

The distribution of total and specific serum IgE in the European Community Respiratory Health Survey

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Background: Variations in the prevalence of atopy could provide important clues to the etiology of atopy and asthma. Although estimates of prevalence are available from different studies, a lack of standardization makes comparisons difficult. **Objective:** This study was conducted to estimate the variation of geometric mean levels of serum IgE and the prevalence of specific IgE to common allergens between populations as part of the European Community Respiratory Health Survey (ECRHS), a multicenter survey of asthma and risk factors for asthma. **Methods:** Random samples of subjects living in 37 centers in 16 countries who had answered a questionnaire about their respiratory symptoms were invited for further assessment including total serum IgE and the presence of specific IgE against house dust mite (*Dermatophagoides pteronyssinus*), timothy grass, cat, *Cladosporium herbarum*, and a local allergen. Sera were tested from 13,883 persons. **Results:** The estimated prevalence of atopy, defined as the presence of at least one positive specific IgE, ranged from 16% in

Albacete (Spain) to 45% in Christchurch (New Zealand). The geometric mean total serum IgE varied from 13 kU/L in Reykjavik (Iceland) to 62 kU/L in Bordeaux (France). There was no relation between the geometric mean total serum IgE in a center and the prevalence of atopy.

Conclusions: There are substantial variations in the prevalence of atopy and the level of serum IgE. These variations are independent of each other and likely to be largely environmental in origin. (J Allergy Clin Immunol 1997;99:314-22.)

Key words: Serum IgE, prevalence, *Dermatophagoides pteronyssinus*, grass, cat, *Cladosporium herbarum*, birch, ragweed, *Parietaria judaica*

The European Community Respiratory Health Survey (ECRHS)¹ is a multicenter collaborative study that was set up to measure: (1) the variation in the prevalence of asthma, asthma-like symptoms, and bronchial lability; (2) exposure to known and suspected risk factors for asthma, their association with asthma, and the extent to which they explain variations in asthma prevalence; and (3) variations in treatment for asthma. The study was set up in response to the increasing mortality rates associated with asthma in many parts of Europe and elsewhere in the mid 1980s^{2,3} and in response to emerging evidence for an increase in the prevalence of asthma and of allergic diseases more generally.⁴⁻⁶

Atopy, defined as the propensity to raise specific IgE to common allergens,⁷ has long been recognized as a characteristic of many patients with asthma, and the relation between atopy and airway responsiveness has been confirmed by using both skin test results⁸ and total IgE⁹ as markers of atopy. Although early studies suggested that total IgE, particularly in tropical countries where parasites are the major cause of a high IgE level, might protect against asthma,¹⁰ interest has more recently been focused on the possibility that total serum IgE may be an independent risk factor for asthma, and possibly an even better predictor than positive skin test results.¹¹

Evidence from Switzerland that the prevalence of specific IgE against local allergens has been increasing over the last one and a half to two decades¹² suggests that atopy itself might be increasing in prevalence and makes it plausible that the increase that has been noted in the atopic diseases has been a consequence of this. The assessment of atopy and total IgE levels is therefore

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Abbreviation used

ECRHS: The European Community Respiratory Health Survey

likely to be an important component of explaining the current distribution of asthma.

Indirect evidence, based mostly on the results of skin tests, suggests that there are differences in the prevalence of atopy from one area to another.¹³ However, skin tests are difficult to standardize, and there are concerns over the choice of allergens with which to test and compare populations living in different environments. This article presents descriptive data on the distribution of total serum IgE and specific IgE against selected allergens in the centers participating in the ECRHS.

METHODS

The methods used in the ECRHS are described in more detail elsewhere.^{1,14} Briefly, participating centers selected areas for study, which were defined by preexisting administrative boundaries, had populations of at least 150,000 persons, and, when possible, had up-to-date sampling frames of 20- to 44-year-olds. In the first phase of the study, randomly selected samples of at least 1500 persons of each sex were sent questionnaires enquiring about respiratory symptoms, attacks of asthma, use of asthma medication, and hay fever or nasal allergies in the previous 12 months together with questions about the age and sex of the respondent. In the second part of the study, a random sample of subjects responding to this postal questionnaire were invited to come for a more detailed interview, blood tests, skin tests, assessment of lung function by spirometry, and airway challenge with methacholine.

For measurement of serum IgE, 10 ml of venous blood was taken from each subject and left to coagulate either for 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; the serum was removed with a pipette and transferred to 2 ml polypropylene microtubes with screw tops (Sarstedt, Nümbrecht, Germany). Aliquots were stored at -20° C, packed in Styrofoam boxes (Sarstedt), and sent on dry ice to a central laboratory at Pharmacia Diagnostics AB, (Uppsala, Sweden) for analysis. The only exception to this practice was in Melbourne where specimens were handled locally by using the CAP system and reagents, which were supplied by Pharmacia Diagnostics AB.

Specific and total IgE were measured by using the Pharmacia CAP System. The working range for the assay of total IgE was 2 kU/L to 2000 kU/L. Subjects with no detectable IgE were assigned a value of 1 kU/L, and those with a value greater than 2000 kU/L were assigned 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 of the specific allergen, the limit of detection of the assay. In all centers specific IgE was measured against *Dermatophagoides pteronyssinus*, timothy grass, cat, *Cladosporium herbarum*, and a local allergen. The local allergen was birch for northern Europe; *Parietaria judaica* for southern Europe; and ragweed for North America, New Zealand, and Australia.

Prevalence of specific IgE and mean log total serum IgE for each age-sex group (men and women aged 20 to 24, 25 to 34, and 35 to 44 years) were estimated, first with no adjustment for

nonresponse, and second taking into account nonresponders, whose prevalences and mean log serum total IgE were assumed to be the same as those of responders of the same age-sex group in the same center with the same symptoms reported on the screening questionnaire. Direct age-sex-standardized prevalence and mean serum total IgE were then calculated from the adjusted and unadjusted prevalences by a weighted average of the six groups, giving half the weight to the smaller 20- to 24-year-old groups. Thus each estimate allowed for differential response by age and sex, but the "adjusted" estimates also allowed for response bias in relation to symptoms.

Age-sex-standardized results were calculated with 95% confidence limits. The confidence limits for the prevalences of positive specific IgE were based on the usual formula for the variance of a proportion,¹⁵ summed and weighted over the six age-sex groups. The confidence interval for the mean total serum IgE was calculated on the log scale, pooling the standard deviation over the six age-sex groups and antilogging the limits to give the 95% confidence interval for the geometric mean serum total IgE. Analysis of variance for log IgE and log linear models for the presence of specific IgE were used to estimate the significance of differences between countries and between centers within countries and to assess whether the effects of age and sex were different between centers.

RESULTS

Data are included from 37 centers in 16 countries, 11 fewer centers than in the previous report on symptoms.¹⁶ The majority of the centers not included did not send serum samples for testing, though three centers (Vienna [Austria], Coimbra [Portugal], and Oporto [Portugal]) have been omitted because of difficulties in matching the symptom data to the serum results. Table I shows the distribution of the participation rates. Participation in the clinical examination as a whole (stage II) varied from 9% in Athens (Greece) to 90% in Umeå (Sweden), and within stage II agreement to provide a serum sample ranged from 43% in Portland (United States) to 98% in Erfurt (Germany) and Verona (Italy). The symptoms reported in the initial questionnaire were significantly associated with the probability that a blood sample was provided in 15 of the 37 centers, and adjustment for nonparticipation by different symptom categories led to statistically significant changes in the estimated prevalence of specific IgE to the allergens tested in a majority of centers, with the exception of the responses to *Cladosporium* species. However, though many of these changes were statistically significant, the extent of the adjustments was small even when the participation rates were less than 25%.

Fig. 1 shows the adjusted age-sex specific prevalence plotted against the unadjusted age-sex specific prevalence of IgE to *D. pteronyssinus*, indicating little effect of adjustment. Findings for IgE to cat were similar (not shown). Fig. 2 shows the effect of adjusting estimates of geometric mean total IgE for nonparticipation. The changes in the estimates are slightly greater, but the adjusted estimates are still generally within 20% of the initial estimates. However, one center did show important differences in both the geometric mean total IgE and the prevalence of sensitivity to grass after adjust-

TABLE I. Participation rates by center

Country/Center		No. selected from random sample	No. responding		Percent responding	
			Stage II	IgE	Stage II	IgE*
Iceland	Reykjavik	672	564	518	84	92
Norway	Bergen	959	835	749	87	90
Sweden	Goteborg	772	682	573	88	84
	Umea	611	552	425	90	77
	Uppsala	709	622	525	88	84
Netherlands	Bergen op Zoom	638	452	418	71	92
	Geleen	671	415	388	62	93
	Groningen	599	380	355	63	93
Belgium	Antwerp city	867	564	267	65	47
	Antwerp south	800	558	325	70	58
Germany	Erfurt	1076	731	718	68	98
	Hamburg	3312	1252	775	38	62
Switzerland	Basel	1192	853	567	72	66
France	Bordeaux	2936	544	512	19	94
	Grenoble	1165	473	429	41	91
	Montpellier	3736	456	364	12	80
U.K.	Paris	3113	652	555	21	85
	Caerphilly	532	381	321	72	84
	Cambridge	527	277	192	53	69
	Ipswich	682	448	365	66	81
	Norwich	655	473	365	72	77
Ireland	Dublin	599	454	232	76	51
Greece	Athens	3325	309	145	9	47
Italy	Pavia	816	310	250	38	81
	Turin	518	244	177	47	73
	Verona	504	340	332	68	98
Spain	Albacete	658	435	390	66	90
	Barcelona	534	393	175	74	45
	Galdakao	576	486	365	84	75
	Huelva	478	271	215	57	79
	Oviedo	522	357	244	68	68
New Zealand	Seville	400	212	162	53	76
	Christchurch	712	458	268	64	59
	Hawkes Bay	549	316	142	58	45
	Wellington	741	485	301	65	62
Australia	Melbourne	1644	669	520	41	78
U.S.A.	Portland	1604	723	314	45	43

*As a percent of those responding to stage II.

No samples were received from Tartu (Estonia), Aarhus (Denmark), Nancy (France), Dundee (Great Britain), Kilkenny-Wexford (Ireland), Algiers (Algeria), Bombay (India), or Auckland (New Zealand). The data from Vienna (Austria), Oporto (Portugal), and Coimbra (Portugal) could not be linked reliably to the stage I data.

ment for nonparticipation. This was due to differences in the sampling strategy in Basel (Switzerland). The prevalences quoted in the rest of this article are unadjusted for the symptoms of the nonresponders because the effects of adjustment are small compared with the other sources of variation seen and because the adjusted prevalences could not be given for some centers in which the models used to derive them did not converge.

Table II gives the distributions of the geometric mean total serum IgE and the prevalences of specific IgE to different allergens in the different centers. Basel (Switzerland) has been omitted from the table and statistics, though not from the figures, because of the large apparent effect of adjusting for nonparticipation. Melbourne

(Australia) has also been excluded from Table II and the statistics, though not from the figures or appendix, because the samples were tested separately. The variation in the prevalence of a response to at least one specific IgE ranged between 16% in Albacete (Spain) and 45% in Christchurch (New Zealand). Melbourne (Australia) had an even higher prevalence of 46%, and there is no reason to assume that this was unduly influenced by the method of analysis. It is notable that the addition of a local allergen-birch in northern Europe, *P. judaica* in southern Europe, and ragweed in the United States and Australasia did not greatly affect the prevalence of atopy, defined as a positive specific IgE. The four allergens tested in all centers accounted for

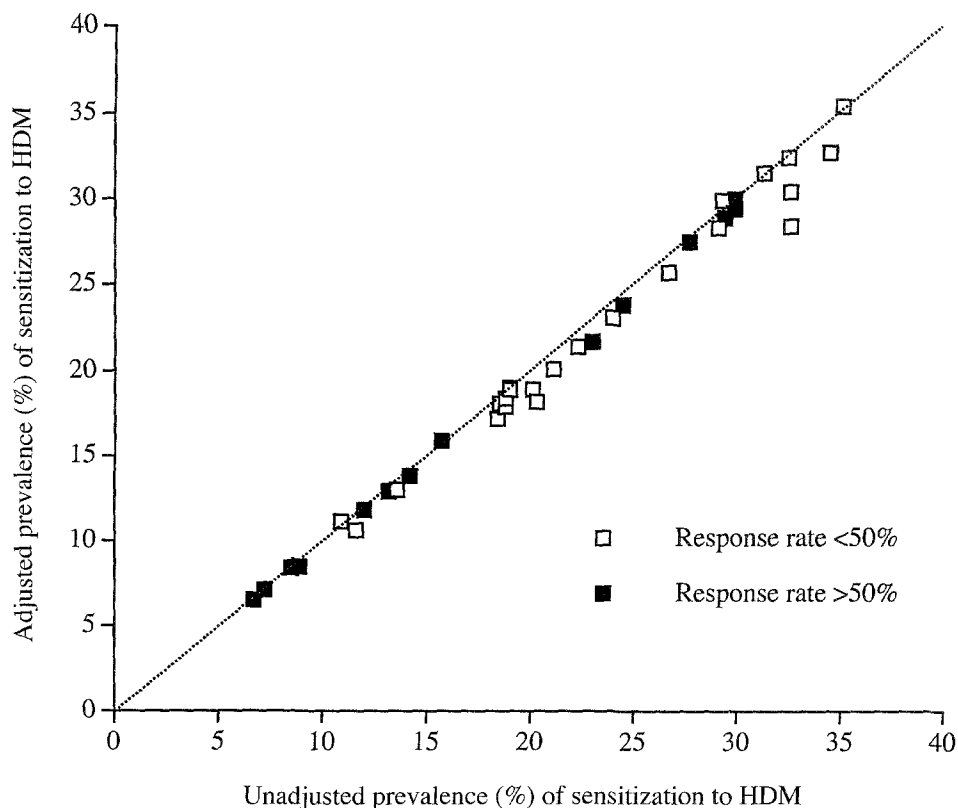


FIG. 1. Adjusted and unadjusted prevalence of sensitization to house dust mite in centers with participation rates higher (filled squares) and lower (open squares) than 50%. The participation rate is the proportion of all those who completed stage 1, were selected for stage 2, and provided blood samples for IgE testing. Dotted line is line of identity. HDM, House dust mite.

96% of the variance in the prevalence of atopy, defined as a response to any of these four allergens or the local allergen.

The geometric mean total serum IgE varied from 13.2 kU/L in Reykjavik (Iceland) to 62.5 kU/L in Bordeaux (France). There were significant variations between countries for total IgE ($p < 0.001$) and for the prevalence of any specific IgE ($p < 0.001$). The relation between age and sex and the geometric mean total serum IgE were consistent across centers. Compared with total serum IgE in 20- to 24-year-olds, total serum IgE was 7% lower in 25- to 34-year-olds and 18% lower in 35- to 44-year-olds. At all ages, women had a 26% lower total serum IgE than men. The relation between gender and the prevalence of a specific sensitivity differed between centers ($p < 0.001$), making it difficult to summarize this association.

Fig. 3 shows the distribution of geometric mean total serum IgE by country and by center, and Fig. 4 shows the same distribution for the prevalence of atopy (defined as a positive response to any of the five allergens tested in each center).

Fig. 5 shows the lack of association between the prevalence of atopy, defined as a positive response to any of the four specific allergens tested in all centers,

and the geometric mean total serum IgE. The association between total IgE and the prevalence of specific sensitivity to different allergens is inconsistent, being negative with grass, *Cladosporium*, birch, and ragweed; positive with *D. pteronyssinus* and *P. judaica*; and having no relation to cat sensitivity. However, the prevalence of specific sensitivity to one allergen is, in general, positively associated with specific sensitivity to other allergens. The only clear exceptions to this are the negative associations between mite sensitivity and two of the "local" allergens, birch and ragweed.

DISCUSSION

The participation rate in response to the request to give blood in these surveys was highly variable. Nevertheless, after adjusting for the age and sex of the populations surveyed, there was little evidence that the poor participation rates in some centers had a strong influence on the estimated prevalence of atopy or the geometric mean serum IgE. This conclusion is based on the very modest effect of adjusting the results on the assumption that nonresponders in the second sample had the same IgE levels as those who had given samples, of the same age and sex, living in the same centers and reporting the same symptoms.

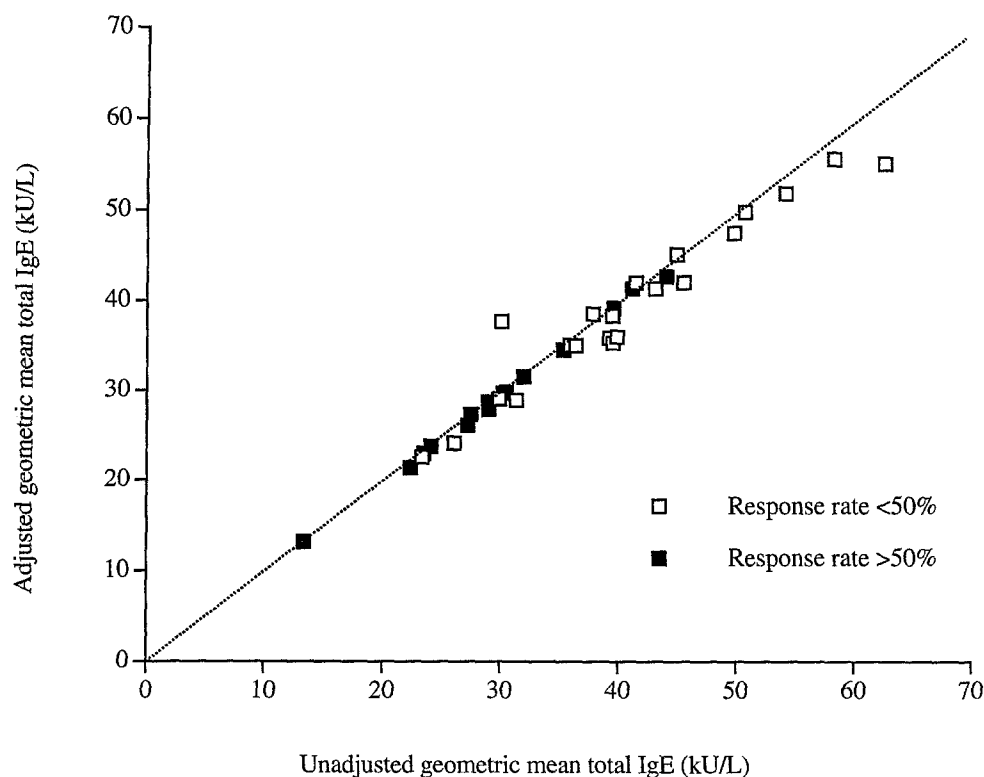


FIG. 2. Adjusted and unadjusted geometric mean total serum IgE in centers with participation rates higher (filled squares) and lower (open squares) than 50%. The participation rate is the proportion of all those who completed stage 1, were selected for stage 2, and provided blood samples for IgE testing. Dotted line is line of identity.

TABLE II. Distribution of geometric mean total serum IgE and prevalences of IgE to specific allergens for the 35 centers included in the study

Measure	No. of centers	Min	First quartile	Median	Third quartile	Max
Geometric mean total serum IgE (kU/L)	35	13.2	29.1	35.9	42.9	62.2
Prevalence of specific IgE to						
Common allergens						
Mite (%)	35	6.7	13.6	20.3	29.3	35.1
Cat (%)	35	2.7	6.0	8.5	11.6	14.8
Grass (%)	35	8.1	15.0	18.0	21.8	34.6
Cladosporium spp. (%)	35	0.3	1.5	2.4	3.9	13.6
Local allergens						
Birch (%)	18	1.9	5.8	9.5	14.6	23.0
Parietaria spp. (%)	13	2.6	4.1	7.4	10.7	13.3
Ragweed (%)	4	6.9	7.6	12.5	15.9	16.1
Any common allergen (%)	35	16.2	26.7	33.1	39.9	44.5
Any allergen (%)	35	16.4	29.5	35.6	40.8	45.2

Basel and Melbourne are omitted.

Min, Minimum; Max, maximum.

There are wide variations in the geometric mean levels of total serum IgE. These vary over a fourfold range between the centers. Within countries the variation was less marked, though there was a highly

significant difference in the geometric mean level in Hamburg in the former West Germany (26 kU/L) compared with that in Erfurt in the former East Germany (41 kU/L).

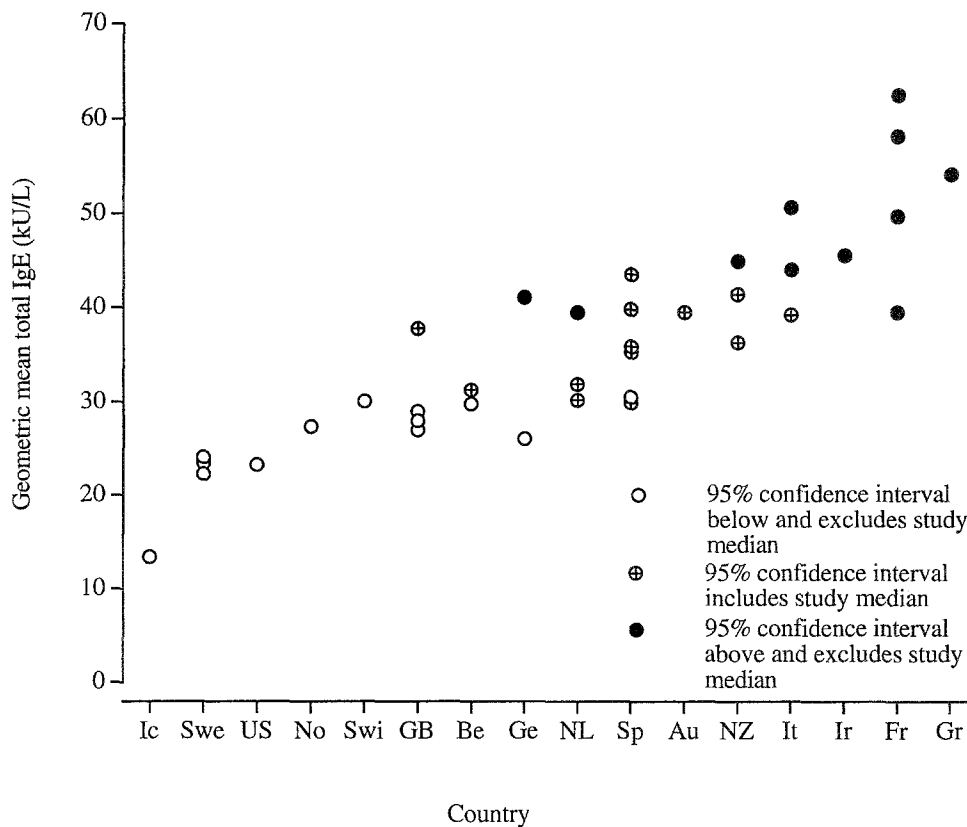


FIG. 3. Geometric mean total serum IgE (in kilounits per liter) plotted by country and center. Each symbol represents the value for one center; countries are ordered along the x axis. Values significantly above or below the median for 35 centers are indicated. *Ic*, Iceland; *Swe*, Sweden; *US*, United States; *No*, Norway; *Swi*, Switzerland; *GB*, Great Britain; *Be*, Belgium; *Ge*, Germany; *NL*, Netherlands; *Sp*, Spain; *Au*, Australia; *NZ*, New Zealand; *It*, Italy; *Ir*, Ireland; *Fr*, France; *Gr*, Greece.

Much of the discussion of the determinants of IgE levels has concentrated on the genetics of total IgE. Many authors have concluded that there is a single gene polymorphism that accounts for much of the variation in total serum IgE, a belief recently supported by reports of linkage between log total IgE and markers on chromosome 5 close to the gene for IL-4 and other important regulatory cytokines.¹⁷ This association was particularly strong in those who did not have specific IgE to common aeroallergens. In addition to this association, there is a clearly recognized ability of some parasitic worms to stimulate both specific and nonspecific IgE production.¹⁸ Although smoking has been reported to affect total serum IgE,¹⁹ it appears to have little effect in this age group when age and gender have been taken into account.²⁰⁻²²

The variations noted here seem unlikely to be due in any great measure to genetic heterogeneity. The genetic distance between the centers is not wide enough to provide a convincing account of the differences, and the wide variation within Germany is much more likely to be explained by differences in environment and lifestyle. The reasons for the variations noted here are more difficult to guess. Although variations in the prevalence

of parasitic worms are a possible explanation, we have no information on worm infestations from the survey and can find no comparable prevalence data from the different centers from other sources. It is of interest to note that the within-center standard deviation in the total IgE increases proportionately as the geometric mean total serum IgE increases. This might argue against the view that the mean serum IgE is being increased by a subgroup of individuals with very high levels of serum IgE. Therefore the evidence, such as it is, does not give strong support to the hypothesis that this variation is due to variations in parasitic infestations between the different centers.

In the preparation of this survey, considerable time was spent discussing the appropriate allergens to use when assaying specific IgE. In the end we decided on a common panel of allergens with one regional allergen to be added for each center. The three regional allergens were birch in northern Europe, *P. judaica* in southern Europe, and ragweed in North America and Australasia. Despite the undoubted importance of the regional allergens, their addition to the original panel of allergens made little difference to the proportion of the popula-

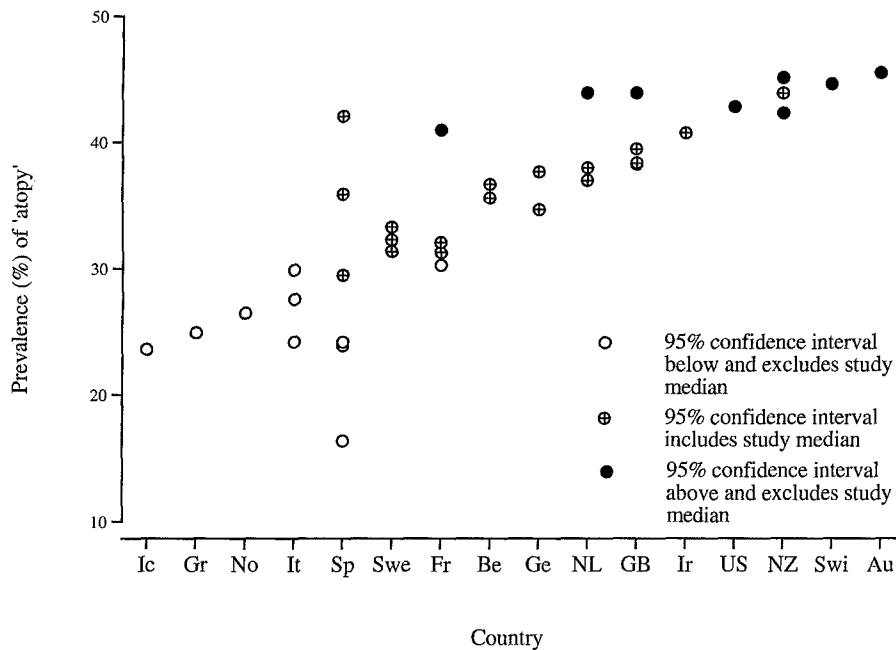


FIG. 4. Prevalence of atopy, defined as specific IgE to any of the five allergens tested in each center, plotted by country and center. Each symbol represents the value for one center; countries are ordered along the x axis. Values significantly above or below the median for 35 centers are indicated. *Ic*, Iceland; *Gr*, Greece; *No*, Norway; *It*, Italy; *Sp*, Spain; *Swe*, Sweden; *Fr*, France; *Be*, Belgium; *Ge*, Germany; *NL*, Netherlands; *GB*, Great Britain; *Ir*, Ireland; *US*, United States; *NZ*, New Zealand; *Swi*, Switzerland; *Au*, Australia.

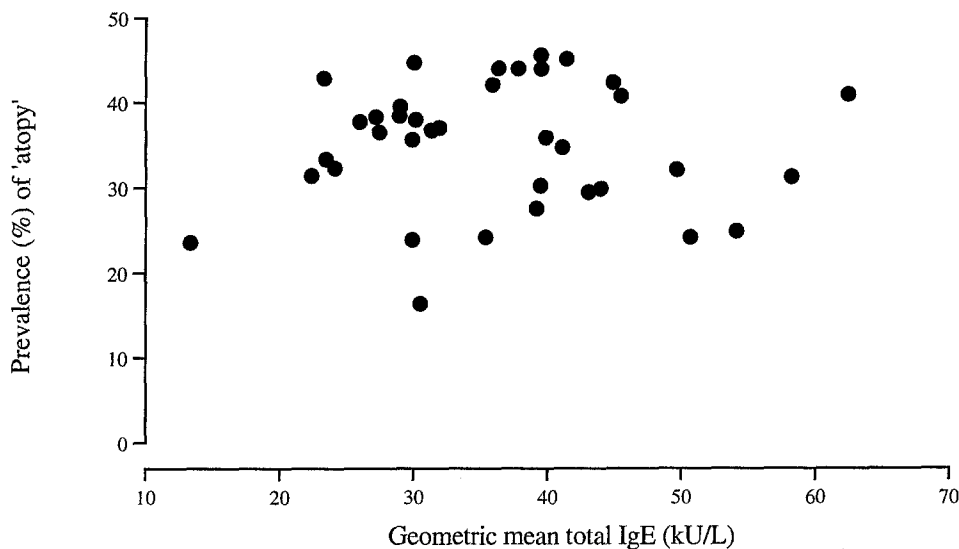


FIG. 5. Prevalence of atopy, defined as specific IgE to any of the four common allergens tested in each center plotted against geometric mean total serum IgE.

tion designated as atopic in any center. Although it is possible that some highly influential allergens were missed, this gives us some encouragement that the prevalence of "atopy" reported here is not greatly influenced by the selection of allergens. It also has important implications for planning efficient surveys of atopy.

This study clearly shows that the prevalence of atopy

varies considerably from one area to another, from 16% in Albacete (Spain) to 45% in Christchurch (New Zealand). The distribution is independent of the distribution of geometric mean total serum IgE, an observation that is not replicated in single-center studies in which, at least outside the tropics, total IgE often provides a good prediction of whether an individual will be atopic.²³

These findings give weight to the argument that total and specific IgE are influenced differently by the environment. Genetic studies of atopy, as differentiated from total serum IgE, are less common; and some are difficult to interpret because they conflate total IgE and specific IgE in their definition.²⁴ There is, however, some evidence that responses to low-molecular-weight, highly purified allergens may be influenced by the HLA phenotype of the subject.²⁵ Again, however, it is unlikely that any major part of the variation noted here is due to genetic variation between centers. The wide variations in prevalence seen in Spain, for instance, would seem unlikely if genes were the major source of variation.

Although the analysis so far is only descriptive in nature, it is of interest that the centers with the highest prevalence of atopy represent predominantly English-speaking populations. This is consistent with the finding of an earlier study describing the distribution of symptoms.¹⁶ Although this ecological association between atopy and symptoms of asthma is not surprising, given the clearly established association between the two, it is nevertheless of interest because it partially validates the earlier finding. The distribution of symptoms might well be an artefact related to language or the cultural response to illness. This explanation is, however, unlikely to account for variations in the prevalence of atopy as assessed in this study. The reasons for these wide variations, however, remain unknown.

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APPENDIX

List of principal participants

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