



Assessment of Allergen Sensitization in a General Population-Based Survey (European Community Respiratory Health Survey I)

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PURPOSE: Exposed to a common environment, the IgE-mediated immune response differs, for instance, among sensitized subjects, some of them reacting toward one allergen (monosensitized) whereas others are sensitized to a wide array of allergens (polysensitized). However, a better phenotypic characterization is needed for epidemiologic studies. Using the data collected during the ECRHS I (European Community Respiratory Health Survey), several assessments of skin prick tests and serum-specific IgE to identify mono- and polysensitized patients were compared.

METHODS: Subjects took part in the ECRHS-I. The CAP-System was used for serum allergen-specific IgE, and allergen-coated Phazet was used for prick tests. Four allergens (*Dermatophagoides pteronyssinus*, cat, timothy grass, and *Cladosporium*) were measured using IgE and nine (the same ones plus olive pollen, birch, *Alternaria*, *Parietaria*, and ragweed) were skin tested. One to two local allergens were also tested, depending on countries.

RESULTS: Prevalence of sensitization in 11,355 subjects (34.0 [27.9–40.1] years, 49.9% men) ranged from 32.3% (four specific IgE, 19.3% mono- and 13.0% polysensitized) to 41.8% (four specific IgE combined to nine prick tests, 19.6% mono- and 22.2% polysensitized). Concordance between four specific IgE and four prick tests was weak (weighted κ 0.65 [0.64–0.66]). Concordance between seven and nine prick tests was high (weighted κ 0.99 [0.98–1.00]). Local allergens induced small changes in the prevalence of sensitization, and reclassified some subjects from mono- to polysensitized.

CONCLUSIONS: Skin tests or serum-specific IgE may be chosen to identify allergenic sensitivity, mono- and polysensitized subjects without being strictly interchangeable.

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INTRODUCTION

Exposed to a common environment, the IgE-mediated immune response differs, for instance, among sensitized subjects, some of them reacting toward one allergen (monosensitized) whereas others are sensitized to a wide array of allergens (polysensitized) (1). Clearly defined phenotypes are needed in epidemiologic studies, and individuals must be appropriately characterized as not sensitized, monosensitized, and polysensitized.

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Mono- and polysensitized subjects differ in terms of their immune response (2–5). Monosensitized patients are more commonly children who may develop polysensitization later in life, or adults who will only develop a single allergenic sensitivity (3, 6). In some subjects, however, sensitization may not be determined by skin tests and/or allergen-specific serum IgE because of a local IgE production (7), or a sensitization to unknown allergens.

Sensitization to allergens can be determined by skin prick tests or by measurement of allergen-specific IgE antibodies in serum. However, skin prick tests and serum allergen-specific IgE may not have the same biological and clinical relevance and may not be interchangeable (8, 9).

Using the data collected during the European Community Respiratory Health Survey (ECRHS I), we compared the respective role of skin prick tests and serum allergen-specific IgE to define sensitized subjects and differentiate mono- and polysensitized patients.

METHODS

Population and Inclusion Criteria

The population of this study is based on the ECRHS I (10, 11). Only centers that carried out serum allergen-specific

Selected Abbreviations and Acronyms

IgE = immunoglobulin E
 A. alternata = *alternaria alternata*
 C. herbarum = *cladosporium herbarum*
 D. pteronyssinus = *dermatophagoides pteronyssinus*
 D. farinae = *dermatophagoides farinae*
 ECRHS = European Community Respiratory Health Survey
 P. judaica = *parietaria judaica*

IgE and skin prick tests were included in the study. Subjects without all serum-specific IgE measurement and skin prick tests were also excluded from the analysis. Centers started the study between 1990 and 1998.

Serum-Specific IgE

Serum allergen-specific IgE was tested using the CAP-System (Pharmacia Diagnostics, Uppsala, Sweden) in a central laboratory (12, 13). Four allergens (*D. pteronyssinus*, timothy grass pollen, cat, and *Cladosporium herbarum*) were tested in all centers. In addition, one local allergen was tested: birch pollen for Northern Europe, *Parietaria judaica* pollen for southern Europe, and ragweed pollen for United States and Canada. Sensitization was considered to be present if the IgE level was greater than 0.35 U/ml.

Skin Prick Tests

The allergen-coated Phazet was used (13, 14) including the four allergens tested by CAP-System plus *Alternaria alternata*, birch, olive, *P. judaica*, and ragweed pollen. Additionally, one to two local allergens were tested in some centers if they were relevant in the local area (*Aspergillus*, chestnut pollen, cockroach, *Dermatophagoides farinae*, dog, horse, *Leptidoglyphus destructor*, mugwort pollen, plantain pollen, and/or rye grass pollen). A histamine-positive control and a saline-negative control were also tested. Skin prick tests were considered positive if the mean wheal size was greater than 0 mm (15, 16).

Assessment of Mono- and Polysensitization

Sensitization was defined in three categories: (1) not sensitized; (2) sensitized to one allergen (monosensitized); and (3) sensitized to more than one allergen (polysensitized). Several definitions of sensitization were used and compared to assess the relevance of skin prick tests and serum allergen-specific IgE. The number of tested allergens and the impact of local allergens were also assessed.

IgE Group. Serum allergen-specific IgE for the 4 allergens tested in all centers (*Dermatophagoides pteronyssinus*, timothy grass pollen and cat, *Cladosporium herbarum*): 4 IgE group.

Skin tests included:

1. Prick tests for the 4 allergens tested in all centers (*Dermatophagoides pteronyssinus*, timothy grass pollen and cat, *Cladosporium herbarum*): 4 prick tests group.
2. Prick tests for a battery of 7 allergens (4 allergens plus olive pollen, birch and *Alternaria*). These allergens were selected in a previous study that was performed in the same population, in order to define the number of allergens to be tested to assess allergenic sensitization (13): 7 prick tests group.
3. Prick tests for all 9 allergens studied in all centres (7 allergens plus *Parietaria judaica*, and ragweed pollen), without local allergens: 9 prick tests group.

Skin tests and IgE groups:

4. Prick tests for the 5 allergens (olive pollen, birch, *Parietaria*, *Alternaria*, ragweed) and serum allergen-specific IgE for 4 allergens (*Dermatophagoides pteronyssinus*, cat, timothy grass pollen and *Cladosporium*): 4 IgE + 5 prick tests group.
5. Prick tests for all 9 allergens tested in all centers and serum allergen-specific IgE for the 4 allergens. In this particular group some allergens are tested both by prick test and serum allergen-specific IgE, positivity being established if at least one of the two measurements was positive: 4 IgE + 9 prick tests group.

In addition, the impact of local allergens was also studied.

Statistical Analysis

The population was described using frequencies and percentages (qualitative variables), and median and 25th and 75th percentiles (quantitative variables, distribution assessed by Shapiro-Wilks normal test, and by Kurtosis and Skewness tests, if not normal). Distribution of non, mono-, and polysensitized subjects was assessed for each definition using frequencies and percentages. Comparisons were also carried out and concordances between definitions were established using the weighted κ and generalized McNemar-Bowker test of symmetry. Categories were ordered as nonsensitized, then monosensitized, and finally polysensitized. A minimal weighted κ score of 0.80 was considered as good concordance between two definitions. Under this level, the concordance was considered as weak.

The statistical analysis was carried out using Stata 9.1 (StataCorp LP, College Station, TX). The *p* for normality tests was considered significant if less than 0.05.

RESULTS**Participants**

Overall, 18,794 participants in 37 centers and 17 countries (Australia, Belgium, France, Germany, Iceland, Ireland, Italy, Lithuania, New Zealand, Norway, Poland, Spain,

Sweden, Switzerland, The Netherlands, United Kingdom, and the United States), had at least one serum allergen-specific IgE measurement or one skin prick test for the most common allergens. Among them, 7439 had to be removed from the analysis (see Bousquet et al. (13) for complete description). Therefore, the study focused on 32 centers from 13 countries. The median age of the 11,355 subjects (5669 [49.9%] men and 5686 [50.1%] women) studied was 34.0 (27.9–40.1) years. Only 5.1% of subjects had current asthma (reported an attack of asthma or the use of treatment of asthma in the last year and/or used of medication for asthma), including 3.6% rhinitics and 27.3% rhinitis including 3.6% current asthmatics.

Assessment of Sensitization

Depending on the definition, the percentage of nonsensitized and sensitized subjects varied. The prevalence of non-sensitized subjects decreased from 67.8% (four prick tests: *D. pteronyssinus*, cat, timothy grass pollen, and *Cladosporium*) to 67.7% (4 IgE: *D. pteronyssinus*, cat, timothy grass pollen, and *Cladosporium*), 64.4% (nine prick tests), 63.4% (four IgE [*D. pteronyssinus*, cat, timothy grass pollen, and *Cladosporium*]) and five prick tests [olive pollen, birch, *Alternaria*, *Parietaria*, and ragweed]) and 58.2% (four IgE and nine prick tests) (Table 1). Using the same definition, the proportion of polysensitized subjects was 12.8%, 13.0%, 17.6%, 18.1%, and 22.2%, respectively.

Comparisons between definitions of sensitization are reported in Table 2. When four prick tests and four IgE were compared, there were 6.9% of subjects with undetectable IgE and positive skin tests and 7.0% of subjects with detectable IgE and negative skin tests.

Impact of Local Allergens

Adding prick tests to local allergens induced small variations in sensitization prevalence (<1.4%, Table 1). However, the impact on mono- and polysensitized was more important. Prevalence of polysensitized subjects increased by 2.8% (compared to four IgE), 2.9% (compared to nine prick tests), 3.3% (compared to four IgE and five prick tests), and 3.1% (compared to four IgE and nine prick tests).

Concordance Between Definitions

Depending on definitions, the concordance (weighted κ) ranged from 0.65 to 0.99 (Table 2 and Table 3). The lowest weighted κ coefficient was observed between four IgE and four prick tests (*Dermatophagoides pteronyssinus*, cat, timothy grass pollen, and *Cladosporium*). The highest was observed between seven (*D. pteronyssinus*, cat, timothy grass pollen, olive pollen, birch, *Cladosporium*, *Alternaria*) and nine (the same ones plus *Parietaria* and ragweed) skin prick tests (0.99 [0.98–1.0]).

Concordance was also very good (>0.85) between seven or nine prick tests and four IgE plus nine prick tests, four IgE (*D. pteronyssinus*, cat, timothy grass pollen, and *Cladosporium*) plus five prick tests (birch, olive pollen, *Parietaria*, *Alternaria*, and ragweed) and four IgE plus nine prick tests.

In all cases, except between four IgE and four prick tests, an asymmetric distribution was observed ($p < 0.0001$; McNemar-Bowker test of symmetry).

As a whole, the impact of local allergens was weak, the weighted κ coefficient being always greater than 0.92. The major impact of local allergens was the reclassification of several subjects from mono- to polysensitized.

TABLE 1. Proportion of non-, mono-, and polysensitized subjects depending on definition

	Nonsensitized (%)	Monosensitized (%)	Polysensitized (%)
IgE only			
4* allergens	7684 (67.7)	2196 (19.3)	1475 (13.0)
4* + 1 local allergens	7531 (66.3)	2026 (17.8)	1798 (15.8)
Prick tests only			
4* allergens	7696 (67.8)	2203 (19.4)	1456 (12.8)
4* + 2 local allergens	7537 (66.4)	1898 (16.7)	1920 (16.9)
7 [†] allergens	7360 (64.8)	2045 (18.0)	1950 (17.2)
9 [‡] allergens	7313 (64.4)	2046 (18.0)	1996 (17.6)
9 [‡] + 2 local allergens	7196 (63.4)	1836 (16.2)	2323 (20.5)
IgE or prick tests			
4* IgE + 5 [§] prick tests	7203 (63.4)	2096 (18.5)	2056 (18.1)
4* + 1 local IgE and 5 [§] + 2 local prick tests	7057 (62.2)	1864 (16.4)	2434 (21.4)
IgE and prick tests			
4* IgE + 9 [‡] prick tests	6609 (58.2)	2227 (19.6)	2519 (22.2)
4* + 1 local IgE and 9 [‡] + 2 local prick tests	6477 (57.0)	2001 (17.6)	2877 (25.3)

For skin prick test, 0 mm was considered as the cut-off.

**D. pteronyssinus*, cat, timothy grass, and *Cladosporium*.

[†]*D. pteronyssinus*, cat, timothy grass, *Cladosporium*, *Alternaria*, birch, and olive tree.

[‡]*D. pteronyssinus*, cat, timothy grass, *Cladosporium*, *Alternaria*, birch, olive tree, ragweed, and *Parietaria*.

[§]Birch, olive tree, *Parietaria*, ragweed, and *Alternaria*.

Skin Prick Test Cut-Off: Sensitivity Analysis

The sensitivity analyses were also carried out using a 3-mm and 5-mm cut-off for the four skin prick tests. Similar findings were observed. Thus, the weighted κ between four serum-specific IgE and four skin prick tests was 0.65 (0.64–0.66) for a cut-off of greater than 0 mm, 0.66 (0.65–0.67) for 3 mm, and 0.52 (0.51–0.53) for 5 mm.

DISCUSSION

Based on a study involving greater than 11,000 subjects, it was found that skin tests and serum allergen-specific IgE do not provide the same prevalence of sensitization. Not surprisingly, combining the results of serum IgE for four allergens and skin prick tests for nine allergens provided the highest estimate of sensitization by comparison to serum allergen-specific IgE to four allergens or skin tests to four allergens. The assessment of local allergens did not change markedly the prevalence of sensitized subjects but induced a reclassification of some subjects from the mono- to the polysensitized state.

Skin prick tests and serum allergen-specific IgE may not have the same biological and clinical relevance and may not be interchangeable (8, 9). In clinical practice, to assess sensitization, skin tests seem to be more sensitive, whereas the IgE test is more specific because the cut-off level for a positive IgE test is arbitrarily set at 0.35 kU/L to avoid false/positive results (17). It is known that a few patients with positive nasal or bronchial allergen challenges with pollen and house dust mites can have serum allergen-specific IgE levels under this cutoff (18–20). In food allergy, undetectable serum allergen-specific IgE may be found in patients with a proven allergic clinical reaction assessed by oral food challenge, even for well-characterized allergens such as peanut (21, 22). In large epidemiologic studies, it is easier to achieve standardization of criteria for positive and negative results with serum allergen-specific IgE when the measurement is carried out in a central laboratory. Skin prick tests can also be used in multicenter studies. However, although methods are standardized, some variability in the performance of the tests and interobserver variation can be observed. The present study is of particular interest in comparing the two tests because the same allergens of the same company were used in both assays. Thus, differences that are reported in this study can be related only to the tests or to their performance, and not to the allergens.

In this study, sensitization was assessed using two different measurements (skin prick tests and serum-specific IgE) and it was found that skin tests and serum allergen-specific IgE do not lead to the same results. A similar study was carried out for the diagnosis of cockroach allergy (23). However, results of such study could not be generalized

TABLE 2. Sensitivity analysis: comparison between several definitions of sensitization

	Nonsensitized (%)	Monosensitized (%)	Polysensitized (%)
4* IgE + 9 [‡] skin tests			
4* IgE			
Nonsensitized	6609	766 (34.4)	309 (12.3)
Monosensitized		1461 (65.6)	735 (29.2)
Polysensitized			1475 (58.6)
7* skin tests			
Nonsensitized	6609	568 (25.5)	183 (7.3)
Monosensitized		1659 (74.5)	386 (15.3)
Polysensitized			1950 (77.4)
9 [‡] skin tests			
Nonsensitized	6609	533 (23.9)	171 (6.8)
Monosensitized		1694 (76.1)	352 (14.0)
Polysensitized			1996 (79.2)
4* IgE + 5 [§] skin tests			
Nonsensitized	6609	498 (22.4)	96 (3.8)
Monosensitized		1729 (77.6)	367 (14.6)
Polysensitized			2056 (81.6)
4* IgE			
4* skin tests			
Nonsensitized	6896 (89.7)	605 (27.6)	195 (13.2)
Monosensitized	605 (7.9)	1263 (57.5)	335 (22.7)
Polysensitized	183 (2.4)	328 (14.9)	945 (64.1)
7 [†] skin tests			
Nonsensitized	6645 (86.5)	542 (24.7)	173 (11.7)
Monosensitized	744 (9.7)	1052 (47.9)	249 (16.9)
Polysensitized	295 (3.8)	602 (27.4)	1053 (71.4)
9 [‡] skin tests			
Nonsensitized	6609 (86.0)	533 (24.3)	171 (11.6)
Monosensitized	766 (10.0)	1038 (47.3)	242 (16.4)
Polysensitized	309 (4.0)	625 (28.5)	1062 (72.0)
4* IgE + 5 [§]			
Nonsensitized	7203		
Monosensitized	405 (5.3)	1691 (77.0)	
Polysensitized	76 (1.0)	505 (23.0)	1475
9 [‡] prick tests			
7 [†] skin tests			
Nonsensitized	7313	46 (2.3)	1 (0.1)
Monosensitized		2000 (97.8)	45 (2.3)
Polysensitized			1950 (97.7)
4* IgE + 5 [§] skin tests			
Nonsensitized	6609 (90.4)	498 (24.3)	96 (4.8)
Monosensitized	533 (7.3)	1242 (60.7)	321 (16.1)
Polysensitized	171 (3.4)	306 (15.0)	1579 (79.1)

For skin prick test, 0 mm was considered as the cut-off.

**D. pteronyssinus*, cat, timothy grass, and *Cladosporium*.

[†]*D. pteronyssinus*, cat, timothy grass, *Cladosporium*, *Alternaria*, birch, and olive tree.

[‡]*D. pteronyssinus*, cat, timothy grass, *Cladosporium*, *Alternaria*, birch, olive tree, ragweed, and *Parietaria*.

[§]Birch, olive tree, *Parietaria*, ragweed, and *Alternaria*.

because the extracts used for skin test had highly variable protein contents (24). Focusing on the link between skin prick tests and serum specific IgE measurement for the same allergens, in this study, approximately 10.3% of the subjects defined as nonsensitized using the measurement of four serum-specific IgE were positive for at least one of

TABLE 3. Concordance between definitions

	Weighted κ	McNemar
Excluding local allergens		
4 IgE vs. 4 prick tests	0.65 [0.64–0.66]	0.93
4 IgE vs. 9 prick tests	0.76 [0.75–0.77]	<0.001
4 IgE vs. 4 IgE + 5 prick tests	0.87 [0.86–0.88]	<0.001
4 IgE vs. 4 IgE + 9 prick tests	0.76 [0.74–0.76]	<0.001
4 IgE + 5 prick tests vs. 4 IgE + 9 prick tests	0.88 [0.87–0.89]	<0.001
4 IgE + 5 prick tests vs. 9 prick tests	0.74 [0.73–0.75]	<0.001
4 IgE + 9 prick tests vs. 9 prick tests	0.86 [0.85–0.87]	<0.001
7 prick tests vs. 9 prick tests	0.99 [0.98–1.00]	<0.001
7 prick tests vs. 4 IgE	0.62 [0.61–0.63]	<0.001
7 prick tests vs. 4 IgE + 9 prick tests	0.85 [0.84–0.86]	<0.001
Including local allergens		
4 vs. 4 + 1 local IgE	0.94 [0.93–0.95]	<0.001
4 vs. 4 + 2 local prick tests	0.92 [0.91–0.93]	<0.001
9 vs. 9 + 2 local prick tests	0.95 [0.94–0.96]	<0.001
4 IgE and 5 prick test vs. 4 + 1 local IgE and 5 + 2 local prick tests	0.92 [0.91–0.93]	<0.001
4 IgE and 9 prick test vs. 4 + 1 local IgE and 9 + 2 local prick tests	0.95 [0.94–0.96]	<0.001

four skin prick tests, and vice versa. It is possible that, using a skin test cut-off level of greater than 0 mm, some patients have false/positive skin tests without a true IgE sensitization. This issue has already been studied in the ECRHS-I, and 0 mm was considered to be the most discriminative measure that minimized error in comparison of interobserver variation (15, 16). It is of importance in this study that increasing the cut-off level of skin tests from greater than 0 mm to 3 mm and 5 mm did not change the general conclusion. When the number of skin tests was increased to nine, the same difference was seen between the two assays. Some extracts can induce false/positive reactions by nonimmunologic mechanisms using intradermal tests, but this is not the case with prick tests (19, 25). On the other hand, an abnormal performance inducing a false/positive of skin prick test in some subjects cannot be ruled out. This study cannot indicate, however, which test is better than the other one to assess IgE sensitization.

Approximately 25% of the subjects was sensitized according to the different methods. However, the sensitization rate varied a lot between centers and countries. A previous report based on skin prick tests in the same population observed (26) the lower rate in Oviedo, Spain (17.1% [12.4–21.8]) and the higher in Geleen, The Netherlands (54.8% [49.4–60.2]). In Portland, OR, 52.1% (46.2–58.0) of the subjects were sensitized. The Third National Health and Nutrition Examination Survey (27) reported a similar rate, with 53.9% plus or minus 1.02% of the participant sensitized to at least on indoor or outdoor allergen.

The second question is the best number of allergens to be tested to assess sensitization. It is clear that increasing the number of allergens using skin tests, there is an increased

prevalence of sensitized subjects and of polysensitized patients. In a previous study, we showed that seven selected allergens (*D. pteronyssinus*, cat, timothy grass, birch, olive pollen, *Alternaria*, and *Cladosporium*) allow the identification of almost all sensitized subjects in epidemiologic studies (13). This study suggests that this number was sufficient to determine sensitization (nonsensitized/sensitized; as well as non-, mono-, and polysensitized).

The third question was the relevance of local allergen testing. The prevalence of sensitization is little changed (1% difference) when 9 or 11 skin tests were carried out. As expected, local allergen testing increased the prevalence of polysensitization. Not all relevant allergens were tested in this study. This is particularly true in the Mediterranean area in which cypress pollen was not tested. It was decided not to test this particular pollen because it was not standardized at the time of the study and many patients with a clinically-evident allergy had negative skin tests and serum-specific IgE (28). Bermuda grass might have been tested (27), but it does not seem to represent major allergens in most of the centers.

In epidemiological studies, a single method may be chosen to assess allergenic sensitivity (none, mono-, and polysensitization), but the results differ between skin tests and IgE measurements.

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REFERENCES

1. Pepys J. Types of allergic reaction. *Clin Allergy*. 1973;3(Suppl):491-509.
2. Bousquet J, Coulomb Y, Arrendal H, Robinet-Levy M, Michel FB. Total serum IgE concentrations in adolescents and adults using the Phadebas IgE PRIST technique. *Allergy*. 1982;37:397-406.
3. Bousquet J, Knani J, Hejjaoui A, Ferrando R, Cour P, Dhivert H, et al. Heterogeneity of atopy. I. Clinical and immunologic characteristics of patients allergic to cypress pollen. *Allergy*. 1993;48:183-188.
4. Rudin A, Macaubas C, Wee C, Holt BJ, Sly PD, Holt PG. "Bystander" amplification of PBMC cytokine responses to seasonal allergen in polysensitized atopic children. *Allergy*. 2001;56:1042-1048.
5. Bousquet J, Anto JM, Bachert C, Bousquet PJ, Colombo P, Cramer R, et al. Factors responsible for differences between asymptomatic subjects and patients presenting an IgE sensitization to allergens. A GA2LEN project. *Allergy*. 2006;61:671-680.
6. Silvestri M, Rossi GA, Cozzani S, Pulvirenti G, Fasce L. Age-dependent tendency to become sensitized to other classes of aeroallergens in atopic asthmatic children. *Ann Allergy Asthma Immunol*. 1999;83:335-340.
7. Rondon C, Romero JJ, Lopez S, Antunez C, Martin-Casanez E, Torres MJ, et al. Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. *J Allergy Clin Immunol*. 2007;119:899-905.
8. Witteman AM, Stapel SO, Perdok GJ, Sjaamsoedin DH, Jansen HM, Aalberse RC, et al. The relationship between RAST and skin test results in patients with asthma or rhinitis: a quantitative study with purified major allergens. *J Allergy Clin Immunol*. 1996;97:16-25.
9. Droste JH, Kerhof M, de Monchy JG, Schouten JP, Rijcken B. Association of skin test reactivity, specific IgE, total IgE, and eosinophils with nasal symptoms in a community-based population study. The Dutch ECRHS Group. *J Allergy Clin Immunol*. 1996;97:922-932.
10. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J*. 1994;7:954-960.
11. Janson C, Anto J, Burney P, Chinn S, de Marco R, Heinrich J, et al. The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II. *Eur Respir J*. 2001;18:598-611.
12. Burney P, Malmberg E, Chinn S, Jarvis D, Luczynska C, Lai E. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. *J Allergy Clin Immunol*. 1997;99:314-322.
13. Bousquet PJ, Hooper R, Kogevinas M, Jarvis D, Burney P. Number of allergens to be tested to assess allergenic sensitization in epidemiologic studies: results of the European Community Respiratory Health Survey I. *Clin Exp Allergy*. 2007;37:780-787.
14. Chanal I, Horst M, Segalen C, Dreborg S, Michel FB, Bousquet J. Comparison between modified skin prick test with standardized allergen extracts and Phazet. *J Allergy Clin Immunol*. 1988;82:878-881.
15. Chinn S, Jarvis D, Luczynska CM, Lai E, Burney PG. Measuring atopy in a multi-center epidemiological study. *Eur J Epidemiol*. 1996;12:155-162.
16. Bousquet PJ, Chatzi L, Jarvis D, Burney P. Assessing skin prick tests reliability in ECRHS-I. *Allergy*. 2008;63:341-346.
17. Choi IS, Koh YI, Koh JS, Lee MG. Sensitivity of the skin prick test and specificity of the serum-specific IgE test for airway responsiveness to house dust mites in asthma. *J Asthma*. 2005;42:197-202.
18. Yunginger JW, Ahlstedt S, Eggleston PA, Homburger HA, Nelson HS, Ownby DR, et al. Quantitative IgE antibody assays in allergic diseases. *J Allergy Clin Immunol*. 2000;105:1077-1084.
19. Demoly P, Michel F, Bousquet J. In vivo methods for study of allergy. Skin tests, techniques and interpretation. In: Middleton E, Reed C, Ellis E, Adkinson N, Yunginger J, Busse W, eds. *Allergy, Principles and Practice*. 5th ed. St. Louis (MO): Mosby; 1998:530-539.
20. Pastorello EA, Incorvaia C, Ortolani C, Bonini S, Canonica GW, Romagnani S, et al. Studies on the relationship between the level of specific IgE antibodies and the clinical expression of allergy: I. Definition of levels

- distinguishing patients with symptomatic from patients with asymptomatic allergy to common aeroallergens. *J Allergy Clin Immunol.* 1995;96:580–587.
21. Rance F, Abbal M, Lauwers-Cances V. Improved screening for peanut allergy by the combined use of skin prick tests and specific IgE assays. *J Allergy Clin Immunol.* 2002;109:1027–1033.
 22. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol.* 2001;107:891–896.
 23. Lopes MI, Miranda PJ, Sarinho E. Use of the skin prick test and specific immunoglobulin E for the diagnosis of cockroach allergy. *J Pediatr (Rio J).* 2006;82:204–209.
 24. Patterson ML, Slater JE. Characterization and comparison of commercially available German and American cockroach allergen extracts. *Clin Exp Allergy.* 2002;32:721–727.
 25. Calabria C, Hagan L. The role of intradermal skin testing in inhalant allergy. *Ann Allergy Asthma Immunol.* 2008;101:337–347.
 26. Bousquet PJ, Leynaert B, Neukirch F, Sunyer J, Janson CM, Anto J, et al. Geographical distribution of atopic rhinitis in the European Community Respiratory Health Survey I. *Allergy.* 2008;63:1301–1309.
 27. Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol.* 2005;116:377–383.
 28. Paris-Kohler A, Demoly P, Persi L, Lebel B, Bousquet J, Arnoux B. In vitro diagnosis of cypress pollen allergy by using cytofluorimetric analysis of basophils (Basotest). *J Allergy Clin Immunol.* 2000;105:339–345.