = 5526)		Test for heterogeneity†	Cat‡ (n = 5188)		Test for heterogeneity†
Age group									
<30 y	1.00			1.00			1.00		
≥30 y	0.72 (0.59-0.85)	$P < .001$	$P = .06$	0.66 (0.54-0.75)	$P < .001$	$P = .2$	0.69 (0.58-0.84)	$P < .001$	$P = .5$
Sex									
Women	1.00			1.00			1.00		
Men	1.43 (1.23-1.67)	$P < .001$	$P = .2$	1.34 (1.10-1.65)	$P = .004$	$P < .001$	1.03 (0.85-1.26)	$P = .7$	$P = .3$

*Adjusted for maternal smoking and family size and combined by using random-effects meta-analysis.

†Test for heterogeneity between centers.

‡Galdakao, Albacete, and Huelva were dropped from analysis because of low prevalence of sensitization to cat allergen.

TABLE II. OR* (95% CI) for sensitization to house dust mite, grass, and cat allergens with current smoking status†

	House dust mite		Test for heterogeneity‡	Grass		Test for heterogeneity‡	Cat		Test for heterogeneity‡
Nonsmokers	1.00			1.00			1.00		
Exsmokers vs nonsmokers	0.96 (0.84-1.09)	$P = .7$	$P = .7$	0.77 (0.67-0.86)	$P < .001$	$P = .7$	0.77 (0.63-0.94)	$P = .014$	$P = .1$
Current vs nonsmokers	1.13 (1.02-1.26)	$P = .019$	$P = .6$	0.76 (0.67-0.88)	$P < .001$	$P = .03$	0.69 (0.63-0.94)	$P < .001$	$P = .9$

*Adjusted for age group, sex, maternal smoking history, and family size and combined by using random-effects meta-analysis.

†Analysis of all 13,002 individuals.

‡Test for heterogeneity between centers.

sitization to each allergen was observed. These details have been presented elsewhere.¹⁸

Specific IgE

Age and sex in lifetime nonsmokers. Sensitization to all allergens was higher in those aged less than 30 years, and sensitization to mite and grass allergens, but not cat allergen, was significantly higher in men than women. There was significant variation between centers in the association between age and mite sensitization and sex and grass sensitization (Table I).

Smoking in the random sample. The prevalence of sensitization to grass and cat allergens was lower in both smokers and exsmokers than in nonsmokers. Sensitization to house dust mite allergen showed a very different pattern, with more sensitization in smokers than nonsmokers and little difference between exsmokers and nonsmokers (Table II).

Table III shows the changes that occurred in these associations when adjustment was made for the healthy-smoker bias by first excluding those with asthma before the age of 14 years and then also excluding those with respiratory symptoms. Exclusion of people with asthma before the age of 14 years did not greatly alter the estimated risk of sensitization to any of the allergens in smokers, but further exclusion of those with current res-

piratory symptoms increased the estimated risk of sensitization to house dust mite allergen. The low prevalence of sensitization to cat allergen in the sample precluded a similar analysis for sensitization to cat allergen.

Dose response. Table IV shows the association between the number of cigarettes smoked per day and sensitization in current smokers. Heavy smokers were less likely to be sensitized to grass and cat allergens than those who smoked less than 5 cigarettes per day, but these differences did not reach conventional levels of statistical significance. No association was observed between the amount currently smoked and sensitization to house dust mite allergen.

Among current smokers, a decreased risk of sensitization to grass and cat allergens was observed with increasing amounts ever smoked (grass: OR [associated with increase of 10 pack-years], 0.91 and 95% confidence interval [CI], 0.83-1.00; cat: OR, 0.79 and 95% CI, 0.73-0.97). This relation was not observed among exsmokers. In exsmokers the risk of sensitization to house dust mite, grass, or cat allergen did not change as the length of time of abstinence increased.

For all the above analyses, specific IgE levels were considered positive if greater than 0.35 kU/L IgE was found. Similar results were obtained by using a higher cut-off level of 0.70 kU/L, although for some analyses

TABLE III. OR* (95% CI) for smokers (vs nonsmokers) for sensitization to house dust mite and grass allergens excluding those with asthma in childhood and those with symptoms suggestive of current asthma

	Complete sample	Excluding those with asthma before the age of 14 years (n = 12398)	Excluding those with asthma before age of 14 years and those with symptoms suggestive of current asthma† (n = 7082)
House dust mite	1.12 (1.00-1.25)	1.16 (1.04-1.29)	1.29 (1.11-1.50)
Grass	0.77 (0.66-0.86)	0.76 (0.66-0.87)	0.83 (0.69-0.99)

*Adjusted for age group and sex and combined by using random-effects meta-analysis.

†Symptoms suggestive of current asthma are wheeze, cough, chest tightness, waking with breathlessness or asthma attacks in the last 12 months, or current use of asthma medication.

TABLE IV. OR* (95% CI) for sensitization to common allergens in current smokers by amount smoked

Cigarettes currently smoked	House dust mite	Test for trend	Grass	Test for trend	Cat	Test for trend
<5	1.00		1.00		1.00	
5-14	1.10 (0.85-1.44)		0.89 (0.68-1.17)		0.72 (0.50-1.04)	
15-24	1.17 (0.90-1.51)		0.82 (0.63-1.07)		0.68 (0.48-0.97)	
≥25	1.07 (0.79-1.44)	P = .54	0.75 (0.55-1.04)	P = .06	0.70 (0.46-1.08)	P = .12

*OR from logistic regression model using all data and adjusted for age group, sex, and center.

TABLE V. Unadjusted geometric mean total IgE and the adjusted OR* (95% CI) of geometric mean total IgE levels by age in men and women who are lifetime nonsmokers

Age group	Unadjusted geometric mean total IgE (kU/L)		Ratio of geometric means	
	Women	Men	Women	Men
20-24	27.5	41.6	1.00	1.00
25-34	26.9	35.5	0.93 (0.79-1.08)	0.87 (0.73-1.02)
35-44	22.9	32.3	0.81 (0.68-0.93)	0.74 (0.62-0.89)

*Combined by using random-effects meta-analysis.

the power to detect significant differences was reduced, and some centers had to be dropped from the analysis because of the reduction in the number of individuals defined as being sensitized.

Total IgE

Age and sex in lifetime nonsmokers. Total IgE levels were higher in men than women (ratio between age-area adjusted geometric means, 1.38; 95% CI, 1.27-1.48), and in both sexes levels were higher in younger than older adults (Table V). These associations showed no significant variation between centers. Although 24 (0.43%) subjects had total IgE levels in excess of 2000 kU/L and 291 (5.26%) had levels below the lowest detection limit of the assay, these associations were still observed when calculations were made allowing for censoring of high and low values. Omission of those in whom asthma developed before the age of 14 years did not alter these associations.

Smoking. The geometric mean total IgE level was higher in smokers than nonsmokers, with no significant difference between exsmokers and lifetime nonsmokers (Table VI). This association did not differ between centers nor did it differ between men and women. Seventy-five (0.56%) subjects had total IgE levels in excess of

2000 kU/L, and 606 (4.7%) had levels below the lowest detection limit of the assay. The association between smoking history and total IgE level was not changed when calculations were conducted by using censored regression or when those in whom asthma developed before the age of 14 years were omitted.

Although smoking was a significant predictor of the total IgE level, it explained less than 1% of the residual variation in total IgE levels after adjustment for age, sex, and center.

Dose response and smoking. Among smokers, geometric mean total IgE levels increased with the number of cigarettes smoked per day (Table VII) but also increased with increasing numbers of cigarettes ever smoked. People who currently were heavy smokers were highly likely to have a high lifetime consumption, and it was not possible to determine whether current smoking or total pack-years smoked was more important. Neither explained more than 1% of the variation in total IgE levels in smokers.

There was no association between total IgE and the number of pack-years of smoking in exsmokers, suggesting that current smoking behavior may be more important than lifetime consumption. Among exsmokers, however, the total IgE levels were marginally lower in those who had given up for the longest time (ratio of age-gen-

TABLE VI. Ratio of adjusted geometric mean total IgE levels by smoking status

	Adjusted OR (95% CI)	Test for hetero- geneity
Nonsmoker	1.00	
Exsmokers vs nonsmokers	0.96 (0.86-1.03)	<i>P</i> = .3
Smokers vs nonsmokers	1.29 (1.21-1.37)	<i>P</i> = .8

*Adjusted for center and combined by using random-effects meta-analysis.

der-area adjusted mean for 1 extra year of abstinence, 0.99; 95% CI, 0.98-1.00).

DISCUSSION

This study has shown that smoking was associated differently with sensitization to 3 common environmental allergens while being consistently associated in a dose-dependent fashion with high total IgE levels. Because of the cross-sectional design of the study and the potential for healthy-smoker bias, analyses have been conducted including and excluding those with current respiratory symptoms. These analyses confirm that current smoking is an important risk factor for sensitization to house dust mite allergen, but that it has a significant negative association with sensitization to grass and cat allergens.

All individuals taking part in this study were selected at random from suitable population-sampling frames. Although response rates were higher in some centers than others, it is unlikely that the association between sensitization and smoking in responders was different from that found in nonresponders or that smokers sensitized to grass allergen were less likely to respond than smokers who were sensitized to house dust mite allergen.

The most important potential bias within the study is the healthy-smoker bias, and within this cross-sectional study it is not possible to fully account for its potential effect. When individuals who have no symptoms are excluded from the analysis, the association of smoking with sensitization to house dust mite allergen becomes stronger, whereas the negative association between smoking and sensitization to grass allergen becomes less apparent and closer to 1.00. The healthy smoker bias is therefore influencing the estimates for both sensitization to house dust mite allergen and sensitization to grass allergen. It is not possible to determine whether the bias is greater for grass or house dust mite allergen, and we are limited to concluding that if the healthy-smoker bias is present, the ORs for house dust mite allergen are likely to be greater than has been estimated, and the ORs for sensitization to grass allergen are likely to be closer to 1.00. If sensitization to grass allergen was strongly associated with severe allergic symptoms or with symptoms that were more likely to be aggravated by smoking than sensitization to house dust mite allergen, we would expect those who are sensitized to grass allergen to be more likely to refrain from smoking than those who are sensitized to house dust mite allergen. Although sensi-

TABLE VII. Ratio of adjusted* geometric mean total IgE with amount currently smoked

Amount smoked	Ratio* of geometric mean total IgE	Test for trend
<5/d	1.00	
5-14/d	1.19 (1.02-1.39)	
15-24/d	1.16 (1.00-1.34)	
≥25/d	1.33 (1.12-1.59)	<i>P</i> = .008

zation to house dust mite allergen has most consistently been associated with the development, persistence, and severity of asthma, it is not possible to determine whether there is a substantial difference in the magnitude of the healthy-smoker bias as it influences the association of smoking and sensitization to these 2 allergens.

There are several reports showing that smokers have higher total IgE levels than nonsmokers and that this association is dose dependent, with heavy smokers having higher total IgE levels than light smokers.^{12,13,19} Our findings are consistent with these observations, and in addition, we have shown that in exsmokers total IgE levels are lower in those who have given up for the longest period. Why total IgE levels should be higher in smokers than nonsmokers is poorly understood but may reflect either increased levels of specific IgE to a range of allergens or increased levels of specific IgE to tobacco antigens or bacterial antigens. Whatever the reason, our results suggest that after stopping smoking, total IgE levels will fall.

Longitudinal studies of occupational groups have reported that smoking is associated with sensitization to some occupational allergens, but the association between smoking and sensitization to environmental allergens is less clear. One of the largest cohort studies to describe the incidence of atopy in adults reported lower rates in smokers than nonsmokers or exsmokers.¹¹ However, the definition of atopy was broad, being sensitization to any of the allergens tested, and acquisition rates for sensitization to the individual allergens were not presented.

Heavy smoking causes an increase in suppressor T cells, a decrease in helper T cells, and a significant decrease in natural killer cell activity.²⁰ These changes may result in a decreased risk of sensitization to allergens and explain our observation that smoking is negatively associated with sensitization to grass and cat allergens. If this is the case, however, we need some explanation for why the sensitization to mite allergen and some occupational allergens is increased in smokers and why total IgE has been found to be consistently higher in smokers.

Four of the allergens from the genus *Der-matophagoides* have been found to be enzymes with proteolytic activity.²¹ It has been demonstrated in vivo that they can cleave CD23,²² the low-affinity IgE Fc receptor, and CD25,²³ the α -subunit of the IL-2 receptor. Both of these actions could enhance IgE production in response to allergens. Lung antiproteases (in particular α -1-anti-trypsin) provide a natural defense against proteolytic

enzymes, but in smokers functional antiprotease activity is considerably reduced.²⁴ It may be that smoking, by reducing α -1-antitrypsin (or other lung antiproteases), prevents the normal inactivation of house dust mite allergen proteases, leading to an increased risk of sensitization to house dust mite allergen. Pertinent to this hypothesis, smoking has been shown to promote sensitization to other proteolytic enzymes, including those encountered by workers in the detergent^{25,26} and pharmaceutical industries.²⁷ However, smoking has been identified as a risk factor for sensitization to occupational agents not currently recognized as proteases, such as platinum salts,^{1,2} coffee and castor bean allergens,³ reactive dyes,⁵ and prawn antigens,⁶ and other mechanisms must also be important.

Smoking increases the permeability²⁸ of the bronchus and may increase access of antigen to antigen-presenting cells. If so, smoking at the time of first exposure to allergen, as occurs in the occupational setting, will promote sensitization. In contrast, first exposure to common environmental allergens occurs in childhood or earlier, before smoking begins, and this may be why the associations are less consistent and clear.

In conclusion, the association of smoking with sensitization to common environmental allergens varies for different allergens, and smoking may be an important risk factor for sensitization to house dust mite allergen but not for grass allergen. Smoking is associated in a dose-dependent fashion with high total IgE levels. Only longitudinal studies can clarify whether smoking is an important cause of sensitization to common environmental allergens, particularly house dust mite allergen, in a general population in adults.

We thank Dr Jonathan Sterne for his support and advice. We also thank the late Colette Baya and Dr Manuel Hallen for their help during the study and Professor K. Vuytsteek and the members of the COMAC for their support.

REFERENCES

- Calverley A, Rees D, Dowdeswell R, Linnet P, Kielkowsky D. Platinum salt sensitivity in refinery workers: incidence and effects of smoking and exposure. *Occup Environ Med* 1995;52:661-6.
- Niezborala M, Garnier R. Allergy to complex platinum salts: a historical prospective cohort study. *Occup Environ Med* 1996;53:252-7.
- Romano C, Sulotto F, Piolatto G, et al. Factors related to the development of sensitization to green coffee and castor bean allergens among coffee workers. *Clin Exp Allergy* 1995;25:643-50.
- Zetterstrom O, Osterman K, Machado L, Johansson SG. Another smoking hazard: raised serum IgE concentration and increased risk of occupational allergy. *BMJ* 1981;283:1215-7.
- Park HS, Lee MK, Kim BO, et al. Clinical and immunologic evaluations of reactive dye-exposed workers. *J Allergy Clin Immunol* 1991;87:639-49.
- Chan-Yeung M. Immunologic and non-immunologic mechanisms in asthma due to the western red cedar (*Thuja plicata*). *J Allergy Clin Immunol* 1982;70:32-7.
- Omenaas E, Bakke P, Elsayed S, Hanoa R, Gulsvik A. Total and specific serum IgE levels in adults: relationship to sex, age and environmental factors. *Clin Exp Allergy* 1994;24:530-9.
- Becklake M, Lallo U. The 'healthy smoker': a phenomenon of health selection? *Respiration* 1990;57:137-44.
- Oryszczyn M, Annesi I, Neukirch F, Dore M, Kauffmann F. Longitudinal observations of serum IgE and skin prick test response. *Am J Respir Crit Care Med* 1995;151:663-8.
- Lin F, Kennedy S, Chan-Yeung M. Effect of grain exposure and smoking on the longitudinal changes in immediate skin reactivity. *Clin Exp Allergy* 1994;24:949-54.
- Barbee RA, Kaltenborn W, Lebowitz MD, Burrows B. Longitudinal changes in allergen skin test reactivity in a community population sample. *J Allergy Clin Immunol* 1987;79:16-24.
- Burrows B, Halonen M, Barbee RA, Lebowitz MD. The relationship of serum immunoglobulin E to cigarette smoking. *Am Rev Respir Dis* 1981;124:523-5.
- Warren C, Holford-Stevens V, Wong C, Manfreda J. The relationship between smoking and total immunoglobulin E levels. *J Allergy Clin Immunol* 1982;69:370-5.
- Jarvis D, Luczynska C, Chinn S, Burney P. The association of age, gender and smoking with total IgE and specific IgE. *Clin Exp Allergy* 1995;25:1083-91.
- European Community Respiratory Health Survey. Protocol for the European Community Respiratory Health Survey. London: Department of Public Health Sciences, Kings' College; 1993.
- Burney P, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954-60.
- Der Simonian R, Liard N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
- Burney P, Malmberg E, Chinn S, Jarvis D, Luczynska CM, Lai E. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1997;99:314-22.
- Oryszczyn M, Annesi I, Neukirch F, Dore M, Kauffmann F. Relationships of total IgE level, skin prick tests response and smoking habits. *Ann Allergy* 1990;67:355-8.
- Holt P. Immune and inflammatory function in cigarette smokers. *Thorax* 1987;42:241-9.
- Robinson C, Kalsheker N, Srinivasan N, et al. On the potential significance of the enzymatic activity of mite allergens to immunogenicity. Clues to structure and function revealed by molecular characterization. *Clin Exp Allergy* 1997;27:10-21.
- Hewitt C, Brown A, Hart B, Pritchard D. A major house dust mite allergen disrupts the immunoglobulin E network by selectively cleaving CD23: innate protection by antiprotease. *J Exp Med* 1995;182:1537-44.
- Schulz O, Sewell HF, Shakib F. Proteolytic cleavage of CD25, the alpha subunit of the human T cell interleukin 2 receptor, by Der p 1, a major mite allergen with cysteine protease activity. *J Exp Med* 1998;187:271-5.
- Gadek J, Fells G, Crystal R. Cigarette smoking induces functional antiprotease deficiency in the lower respiratory tract of humans. *Science* 1979;206:1315-6.
- Greenberg M, Milne J, Watt A. Survey of workers exposed to dusts containing derivatives of bacillus subtilis. *BMJ* 1970;2:629-33.
- Flood D, Blofeld R, Bruce C, Hewitt J, Juniper C, Roberts D. Lung function, atopy, specific hypersensitivity, and smoking of workers in the enzyme detergent industry over 11 years. *Br J Ind Med* 1985;42:43-50.
- Johnsen CR, Sorensen TB, Ingemann Larsen A, et al. Allergy risk in an enzyme producing plant: a retrospective follow up study. *Occup Environ Med* 1997;54:671-5.
- McSharry C, Anderson K, McKay I, Colloff M, Feyerabend C, Wilson R. The IgE and IgG antibody responses to aerosols of *Nephrops norvegicus* (prawn) antigens: the association with clinical hypersensitivity and with cigarette smoking. *Clin Exp Immunol* 1994;97:499-504.
- Gareth Jones J, Minty B, Royston D, Royston J. Carboxyhaemoglobin and pulmonary epithelial permeability in man. *Thorax* 1983;38:129-33.

APPENDIX

List of principal participants

Coordinating center (London): P. Burney, S. Chinn, C. Luczynska, D. Jarvis, E. Lai.

Project management group: P. Burney (Project leader); S. Chinn, C. Luczynska, D. Jarvis, P. Vermeire (Antwerp); H. Kesteloot (Leuven); J. Bousquet (Montpellier); D. Nowak (Hamburg); the late J. Prichard (Dublin); R. de Marco (Verona); B. Rijcken (Groningen); J. M. Anto (Barcelona); J. Alves (Oporto); G. Boman (Uppsala); N. Nielsen (Copenhagen); P. Paoletti (Pisa).

Participating centers: Austria: W. Popp (Vienna); Australia: M.

Abramson, J. Kutin (Melbourne); Belgium: P. Vermeire, F. van Bastelaer (Antwerp South, Antwerp Central); France: J. Bousquet, J. Knani (Montpellier), F. Neukirch, R. Liard (Paris), I. Pin, C. Pison (Grenoble), A. Taytard (Bordeaux); Germany: H. Magnussen, D. Nowak (Hamburg); H. E. Wichmann, J. Heinrich (GSF Institute of Epidemiology, Erfurt); Greece: N. Papageorgiou, P. Avarlis, M. Gaga, C. Marossis (Athens); Iceland: T. Gislason, D. Gislason (Reykjavik); Ireland: the late J. Prichard, S. Allwright, D. MacLeod (Dublin); Italy: M. Bugiani, C. Bucca, C. Romano (Turin) R. de Marco Lo Cascio, C. Campello (Verona), A. Marinoni, I. Cerveri, L. Casali (Pavia); The Netherlands: B. Rijcken, A. Kremer (Groningen, Bergen-op-Zoom, Geleen); New Zealand: J. Crane, S. Lewis (Wellington, Christchurch, Hawkes Bay); Norway: A. Gulsvik, E.

Omenaas (Bergen); Portugal: J. A. Marques, J. Alves (Oporto); Spain: J. M. Antó, J. Sunyer, F. Burgos, J. Castellsagué, J. Roca, J. B. Soriano, A. Tobías (Barcelona), N. Muniozguen, J. Ramos González, A. Capelastegui (Galdakao), J. Castillo, J. Rodriguez Portal (Seville), J. Martinez-Moratalla, E. Almar (Albacete), J. Maldonado Pérez, A. Pereira, J. Sánchez (Huelva), J. Quiros, I. Huerta, F. Pavo (Oviedo); Sweden: G. Boman, C. Janson, E. Björnsson (Uppsala), L. Rosenhall, E. Norrman, B. Lundbäck (Umeå), N. Lindholm, P. Plaschke (Göteborg); Switzerland: U. Ackermann-Liebrich, N. Künzli, A. Perruchoud (Basel); United Kingdom: M. Burr, J. Layzell (Caerphilly), R. Hall (Ipswich), B. Harrison (Norwich), J. Stark (Cambridge); USA: S. Buist, W. Vollmer, M. Osborne (Portland).

Availability of Journal Back Issues

As a service to our subscribers, copies of back issues of *The Journal of Allergy and Clinical Immunology* for the preceding 5 years are maintained and are available for purchase until inventory is depleted from Mosby at a cost of \$17.00 per issue. The following quantity discounts are available: 25% off on quantities of 12 to 23, and one third off quantities of 24 or more. Please write to Mosby, Inc., Subscription Services, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318, or call (800) 453-4351 or (314) 453-4351 for information on availability of particular issues. If unavailable from the publisher, photocopies of complete issues may be purchased from Bell & Howell Information and Learning, 300 N. Zeeb Rd., Ann Arbor, MI 48106, (313) 761-4700 or (800) 521-0600.