

Can subjects with a positive allergen skin test be selected by a short questionnaire?

The Glostrup Allergy Study, Denmark

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The objective was to evaluate a postal questionnaire screening procedure for selection of subjects with positive reactions to skin prick tests with common allergens. The project consisted of a screening, with subsequent skin prick test of two selected groups. The setting was the Glostrup Population Studies institute in Copenhagen, Denmark. Participants in the screening included 8000 subjects, aged 15–69 years. The subjects were randomly selected from the population of western Copenhagen County, Denmark. From the 6998 respondents (87.5%), 793 subjects were randomly selected (Random Group), and 788 subjects were chosen on the basis of their answers to the questionnaire (Symptom Group). Both groups were invited to take skin prick tests. Attendance rates were 75.5% (Random Group) and 80.6% (Symptom Group).

The main outcome measures were responses (yes or no) to the specific questions and the subjects' skin reaction (positive or negative). The association between symptoms and skin reactivity, adjusted for the effects of sex and age, was summarized by odds ratios. Symptoms on exposure to allergens were highly associated with positive skin reactivity. In the Symptom Group the percentage of subjects with at least one positive skin reaction was 57.7%, which was twice as much (28.4%) as in the Random Group. The results show that it was possible to select a group with high skin reactivity on the basis of the symptoms reported in the screening. Questions about exposure to allergens were the most appropriate for selection of this group.

Key words: epidemiology; general population; immediate hypersensitivity; odds ratio; screening; skin tests.

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The percentage of subjects with allergic diseases in a population has been estimated by means of questionnaires, and in several studies (1, 3, 11, 18) skin prick tests were used as an objective measurement of IgE-mediated hypersensitivity. The Glostrup Allergy Study is one such study investigating allergic disorders in the general population.

Because a screening procedure for large population groups by postal questionnaire is often more appropriate than allergen skin testing, a questionnaire aiming to select subjects with positive allergen skin tests might be useful in the study of the epidemiology of asthma and allergic rhinitis. The problems of selection bias will probably be fewer if subjects with skin test reactivity to allergens are identified

in a population by postal questionnaire than by studies of patients in allergy clinics.

This paper presents the results of a screening by a short questionnaire in a large group of randomly selected subjects. The screening procedure aimed at selecting a group of subjects who would exhibit a high percentage of positive reactions to skin prick tests with common allergens. The hypothesis that this could be achieved by selecting subjects reporting clinically relevant symptoms was tested.

The percentages of subjects reporting certain respiratory symptoms in the whole group and in the two skin-prick-tested groups are presented, as well as the association between symptoms and degree of skin reactivity to allergens.

Material and methods

Sampling and screening

In October 1989, a random sample of 14 858 men and women aged 15–69 years, living in the western part of Copenhagen County, Denmark, was drawn by the National Personal Register (16). The total population of the area of the Glostrup Population Studies was 324 931 subjects, which is 54% of the total population of Copenhagen County and 6% of the total population of Denmark. The sample was restricted by citizenship (Danish), place of birth (Denmark), and date of birth (first or 15th of the month). A total of 8000 men and women was selected randomly from the restricted sample (14 858 subjects), comprising the study population for the screening. The study design is summarized in Fig. 1.

The screening took place between November 1989 and June 1990. A postal questionnaire, including a

letter of explanation and a prepaid reply envelope, was sent to the 8000 subjects. To minimize selection bias, we did not inform the subjects about the aim of the screening procedure, although it was stated that randomly selected respondents would be invited later for a general health examination including allergy. The questionnaire had been piloted in an allergy clinic. The questionnaire (symptoms a. to k. in Table 1) asked about symptoms of seasonal and allergic rhinitis (symptoms a. to d. in Table 1), about breathlessness at rest in the past 12 months (symptom e. in Table 1), and about breathlessness related to exposure to allergens (symptoms f. to h. in Table 1). Finally, a section of the inquiry about breathlessness related to walking (symptoms i. to k. in Table 1) was taken from a Danish translation of the UK Medical Research Council (MRC) questionnaire on respiratory symptoms (13). The questionnaire was sent to nonrespondents up to three times.

Invitation and examination

Two groups selected among the respondents were invited for skin prick tests. Respondents who reported symptoms (symptoms b. or c., or symptoms e. and f., or symptoms e. and g. (category 1., Table 1)) were identified, and an equal number of all respondents was selected randomly. In the random sample, subjects who reported symptoms were included in both groups. From February 1990 to February 1991, subjects were invited in random order. By the end, a total of 1435 subjects had been invited, 793 subjects had been randomly selected from among all respondents, and 788 subjects had been selected from among those reporting symptoms (146 subjects were included in both groups).

The subjects were invited to a general health examination by a standard letter containing information about the project. It was stated that the aim was to study the distribution of some important disorders in the general population, especially allergy. Those who failed to attend the examination were reinvited. Those who refused to attend the examination and those who did not respond at all were contacted by telephone.

Phazet (Pharmacia Diagnostics AB, Sweden) (4) was used for the skin prick tests. The Phazet lancets were coated with allergen solutions standardized for total allergenic activity (100 000 biologic units per ml), or with histamine dihydrochloride (10 mg/ml) (the positive control). The point length was 1 mm. The panel of allergens comprised birch, grass (timothy), mugwort, cat, dog, horse, house-dust mite (*Dermatophagoides pteronyssinus* and *D. farinae*), and two molds (*Alternaria* and *Cladosporium*). A negative control (uncoated lancet) and a positive control were included. The test sites were placed at intervals of

SCREENED GROUP

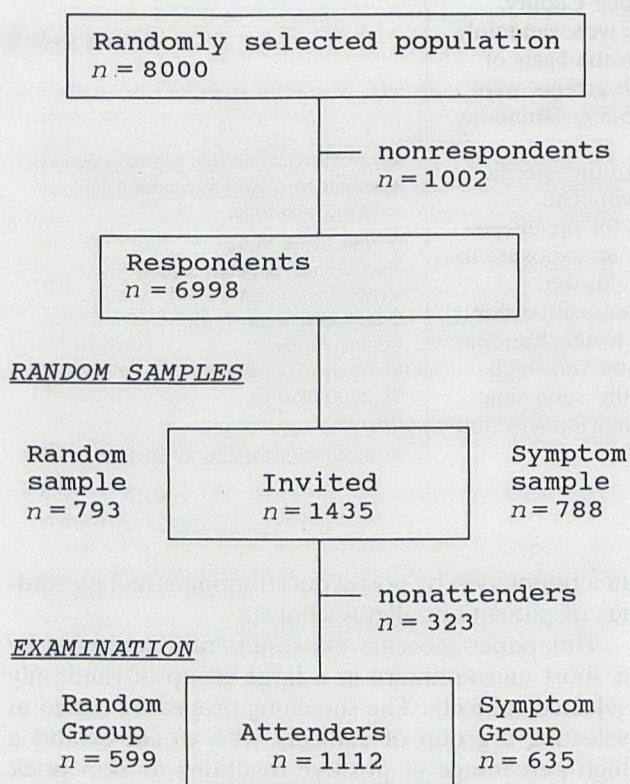


Fig. 1. Study design and participants. Screening was performed among 8000 randomly selected subjects, aged 15–69 years. Non-respondents numbered 1002 subjects. Among respondents, two groups were selected; one randomly and the other by reported symptoms. The two groups were invited to further examinations. They comprised a total of 1435, of whom 146 subjects in the Random Group reported symptoms and were therefore included in both groups. Of the subjects invited, 1112 subjects (77.5%) attended, and 122 were included in both groups.

Table 1. Distribution of response among the 6998 who completed the screening questionnaire (respondents) and two subgroups (Random Group and Symptom Group) who attended further examinations

Question	Respondents (n=6998)			Random Group (n=599)			Symptom Group (n=635)		
	Yes (%)	No (%)	Missing (%)	Yes (%)	No (%)	Missing (%)	Yes (%)	No (%)	Missing (%)
a. Itchy or stuffy nose or sneezing during the summer months	20.0	79.4	0.6	23.7	75.6	0.7	71.8	28.2	0.2
b. Itchy or stuffy nose or sneezing when near grass, trees, or flowers	14.7	84.6	0.7	16.4	83.5	0.2	77.0	22.8	0.2
c. Itchy or stuffy nose or sneezing when near animals	8.1	91.3	0.6	9.0	90.8	0.2	43.8	55.7	0.5
d. Itchy or stuffy nose or sneezing when cleaning rooms or making beds, or when in bed	17.1	82.2	0.7	18.9	80.8	0.3	46.5	52.8	0.8
e. Attack of shortness of breath when at rest at any time in last 12 months	14.4	85.1	0.5	13.2	86.3	0.5	34.5	65.2	0.3
f. Shortness of breath when near grass, trees, or flowers	3.7	95.6	0.7	3.3	96.0	0.7	17.8	80.9	1.3
g. Shortness of breath when near animals	2.9	96.2	0.9	2.3	97.0	0.7	15.7	83.1	1.1
h. Shortness of breath when cleaning rooms or making beds, or when in bed	4.8	94.3	0.9	3.7	95.5	0.8	16.4	83.0	0.6
i. Shortness of breath when hurrying on level ground or walking up slight hill	29.5	69.7	0.8	30.9	68.9	0.2	39.7	60.2	0.2
j. Shortness of breath when walking with other people of your own age on level ground	8.5	90.9	0.6	7.8	92.0	0.2	11.8	87.9	0.3
k. Having to stop for breath when walking at your own pace on level ground	4.8	94.6	0.5	3.7	96.2	0.2	6.8	92.9	0.3
l. Symptoms a. or b., or e. and f., or e. and g.	18.5	81.1	0.4	20.4	79.5	0.2	100.0	0.0	0.0

20 mm on the volar side of the forearms in a straight line from approximately 5 cm below the elbow flexure to about 10 cm above the wrist. The Phazet was applied to the skin next to the respective numbers, at an angle of 90°, pressed for 1 s, and then removed with an upward motion. The skin reactions were read after 15 min by drawing around the perimeter of the wheal with a fine-point, felt-tip pen, and transferred by transparent tape to the data collection sheet. The largest and the smallest diameters (at the widest point and at the midpoint at 90°) of the wheals were measured with a transparent ruler, and the mean diameter was recorded in millimeters. The response to the negative control was subtracted when reporting reactions to allergens. All skin prick tests were performed between February 1990 and February 1991 by the same technician. Before the study, the reproducibility of the test by the technician was established by performing two histamine skin tests on 20 volunteers. The coefficient of variation was 0.14.

Nonrespondents and nonattenders

Nonrespondents to the screening were defined as those with unknown addresses, those who did not return the questionnaire, and those who were seriously ill. Furthermore, subjects who refused contact were defined as nonrespondents. Information on nonrespondents was obtained from the National Personal Register.

Nonattenders were defined as those who did not attend the examination. Nonattenders were asked to return the questionnaire. If possible, they were interviewed by telephone, or a final questionnaire was mailed to them.

Ethics

The study was approved by the Ethics Committee of Copenhagen County. Pregnant women were excluded from the examination.

Statistical analysis

Statistical analysis was performed by computer programs from SPSS, Inc. (Chicago, IL, USA), and BMDP Statistical Software, Inc. (Los Angeles, CA, USA). All questions were answered by either yes or no. In the analyses of the screening, the following simplifications were performed: if the answer to question e. (Table 1) was no, the answers to questions f., g., and h. (Table 1) were defined as no, since these three questions were subcategories of question e. (Table 1). Three age groups were defined: 15–34 years (young), 35–49 years (middle), and 50–69 years (old). Differences between attendance rates in the groups were examined by the chi-square test. The coefficient of variation of the skin prick test was calculated (8).

The associations between the degree of skin reactivity and the symptoms have been calculated for the Random Group. The degree of skin reactivity was dichotomized by a borderline diameter, dividing the subjects into those who had at least one reaction of at least borderline size and those with all reactions smaller than the borderline diameter. Odds ratios for questions and skin reactions were estimated in a logistic regression model for borderline diameters from 3 to 8 mm, adjusted for the effects of sex and age.

Statistical significance was defined as $P < 0.05$.

Table 2. The response pattern among the subjects in the screening (screened group), and the attendance rates among two groups invited for skin prick tests, the Random Group and the Symptom Group

Age group (yr)	Screened Group						Random Group						Symptom Group					
	Men			Women			Men			Women			Men			Women		
	No.	Resp. (%)	χ^2	No.	Resp. (%)	χ^2	No.	Attend. (%)	χ^2	No.	Attend. (%)	χ^2	No.	Attend. (%)	χ^2	No.	Attend. (%)	χ^2
15-34	1586	82.9		1544	88.3		139	68.3		154	76.6		184	71.7		183	77.0	
35-49	1249	87.1	***	1315	90.0	NS	130	77.7	*	138	76.8	NS	94	87.2	***	150	86.6	NS
50-69	1150	88.3		1156	89.3		123	82.9		109	75.5		74	90.5		103	73.3	
Total	3985	85.8	***	4015	89.2		392	76.0	NS	401	75.1		352	79.8	NS	436	81.2	

NS: $P > 0.05$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Response rate: Resp.; attendance rate: Attend. chi square: χ^2 .

Results

Response pattern

A total of 6998 (88.7%) subjects completed the questionnaires (Table 2). Among men, a slightly lower response rate was found among the young than among the middle-aged and the old age groups ($P < 0.001$). No significant difference in response rate was found among women. Significantly more women than men responded ($P < 0.001$).

Information on nonrespondents was obtained from 176 (17.6%) of the 1002 nonrespondents (Table 3).

The difference in attendance rate between the age groups among men selected for the Random Group was due to a relatively low attendance rate among the young and a high rate among the middle-aged and old ($P < 0.05$). The difference in attendance rate found between men and women was not statistically significant.

Among those eligible for the Random Group, attendance was dependent on symptoms (symptoms a., b., and d. (Table 1)) ($P < 0.05$). The highest attendance rates were found among those who reported symptoms. Attendance rates among those who reported symptoms a., b., and d. (Table 1) were 84.0%, 84.5%, and 83.5%, respectively, as compared with 73.3%, 74.1%, and 73.8% among those who did not report these symptoms.

Information was obtained from 146 (75.3%) of the 194 nonattenders of the Random Group (Table 3). Among those eligible for the Symptom Group, the attendance rates were independent of age, sex (Table 2), and symptoms. Information was obtained from 107 (69.9%) of the 153 nonattenders of the Symptom Group (Table 3).

Screening

Some of the respondents did not answer all the questions, and information on symptoms was missing for up to 2.7% of the subjects. Table 4 shows the distribution of missing information and the prevalence of each symptom among those who answered the questions. The most frequently reported symptoms were shortness of breath when hurrying on level ground or walking up a slight hill (29.5%); an itchy or stuffy nose or sneezing during the summer months (20.0%); an itchy or stuffy nose or sneezing when cleaning rooms or making beds, or when in bed (17.1%); an itchy or stuffy nose or sneezing when near grass, trees, or flowers (14.7%); and breathlessness at rest in the last 12 months (14.4%).

Skin prick tests

All subjects, except three, were skin prick tested with the panel of allergens and the controls. Two subjects

Table 3. Information about the nonrespondents (screened group) and nonattenders (Random Group and Symptom Group) to examination

Group	Dead (n)	Emigrated (n)	Seriously ill (n)	Pregnant (n)	Address unknown (n)	Refused contact (n)	Telephone interview (n)	Postal (n)	No information (n)	Total (n)
Nonrespondents										
Screened Group	13	11	58	*	44	50	*	*	826	1002 (12.5%)
Nonattenders										
Random Group	0	2	13	3	*	11	61	56	48	194 (24.5%)
Nonattenders										
Symptom Group	1	6	3	4	*	7	42	44	46	153 (19.4%)

* No information obtained.

Table 4. Distribution of missing information and overall percentage of symptoms among subjects who attended examination

Symptom	No. of subjects who answered question		Percentage (%) of those who answered	
	Random Group	Symptom Group	Random Group	Symptom Group
a. Itchy or stuffy nose or sneezing during summer months	595	634	23.9	71.8
b. Itchy or stuffy nose or sneezing when near grass, trees, or flowers	598	634	16.4	77.1
c. Itchy or stuffy nose or sneezing when near animals	598	632	9.0	44.0
d. Itchy or stuffy nose or sneezing when cleaning rooms or making beds, or when in bed	597	630	18.9	46.8
e. Shortness of breath when at rest at any time in last 12 months	595	631	13.3	34.5
f. Shortness of breath when near grass, trees, or flowers	594	625	3.4	17.9
g. Shortness of breath when near animals	594	626	2.4	16.0
h. Shortness of breath when cleaning rooms or making beds, or when in bed	593	629	3.7	16.4
i. Shortness of breath when hurrying on level ground or walking up slight hill	597	632	30.8	39.7
j. Shortness of breath when walking with other people of your own age on level ground	597	631	7.7	11.7
k. Having to stop for breath when walking at your own pace on level ground	597	631	3.7	6.7
l. Symptom a., or b., or e. and f., or e. and g.	598	635	20.4	100.0

refused to be skin prick tested, and one refused the skin prick test with the positive control. The negative control elicited a skin reaction of 3 mm in five subjects (one in the Random Group and four in the Symptom Group). In all other subjects (1110 were tested), the reaction to the negative control was less than 3 mm. All skin reactions to the positive control were 3 mm or more.

The percentages of subjects with at least one skin reaction of a given diameter (3–8 mm) appear in

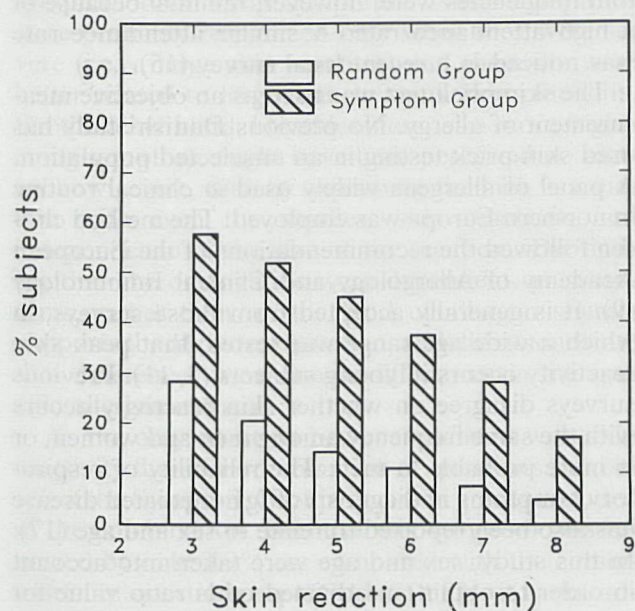


Fig. 2. Skin reactivity to allergens. Y-axis gives the percentage of subjects with one or more skin reactions of at least the borderline diameter indicated on x-axis. Random Group ($n = 599$) (filled bars), and Symptom Group ($n = 635$) (empty bars).

Fig. 2. Significantly more subjects in the Symptom Group had at least one wheal with a diameter of 3–8 mm than in the Random Group. The percentages for subjects who had wheals with a diameter of 3 mm were 57.7% and 28.4%, respectively ($P < 0.0001$).

Association between skin reactions to allergens and symptoms

The odds ratios did not indicate that a specific degree of skin reactivity could be considered to be a genuine cutoff point between reactivity associated with symptoms and that not associated with symptoms. By their association with skin reaction, the questions about symptoms could be classified into three groups. One group comprised most of the questions; that is, the questions about breathlessness of a more general nature, as when walking, and attacks of breathlessness at rest during the last 12 months, as well as two questions about nasal symptoms: one on exposure to animals and the other on exposure to dust (symptoms h., i., j., k., e., c., and d. (Fig. 3)). The questions in this group were weakly or not at all associated with skin reactions, as the probability of answering yes to these questions did not increase, or only weakly increased, by increasing skin reaction. The second group comprised two questions about pollen-related nasal symptoms; one about nasal symptoms during the summer, and the other about symptoms on exposure to plants (symptoms a. and b. (Fig. 3)). The probability of answering yes to these questions increased by increasing skin reaction. The third group comprised two questions related to pulmonary symptoms, i.e. attacks of

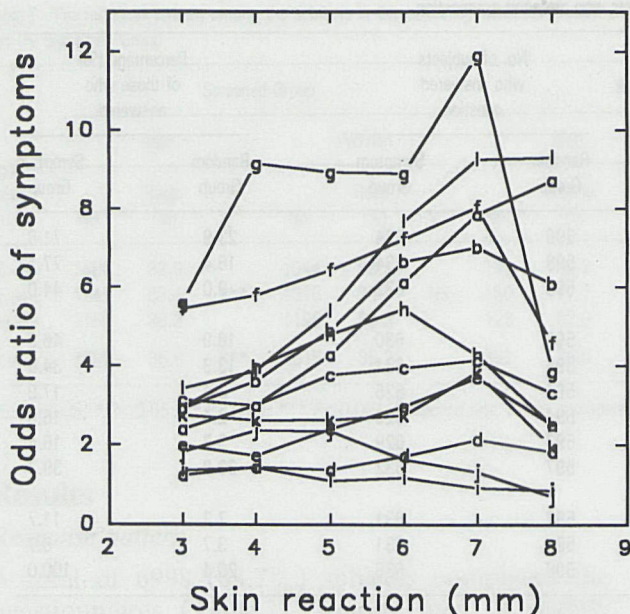


Fig. 3. The association between questions and skin reactivity summarized by the odds ratios. The degree of skin reactivity is expressed as the largest skin reaction to skin prick tests with the panel of 10 allergens. The odds ratios were calculated at different borderline diameters in the Random Group ($n = 599$). The questions are indicated by the same letters that appear in Table 1.

breathlessness at rest during the last 12 months and attacks of breathlessness on exposure to plants or animals (symptoms f. and g. (Fig. 3)). These questions were highly associated with skin reactions, whatever the size of the skin reaction.

Three of the four questions used for selecting the Symptom Group were symptoms in the two last groups mentioned above (symptoms b., f., and g. (Fig. 3)).

Nonattenders at examination

Interviewed by telephone, the 61 subjects eligible for the Random Group stated the following reasons for not attending: 5% felt too healthy; 57% were too busy with education, work, or family; and 5% had fear of hospitals, diagnosis, and registries. The remaining 33% gave no explanation. Interviewed by telephone, the 42 subjects eligible for the Symptom Group stated the following reasons for not attending: 2% felt too healthy; 36% were too busy with education, work, or family; and 12% had fear of hospitals, diagnosis, and registries. The remaining 50% gave no explanation.

Discussion

A generally accepted questionnaire to select subjects with positive skin reactions was not available. As a way of inducing the greatest possible number of sub-

jects to respond, the questionnaire employed was short, with questions about certain common respiratory symptoms and their relation to exposure to well-known allergen sources. The questions were phrased, "Do you get ...?" or "Have you had ...?" Despite disagreement on the terminology of allergic disorders among surveys, question on diagnoses have generally been used in surveys on allergy (2, 5–7, 10). However, questions about diagnoses were excluded in this survey. Since symptoms of allergy would not necessarily cause the subject to consult a doctor, some subjects had never had a diagnosis. The criteria for diagnosis might vary. Therefore, the questionnaire did not include questions about whether the subject regarded symptoms as a disease. Presumably, questions about diagnosis or questions phrased "Do you suffer from ... [a specific symptom]?" give a lower frequency of symptoms than questions phrased "Do you get ...?" or "Have you had ...?"

The response rate to the screening was similar to rates obtained in other surveys in the Scandinavian countries (2, 12, 14). The frequencies of symptoms in answers to the MRC questions in Denmark were similar to those found in a Norwegian study of the same age group (2).

An overrepresentation of subjects with allergic symptoms could be expected among the attenders. The overrepresentation of respiratory symptoms among the attenders, as compared with the nonattenders, indicates that the observed frequencies of these symptoms were slightly higher than in the general population. The reported discrepancies in symptom frequencies were, however, minimal because of a high attendance rate. A similar attendance rate was noticed in a recent local survey (15).

The skin prick test was used as an objective measurement of allergy. No previous Danish study has used skin prick testing in an unselected population. A panel of allergens widely used in clinical routine in northern Europe was employed. The method chosen followed the recommendations of the European Academy of Allergology and Clinical Immunology (9). It is generally accepted from those surveys, in which a wide age range was tested, that peak skin reactivity occurs in young subjects (3, 11). Previous surveys disagree on whether skin reactivity occurs with the same frequency among men and women, or is more probable in men. The reliability of respiratory symptoms in diagnosis of IgE-mediated disease has also been reported to relate to sex and age (17). In this study, sex and age were taken into account in order to obtain an adjusted odds ratio value for each association.

How to separate clinically important skin reactions associated with symptoms from insignificant reactions unassociated with allergic symptoms has

always been a matter of debate. In the search for a cutoff point, odds ratios for questions about symptoms and skin reactivity were calculated for successive borderline sizes of the skin wheal from 3 to 8 mm. For technical reasons, it was not possible to go below 3 mm. A true cutoff point should be characterized by a peak in the odds ratio, with lower values for smaller wheals and larger sizes of the borderline wheal. However, no such borderline skin reaction was found in the present study, nor has it been reported in previous surveys (1, 3, 7, 10, 11, 18). An arbitrary borderline value of 3 mm has been recommended as an indication of sensitization (9).

The odds ratios were also used to identify the applicable questions for the selection of subjects with skin reactivity. It was not expected that all common respiratory symptoms would be associated with immediate hypersensitivity. Therefore, the finding that most questions were only weakly or not at all associated with skin reactivity was not surprising. The questions associated with skin reactivity were more specific than the questions not associated.

Two distinct patterns of association summarized by the odds ratios were found among the questions associated with skin reactions. One pattern was an increase in the probability of symptoms with increasing skin reaction. This pattern was found for the questions on nasal symptoms. The other pattern was a constantly high association independent of the skin reactivity found for some questions of breathlessness. This might, to some extent, be explained by the perception that breathlessness is a more serious symptom than nasal symptoms. Nasal symptoms were probably recognized only when they were severe (i.e. a large skin reaction) and therefore were better related to large than to small skin reactions. On the other hand, breathlessness, as a more frightening symptom, might have been perceived no matter how severe, thereby explaining the high association with even the smallest skin reactions and independence of the size of the reaction. The finding that the odds ratios were dependent on symptoms, rather than on the kind of allergen source, supports the above explanation, and did not indicate that differences were due to differences in the specific allergen extracts.

As the only question better associated with skin reactivity than the combination of questions used to select the Symptom Group, question g. was included in the combination. Because this symptom was reported by only 2.9%, as compared with the combination of questions reported by 18.5%, it is not advisable to reduce the number of questions in the combination used to select subjects with skin reactions. Questions from the UK MRC questionnaire included in the present inquiry were not associated

with skin reactions, and these questions could probably be excluded in future questionnaires.

In conclusion, it was possible to select a group with high skin reactivity on the basis of the symptoms reported in the screening. Questions about symptoms on exposure to allergens were the most appropriate for selecting the group with high skin reactivity.

Acknowledgments

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