

Original article

Role and interpretation of total serum IgE measurements in the diagnosis of allergic airway disease in adults

Background: While total IgE measurements are often used in clinical practice, it is unclear how they should be interpreted for the diagnosis of allergic disorders. We studied whether total IgE may be used to rule out or predict sensitization and whether there are age or gender differences.

Methods: ROC curves were assessed in subjects with asthma or allergy symptoms from a general population sample. We studied predictive values and likelihood ratios. At least one positive skin test (Phazet[®]) or specific IgE measurement (CAP[®]) served as reference.

Results: High negative predictive values, suitable to rule out sensitization, were not found. In younger subjects, high total IgE levels strongly increase the probability of sensitization. The relationship between monosensitization and total IgE was less strong, but meaningful positive likelihood ratios were found at higher levels of total IgE. The discriminating ability of total IgE was better in the age group 20–44 than 45–70 years and comparable in males and females.

Conclusion: Total IgE is not useful to rule out sensitization to common inhalant allergens. High total IgE may indicate a high probability of sensitization and may be useful to decide whether further investigation is warranted in patients with negative specific allergy tests to a panel of common inhalant allergens.

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Sensitization to common inhalant allergens is usually assessed by measuring specific IgE in serum or by performing skin tests. A disadvantage of both tests is that they are directed to specific allergens. As individual patients differ in their pattern of sensitization, an adequate diagnostic work up may involve 10 or more allergens, which is costly and time consuming. Thus, a single test, which, when negative, would be associated with a very low probability of sensitization, would be useful as a first step in the diagnostic work up of a potentially allergic patient. Another application for such a test could be the prediction of a high probability of sensitization in patients where clinical suspicion of an allergic disease persists despite negative results using a screening panel of skin tests or specific IgE measurements. A single measurement that might be usable for these purposes is serum total IgE. A dipstick test for allergy screening enables any practitioner to determine total IgE levels within less than 1 h (1). Measurement of total IgE is easier and less costly than the Phadiatop[®] test, which has been reported to be an accurate screening test for sensitization to common inhalant allergens (2–5).

However, it is unclear how total IgE measurements should be interpreted and to what extent total IgE

measurements may contribute to decision-making in clinical practice as indicated above.

Some authors described considerable overlap between total IgE levels in atopic and nonatopic individuals (6–8), such that no single level of IgE could distinguish atopic from nonatopic individuals. However, this does not exclude the possibility of defining a low cut-off value of total IgE below which sensitization to common inhalant allergens is effectively ruled out, or a high value of total IgE above which sensitization is likely despite negative tests to common inhalant allergens.

It is also not known whether reported lower total IgE levels in females and the decrease of total IgE with age (9, 10) should lead to different cut-off values according to gender and age.

In this study, we examined whether cut-off values of serum total IgE can be used to rule out or predict sensitization to common inhalant allergens in subjects with symptoms that might be allergic. We also examined whether gender and age should be considered when using cut-off values of total IgE. To show the ability of various cut-off values of total IgE to discriminate between subjects with and without sensitization to common inhalant allergens, we created receiver operator characteristic

(ROC) curves. These ROC curves plot true positive rates against false positive rates for different cut-off values of total IgE. To estimate the clinical impact of a positive and negative test result at different cut-off values of total IgE, we calculated positive and negative predictive values. To demonstrate the effect of changes in total IgE on pretest probability of sensitization, likelihood ratios were calculated.

At least one positive skin test or specific IgE test to common inhalant allergens served as a 'gold standard' for sensitization. The analyses were performed stratified by gender and two age groups in subjects from the adult general population who reported airway symptoms that might be allergic.

Methods

Subjects

Subjects were selected from a random sample of 4522 from the general population, aged 20–70 years, in three areas in the Netherlands (the city of Groningen and the towns of Roosendaal and Geleen, both with adjacent rural communities). The sample was stratified by gender and 10-year age groups. All the subjects were asked to participate in the study that consisted of the administration of a respiratory questionnaire by a trained interviewer, lung function testing, measurement of bronchial reactivity by methacholine provocation, skin tests with nine inhalant allergens and venous blood collection for IgE determinations (total IgE and specific IgE to five inhalant allergens) and haematology. Complete data consisting of total and specific IgE results, skin test results and record of asthma and allergy symptoms were obtained from 1215 males (response rate = 53%) and 1112 females (response rate = 50%) of the 4522 subjects.

Methods of measurement

All measurements were performed according to the protocols of the European Community Respiratory Health Survey (11). To determine serum IgE levels, blood samples were centrifuged and the sera were stored at -20°C . Total and specific IgE were measured using the Pharmacia CAP[®] System. The CAP[®] was performed in the laboratories of Pharmacia diagnostics AB, Uppsala. The assay is calibrated against the WHO Standard for IgE, with a range of 0.35–100 kU/l for specific IgE and 2–2000 kU/l for total IgE. A value of 1 kU/l was given to total IgE levels below 2 kU/l. Specific IgE of five common inhalant allergens was measured: *Dermatophagoides pteronyssinus* (house dust mite), cat, Timothy grass pollen, birch pollen and *Cladosporium herbarum*. Specific IgE tests are considered positive at levels of 0.35 kU/l or higher (class 1).

Skin prick tests were performed using Phazet[®] stainless steel lancets precoated with lyophilized allergen (Pharmacia Diagnostics AB, Uppsala, Sweden). The following allergens were tested: *D. pteronyssinus* (house dust mite), cat, Timothy grass pollen, birch pollen, *C. herbarum*, *Alternaria alternata*, olive pollen, common ragweed pollen, *Parietaria judaica*. The test included positive (histamine) and negative (uncoated Phazet[®] lancet) controls. Mean diameters were calculated as the mean of the widest diameter and the perpendicular diameter measured at its midpoint. A mean wheal diameter of ≥ 3 mm was considered a positive response. Skin test results where the mean diameter of the negative control was greater

than 2 mm or the positive control was negative were excluded from the analyses.

Subjects who had at least one of the five specific IgE tests or one of the nine skin tests positive were defined as allergy test positive, while subjects who had all specific IgE tests and skin tests negative were defined as allergy test negative.

Data on symptoms were obtained by questionnaire. The questions were asked in a standardized way and could be answered by 'yes' or 'no'. Questions on asthma were: (a) 'Have you ever had asthma?'; if 'yes', 'Have you had an attack of asthma in the last 12 months?' 'Are you currently taking any medicines, including inhalers, aerosols or tablets, for asthma?' Questions on allergy symptoms were: (a) 'Do you have any nasal allergies, including hay fever?' (b) 'When you are near animals, such as cats, dogs or horses, near feathers, including pillows, quilts or duvets, or in a dusty part of the house, do you ever start to cough, start to wheeze, get a feeling of tightness in your chest, start to feel short of breath, get a runny or stuffy nose or start to sneeze or get itchy or watering eyes?' (c) 'When you are near trees, grass or flowers, or when there is a lot of pollen about, do you ever start to cough, start to wheeze, get a feeling of tightness in your chest, start to feel short of breath, get a runny or stuffy nose or start to sneeze or get itchy or watering eyes?'

For defining the upper 5% of total IgE values in 'normal' subjects, normal subjects were defined as those who were allergy tests negative and reported none of the symptoms above and 'no' to the question: 'Have you ever had eczema or any kind of skin allergy?'

Study design

To show whether total IgE can be used to discriminate between allergy test positive and allergy test negative subjects, ROC curve analyses were performed. ROC curves show the relationship between the true positive rate (i.e. sensitivity) and the false positive rate (i.e. $1 - \text{specificity}$) for different cut-off values of total IgE. The ability of total IgE to discriminate between allergy test positive and negative subjects increases as the ROC curve approaches the upper left-hand corner (12) (Fig. 1). The best test performance (highest true positive rate, lowest false positive rate) was found with the cut-off value associated with the point of the curve closest to the upper left-hand corner of the graph. In order to estimate the performance of total IgE measurements in a clinical context, we calculated positive and negative predictive values at different cut-off values of total IgE. The positive predictive value of total IgE at a certain cut-off value is defined as the proportion of allergy test positive subjects among subjects with a positive total IgE (i.e. a level greater than or equal to that cut-off value). The negative predictive value of total IgE at a certain cut-off value is defined as the proportion of allergy test negative subjects among subjects with a negative total IgE (i.e. a level lower than that cut-off value).

In order to examine how much total IgE changes the pretest probability of sensitization, likelihood ratios were calculated, as these have the property of being stable when pretest probability changes (12). The positive likelihood ratio is defined as true positive rate (i.e. sensitivity)/false positive rate (i.e. $1 - \text{specificity}$). The negative likelihood ratio is defined as false negative rate (i.e. $1 - \text{sensitivity}$)/true negative rate (i.e. specificity) (12).

To study whether total IgE might be used to predict the probability of sensitization in case of negative tests to a panel of allergens, likelihood ratios were calculated in a subgroup of subjects with negative allergy tests to eight of the nine allergens.

To study the influence of gender and age, all the analyses were performed after stratification by gender and two age groups (20–44 and 45–70 years).

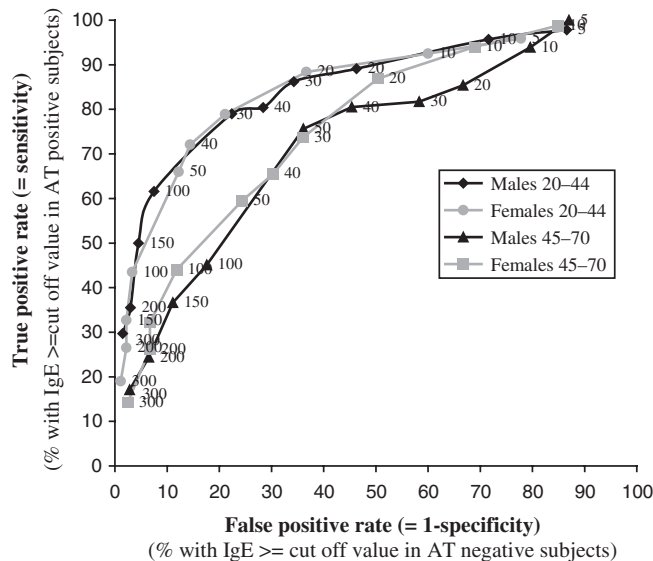


Figure 1. ROC curves of total IgE in subjects with a history of asthma, nasal allergy or symptoms when exposed to dust, animals or pollen by age group and gender (numbers along the curve indicate cut-off values of total IgE). Cut-off values of total IgE that best discriminate between allergy test positive and negative subjects are those associated with the ROC curve as it approaches the upper left-hand corner.

Statistical analysis

As total IgE values follow a log-normal distribution, a logarithmic transformation (natural log) of total IgE was applied. Means were calculated after this transformation and expressed as antilogarithms or geometric means. Comparison of mean IgE levels was done by use of the unpaired Student's *t*-test. Chi-square tests were used to test differences between proportions.

Results

Complete data of total IgE, specific IgE, skin tests and symptoms were obtained from 1215 males and 1112 females (Table 1). Of these individuals, 395 (33%) males and 440 (40%) females reported symptoms of asthma or allergy. No gender differences in the proportion of allergy test positive subjects were found, but females had lower mean total IgE levels and reported various allergy symptoms more frequently than males in both age groups. Subjects in the age group 20–44 years were more frequently allergy test positive and reported various allergy symptoms more frequently than subjects in the age group 45–70 years. However, males of the age group 45–70 years reported more asthma attacks or medication than males of the age group 20–44 years. Females in the age group 20–44 years had a higher mean total IgE than females in the age group 45–70 years. A similar trend was seen in the corresponding male age groups, but this was not statistically significant.

Subgroups of subjects with symptoms had significantly higher prevalences of at least one positive allergy test than the subgroup without any symptoms, except for males with asthma attacks where this difference did not reach statistical significance (Table 2). Higher prevalences of positive allergy tests in the age group 20–44 years than in the age group 45–70 years were found in both subjects with allergy symptoms and in subjects without any symptoms (Table 2). A similar trend was seen in patients with asthma symptoms where numbers were smaller. No significant gender differences in the proportion of subjects with at least one positive allergy test in subgroups of subjects with symptoms were found.

ROC curves in Fig. 1 show that the ability of total IgE to discriminate between allergy test positive and allergy

Table 1. Characteristics of the subjects by age group and gender

	Age group 20–44 years		Age group 45–70 years	
	Males, <i>n</i> = 576	Females, <i>n</i> = 546	Males, <i>n</i> = 639	Females, <i>n</i> = 566
Mean age (years)	33	33	57	57
≥1 pos. specific IgE (%)	40*	40*	25	24
≥1 pos. skin test (%)	34*	31*	19	17
≥1 pos. spec. IgE or skin test (%)	44*	43*	29	28
Geometrical mean total IgE (ln SD‡) (kU/l)	39 (1.57)†	28 (1.58)*	34 (1.55)†	22 (1.45)
Asthma attack during last 12 months (%)	0.3	2.0†	1.6*	2.5
Asthma attack or medication (%)	1.6	3.1	3.6*	3.4
Self-reported nasal allergy (%)	17*	20	12	17†
Symptoms when exposed to dust/animals (%)	26*	35*,†	21	27†
Symptoms when exposed to pollen (%)	18	22	14	19†
Dust/animal/pollen symptoms lower airways (%)	19*	23†	14	19†
Dust/animal/pollen symptoms upper airways (%)	33*	40*,†	25	31†
Eczema or skin allergy ever (%)	30	42*,†	26	35†

* Significantly higher than other corresponding age group ($P < 0.05$).

† Significantly higher than other corresponding gender ($P < 0.05$).

‡ ln SD = natural logarithm of the standard deviation.

Table 2. Prevalence of at least one positive allergy test among subjects with different airway symptoms stratified by age group and gender

	At least one positive allergy test			
	Age group 20–44 years		Age group 45–70 years	
	Males, % (n)	Females, % (n)	Males, % (n)	Females, % (n)
Asthma attack during last 12 months	50 (1)	64 (7)*	30 (3)	43 (6)*
Asthma attacks during last year or medication	78 (7)*	77 (13)*	44 (10)*	58 (11)*
Self-reported nasal allergy	83 (79)*,†	75 (81)*,†	50 (37)*	57 (55)*
Symptoms when exposed to dust/animals	70 (107)*,†	65 (126)*,†	42 (56)*	44 (67)*
Symptoms when exposed to pollen	75 (76)*,†	66 (78)*,†	47 (41)*	53 (58)*
Dust/animal/pollen symptoms lower airways	70 (75)*,†	65 (83)*,†	46 (41)*	42 (44)*
Dust/animal/pollen symptoms upper airways	68 (131)*,†	64 (142)*,†	43 (69)*	43 (75)*
Eczema or skin allergy ever	49 (86)†	51 (117)*,†	34 (55)	29 (58)
None of the symptoms above	31 (113)†	29 (89)†	24 (106)	20 (72)

* Significantly higher than subgroup of subjects without symptoms ($P < 0.05$).

† Significantly higher than other corresponding age group (χ^2 1 df; $P < 0.05$).

Table 3. Positive and negative predictive value of total IgE for at least one positive allergy test and the proportion with positive total IgE at different cut-off values of total IgE in subjects with asthma or allergy symptoms, stratified by age group and gender

Cut-off value	Positive predictive value		Negative predictive value		% positive total IgE	
	Males, % (n)	Females, % (n)	Males, % (n)	Females, % (n)	Males, % (n)	Females, % (n)
20–44 years						
Pretest prob.	67 (138)	62 (147)	–	–	$n = 205$	$n = 237$
5 kU/l	70 (135)	67 (141)	75 (9)	77 (20)	94 (193)	89 (211)
50 kU/l	88 (109)	90 (97)	64 (52)	61 (79)	61 (124)	46 (108)
100 kU/l	94 (85)	96 (64)	54 (62)	51 (87)	44 (90)	28 (67)
150 kU/l	96 (69)	96 (48)	48 (64)	47 (88)	35 (72)	21 (50)
200 kU/l	96 (49)	95 (39)	42 (65)	45 (88)	25 (51)	17 (41)
300 kU/l	98 (41)	97 (28)	41 (66)	43 (89)	21 (42)	12 (29)
45–70 years						
Pretest prob.	43 (82)	41 (84)	–	–	$n = 190$	$n = 203$
5 kU/l	47 (82)	45 (83)	100 (14)	95 (18)	93 (176)	91 (184)
50 kU/l	61 (62)	63 (50)	78 (69)	73 (90)	53 (101)	39 (79)
100 kU/l	66 (37)	73 (37)	66 (89)	69 (105)	30 (56)	25 (51)
150 kU/l	71 (30)	77 (27)	65 (96)	66 (111)	22 (42)	17 (35)
200 kU/l	74 (20)	73 (22)	62 (101)	64 (111)	14 (27)	15 (30)
300 kU/l	82 (14)	80 (12)	61 (105)	62 (116)	9 (17)	7 (15)

test negative subjects was better for the age group 20–44 years than for the age group 45–70 years. The relationship between true positive rate and false positive rate was comparable for males and females, as shown by the comparable course of the ROC curves. However, for a given true positive and false positive rate, the cut-off value for total IgE is lower for females than males.

No suitable low cut-off value of total IgE was found to efficiently rule out sensitization to common inhalant allergens in subjects with asthma or allergy symptoms (Table 3). Cut-off values with a sufficiently high negative predictive value could not be found in the age group 20–44 years. In the age group 45–70 years, a negative predictive value of 100% was found in males at a cut-off value of 5 kU/l (Table 3), indicating that in this age group all the males with a total IgE less than 5 kU/l were allergy test negative. However, this applies to only a very

few subjects [i.e. 14 males (7%) in the age group 45–70 years with allergy symptoms].

Cut-off values with high positive predictive values were found in the age group 20–44 years with a history of asthma or allergy symptoms (Table 3). Ninety-six percent of the subjects with total IgE levels higher than 150 kU/l were allergy test positive. Such high positive predictive values were not found in the age group 45–70 years.

We also studied positive and negative predictive values when cut-off values are used that are generated by determining the upper 5% of total IgE values in ‘normal’ subjects. One hundred and ninety-one (33%) males and 148 (27%) females in the age group 20–44 years and 268 (42%) males and 203 (36%) females in the age group 45–70 years could be defined as ‘normal’. The upper 5% of total IgE values in these ‘normal’ subjects was 162 kU/l in males and 140 kU/l in females in the age group

Table 4. Positive and negative likelihood ratios at different cut-off values of total IgE in subjects with asthma or allergy symptoms, stratified by age group and gender

Cut-off value	Positive likelihood ratio		Negative likelihood ratio	
	Males	Females	Males	Females
<i>20–44 years</i>				
5 kU/l	1.1	1.2	0.2	0.2
50 kU/l	3.5	5.4	0.3	0.4
100 kU/l	8.3	13.1	0.4	0.6
150 kU/l	11.2	14.7	0.5	0.7
200 kU/l	11.9	11.9	0.7	0.8
300 kU/l	19.9	17.1	0.7	0.8
<i>45–70 years</i>				
5 kU/l	1.2	1.2	0	0.1
50 kU/l	2.1	2.4	0.4	0.5
100 kU/l	2.6	3.7	0.7	0.6
150 kU/l	3.3	4.8	0.7	0.7
200 kU/l	3.8	3.9	0.8	0.8
300 kU/l	6.2	5.7	0.9	0.9

20–44 years and 205 kU/l in males and 116 kU/l in females in the age group 45–70 years. Table 3 shows that using these values as cut-off values of total IgE in subjects with symptoms resulted in high positive and low negative predictive values.

Likelihood ratios show how much total IgE changes the pretest probability of sensitization (Table 4). The odds of sensitization at different cut-off values of total IgE can be calculated by multiplying the pretest odds with the likelihood ratio. For example, when a cut-off value of 150 kU/l is used in a group of males aged 20–44 years with the pretest probability of sensitization of 67.3% (pretest odds = 2.1), the posttest odds will be 23.5 (i.e. 2.1×11.2) when a positive test is found. Thus, the posttest probability of sensitization will be 96% (Table 3). When the total IgE level is lower than 150 kU/l, the posttest odds will be 1.1 (i.e. 2.1×0.5) with a probability of sensitization of 52%. Thus, the probability of not being sensitized is 48% (Table 3).

Likelihood ratios were lower in a subgroup of subjects with negative allergy tests to at least eight of the nine allergens (Table 5). If the pretest odds were, for example, 1% in a particular setting, a total IgE higher than 300 kU/l in younger males would increase the probability of sensitization to 8%.

Discussion

This study shows that serum total IgE measurements cannot be used to efficiently rule out sensitization to common inhalant allergens in adult subjects with symptoms that might be allergic. To rule out sensitization, high negative predictive values are needed. The high prevalence of sensitization and the relatively weak association of total IgE with sensitization lead to low negative predictive values, even at very low cut-off values of total

Table 5. Positive and negative likelihood ratios at different cut-off values of total IgE in subjects with asthma or allergy symptoms and negative allergy tests to eight of nine allergens, stratified by age group and gender

Cut-off value	Positive likelihood ratio		Negative likelihood ratio	
	Males	Females	Males	Females
<i>20–44 years</i>				
5 kU/l	1.1	1.2	0.6	0.3
50 kU/l	2.4	4.1	0.6	0.6
100 kU/l	4.3	8.3	0.6	0.8
150 kU/l	5.9	5.0	0.7	0.9
200 kU/l	6.7	3.3	0.8	1.0
300 kU/l	8.4	5.0	0.9	1.0
<i>45–70 years</i>				
5 kU/l	1.1	1.2	0	0.3
50 kU/l	1.8	2.1	0.5	0.6
100 kU/l	1.4	3.0	0.9	0.7
150 kU/l	1.6	3.8	0.9	0.8
200 kU/l	1.4	3.0	1.0	0.9
300 kU/l	2.2	3.0	1.0	1.0

IgE in younger subjects. In subjects 45–70 years with allergy symptoms, sensitization to common inhalant allergens is very unlikely with total IgE lower than 5 kU/l. However, this applies to less than 10% of the cases. Therefore, total IgE is not useful as the first step in the diagnostic work up of patients with allergic disease and cannot be used to exclude individuals from skin tests or specific IgE determinations.

Higher values of total IgE may indicate a high risk of sensitization in younger subjects but this has limited practical utility, as identification of the inhalant allergens in question, necessitating further testing of individual allergens is required for proper management in most cases.

Likelihood ratios show that high total IgE levels strongly increase the probability of sensitization, especially in younger subjects. Clinically, total IgE might be useful in deciding which patients with negative specific allergy tests to a panel of common inhalant allergens have an increased probability of being sensitized to an allergen not included in such a panel. Such patients would then be candidates for further testing with less common inhalant allergens. An important consideration in this regard is that such patients are likely to be monosensitized, as total IgE increases with the number of positive allergy tests.

In our data, the geometric mean total IgE of subjects sensitized to more than one allergen is significantly higher than the mean of subjects sensitized to only one allergen (119 vs. 53 kU/l, $P < 0.01$). Thus, total IgE will better discriminate multisensitized than monosensitized subjects from non-sensitized subjects. In order not to overestimate the power of total IgE in this regard, we calculated likelihood ratios for different cut-off values of total IgE in symptomatic patients having negative specific allergy tests to at least eight of the nine allergens tested (Table 5). The positive likelihood ratios shown thus represent the factor

by which the odds of sensitization increases for a given level of total IgE. As may be seen, higher levels of total IgE are associated with high positive likelihood ratios, especially in younger males. This relationship is less consistent in females and less pronounced in the older age group. These data show that the relationship between a single sensitization and total IgE is strong enough that meaningful positive likelihood ratios may be generated for higher levels of total IgE. Assuming that the relationship between total IgE and an untested allergen of interest is as strong as is the case in our study population (where this was most often house dust mite), measuring total IgE may aid the clinician in selecting patients from amongst those with negative allergy screening tests who warrant further investigation.

In the literature, reference values of total IgE are often assessed from the distribution of total IgE in 'normal' subjects with no history of atopic disease and no positive skin test to common inhalant allergens (6, 8, 10, 13, 14). Our results confirmed the findings of other studies (6, 8) that reference values developed from a 'normal' population are not usable to distinguish allergy test positive from allergy test negative subjects, because of extensive overlap of values. Other authors also describe this considerable overlap. Bousquet et al. (6) found that in the age group 13–76 years, 38% of subjects with allergic disease and 25% of subjects with nonallergic asthma, rhinitis or conjunctivitis had total IgE concentrations within a 'normal' range. Klink et al. (8) described the percentages of subjects with asthma or positive skin tests that had lower total IgE levels than different percentiles of total IgE of a reference group and showed considerable overlap. However, overlap does not exclude the possibility to use total IgE to rule out sensitization. A low cut-off value might be used for this purpose despite the fact that many 'normal' subjects have total IgE levels higher than this cut-off value. Results of Klink et al. (8) suggested that a very low cut-off value of total IgE (10th to 25th percentile of the reference group) might be used to rule out current asthma or allergic rhinitis in a limited number of subjects. This is in agreement with our results.

A part of the overlap may be explained by misclassification. In our study, 'normal' subjects had no positive skin test to nine allergens and no specific IgE to five allergens. Although the prevalence of sensitization to allergens other than those tested might be considerable (e.g. sensitization to dog), the majority of these subjects will be sensitized to the allergens tested. In our study, 10% of the younger age group had specific IgE or a skin test positive to cat, but only 16 subjects (1%) had a positive allergy test to cat exclusively. In subjects with negative allergy tests to the most common inhalant allergens house dust mite, cat, timothy grass and birch, sensitization to the other five allergens was very rare. Thus, misclassification is unlikely to be a major cause of overlap of total IgE values in patients and normals.

Although no gender differences in the prevalence of sensitization to inhalant allergens and the shape of the ROC curves were found, total IgE levels were lower in females than in males. The ROC curves show that to obtain equal sensitivity and specificity of total IgE for males and females, a lower cut-off value of total IgE for females than for males should be used.

The superior discriminating ability of total IgE in the age group 20–44 as compared to 45–70 years might be because of the fact that younger allergy test positive subjects have a higher mean number of positive allergy tests than older subjects. In our data, total IgE increased with the number of positive allergy tests.

As the shape of the ROC curve was better in the age group 20–44 years than in the older age group of 45–70 years, it might even be better in children. Indeed, Lindberg et al. (15) were able to establish cut-off values of total IgE with high diagnostic sensitivity and specificity in children.

A limitation of this study is that in a random population sample the symptomatic individuals are likely to have less severe symptoms and a lower prevalence of sensitization than individuals from clinical populations. However, a higher prevalence of positive allergy tests yields a lower negative predictive value. Using a low value of total IgE to rule out sensitization will therefore be even less feasible in a clinical population.

The possibility that confounders, such as smoking, may be involved cannot be excluded. Indeed, in our data there is a negative association between current smoking and the presence of nasal allergy symptoms and allergy test positivity. Also, current smoking appeared to be positively associated with total IgE. However, excluding all current smokers from the analyses did not alter the results.

Another factor that may influence the association between positive allergy tests and total IgE is the presence of atopic eczema. We did not have information about the current presence of eczema, only about the lifetime presence. In our study population of subjects with symptoms of asthma or respiratory allergy, subjects with a history of 'eczema or skin allergy ever' had similar mean total IgE levels as subjects with no history of eczema in all the four strata of sex and age groups.

The advantage of our study is that both the 'normal' population and the sensitized subjects are obtained from the same population sample using the same diagnostic methods. Systematic errors resulting from patient selection differences or diagnostic methodological differences are reduced, allowing for better assessment of reference values.

In conclusion, our results demonstrated that total IgE cannot be used to rule out the presence of sensitization to common inhalant allergens in adult subjects with symptoms suggesting allergy. Its role as part of a routine diagnostic work up in patients suspected of having allergic disease is therefore limited. It may be used,

however, to indicate the probability of sensitization and aid the clinician to decide whether further investigation is warranted in patients with negative specific allergy tests to a panel of common inhalant allergens.

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