

Interpretation of skin tests to house dust mite and relationship to other allergy parameters in patients with asthma and chronic obstructive pulmonary disease

Paul L. P. Brand, MD,^a Huib A. M. Kerstjens, MD,^a
Henk M. Jansen, MD, PhD,^b Henk F. Kauffman, PhD,^c
Jan G. R. de Monchy, MD, PhD,^c and the Dutch CNSLD Study Group*
The Netherlands

Background: The relationships between allergic symptoms after exposure to house dust, allergy parameters (skin test to house dust mite [HDM], total IgE, HDM-specific IgE, and blood eosinophil counts), and several confounding variables (age, sex, smoking habits, and airway hyperresponsiveness) were evaluated in 235 patients with asthma and chronic obstructive pulmonary disease (COPD).

Results: Skin tests had higher diagnostic value (sensitivity plus specificity) for symptomatic allergy than specific IgE (1.45 versus 1.36) or total IgE (1.16). The other allergy parameters gave no additional information on symptoms once the skin test was known. Expressing the skin test relative to the histamine control proved slightly better than uncorrected wheal size, but this probably has limited clinical value. The best cutoff level for a positive skin test was 0.7 when the histamine wheal size was accounted for by division, -6 mm when subtraction was used, and 7 mm for absolute wheal size. These cutoff levels proved equally applicable in various subgroups of patients with asthma and COPD. Only the skin test and female sex were independent predictors of allergic symptoms.

Conclusion: We conclude that skin tests to HDM are better predictors for clinical allergy than total or specific IgE levels and eosinophil count, and that they are applicable in most patients with asthma and with COPD. (*J ALLERGY CLIN IMMUNOL* 1993;91:560-70.)

Key words: Intradermal tests, allergy, respiratory hypersensitivity, asthma, chronic obstructive pulmonary disease

From the Departments of Pulmonology^a and Allergy,^c University Hospital Groningen, and the Department of Pulmonology, University Hospital of Amsterdam,^b the Netherlands.

*The Dutch CNSLD study group consists of a steering committee (K. F. Kerrebijn, Ph. H. Quanjer, and H. J. Sluiter); members from the departments of Pulmonology of the University Hospitals of Amsterdam (E. M. Pouw, D. F. M. E. Schoonbrood, C. M. Roos, H. M. Jansen), Groningen (P. L. P. Brand, A. de Gooyer, H. A. M. Kerstjens, D. S. Postma, Th. W. van der Mark, H. J. Sluiter, G. H. Koëter), Leiden (P. M. de Jong, P. J. Sterk, A. M. J. Wever, J. H. Dijkman), Nijmegen (P. N. R. Dekhuijzen, H. T. M. Folgering, C. L. A. van Herwaarden), Rotterdam (S. E. Overbeek, J. M. Bogaard, C. Hilvering), and Utrecht (S. J. Gans, H. J. J. Mengelers, B. van der Bruggen, J. Kreukniet); members from the departments of Pediatric Pulmonology of the Sophia Children's Hospital, Rotterdam (E. E. M. van Essen-Zandvliet, K. F. Kerrebijn); the Juliana Children's Hospital, the Hague (E. J. Duiverman, J. M. Kouwenberg, J. E. Prinsen); University Hospital of Groningen

(H. J. Waalkens, J. Gerritsen, K. Knol); members from the department of Allergy, University of Groningen (J. G. R. de Monchy), from the department of General Practice, University of Leiden (A. A. Kaptein, F. W. Dekker), and from the department of Physiology, University of Leiden (P. J. F. M. Merkus, Ph. H. Quanjer). Scientific counsel: S. J. Pocock, M. D. Hughes (London, U.K.), E. R. Bleeker, D. A. Meyers (Baltimore, Md.).

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Reprint requests: Jan G. R. de Monchy, MD, PhD, Department of Allergy, University Hospital, Oostersingel 59, 9713 EZ Groningen, the Netherlands.

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Immunoglobulin E (IgE)-mediated allergy is a major characteristic of asthma in younger age groups,^{1,2} the relevance of allergy in the development of chronic obstructive pulmonary disease (COPD) is currently being reevaluated.³ Diagnosis of an allergic disorder is largely based on medical history and can be confirmed by means of measurement of antigen-specific IgE levels or skin tests.^{4,5} The latter are considered to be the cornerstone of allergy diagnosis and are therefore commonly applied in patients with asthma and COPD.⁶

Advances in purification and standardization of allergen extracts are being made,⁷ but it remains difficult to compare skin test results from different studies because of differences in test technique (e.g., prick, scratch, or intradermal tests) and the use of different allergen extracts.⁸ Furthermore, atopic status is confounded by several patient characteristics, such as age,⁹⁻¹¹ sex,^{9,10,12,13} and smoking habits.^{11,12,14,15} The presence and severity of allergic symptoms in patients with obstructive airway diseases (both in asthma and in COPD) may be modulated by the level of airway responsiveness.^{16,17} Thus interpretation of skin test data and their relationship to allergic symptoms is also dependent on the patient population under study.

The wheal size of a skin test is usually assessed as the mean of the largest wheal diameter and that perpendicular to it (MWD).⁸ MWDs of skin tests may be expressed as absolute values (in millimeters), or they may be related to the size of the negative or positive control. There is no agreement on a threshold value for a positive skin test result.⁸

Epidemiologic studies have shown relationships between certain respiratory symptoms and distinct patterns of various allergy parameters.^{1,18,19} These findings may not be directly applicable to the clinical situation. The value of skin tests and specific IgE for predicting symptomatic allergy in patients has only been evaluated in a few studies with small samples of selected patients,^{4,20-22} none of which accounted for confounding variables such as age, sex, smoking, and airway hyperresponsiveness. To our knowledge, also no study has been performed comparing patients with asthma with those with COPD in this respect.

We have compared the diagnostic value of intradermal skin tests and specific IgE for allergy-like symptoms on exposure to house dust. The house-dust mite (HDM) is the most common aeroallergen in countries with a moderate climate.²³ Receiver-operating characteristic (ROC) analysis was used to find the best cutoff value of the skin test for predicting symptomatic allergy. The diagnostic value was compared in several subgroups of patients (with asthma and COPD) and was corrected for several confounding variables.

Abbreviations used

COPD:	Chronic obstructive pulmonary disease
FEV ₁ :	Forced expiratory volume in 1 second
HDM:	House dust mite
HEWS:	Histamine equivalent wheal size
IgE:	Immunoglobulin E
IU:	International units
MWD:	Mean wheal diameter
PC ₂₀ :	Provocative concentration of histamine that causes a 20% decline in FEV ₁
PRU:	Phadebas RAST units
RAST:	Radioallergosorbent test
ROC:	Receiver-operating characteristic
SD:	Standard deviation
CI:	Confidence interval

MATERIAL AND METHODS

Patients

For this report we used baseline data from a multicenter trial sponsored by the Dutch government. The main goal of this trial is to compare the effect of three different treatment regimens (beta agonist plus either placebo, anticholinergic agent, or corticosteroid, all by inhalation) on the long-term course and outcome of 274 patients (ages 18 to 60 years) with obstructive airways disease. The study design and methods have been described in detail previously.²⁴

With use of data from a standardized history, and by adhering to the criteria proposed by the American Thoracic Society,²⁵ different clinical syndromes were identified.²⁴

Patients reporting attacks of breathlessness and wheeze (asthmatic attacks) without chronic (i.e., for more than 3 months per year) cough or sputum production were labeled the *asthma* group.

Current or former smokers without a history of asthmatic attacks, reporting either chronic cough or sputum production or dyspnea when walking quietly on level ground, or both, were included in the *COPD* group.

Patients with both asthmatic attacks or recurrent wheeze and chronic cough and sputum production could not be attributed to the asthma or COPD group and were labeled the *asthmatic bronchitis* group.

A detailed smoking history was recorded. Pack years of smoking were calculated as number of packs of 20 cigarettes smoked per day times the number of years of active smoking.

The study protocol was approved by the medical ethics committees of all participating centers; all patients gave written informed consent.

Data acquisition

Before entering the study patients discontinued their usual maintenance treatment as described previously.²⁴ Spirometry was performed on water-sealed spirometers according to standardized guidelines.²⁶ Histamine provocation tests were

performed with a 2-minute tidal breathing method.²⁴ PC₂₀ histamine was defined as the provocative concentration of histamine that caused a 20% decline in forced expiratory volume in 1 second (FEV₁).

Symptomatic allergy

Symptomatic allergy was determined from a standardized questionnaire. Allergic pulmonary symptoms to house dust were defined as a positive answer to the question "do you ever have shortness of breath, or wheeze after contact with house dust?" Allergic nose or eye symptoms to house dust were defined as a positive answer to the question "do you ever sneeze or have a runny nose or red or itchy eyes after contact with house dust?" The presence of any allergic symptom to house dust was defined as a positive answer to any of these questions. Similar questions were asked for exposure to pollen, cat, dog, horse, fungi, and feathers.

Allergenic extracts

Twelve common aeroallergenic extracts were selected for intradermal skin testing: HDM,* several grass and tree pollens,* *Aspergillus*, *Alternaria*, dog,* cat,* horse,* rodents,* and bird feathers. The purified extracts were prepared at ALK, Copenhagen, Denmark, and made available by Diephuis Laboratory, Groningen, The Netherlands. All extracts were kept at 5° to 8° C to maintain stability during the study. Extracts were dissolved in phosphate-buffered saline solution (pH 7.4), which contained 0.3 mg/ml human serum albumin as stabilizer and 5 mg/ml phenol as preservative. The purified HDM extract we used contained *Dermatophagoides pteronyssinus* 30 Nordic biological units (BU)/ml, equaling 138 international units (IU) of the major allergen *Der p* I and 207 IU of *Der p* II.²⁷ 1000 BU/ml denotes the potency of an extract that elicits an identical reaction as that to histamine dihydrochloride 1 mg/ml in most individuals who are allergic to the material in the skin prick test.²⁷ Histamine dihydrochloride (0.01 mg/ml) and solvent were used as positive and negative controls, respectively.

Intradermal skin testing

All skin tests were performed by experienced technicians who received specific training for this study. Skin tests were performed between 9 AM and noon on the alcohol-cleansed volar surfaces of both forearms. A volume of 0.03 ml allergenic extract from disposable 0.5 ml syringes (28 G Monoject; Sherwood Medical, St Louis, Mo.) was injected intradermally. Tests were applied in a fixed order and numbered accordingly at least 5 cm apart from each other. Results were read after exactly 15 minutes. Only wheals accompanied by a flare reaction were read. The wheal area was determined by circumscribing the wheal in ink and transferring this to adhesive tape. The MWD was calculated as the mean of the largest wheal diameter and that perpendicular to it. The precision and reproducibility of this method have been studied previously: the coefficient of variation of the intradermal skin test was 5.7% within patients and 11.6% between patients.²⁸

*Standardized according to the Nordic guidelines.

IgE assay and specific IgE

All sera were stored at -20° C until the assays were performed in a single batch. Total IgE concentrations were quantified with the enzyme immunoassay procedure (Pharmacia, Uppsala, Sweden), and expressed in international units per milliliter. Specific IgE levels against HDM were determined by enzyme radioallergosorbent test (RAST) (disk procedure, Pharmacia) and expressed in classes and in Phadebas RAST units per milliliter.

Diagnostic value of skin tests, total IgE, specific IgE, and eosinophils for symptomatic allergy

Criteria for the definition of a positive skin test can be divided into four categories: (1) criteria based on the absolute allergen wheal size expressed as the mean of the largest wheal diameter and that perpendicular to it (MWD in mm); (2) criteria based on the difference in absolute size between the allergen wheal and the negative (solvent) control wheal in millimeters; (3) criteria based on the difference in absolute size between the allergen wheal and the positive (histamine) control wheal (MWD-histamine) in millimeters; (4) histamine equivalent wheal size (HEWS), that is, MWD of the HDM skin test divided by the MWD of the histamine skin test.

First, sensitivity and specificity for symptomatic HDM allergy were calculated for different cutoff levels of the above-mentioned expressions for a positive skin test.²⁹ For example, the diagnostic value of skin tests expressed as MWD were calculated for cutoff levels of 1, 2, 3, 4 mm, and so on. In a similar manner, diagnostic values were computed for HEWS of 0.1, 0.2, 0.3, 0.4, and so on. Because skin tests are used both as a tool to confirm and to exclude the suspicion of clinical allergy, the cutoff level with the highest sum of sensitivity plus specificity for allergic symptoms was determined.³⁰ This sum may be labeled the diagnostic value of a test.

Subsequently, the diagnostic values of the skin test were compared with those of total IgE, HDM-specific IgE, and blood eosinophils. No agreement exists as to proper threshold values for abnormal tests. Because the purpose of this report was to examine the interpretation of skin test data, we collected threshold values for total-IgE (>100 IU/ml) and eosinophils (>275/mm³) from the literature.^{18, 31}

Data analysis

Total IgE, blood eosinophils, and PC₂₀ levels were analyzed parametrically after logarithmic transformation. Group differences were evaluated with Student's *t* tests, one-way analysis of variance (ANOVA), and chi-square tests. Correlations were expressed as Pearson's *r* (Spearman's *ρ* for skewed distribution of specific IgE). Multiple linear regression was performed to analyze the influence of confounding variables on skin tests.

To correct the diagnostic values of skin tests and specific IgE for possible confounding variables, multiple logistic regression models were built with likelihood ratio tests.³² The bootstrap procedure was used with 100 samples to es-

TABLE I. Clinical characteristics of 235 patients under study

	Mean (SD)	Median (range)	No. (%)
FEV ₁ (%pred)	63.7 (15.8)		
log ₂ PC ₂₀ histamine (mg/ml)	-1.9 (2.3)		
Geometric mean	0.27		
log ₁₀ IgE (IU/ml)	2.1 (0.72)		
Geometric mean	121		
log ₁₀ eosinophils ($\times 10^6$ /L)	2.3 (0.42)		
Geometric mean	204		
Solvent wheal size (mm)	1.0 (2.2)		
Histamine wheal size (mm)	11.7 (2.1)		
MWD of HDM (mm)	13.1 (5.4)		
Age (yr)		40.4 (18-60)	
HDM-specific IgE (PRU/ml) for 122 non-zero values		8.1 (0.4-17.5)	
Pack years smoking		4.6 (0-123)	
Smoker: Current			85 (36%)
Ex			74 (31%)
Never			76 (32%)
Diagnosis: Asthma			96 (41%)
Asthmatic bronchitis			88 (37%)
COPD			51 (22%)
Pulmonary symptoms after house dust			128 (54%)
Any allergic symptom after house dust			144 (61%)

timize the standard error of the diagnostic value.³³ All analyses were performed with the SPSS/PC+ package.

RESULTS

Patients

Thirty-nine of the 274 patients enrolled in the study were excluded from analysis in this report: skin test data were incomplete in one patient; another two patients had negative skin tests to histamine, which makes interpretation of skin test results difficult⁶; in 36 patients history data were insufficient to identify a clinical syndrome. These excluded patients did not differ significantly (all *p* values >0.1) from the remaining 235 patients with respect to HDM-MWD, histamine-MWD, total IgE, specific IgE, blood eosinophils, FEV₁, PC₂₀, symptoms after house dust exposure, age, sex, and smoking habits. Clinical characteristics of the remaining 235 patients are presented in Table I. Ninety-six of the 235 patients were found to have asthma on the basis of history data; 51 had COPD; and the remaining 88 were labeled the *asthmatic bronchitis* group.

Skin test results

The mean (SD) histamine wheal size was 11.7 (2.1) mm. The allergen that most patients reacted to was HDM: 173 patients (74%) showed a measurable wheal (≥ 1 mm when accompanied by a flare reaction) after

HDM injection, followed by 72% to bird feathers, 66% to dog, 61% to cat, and 54% to grass pollen. Fewer than 50% of patients reacted to the other aeroallergens. In patients with a measurable wheal to HDM, the mean (SD) wheal size was 13.1 (5.4) mm as compared with 9.1 (2.9) for feathers, 10.7 (4.4) for dog, 11.9 (5.9) for cat, and 10.8 (5.2) for grass pollen. Because HDM proved to be the most common aeroallergen in this population, further analyses were restricted to HDM. No adverse effects of intradermal skin testing were noted, in particular no anaphylactic or systemic reactions were noted.

Diagnostic value of skin tests, total IgE, specific IgE, and eosinophils for clinical allergy

First, the best cutoff values for different expressions of skin test positivity were established. For example, MWD 7 mm had a higher diagnostic value (1.44; sensitivity 0.78, specificity 0.66) than the other cutoff levels for MWD (e.g., MWD >10 mm; 1.42; 0.69 and 0.73). In a similar manner HEWS >0.7 proved better (1.45; 0.76 and 0.69) than the other cutoff levels of HEWS (e.g., HEWS >0.5; 1.39; 0.84 and 0.55). The most discriminative values were 0.7 for HEWS, -6 mm for (MWD-histamine), and 7 mm for MWD (Fig. 1). Comparable results were obtained for the other allergens.

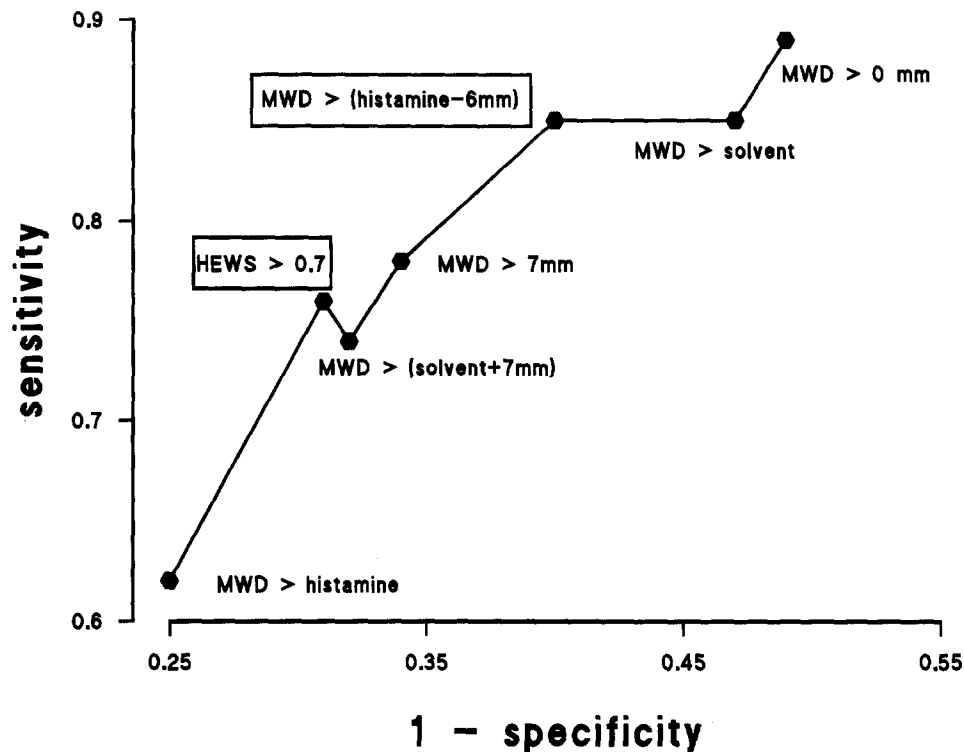


FIG. 1. Combined ROC curve shows diagnostic value of HDM skin test, expressed in various ways, for allergic symptoms. Sensitivity is plotted against (1 - specificity). The point closest to the upper left-hand corner of the plot identifies the expression with the highest diagnostic value of a positive skin test result. *Solvent*, Size of solvent wheal; *histamine*, size of histamine wheal.

TABLE II. Cutoff levels of skin test, IgE, specific IgE, and eosinophils with the highest diagnostic values for symptomatic house dust allergy

Skin test	Any allergic symptom			Allergic pulmonary symptoms only diagn. value
	Sensitivity	Specificity	Diagn. value	
MWD >7 mm	0.78	0.66	1.44	1.35
MWD >(solvent + 7 mm)	0.74	0.68	1.42	1.32
MWD >(histamine-6 mm)	0.85	0.60	1.45	1.36
HEWS >0.7	0.76	0.69	1.45	1.37
IgE >100 IU/ml	0.51	0.65	1.16	1.07
Specific IgE class >0	0.68	0.69	1.36	1.30
Eosinophils >275/mm ³	0.45	0.69	1.13	1.08

Diagn. value, diagnostic value (sum of sensitivity and specificity).

Skin test parameters, in whatever way expressed, had higher diagnostic values for symptomatic allergy than IgE and eosinophil level and also higher than specific IgE class for HDM (Table II). The sum of sensitivity and specificity was maximally 1.45 for the skin test, compared with 1.16 for total IgE, 1.36 for specific IgE, and 1.13 for eosinophils.

Diagnostic values of all allergy parameters for

symptoms of allergy were markedly higher when any allergic symptoms were studied than when respiratory symptoms only were analyzed (Table II).

Differences in diagnostic values for various ways of expressing the skin test were very small (Table II). Because adjusting the MWD of the HDM for the histamine control yielded somewhat higher diagnostic values (1.45 versus 1.44 for the uncorrected MWD

TABLE III. Adjusted odds ratios (and 95% CI) for the independent influences of different allergy parameters on allergic symptoms

Allergy parameter	Adj. odds ratio	95% CI	
		Lower limit	Upper limit
HEWS >0.7	5.4	2.0	15.1
IgE (10-fold increase)	1.2	0.7	2.2
HDM-specific IgE class	1.0	0.7	1.5
Eosinophils (10-fold increase)	0.6	0.3	1.4
Prior knowledge of skin test results	1.7	0.8	3.7

Adj. odds ratio. Adjusted odds ratio with any allergic symptom as dependent variable (see text).

and 1.42 for the solvent corrected MWD (Table II, Fig. 1), this expression was used for further analyses. The standard error of the diagnostic values as determined by bootstrap procedure was 0.05 for both histamine corrected skin test expressions.

Interrelationship between allergy parameters and their usefulness in predicting allergic symptoms

Skin test, total IgE, specific IgE, and eosinophil counts were all intercorrelated: correlation coefficients between HEWS and total IgE ($r = 0.51$), between HEWS and specific IgE class ($p = 0.77$), and between HEWS and eosinophil count ($r = 0.22$) were all highly significant ($p < 0.001$).

To establish whether different allergy parameters were related to allergic symptoms independently of one another, a multiple logistic regression model was built with allergic symptoms to house dust as the dependent variable. The results of the logistic model for allergic symptoms are presented in Table III. If the confidence interval (CI) for the odds ratio does not contain the number 1, the variable may be regarded as an independent predictor of allergic symptoms.³² The skin test to HDM (expressed as HEWS) was found to be the only independent predictor of symptoms. Similar results were obtained when MWD was used in this model, with a slightly lower overall significance. After entering the HDM skin test into the model, the other allergy parameters did not contribute significantly to the prediction of allergic symptoms. With a HEWS of >0.7, the chance of having allergic symptoms after exposure to house dust was 5.4 times as great compared with having a HEWS ≤ 0.7 . Prior knowledge of HDM allergy test results did not improve the overall significance of the model (Table III). Computation of the same model as in Table III, with pulmonary allergic symptoms instead of any allergic symptom, yielded a slightly lower adjusted odds ratio

TABLE IV. Diagnostic values* of histamine corrected HDM skin test in different patient subgroups

	HEWS >0.7 Diagnostic value	MWD > (histamine-6 mm) Diagnostic value
Asthma (96)	1.36	1.43
Asthmatic bronchitis (88)	1.46	1.47
COPD (51)	1.32	1.30
Male (155)	1.44	1.45
Female (80)	1.53	1.50
Smoker (85)	1.48	1.48
Nonsmoker (150)	1.39	1.42
<40 yr (115)	1.39	1.43
≥ 40 yr (120)	1.40	1.40
PC ₂₀ <1 (187)	1.49	1.48
PC ₂₀ ≥ 1 (48)	1.15	1.25

Number of patients in each group in parentheses.

for HEWS (odds ratio, 5.0; 95% CI, 1.9 to 13.6) and no other significant odds ratios.

Applicability of skin test cutoff values for different diagnosis groups, sexes, ages, smoking status, and PC₂₀ levels

To establish whether cutoff values for a positive skin test derived for the whole study population (Table II) were applicable in different types of patients, diagnostic values were calculated for different subgroups of patients (Table IV). Diagnostic values were comparably high in asthma and asthmatic bronchitis but slightly lower in COPD. Changing the cutoff level in the latter group gave no improvement in the diagnostic value. In 19 of 51 (37%) of patients with a history-based diagnosis of COPD, a positive skin test for HDM (defined as HEWS >0.7) was found.

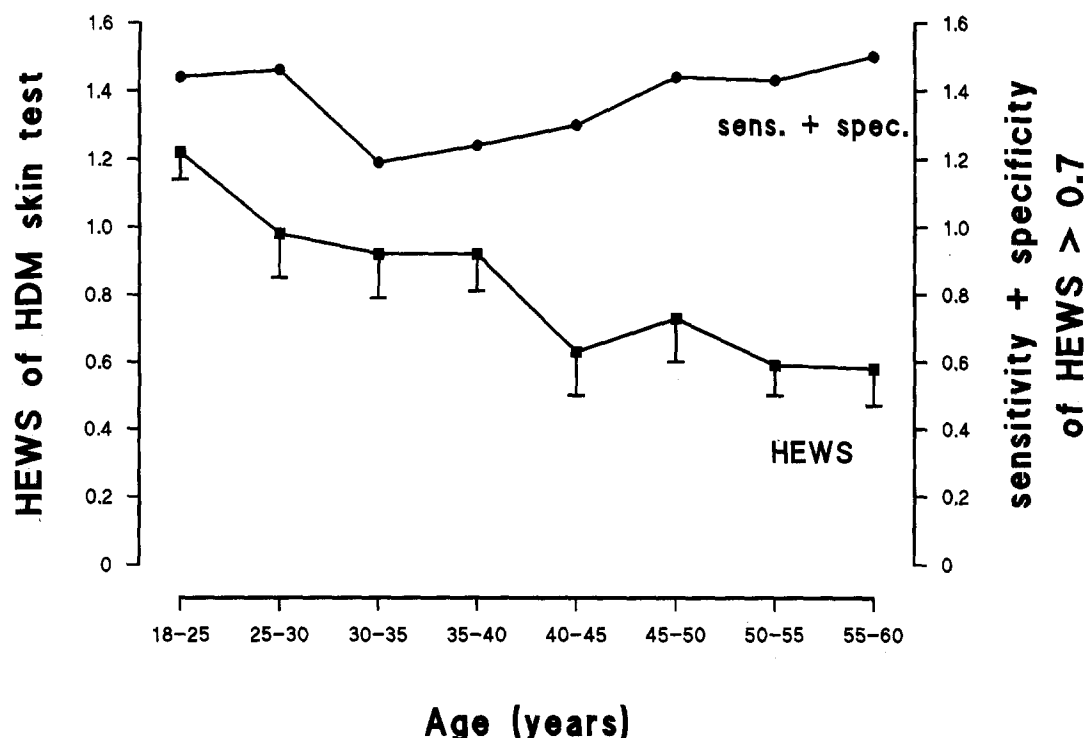


FIG. 2. Mean HEWS of HDM skin test (squares) and the diagnostic value (sensitivity + specificity) of a positive (HEWS > 0.7) HDM skin test (circles) in different age groups. Bars represent standard errors of the mean.

The diagnostic values of the HDM skin tests were also compared with respect to sex, smoking habits, age, and level of PC_{20} . The criteria for a positive skin test after correction for the histamine skin test were found to be applicable in all categories (Table IV). Only in the subgroup of patients with a smaller degree of airway hyperresponsiveness was a low diagnostic value detected (Table IV), which could not be increased by changing the cutoff level for a positive skin test.

Confounders of atopic status

Age, smoking status, sex, and PC_{20} were all considered confounding variables of atopic status. The univariate intercorrelations of these variables were first assessed, and subsequently multiple logistic regression models were built.

The following allergy parameters all decreased with age: HEWS ($r = -0.35$, Fig. 2), total IgE ($r = -0.37$), specific IgE ($p = -0.41$), and eosinophil count ($r = -0.26$) ($p < 0.001$). Although the size of the HDM skin test diminished in patients with increasing age, the diagnostic value remained rather stable over different age groups (Fig. 2).

Smokers had significantly ($p < 0.05$) lower levels of total IgE, specific IgE, and eosinophils and had

smaller HEWS. There was a negative correlation between pack years of cigarette smoking on the one hand and HEWS ($r = -0.38$, $p < 0.001$), total IgE ($r = -0.23$, $p < 0.001$), specific IgE ($p = -0.38$, $p < 0.001$), and eosinophil count ($r = -0.13$, $p < 0.06$) on the other.

No significant differences between sexes were found with respect to HEWS, total IgE, specific IgE, and eosinophils. Women did, however, have more allergic symptoms than men ($\chi^2 5.1$, $p = 0.02$). They also had slightly lower PC_{20} levels (geometric mean 0.20 versus 0.31 mg/ml, $p = 0.04$) and were, on average, younger (37 versus 41 years of age, $p < 0.01$).

An inverse relationship existed between PC_{20} and the allergy parameters: the correlations between $\log_2 PC_{20}$ and HEWS ($r = -0.28$), total IgE ($r = -0.25$), specific IgE ($p = -0.24$), and eosinophils ($r = -0.31$) were all highly significant ($p < 0.001$).

In a multiple regression model 25% of the variance in HEWS could be explained by the above-mentioned confounders. The resulting model was as follows:

$$\text{HEWS} = -0.011 \cdot \text{age} - 0.010 \cdot \text{pack years} - 0.258 \cdot \text{sex} - 0.056 \cdot \log_2 PC_{20} + 1.36$$
(male = 0, female = 1).

TABLE V. Adjusted odds ratios (and 95% CI) for different patient characteristics for allergic symptoms

Patient characteristic	Adj. odds ratio	95% CI	
		Lower limit	Upper limit
HEWS >0.7	5.0	2.1	11.8
5 pack years of smoking	0.9	0.8	1.0
Sex, female:male	2.8	1.3	5.9
PC ₂₀ (1 doubling dose)	1.1	0.9	1.3
5 years of age	1.0	0.8	1.1
Prior knowledge of skin test results	1.8	0.8	3.9

Finally, multiple logistic regression models were used to determine how these different confounders contributed independently in predicting allergic symptoms. Independent variables were HEWS of HDM skin test, age, sex, pack years of smoking, PC₂₀ (expressed as doubling doses of histamine), and prior knowledge of HDM allergy test results. The influence of confounders was small (Table V). Only female sex was independently related to allergic symptoms. The adjusted odds ratio for allergic symptoms in patients with a HEWS larger than 0.7 was 5.0 (Table V). This means that patients with a positive HDM skin test (HEWS >0.7) were five times more likely to report allergic symptoms after exposure to house dust than patients with a negative skin test, after correction for age, sex, smoking habits, level of airway hyperresponsiveness, and prior knowledge of atopic status. In a similar manner the adjusted odds ratio for pulmonary allergic symptoms only was 4.7 (95% CI, 2.0 to 10.6). The addition of type of disease (asthma, asthmatic bronchitis, COPD) to the above full model yielded no significant odds ratios for type of disease nor did it change the other odds ratios; no interactions between skin test, pack years, PC₂₀, and sex or age were found in this model.

DISCUSSION

The aim of the analyses presented here was to compare the diagnostic values of skin tests, total and specific IgE measurements, and eosinophil counts in detecting allergic symptoms in patients with asthma and COPD. This is a relevant issue to the respiratory physician or allergist who wants to screen his patients with an obstructive airways disease for signs of atopy. Other clinical studies have investigated the relationship between allergic symptoms and atopy parameters (skin tests, RAST, and the like), but these were all performed in groups of patients selected on prior knowledge or suspicion of allergy.^{4, 20-22} Furthermore, in none of these other clinical studies were confound-

ing variables of atopic status accounted for. Our results indicate that in patients with obstructive airway diseases, skin tests have a higher sensitivity than specific IgE for allergy-like symptoms on exposure to house dust. This finding is in accordance with earlier work on other allergens,³⁴⁻³⁶ probably because of the lack of sensitivity of specific IgE determinations at low levels of antigen-specific IgE.^{5, 34, 37} Different sources of allergen, a possible sensitizing role of IgG₄ or an increased susceptibility of the complement system, have recently been found not to be the likely explanation of this phenomenon.³⁷ Of all allergy parameters, only the skin test (in whatever way expressed) was an independent predictor of allergic symptoms (Table III). Once the skin test was known, the other allergy parameters provided no additional prediction of allergic symptoms. Thus skin tests provided the best indicator of symptomatic house dust allergy in our population of patients with obstructive airways disease. More specific information might have been obtainable from HDM inhalation provocation tests, but they were regarded not to be feasible in the context of this study.

When comparing diagnostic values of various allergy parameters, the choice of a "gold standard" for allergic symptoms is not easy. Epidemiologic studies have shown associations between distinct patterns of respiratory symptoms and certain markers of atopy in general population samples.^{1, 13, 18, 19} For example, Burrows et al.¹ found significant increases in asthma prevalence with increases in both skin test scores and IgE levels. The linear association between asthma prevalence and age and sex standardized IgE scores was closer than between asthma and skin test scores. The reverse applied to the association with allergic rhinitis. Mensinga et al.¹⁸ found that skin test reactivity without eosinophilia was associated with persistent wheeze and asthmatic attacks, whereas eosinophilia without skin test reactivity was related to chronic cough and phlegm. For the purpose of our

study, such analyses were not considered feasible because all patients in our study sample had chronic respiratory symptoms. Therefore we recorded symptoms that patients specifically recognized as being caused by an allergen source. Since HDM is the most common aeroallergen in countries with a moderate climate such as ours,²³ this allergen was used in our analyses. It is our experience that most patients can reliably recognize symptoms that are brought about by exposure to house dust, although symptoms that are caused by airway inflammation as a result of chronic low-dose allergen exposure may not always be classified as allergic with our method. Our methods of recording respiratory symptoms brought about by house dust allergy have been proposed,³⁸ but it is unknown whether these are more valuable for diagnosing house dust allergy than our method.

We compared different expressions and cutoff levels for a positive skin test with respect to their diagnostic value in identifying symptomatic patients with house dust allergy. The results show that subtracting the solvent wheal from the allergen wheal does not improve the diagnostic value of the skin test. Correction for the histamine wheal yielded slightly higher diagnostic values than the MWD, but differences were very small (Table II). Theoretically it may be advantageous to correct for the histamine wheal. The size of any allergen skin test is partly dependent on the individual's overall skin reactivity,^{39, 40} which may be reflected by the size of the histamine skin test. It might also correct to a certain extent for between-technician differences.⁴¹ As a result, between-patient reproducibility of histamine-corrected skin test results is lower than that of uncorrected wheal sizes.⁴² Our finding of slightly higher diagnostic values for HEWS than for MWD is in accordance with another study.²⁰ From our results it appears to be justified to conclude, however, that this probably has little clinical relevance.

The choice of an appropriate cutoff level for a positive skin test is dependent on the reason why the test is used. If a skin test is applied as a screening instrument for allergy, a sensitive test is desirable.^{29, 40} On the other hand, if one wants to confirm a clinical suspicion of a disease, a test with high specificity may be more appropriate. As sensitivity rises, specificity falls, and vice versa. There is no agreement on the optimal choice for this trade-off between sensitivity and specificity. For the purpose of this study we considered the criterion with the highest sum of sensitivity and specificity as having the best diagnostic value, thus defining the most appropriate cutoff level.^{29, 30} This proved to be a HEWS larger than 0.7, a MWD-histamine larger than -6 mm, or an MWD >7 mm

in our study population with our HDM allergen (Table II). Obviously, this cutoff value may not be the same in different populations or when different allergens are used. However, our results show that the diagnostic value of a positive skin test for symptomatic allergy is comparably high in different groups of patients (Table IV), suggesting that the cutoff levels we derived for a positive skin test should be useful in most patients from 18 to 60 years of age with obstructive airway diseases. The diagnostic value of a positive skin test was slightly lower in COPD, which may be caused by less sensitization in COPD, and in patients with milder hyperresponsiveness ($PC_{20} \geq 1$ mg/ml) than in severely hyperresponsive patients ($PC_{20} < 1$ mg/ml). The explanation for this observation could be that a stronger degree of airway hyperresponsiveness may facilitate recognition of symptoms after allergen exposure.^{16, 17}

Atopic status may be influenced by several confounding variables. Only multivariable methods allow assessment of the relative importance of different confounding variables independently of each other. The results of this study confirm that atopy significantly diminishes with age.^{9-11, 43} Although age and smoking habits are inversely related to skin test size, they appear to have little independent influence on allergic symptoms (Fig. 2, Table V). In this clinical population, patients who smoked tended to be less atopic (and less hyperresponsive). This could be due to a "healthy smoker effect."^{14, 15, 43} Prior knowledge of atopic status did not confound the relationship between skin tests and symptoms. To our surprise, PC_{20} histamine did not show an independent significant effect on symptoms either, in contrast to earlier studies.^{16, 17} This is probably due to the fact that a $PC_{20} < 8$ mg/ml was a selection criterion for our study, possibly obscuring an independent effect of PC_{20} on symptoms. Women had significantly more allergic symptoms than men (Table V), as has been found previously in a population study.¹³ Because women more often perform household activities than men, they may be more apt to be exposed to airborne particles containing mite antigen. Although HDM skin tests and HDM-specific IgE levels tended to be lower in women than in men, this did not reach significance.⁴⁴ Thus differences in exposure to HDM probably do not explain the sex differences in allergic symptoms. Since severity of airway responsiveness cannot explain these findings (Table V), differences in perception of symptoms between men and women cannot be excluded. Alternatively, women may have a different degree of mast cell and basophil releasability in the skin or airways than men. To our knowledge no data exist on this subject.

Intradermal skin tests are considered to have a larger risk of adverse effects, in particular anaphylactic reactions, than prick tests.^{5, 6, 45} However, in our complete group of 274 patients, no side effects of intradermal skin testing were reported.

In summary, skin tests to HDM appear to be better predictors of allergic symptoms than total or specific IgE in patients with obstructive airway diseases. With increasing standardization of allergen extracts, it is due time that consensus is reached on what constitutes a positive skin test. Our study shows that skin test reactivity may be used as a marker of symptomatic house dust allergy in patients with obstructive airways diseases, irrespective of clinical diagnosis, age, sex, level of hyperresponsiveness, or smoking habits.

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