Association of skin test reactivity, specific IgE, total IgE, and eosinophils with nasal symptoms in a community-based population study

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Background: *Skin prick tests and measurement of specific IgE are important markers of the possible allergic causes of disorders of the upper respiratory tract.*
Objective: *In this study we investigated the association of skin test reactivity and specific IgE positivity to five common aeroallergens separately and of total serum IgE and eosinophil count with nasal allergy symptoms in a random sample of the adult population in The Netherlands.*
Methods: *A cross-sectional study was carried out in a sample of 2167 subjects, aged 20 to 70 years, stratified by age and gender. Nasal allergy symptoms were differentiated into three categories: symptoms after exposure to indoor allergens only, symptoms after exposure to outdoor allergens only, and symptoms after exposure to both indoor and outdoor allergens. Associations were investigated by multiple logistic regression analyses with adjustment for area of residence, gender, age, and smoking status.*
Results: *Skin test and specific IgE reactivity to indoor and outdoor allergens were significantly related to their corresponding nasal symptom groups. Odds ratios increased with increasing number of positive skin test results or increasing levels of specific IgE to allergens in all three nasal symptom groups. For each allergen, a positive skin test result together with a positive specific IgE measurement were the strongest predictors of nasal symptoms. Sensitization to house dust mite was the most prevalent in our study population, whereas the association of skin test reactivity and specific IgE positivity with nasal symptoms was strongest for cat allergen. Skin test and specific IgE reactivity to* Cladosporium *species were not significantly related to the prevalence of nasal symptoms. Total serum IgE was related to nasal symptoms only in subjects who reported symptoms in response to both indoor and outdoor allergens and only at high levels of IgE. Eosinophil count was associated with nasal symptoms in all nasal symptom groups.*
Conclusions: *Our findings confirm the close relationship of skin test positivity with reported symptoms of nasal allergy in a general population. Specific IgE positivity also shows a close relationship with nasal symptoms in response to allergen exposure in a general population. Skin testing and specific IgE measurement may be considered complementary to one another in diagnosing allergic rhinitis. Total IgE may be considered an indicator of greater dysregulation of the immune system in atopic allergy. Eosinophil count is associated with nasal symptoms, regardless of type and extent of nasal symptoms. (J ALLERGY CLIN IMMUNOL 1996;97:922-32.)*

Key words: *General population, nasal allergy, skin test reactivity, specific IgE positivity, total serum IgE, eosinophil count*

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Abbreviations used

CI:	Confidence interval
ECRHS:	European Community Respiratory Health Survey
HDM:	House dust mite
OR:	Odds ratio

Skin prick tests and measurement of specific IgE levels are important in identifying the possible allergic causes of disorders of the respiratory tract. In the Tucson survey, Burrows et al.[1] and Barbee et al.[2] found a close relationship between skin test reactivity and reported allergic rhinitis, whereas the prevalence of asthma appeared to be more closely related to total serum IgE levels. Tollerud et al.[3] demonstrated a similar relationship of skin test reactivity with hay fever, independent of serum IgE levels in a study population of 1071 men, aged 41 to 86 years. The relationship of specific IgE, skin test reactivity, and eosinophil count with allergic respiratory symptoms was investigated in a population of 274 adult patients with obstructive airway disease by Brand et al.,[4] who found that skin test reactivity was the only allergy parameter independently related to allergic symptoms. However, in that study the only allergen involved was house dust mite (HDM). Gergen et al.[5] demonstrated the association of skin test reactivity to several individual allergens with nasal allergy and asthma; that study involved a sample of limited age range (6 to 24 years) only and did not include measurement of specific IgE. Furthermore, in the United States the distribution of aeroallergens is substantially different from that in Europe.[5]

The aim of this study was to investigate more thoroughly the relationship between skin test reactivity and specific IgE positivity to five common allergens, total serum IgE, eosinophil count, and the prevalence of nasal symptoms in a general population with a wide range in age. Furthermore, to determine the importance of individual allergens in eliciting nasal symptoms, we investigated the association of skin test reactivity and specific IgE positivity to five aeroallergens with the prevalence of nasal symptoms. We also examined the significance of skin test and specific IgE reactivity to these allergens, alone and in combination, as independent predictors of nasal allergy symptoms. In the analyses nasal symptoms were differentiated into three mutually exclusive phenotypic categories: symptoms after exposure to indoor allergens (house dust and/or animals) only, symptoms after exposure to outdoor allergens (pollen) only, and symptoms after exposure to both indoor and outdoor allergens.

METHODS

Study design

The analyses were performed with data from the Dutch part of the European Community Respiratory Health Survey (ECRHS), a cross-sectional survey, which was carried out in 17 European countries.[6] A random sample, stratified by gender and age (age categories of 10 years) of 4522 persons, aged 20 to 70 years, was drawn from the municipal registers in three different regions of The Netherlands. The subjects were asked to undergo extensive medical tests, which were carried out between February 1992 and January 1993.

Questionnaire and definitions

Data on allergy symptoms, smoking history, and family history of asthma and allergy were obtained by questionnaire. The questionnaire was part of the protocol of the ECRHS.[6] Questions on nasal symptoms were: (1) "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 get a runny or stuffy nose or start to sneeze, or get itchy or watering eyes?" and (2) "When you are near trees, grass or flowers, or when there is a lot of pollen about, do you ever get a runny or a stuffy nose or start to sneeze, or get itchy or watering eyes?"[6] On the basis of these two questions, symptoms of the nose and eyes were differentiated into three mutually exclusive categories: (1) symptoms after exposure to indoor allergens (house dust and/or animals) only, (2) symptoms after exposure to outdoor allergens (pollen) only, and (3) symptoms after exposure to both indoor and outdoor allergens. Smokers were defined as those who smoked at least one cigarette per day or one cigar per week for a period of 1 year and who were still smoking within 1 month before the examination. Ex-smokers were all smokers who had stopped smoking at least 1 month before the examination. All others were considered "never smokers."

Skin prick testing

Skin prick testing with environmental allergens was carried out with Phazets (Pharmacia Diagnostics AB, Uppsala, Sweden). The allergens tested were: *Dermatophagoides pteronyssinus* (HDM), cat, *Cladosporium herbarum, Alternaria alternata,* timothy grass, olive, birch, *Parietaria* species, and common ragweed; positive (histamine) and negative (uncoated Phazet) controls were also used. Wheal diameters were recorded 15 minutes after application of the antigens by circumscribing the wheal in ink and transferring this to adhesive tape. Mean diameters were calculated as the mean of the widest diameter and the perpendicular diameter measured at its midpoint. Responders to the negative control (>2 mm) and nonresponders to the positive control (<1

mm) were excluded from the analyses. A mean wheal diameter of 3 mm or more was considered a positive response.

Total and specific IgE

Venous blood was collected and centrifuged at 2500 rpm for 10 minutes. Serum samples were stored at −20° C before they were transported to the Central Laboratory at Pharmacia Diagnostics (Uppsala, Sweden). Total IgE and specific IgE to *D. pteronyssinus* (HDM), cat, *Cladosporium* spp., timothy grass, and birch were measured with the Pharmacia CAP system (Pharmacia Diagnostics). Specific IgE levels equal to or greater than 0.70 kU/L (IgE class 2) were considered positive. This cutoff point was chosen because of the greater concordance with skin test results for all five allergens as compared with 0.35 kU/L.

Eosinophil count

Venous blood was drawn into collection tubes containing ethylenediaminetetraacetic acid anticoagulant. Eosinophil counts were performed in four hospital laboratories: Martini Hospital, Groningen, with Technicon H1 (Technicon Instruments Corp., Tarrytown, N.Y.); Lievensberg Hospital, Bergen op Zoom, with Technicon H1; St. Franciscus Hospital, Roosendaal, with Technicon H6000; and Maasland Hospital, Geleen, with a Bürker-Turk counting chamber. In automated hematology analyzers, eosinophils were measured as number of cells per milliliter or liter and recalculated as number of cells per cubic millimeter.

Data analyses

All analyses were performed in the study population of subjects with complete data for questionnaire, skin tests, specific and total IgE measurements, and eosinophil count. Subjects with missing data for these variables were excluded from the analyses. Differences in prevalence rates of nasal symptoms by gender and age category were tested by the Mantel-Haenszel chi square test for linear trend. Results were considered significant if the p value was less than 0.05.

The association of skin prick test results and specific IgE measurements with nasal symptom prevalence has been investigated by multivariate logistic regression analysis with adjustment for area of residence, gender, age, smoking status, and reactivity to other allergens. For each of the nasal symptom groups, a separate regression model was fitted; in each regression model, the subjects without nasal symptoms were used as a referential category. Skin test and specific IgE reactivity were entered as categorical variables with the categories one, two, and three or more positive skin test results or specific IgE measurements versus no positive skin test result or specific IgE measurement, and for each allergen individually, as dichotomous variables with positive versus negative skin test results or specific IgE measurements. To determine whether a cumulative effect of skin test reactivity and specific IgE positivity existed on nasal symptom prevalence, for each allergen these parameters were aggregated into one variable with the distinct categories of positive skin test result only, positive specific IgE measurement only, and both positive skin test result and specific IgE measurement versus both negative skin test result and IgE measurement as a referential category. To determine whether the effect of skin test plus specific IgE positivity was significantly different from the main effects of these parameters, an interaction term of skin test result and specific IgE measurement, again for each individual allergen, was added to the regression models. Finally, all allergy parameters (skin test reactivity, specific IgE, total IgE, eosinophils) and other possible risk factors were entered simultaneously into the regression model in order to determine the relationship of these allergy parameters with the nasal symptom groups independently of one another. Results of skin tests and specific IgE measurements of individual allergens were entered as dichotomous variables with negative skin test result or specific IgE measurement as referential categories. Total serum IgE and eosinophil count were continuous variables. To approximate a normal distribution, total IgE and eosinophil count were analyzed after natural logarithmic transformation. Geometric means were calculated by taking the antilog of the means of log total IgE and log eosinophil count. Of the nine allergens used in skin prick tests, only those with concomitant data on specific IgE were used in the analyses. Odds ratios (ORs) were considered significant if the 95% confidence interval (CI) did not include value 1. The statistical analyses were performed with the SPSS-PC + V4.0 statistical program (SPSS Inc., Chicago, Ill.).

RESULTS

Of the 4522 subjects invited to participate in the study, 2711 (60%) took part. Nonresponders differed significantly from responders by age (in the age category 20 to 29 years only: 23.0% in nonresponders vs 18.3% in responders), current smoking (50.4% in nonresponders vs 36.7% in responders), and nasal symptoms (16.1% in nonresponders vs 21.6% in responders). For 2500 subjects, complete questionnaire data on symptoms, medical history, and smoking status were available. Of those, complete data on skin tests were available from 2317 subjects, data on total and specific IgE from 2297 subjects, and on eosinophil count from 2295 subjects. Of these subjects, 2167 without missing data for any variable were included in the analyses.

Characteristics of the study population are listed in Table I, stratified by type of nasal allergy symptoms. Subjects with nasal symptoms were more likely to be women, and never smokers and to have a family history of asthma and/or allergy, as compared with subjects without nasal symptoms.

TABLE I. Population characteristics for subjects with and without nasal allergy symptoms after exposure to indoor and outdoor allergens

	Nasal allergy symptoms			
	None (n = 1527)	Indoor allergens only (n = 276)	Outdoor allergens only (n = 142)	Indoor and outdoor allergens (n = 222)
Area				
Groningen (%)	32.0	35.9	28.2	30.6
Brabant (%)	38.1	31.5	38.7	37.2
Limburg (%)	29.9	32.6	33.1	30.6
Mean age in years (SD)	46 (14)	40 (14)	44 (13)	43 (14)
Gender				
Male (%)	54.5	49.3	51.4	40.5
Female (%)	45.5	50.7	48.6	59.5
Smoking status				
Never (%)	30.8	38.8	36.6	44.1
Ex (%)	31.5	25.0	31.0	27.5
Current (%)	37.7	36.2	32.4	28.4
Parental allergy (%)	7.5	10.5	14.8	18.0
Parental asthma (%)	16.1	25.7	25.4	38.7

SD, Standard deviation.

On average, subjects with nasal symptoms were younger than subjects without reported nasal symptoms. The prevalence of self-reported nasal symptoms in the population at the time of the study was 29.5%: to indoor allergens only: 12.7%, to outdoor allergens only: 6.6%, to both indoor and outdoor allergens: 10.2%. Nasal symptoms were most prevalent in the group of subjects aged 20 to 29 years, and the prevalence decreased with age (Fig. 1). This relationship with age existed in both men and women and was most obvious in subjects with symptoms after exposure to indoor allergens only (chi square for linear trend 38.7, p = 0.000). In subjects allergic to pollen only, the difference in prevalence by age group was not significant (chi square for linear trend 0.98, p = 0.321). In almost all age groups the prevalence of nasal symptoms was higher in women than in men.

Of the subjects who did not report nasal symptoms, 15.5% had a positive skin test reaction to at least one allergen (Table II). The prevalence of at least one positive skin test reaction in subjects with symptoms after exposure to indoor allergens only was 39.1%, and in subjects with symptoms after exposure to outdoor allergens only, 43.7%. Among subjects who reported nasal symptoms after exposure to both types of allergens, 55.4% had at least one positive skin test reaction. Skin test reactivity to HDM was the most prevalent in our study population: from 10.3% in subjects without nasal symptoms to 36.0% in subjects with symptoms after exposure to both types of allergen. The prevalence of at least one positive specific IgE measurement was 14.5% in subjects without nasal symptoms, 36.6% in subjects with symptoms after exposure to indoor allergens only, 41.5% in subjects with symptoms after exposure to outdoor allergens only, and 57.7% in subjects with symptoms after exposure to both types of allergens. Similar to skin test reactivity, specific IgE positivity to HDM was the most prevalent of the five allergens tested: from 9.7% in subjects without nasal symptoms to 37.4% in subjects with symptoms after exposure to both types of allergens.

Skin test scores were strongly associated with nasal symptoms (Table III, A). ORs (adjusted for area of residence, age, gender, and smoking status) increased with increasing number of positive skin test reactions in all three nasal symptom groups, particularly in subjects with symptoms after exposure to both indoor and outdoor allergens (OR, 3.8-33.6). Subjects with positive skin test scores for HDM and cat were more likely to report symptoms after exposure to indoor allergens only (OR, 3.3 and 10.3, respectively) or to both indoor and outdoor allergens (OR, 2.7 and 4.9, respectively), whereas subjects with positive skin test scores for timothy grass and birch were more likely to report nasal symptoms after exposure to outdoor allergens only (OR, 6.6 and 4.1, respectively) or to both

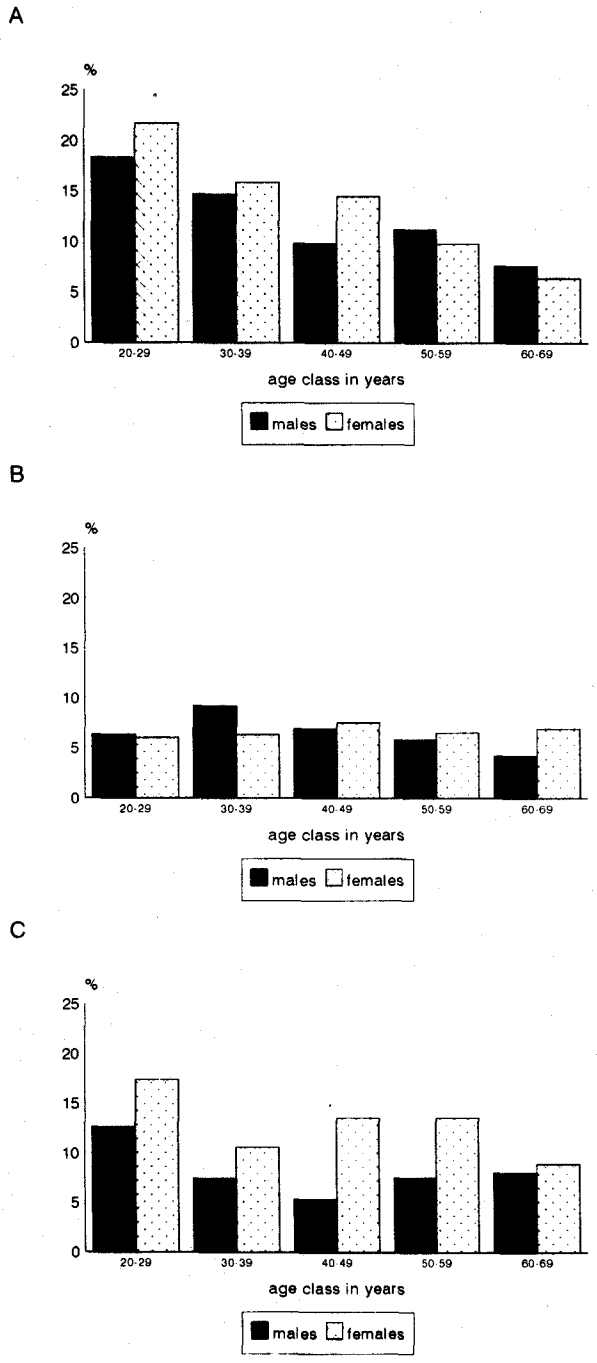

FIG. 1. Prevalences of nasal symptoms after exposure to indoor allergens only **(A)**, to outdoor allergens only **(B)**, and to both indoor and outdoor allergens **(C)**, by gender and age class.

indoor and outdoor allergens (OR, 4.5 and 4.2, respectively). In all three groups of subjects with nasal symptoms, those with skin test reactivity to *Cladosporium* spp. were less likely to report nasal symptoms (OR, 0.2-0.4). The association of specific IgE measurements with nasal symptoms was similar to skin test reactivity (Table III, B). ORs increased with increasing number of positive specific IgE measurements, particularly in subjects with symptoms after exposure to both indoor and outdoor allergens (OR, 4.6-38.0). Elevated levels of specific IgE to HDM and cat were associated with symptoms after exposure to indoor allergens only (OR, 3.1 and 12.9, respectively) and to both indoor and outdoor allergens (OR, 2.9 and 7.8, respectively). Specific IgE to timothy grass and birch were associated with symptoms after exposure to outdoor allergens only (OR, 5.9 and 3.8, respectively) and to both indoor and outdoor allergens (OR, 3.8 and 4.0, respectively). In all three nasal symptom categories an inverse relationship existed between nasal symptoms and specific IgE positivity to *Cladosporium* spp. (OR, 0.3-1.0). Because of very low prevalence and lack of statistical significance of the associations between positive results of tests with *Cladosporium* and nasal symptoms, *Cladosporium* was excluded from the next analyses.

When entered as one categorical variable for each allergen in the regression model, the relationships of a positive skin test result and specific IgE measurement, alone as well as combined, with nasal symptoms, can be determined for each allergen separately (Table IV). In these results we will confine ourselves to the associations between individual allergens and their "matching" symptom categories. In subjects with symptoms after exposure to indoor allergens only, reactivity to HDM as determined by skin test alone (OR, 2.1) and by skin test plus specific IgE measurement (OR, 3.8) was associated with the prevalence of symptoms, whereas in subjects with symptoms after exposure to both indoor and outdoor allergens, a positive specific IgE measurement (OR, 2.8) and positive IgE measurement plus skin test reaction (OR, 2.8) were related to symptoms. For cat allergen, a positive skin test result alone (OR, 4.3), positive specific IgE measurement alone (OR, 7.3), and positive skin test result plus specific IgE measurement (OR, 66.1) were related to symptoms after exposure to indoor allergens only; a positive specific IgE measurement alone (OR, 4.0), or together with a positive skin test result (OR, 18.9), was related to symptoms after exposure to both indoor and outdoor allergens. Skin test and specific IgE reactivity to timothy grass, individually, as well as combined, were associated with symptoms after exposure to outdoor allergens only (OR, 4.2 and 10.6, respectively), whereas in subjects with symptoms after exposure to both indoor and outdoor

TABLE II. Distribution of allergy parameters in subjects with and without nasal allergy symptoms

	Nasal allergy symptoms			
	None (n = 1527)	Indoor allergens only (n = 276)	Outdoor allergens only (n = 142)	Indoor and outdoor allergens (n = 222)
Positive ST result (%)				
HDM	10.3	31.9	16.9	36.0
Cat	1.2	13.4	6.3	14.9
Cladosporium spp.	1.4	1.8	2.8	3.2
Timothy grass	3.6	7.2	26.1	28.8
Birch	3.7	9.1	22.5	25.7
Positive specific IgE (%)				
HDM	9.7	29.3	17.6	37.4
Cat	0.7	12.0	3.5	16.7
Cladosporium spp.	0.9	1.4	0.7	5.0
Timothy grass	4.5	9.4	28.9	32.4
Birch	2.9	6.5	21.1	23.9
One or more positive ST results (%)	15.5	39.1	43.7	55.4
One or more positive specific IgE (%)	14.5	36.6	41.5	57.7
One or more positive ST results or specific IgE (%)	20.2	44.6	48.6	63.1
GM total IgE in kU/L (SD)	24.7 (4.4)	38.6 (4.9)	38.0 (4.6)	69.7 (4.9)
GM eosinophils (n/mm^3) (SD)	98.1 (2.1)	111.2 (2.1)	111.0 (2.0)	124.6 (2.2)

ST, Skin test; *GM,* geometric mean; *SD,* standard deviation.

allergens, the prevalence of symptoms was associated with a positive specific IgE measurement (OR, 2.4) and a positive IgE measurement plus a positive skin test result (OR, 5.5). For birch allergen, only a positive skin test result plus a positive specific IgE measurement were significantly related to symptoms (OR, 6.2 and 5.2), whereas a single positive test score could not predict the occurrence of symptoms. Of skin test–specific IgE interactions, only the interaction of skin test and specific IgE to birch allergen was significantly associated with symptoms after exposure to outdoor allergens (pollen) (OR, 13.0; results not shown).

To determine the independent association of different allergy parameters with nasal symptom prevalence, all allergy parameters were included simultaneously in a multivariate logistic regression model (Table V). Interactions between skin test results and specific IgE measurements were omitted from this model because of missing statistical significance. Skin test reactivity and specific IgE positivity to indoor and outdoor allergens were related to their corresponding nasal symptom groups. Similar to the results in Table IV, in subjects reporting symptoms after exposure to both indoor and outdoor allergens, mainly positive specific IgE measurements were associated, independently of skin test results, with nasal symptoms; whereas for skin test reactivity, only a positive skin test response to birch was significantly related to the presence of symptoms. Log eosinophil count was independently related to nasal symptoms in all symptom groups (OR, 1.2-1.6), whereas log total IgE was significantly associated only with symptoms to both indoor and outdoor allergens (OR, 1.2). Finally, though not always at a statistically significant level, women, younger age groups, never smokers, and subjects with a parent who had asthma or allergy were more likely to report nasal allergy symptoms.

DISCUSSION

Relationship with individual allergens

Nasal allergy symptoms can be induced by a wide range of allergens. In our study population HDM, timothy grass, and birch were the most prevalent sensitizing allergens in skin tests and specific IgE measurements. This depends mostly on the kind of allergen exposure and is in agreement with results of other European studies, in which HDM is the most prevalent allergen.[7-9] To evaluate the influence of individual allergens on the prevalence of nasal symptoms, the association with nasal symptoms of each allergen has been assessed by accounting for the reactivity to other

TABLE III. Association between nasal allergy symptoms as dependent variable and skin test scores (A) and specific IgE measurements (B) as independent variables

Independent variable	*n*	Nasal symptom groups		
		Indoor allergens only	Outdoor allergens only	Indoor and outdoor allergens
A.				
No. of positive ST results				
0	1637	1	1	1
1	339	2.6 (1.8-3.6)	3.0 (1.9-4.6)	3.8 (2.6-5.6)
2	109	5.4 (3.1-9.4)	7.8 (4.0-15.1)	15.9 (9.2-27.6)
≥3	82	7.4 (3.5-15.5)	14.5 (6.6-32.1)	33.6 (17.4-64.9)
Individual ST results				
HDM Pos	350	3.3 (2.3-4.6)	0.7 (0.4-1.4)	2.7 (1.8-3.7)
Cat Pos	98	10.3 (5.1-20.6)	4.2 (1.4-12.0)	4.9 (2.3-10.2)
Cladosporium spp. Pos	37	0.2 (0.1-0.7)	0.3 (0.1-1.3)	0.4 (0.1-1.2)
Timothy Pos	176	0.6 (0.3-1.2)	6.6 (3.7-11.6)	4.5 (2.8-7.4)
Birch Pos	170	1.7 (0.9-3.0)	4.1 (2.4-7.2)	4.2 (2.6-6.8)
B.				
No. of positive specific IgE measurements				
0	1657	1	1	1
1	325	2.6 (1.8-3.6)	2.6 (1.6-4.1)	4.6 (3.2-6.7)
2	111	3.8 (2.1-6.9)	9.6 (5.3-17.6)	17.4 (10.3-29.3)
≥3	74	8.5 (4.0-18.1)	12.5 (5.3-29.9)	38.0 (18.6-77.4)
Individual specific IgE measurements				
HDM Pos	337	3.1 (2.2-4.1)	1.0 (0.6-1.7)	2.9 (2.0-4.4)
Cat Pos	86	12.9 (6.0-27.8)	1.3 (0.3-3.6)	7.8 (3.4-18.0)
Cladosporium spp. Pos	29	0.5 (0.1-2.5)	0.3 (0.0-2.4)	1.0 (0.3-3.2)
Timothy Pos	207	0.7 (0.4-1.4)	5.9 (3.5-10.1)	3.8 (2.4-6.2)
Birch Pos	146	1.1 (0.6-2.3)	3.8 (2.1-6.9)	4.0 (2.4-6.1)

Referential category is no positive skin test result or no specific IgE measurement. Odds ratios (95% CI) adjusted for residential area, gender, age, and smoking status.
ST, Skin test; *Pos,* positive.

allergens. Skin test reactivity and specific IgE positivity to indoor and outdoor allergens were closely related to their corresponding symptom categories. Thus by linking nasal symptoms with exposure to a specific type of allergen, a questionnaire can be useful in differentiating between nasal symptoms induced by indoor allergens and those induced by outdoor allergens.

Although reactivity to HDM was the most prevalent, reactivity to cat allergen had the strongest association with allergy symptoms. This may be explained by the particle size of cat allergen, which is smaller than that of HDM allergen. HDM allergen becomes airborne only after disturbance and falls rapidly, whereas cat allergen remains airborne for long periods, even without disturbance, which may result in a high symptom prevalence in subjects sensitized to cat allergen.[10, 11] The significant relationship of a positive skin test response to cat allergen, even in subjects reporting symptoms after exposure to outdoor allergens only, adds to the conclusion that cat allergen is an important allergen in the development of nasal allergy symptoms. These findings also underline the importance of taking specific measures to reduce exposure to cat allergen in sensitized subjects.

Subjects sensitized to *Cladosporium* spp., according to skin test results and specific IgE measurements, were less likely to report nasal symptoms than those without reaction to *Cladosporium* spp. This finding may be due to the adjustment for other allergens. Reactivity to *Cladosporium* spp. was often accompanied by reactivity to other allergens. Of 37 subjects with skin test reactivity to *Cladosporium* spp., only 10 showed no other positive skin test results, of which eight did not report nasal symptoms. Similarly, of 29 subjects with

TABLE IV. Odds ratios (95% CI) for nasal allergy symptoms of subjects with a positive skin test result only, positive specific IgE only, and positive skin test result with positive specific IgE, compared with subjects with negative skin test results and specific IgE as referential category

Independent variable	Nasal symptom groups		
	Indoor allergens only (*n* = 276/1527)	Outdoor allergens only (*n* = 142/1527)	Indoor and outdoor allergens (*n* = 222/1527)
HDM positive			
ST only	2.1 (1.1-4.0)*	0.7 (0.3-2.0)	1.4 (0.6-3.3)
Specific IgE only	1.4 (0.7-3.1)	1.7 (0.7-4.2)	2.8 (1.4-6.0)*
ST + specific IgE	3.8 (2.6-5.7)*	0.5 (0.3-1.1)	2.8 (1.8-4.4)*
Cat positive			
ST only	4.3 (2.0-9.4)*	4.0 (1.4-11.3)*	2.5 (0.9-6.7)
Specific IgE only	7.3 (3.4-19.0)*	1.7 (0.4-7.2)	4.0 (1.3-11.9)*
ST + specific IgE	66.1 (12.8-341.4)*	0.4 (0.0-5.3)	18.9 (3.8-93.9)*
Timothy positive			
ST only	1.0 (0.4-2.6)	4.2 (1.5-11.5)*	2.0 (0.9-5.0)
Specific IgE only	0.8 (0.4-1.9)	4.1 (1.8-9.6)*	2.4 (1.2-5.0)*
ST + specific IgE	0.2 (0.1-0.7)	10.6 (5.4-20.6)*	5.5 (3.0-9.9)*
Birch positive			
ST only	2.2 (1.0-4.2)*	0.9 (0.3-3.0)	2.3 (1.0-5.3)
Specific IgE only	2.1 (0.7-6.6)	0.5 (0.1-2.7)	2.1 (0.7-6.0)
ST + specific IgE	0.9 (0.4-2.2)	6.2 (3.2-12.0)*	5.2 (2.8-9.4)*

All allergens simultaneously in the regression model. Odds ratios adjusted for residential area, gender, age, and smoking status. (n = number of subjects with/without symptoms in regression model).
ST, Skin test.
*95% CI not including value 1.

specific IgE to *Cladosporium* spp., only six had no other positive specific IgE measurements, and none of them reported nasal symptoms. Without accounting for the other allergens tested, ORs of skin test reactivity to *Cladosporium* spp. were between 1.2 and 2.1 for the different symptom categories, none of which were significant; ORs of specific IgE to *Cladosporium* spp. were between 0.8 and 5.8, of which only the latter, in subjects with symptoms to both indoor and outdoor allergens, was significant. Although these findings should be regarded with some reservation, considering the interrelationship with other allergens and the very low rates of reactivity to *Cladosporium* spp. in this study population, skin test reactivity and specific IgE positivity to *Cladosporium* spp. seem to be of less clinical importance with regard to inducing nasal symptoms.

Relationship with allergy parameters

Our results show that skin test reactivity and specific IgE positivity are both strongly associated with nasal symptoms. The prevalence of reported nasal symptoms increased with increasing numbers of positive skin test results and positive specific IgE measurements. This finding is in agreement with Gergen et al.[5, 12] who found a similar quantitative relationship of skin test reactivity with allergic rhinitis. These associations remained significant after controlling for one another and for total serum IgE and eosinophil count. This finding is in accordance with other population studies in that they also demonstrated a close relationship of skin test reactivity, independent of serum IgE and eosinophilia, with allergic rhinitis[1, 2] and hay fever.[3] On the other hand, Brand et al.[4] found a close relationship only with skin test reactivity, whereas specific IgE appeared not to be an independent predictor of allergic symptoms. These differences may be attributed to the fact that we used the Pharmacia CAP system, which is known to be more sensitive than the conventional RAST system,[13] and Phazets for skin prick tests, which may be less sensitive than the intracutaneous test used by Brand et al.[4] The differences in sensitivity between skin testing and specific IgE measurements may also contribute to the allergen-specific differences of associations with nasal symptoms of skin test and specific IgE reactivity (Table IV). This may be explained by the fact that although the allergens are basically the same, in specific IgE measurement all IgE antibodies specific to all

TABLE V. Independent association of different allergy parameters with nasal allergy symptoms, for each symptom group separately

Independent variable	Nasal symptom groups		
	Indoor allergens only (*n* = 276/1527)	Outdoor allergens only (*n* = 142/1527)	Indoor and outdoor allergens (*n* = 222/1527)
Gender: female vs male	1.3 (1.0-1.7)	1.3 (0.9-1.9)	2.2 (1.6-3.0)*
Age (yr)	0.98 (0.97-0.99)*	1.00 (0.98-1.00)	1.01 (0.99-1.02)
Smoking			
Ex vs never	0.8 (0.6-1.2)	0.9 (0.6-1.3)	0.7 (0.5-1.1)
Current vs never	0.8 (0.6-1.0)	0.8 (0.4-1.0)	0.7 (0.4-0.9)*
Parental asthma	1.5 (0.9-2.2)	2.3 (1.2-3.5)*	2.5 (1.5-3.7)*
Parental allergy	1.6 (1.1-2.1)*	1.8 (1.1-2.6)*	2.5 (2.1-4.1)*
ST results			
HDM positive	2.3 (1.4-3.8)*	0.5 (0.2-1.0)	1.2 (0.7-2.2)
Cat positive	4.3 (2.1-8.8)*	2.6 (1.0-7.2)	2.4 (1.0-5.7)
Timothy positive	0.5 (0.2-1.3)	3.2 (1.5-6.5)*	1.9 (1.0-3.7)
Birch positive	1.6 (0.8-3.4)	2.6 (1.2-5.7)*	2.5 (1.2-4.9)*
Specific IgE			
HDM positive	1.5 (0.9-2.5)	1.5 (0.7-3.2)	1.9 (1.1-3.6)*
Cat positive	7.7 (3.3-17.7)*	0.7 (0.2-3.0)	3.3 (1.2-9.1)*
Timothy positive	0.7 (0.3-1.5)	3.4 (1.7-6.8)*	2.3 (1.3-4.3)*
Birch positive	0.8 (0.3-1.9)	2.1 (0.9-4.8)	2.1 (1.0-4.3)
Log total IgE (kU/L)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.2 (1.1-1.4)*
Log eosinophil count (n/mm^3)	1.2 (1.1-1.6)*	1.5 (1.1-1.8)*	1.6 (1.2-1.8)*

Odds ratios (95% CI) adjusted for area of residence, age, gender, smoking status, and parental predisposition. Each nasal symptom group as dependent variable. (n = number of subjects with symptoms/without symptoms in regression model).
ST, Skin test.
*95% CI not including value 1.

individual components of an allergen are being determined, whereas the purification and sterilization process and the adjustment of concentration, necessary for its safe application in vivo, may have affected the composition of the allergen extract of the Phazets. Nasal symptoms were best predicted by a positive skin test result together with specific IgE positivity to the same allergen. However, the interaction of skin test reactivity and specific IgE positivity did not, in general, improve the regression models significantly. This leads to the conclusion that although skin test and specific IgE reactivity by themselves are adequate predictors of nasal symptoms (as illustrated by Table III in which ORs of skin test and specific IgE reactivity are unadjusted for one another), skin tests and specific IgE measurements may also be considered as complementary to one another. Therefore it may be useful to apply both tests in diagnosing allergic rhinitis. This is also illustrated by the fact that skin test results show the biologic effect of an allergen in vivo in releasing histamine from mast cells, whereas in vitro specific IgE measurement shows the concentration of specific IgE in serum.

After adjustment for other allergy parameters, total serum IgE level was significantly associated with nasal symptoms only in subjects with symptoms after exposure to both indoor and outdoor allergens (OR, 1.2). This association remained unaffected after exclusion of subjects with a doctor's diagnosis of asthma. To elaborate this association, total IgE was also entered as categorical variable, according to its quartile distribution, with the lowest quartile as referential category. Only the highest quartile of total IgE (>87.6 kU/L), as compared with the lowest quartile (<11.3 kU/L), was independently related to nasal symptoms (OR, 2.1; 95% CI, 1.3-3.5). This finding is in accordance with the finding of Burrows et al.[1] that the slight independent relation of allergic rhinitis to total IgE was present at higher levels of IgE. Also, in the Normative Aging Study, only the highest quartile of total serum IgE was significantly related to hay fever.[3] Because the association of a high level of total

serum IgE with the prevalence of nasal symptoms existed only in subjects with symptoms after exposure to multiple allergens, total serum IgE may be considered an indicator of greater dysregulation of the immune system in atopic allergy.

After adjustment for the other allergy markers, blood eosinophil count was significantly related to nasal symptoms. This relationship was similar in all symptom categories and was unaffected by exclusion of subjects with a doctor's diagnosis of asthma. Tollerud et al.[3] found similar ORs of blood eosinophilia for the prevalence of hay fever, though not significant after controlling for other allergy parameters. Also, in the study by Brand et al.[4] blood eosinophil count did not independently predict nasal symptoms of allergy to HDM. In this study, when eosinophil count was entered as a categorical variable according to its quartile distribution, almost all quartiles of the eosinophil count were significantly associated with nasal symptoms in all three symptom groups (OR between 1.2 and 2.2, when compared with the lowest quartile). Unlike total serum IgE, eosinophil count seems to be unrelated to the degree of nasal symptoms.

Possible limitations of our study, which may have affected prevalence rates, are biases caused by nonresponse and misclassification. Responders reported nasal allergy symptoms more often than nonresponders. The prevalence of nasal symptoms may therefore be overestimated. Responders also differed from nonresponders in age in the age group 20 to 29 years and in current smoking status (both less prevalent in responders). Because nasal allergy is more prevalent among younger age groups but less prevalent among current smokers, the ultimate effect may be relatively small. Determining allergic symptoms by questionnaire can lead to some degree of misclassification. Self-reported symptoms may also be of nonallergic origin. Such misclassification may lead to an overestimation of the prevalence of nasal allergy symptoms. On the other hand, allergy symptoms may not be recognized as such. We assume that in symptoms of nasal allergy, only a small degree of misclassification occurred because specific symptoms of the nose and eyes after exposure to house dust, animals, and pollen were explicitly requested. Moreover, Bakke et al.[14] found good agreement between self-reported hay fever and a doctor's diagnosis of allergic rhinitis.

The associations of nasal symptoms with the various allergy parameters cannot be explained by bias caused by misclassification, because such nondifferential misclassification will introduce bias toward the null value, with a consequent underestimation of the associations found. Another potential confounder of our study may be the seasonal variation of symptom prevalence and level of allergy markers, particularly in regard to exposure to pollen. Despite seasonal differences in prevalence of nasal symptoms in subjects with symptoms after exposure to both indoor and outdoor allergens and in specific IgE positivity to HDM and birch (more prevalent in subjects examined in spring or summer), the associations of nasal symptoms with allergy markers were totally unaffected after adjustment of the regression models for these seasonal variations.

In summary, our findings confirm the close relationship of skin test reactivity with reported symptoms of nasal allergy in a general population. In addition, specific IgE positivity, as determined by the CAP system, also shows a close relationship with nasal symptoms in response to allergen exposure in a general population.

Because virtually no significant interactions were found between skin test reactivity and specific IgE positivity, skin test results and specific IgE measurements may be considered complementary to one another in diagnosing allergic rhinitis. Skin test reactivity and specific IgE positivity to individual allergens correlate well with corresponding nasal symptom categories, indicating that by linking the occurrence of symptoms with exposure to specific allergens, questionnaire data are useful to differentiate between reactivity to indoor and outdoor allergens. Though sensitization to HDM was the most prevalent in our study population, the association of skin test reactivity and specific IgE positivity with nasal symptoms was strongest for cat allergen, indicating the potency of cat allergen to elicit allergic symptoms. Total serum IgE is related to nasal symptoms only in subjects who report symptoms after exposure to both indoor and outdoor allergens and only at high levels of IgE. Eosinophil count is associated with the presence of nasal symptoms, regardless of type or extent of these symptoms.

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APPENDIX

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Note: These results come from local analyses of data collected for the ECRHS. Any final international comparison may use a different form of analysis.