

An epidemiological study of atopy in children

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Summary

A sample of 930 children, between 9 years and 15 years old from six Italian towns, were studied. Their family history of allergy, personal allergy and medical history, current allergy symptoms, exposure to environmental allergens, feeding as infants, and their parents' occupations were recorded. They were skin-prick tested (SPT) with a range of common allergens. A subject was defined as atopic if at least one SPT caused a weal greater than 3 mm diameter. The association between the recorded information and atopy was investigated by logistic multiple regression. Atopy was positively associated with: high density housing; medium or high exposure to environmental allergens; a history of rhinitis, asthma or atopic eczema; male gender; and a history of breast-feeding. It was independent of infectious diseases, vaccinations and operations, social class and family history. Thus, there was no evidence of a genetic factor in atopy, other than sex.

Introduction

Several studies have provided new insights into the epidemiologic and genetic basis of allergic diseases [1]. Age and sex effects on skin sensitivity and total serum IgE levels have been extensively investigated in both unrelated subjects and family members [2–6]. However, the possible influence of environmental, social, nutritional and other factors that also operate on the expression of the atopic state should be considered [1].

In children, infections and immunizations [7] have been claimed to worsen, and breast-feeding to reduce, allergy in some patients [8–11].

It can be postulated that several environmental factors [12, 13] may be accentuating allergies in the urban areas (allergenic diet, atmospheric pollution, high-density housing, etc.) and ameliorating allergies in the country (prolonged breast-feeding, low-density housing, etc.) independently of parasitic infection [14].

Allergen skin-prick testing has been demonstrated to correlate well with specific IgE levels and therefore provides a reliable, non-invasive, measure of atopy [15, 16]. It has been reported that prevalence of positive skin-prick tests (SPT) in the general population is as high as 50% [17] but rates as low as 5% have been described, on a selected population without either allergic symptoms or family history of allergy [18]. The nature of the study populations, the number and the strength of the skin-test preparations, and the skin-test method employed, explain this wide variation. More recent data from subjects of all ages, social strata and environmental circumstances [3], and from college students [19], report a prevalence of about 30% of prick-test positive reaction to at least one of the employed allergens.

We set up the present study to investigate the prevalence and causes of atopy in children. We chose a limited age range (9–15 years) to minimize the effect of age and environmental hazards (e.g. cigarette-smoking history) [20–24].

The subjects were skin-prick tested with a range of common allergens and the result was used as the criterion for defining atopy. We tested the hypothesis that genetic (family history of allergy) or environmental (residential history, breast-feeding, infection, immunizations, etc.) variables might be predictors of skin sensitivity.

Subjects and methods

Six towns of the same 'National Sanitary Service—Local Sanitary Unity (NSS-LSU 35)', about 30 km from Naples, were selected. These were: two industrial coastal towns with dense housing; one town about 25 km inland, at sea level, with a mixture of agriculture and light industry, and low- to medium-density housing; three towns, 6–7 km inland, 700–1200 m above sea level, agricultural with low- to very low-density housing.

All General Practitioners (GPs) in the towns (approximately 150) were contacted and asked to participate: the reason for the trial and the effort involved were explained. Approximately 75% of the GPs in each town accepted, including all paediatricians, which covered 90% of the target population. The parents of all 9–15 year olds were contacted and encouraged to take part. Approximately 24% of all 9–15 year olds in each town accepted. About half the volunteers from each town were entered into the study by alternate alphabetical selection, to minimize a possible bias due to self selection (or parent selection) of subjects. Subjects went to their GP, who took their clinical history and completed a standard questionnaire.

A research group task force, including medical allergists and well-trained biologists, then visited schools in the towns and held sessions to enrol the children into the study. All but 10% of the members of the task force remained throughout the study. The subjects were skin-prick tested with a range of eighteen common local aeroallergens and food allergens, using for each allergen a single disposable standardized needle (Dome/Hollister-Stier). Each extract was used once for each subject, using Hollister-Stier or Dome/Hollister-Stier extracts. Positive and negative controls were also used. A subject was defined as atopic if he had at least one positive SPT, i.e. with a weal diameter > 3 mm 15–20 min after testing. This definition was chosen to ensure all atopic subjects were correctly classified. A different definition, e.g. two SPT reactions, may have mis-classified subjects with strong but single allergies. During the SPT session a detailed history was taken and a physical examination

performed when necessary. Questions were asked about personal and family history of allergy, other medical details, current symptoms of allergy, residential history and other relevant information.

Analysis

The data were analysed by logistic multiple regression [25] as implemented by SAS [26] computer software. Numerous analyses were run, initially including the suspected major effectors of SPT results, then on less likely risk factors and confounders. This ensured that the 'best' model was likely to be found without problems from automatic stepwise procedures, very small numbers in some variable combinations, or spurious significances. Most variables were coded as single or multiple binary dummy variables, taking values 0 or 1.

Variables were considered not to be associated with the outcome (SPT result) if their addition to the model did not improve the chi-square test statistics such that $P < 0.05$ (or vice versa for backward selection). Only models with an overall chi-square value such that $P < 0.01$ were used. The parameter estimates were generally stable, with no evidence for co-linearity.

Results

The results are summarized in Tables 1-3 and Figs 1 and 2. Missing data are not given so the totals are less than 930. Percentages are of totals excluding missing values and therefore add up to 100.

A total of 930 subjects, 474 male, 454 female, two not recorded, were studied, with a mean age of 11.6 years (standard deviation 1.2, range 9-15), weight 42.0 kg (s.d. 9.4), and height 146.1 cm (s.d. 9.9).

Overall, 326 subjects had at least one SPT positive reaction and were classed as atopic. All subjects reacted to 1 mg/ml histamine and did not react to 50% glycerol-Coca's. More males were SPT positive (40%) than females (30%) (Fig. 1). There was no difference in SPT between medium- and low-density housing but there was about twice the incidence of atopy in subjects in higher density housing areas. There was no evidence for any difference in incidence by either parent's occupation. Similarly, no difference was found in those with and without a family history of allergy (Fig. 1): 19.3% of subjects had a family history of allergy, 7.8% of mothers and 5.3% of fathers had allergies.

The personal allergy history showed a far greater incidence of positive SPT results among those with a history of allergy (Table 1). The ratio of atopic to non-atopic subjects in all infectious diseases, vaccinations and operations recorded was similar to the entire sample. The subjects' current allergy problems, i.e. present at the time of assessment (Table 2) were well matched to their atopy, as defined by their SPT results, not surprisingly. Urticaria, food and drug intolerance and contact dermatitis were not clearly associated with a positive SPT result.

Among all 930 subjects, 18.7% and 17.3% reacted to *Dermatophagoides pteronyssinus* and *D. farinae*, respectively, 9.2% reacted to *Parietaria* pollen and 6.0% to grass pollen; among food allergens the higher reactivity rates were to mixed legumes (5.9%), maize (5.6%) and tomato (3.9%).

When the SPT-positive subjects' current and previous history were assessed, only 1 subject among the 227 without present allergy problems had symptoms in the past; 29% of SPT positive subjects were reported to have clinical symptoms at the time of

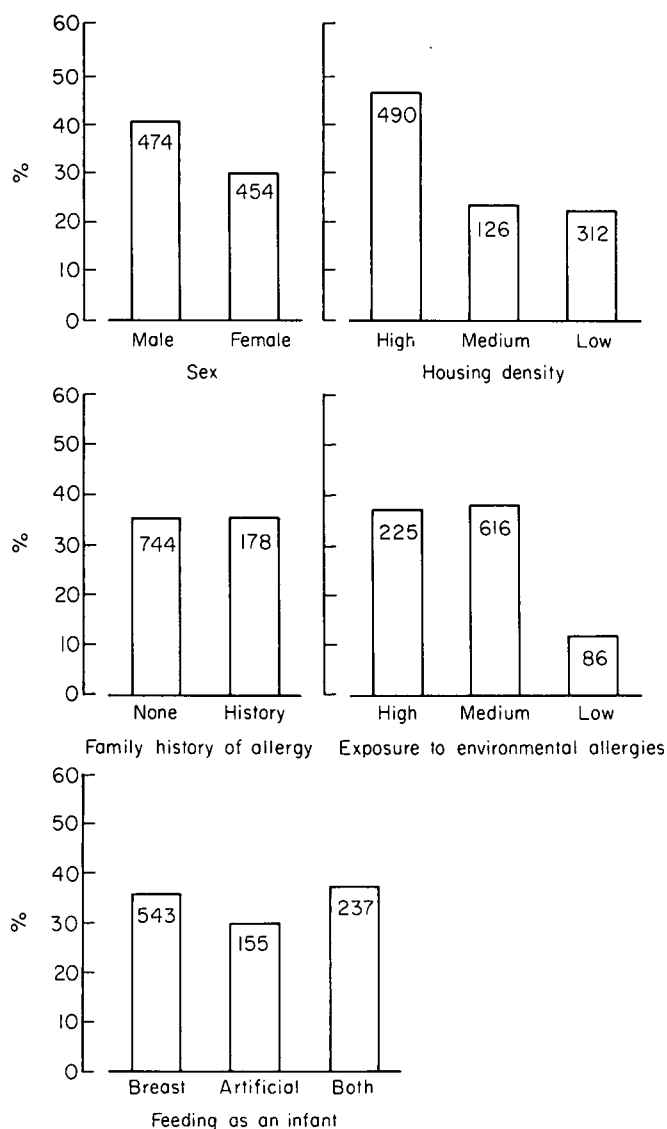


Fig. 1. Percentage of subjects with positive SPT.

assessment. Subjects with low exposure to environmental allergens had a low incidence of positive SPT results (Fig. 1), although only 9% of the total subjects had low exposure. Children fed only on artificial, non-maternal, milk as infants appeared to have a lower incidence of positive SPT reactions than those who had been fed on breast-milk, either exclusively or partially (Fig. 1).

Prior to the analysis, it was felt that amongst the information recorded, the type of housing, family history of allergy and personal allergy history were most likely to influence a subject's results, as SPT positive or negative. A clear association of high-density versus other housing and SPT result was found, but, as indicated in Fig. 1, there was no difference between medium- and low-density housing. A family history of

Table 1. Skin-prick test reactivity by subjects' history of allergy symptoms

Allergy history	SPT					
	Negative		Positive		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
No	337	73.1	124	26.9	461	100
Dubious	23	85.2	4	14.8	27	100
Yes	241	54.9	198	45.1	439	100
Symptoms						
<i>Classic allergic</i>						
Conjunctivitis	2	66.7	1	33.3	3	100
Rhinitis	47	39.2	73	60.8	120	100
Bronchitis	78	48.7	82	51.3	160	100
Asthma	12	30.0	28	70.0	40	100
Otitis	1	33.3	2	66.7	3	100
Urticaria/angio-oedema	27	55.1	22	44.9	49	100
Atopic eczema	77	48.1	83	51.9	160	100
<i>Gastrointestinal</i>						
Recurrent diarrhoea	52	64.2	29	35.8	81	100
Recurrent vomiting	42	53.2	37	46.8	79	100
Irritable colon	80	55.6	64	44.4	144	100
<i>Food and drugs</i>						
Drug intolerance	13	56.5	10	43.5	23	100
Food intolerance	43	55.8	34	44.2	77	100
<i>Other</i>						
Contact dermatitis	1	100	0	0	1	100

allergy had no effect upon outcome, nor did having at least one parent with a history. This was re-examined later in the analyses, using subjects who had at least one atopic parent and those with no history (excluding subjects without an atopic parent but some other atopic relation), leaving 853 subjects. The result was confirmed. It was also confirmed when the definition was restricted to both parents being atopic or no family history at all.

Subjects' history of allergy symptoms were coded into three groups, as shown in Table 1: classic allergic, gastrointestinal, food and drug intolerance. Of these, a classic allergic history was closely associated with positive SPT results but the other two were unrelated. Inspecting Table 1, of the seven symptoms classed as classic allergic, rhinitis and asthma appeared closely associated with SPT results, 61% and 70% of subjects, respectively, were positive; an association was not apparent with the other symptoms. This was confirmed by regression analysis, which also indicated that a history of atopic eczema was a useful predictor of SPT-positive results as previously described [27].

Table 3 shows the results by all three groups. Within each pair, eczema had a higher percentage of positive SPT results. Two-thirds of subjects without any of the three symptoms, but with other allergic symptoms, had negative SPT results. A history of

Table 2. Skin-prick test reactivity by subjects' current allergy symptoms

Current allergy symptoms	SPT					
	Negative		Positive		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
No	540	70.4	227	29.6	767	100
Dubious	7	77.8	2	22.2	9	100
Yes	50	35.2	92	64.8	142	100
Symptoms						
<i>Classic allergic</i>						
Conjunctivitis	3	25.0	9	75.0	12	100
Rhinitis	5	13.2	33	86.8	38	100
Bronchitis	1	8.3	11	91.7	12	100
Asthma	0	0	37	100	37	100
Otitis	0	0	2	100	2	100
Urticaria/angio-oedema	13	52.0	12	48.0	25	100
Atopic eczema	3	30.0	7	70.0	10	100
<i>Gastrointestinal</i>						
Recurrent diarrhoea	0	0	2	100	2	100
Recurrent vomiting	0		0		0	
Irritable colon	5	62.5	3	37.5	8	100
<i>Food and drugs</i>						
Drug intolerance	7	63.6	4	36.4	11	100
Food intolerance	19	73.1	7	26.9	26	100
<i>Other</i>						
Contact dermatitis	10	62.5	6	37.5	16	100

Table 3. Skin-prick test reactivity by subjects' current allergy symptoms in subjects with history of allergy

Rhinitis	Asthma	Atopic eczema	SPT			
			Negative		Positive	
			<i>n</i>	%	<i>n</i>	%
Absent	Absent	Absent	58	67.4	28	32.6
		Present	60	54.1	51	45.9
	Present	Absent	8	33.3	16	66.7
		Present	2	20.0	8	80.0
Present	Absent	Absent	30	40.0	45	60.0
		Present	15	38.5	24	61.5
	Present	Absent	0		0	
		Present	2	33.3	4	66.7

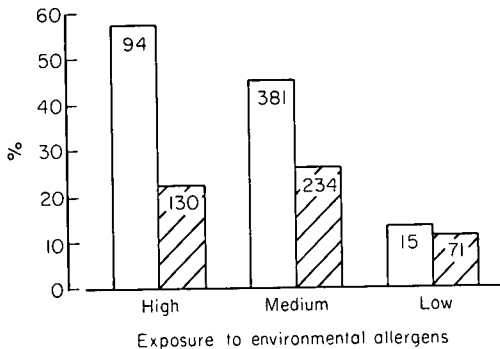


Fig. 2. Percentage of subjects with positive skin-prick test by housing and exposure to environmental allergens. (□) High-density housing, (▨) medium- and low-density housing.

eczema shifts the percentage nearer 50/50. There was no evidence of interactions between these three symptoms. Since a parsimonious model is desirable, including few variables whilst modelling the results as closely as possible, the symptoms were replaced by a single variable, indicating a history, if any, of rhinitis, asthma or atopic eczema, or not. This proved useful.

Previous studies have shown that males have a higher incidence of atopy. This was the situation in this study and sex was included in all regression models.

Breast-feeding has been claimed to induce some protection against atopy although the results of various studies, especially retrospective, have been ambiguous [28–30]. Breast- and artificial feeding, at any time, were entered into the model. Breast-feeding was found to be associated with a higher incidence of positive SPT results, in contradistinction to previous studies. This was not an artifact due to the inclusion of mixed feeders in the breast-fed group as analysis of subjects who were either entirely breast- or entirely artificially fed confirmed the result.

We assessed each subject's degree of risk from environmental allergens, due to overcrowded living conditions, living on a farm, etc. The area the subject lived in affected the assessment. Within each housing condition there was no difference between high and medium exposure on the incidence of SPT-positive results. However, subjects with low exposure had a much lower incidence of SPT-positive results. Analysis of the data (Fig. 2) shows that environmental exposure, classed as low or other, was a useful predictor of outcome, additional to area, with no evidence for an interaction.

The SPT result was independent of the age of the subject; the social class, defined by the father's occupation; and non-allergic medical history, i.e. infectious diseases, vaccinations and operations.

At no stage in the analysis was there evidence for any interaction between any of the variables.

The analysis finally identified five measures that were associated with the SPT results. They were: area, or housing conditions ($\chi^2=28.7$, $P<0.001$); exposure to environmental allergens ($\chi^2=9.8$, $P=0.002$); history of rhinitis, asthma or atopic eczema ($\chi^2=45.3$, $P<0.001$); sex ($\chi^2=5.5$, $P=0.020$); and breast-feeding ($\chi^2=4.2$, $P=0.041$).

These give the logistic model (without the error term) for the data as:

$$\log\left(\frac{P}{1-P}\right) = -1.91 + 0.88x_1 - 1.08x_2 + 1.06x_3 + 0.35x_4 + 0.41x_5$$

Standard errors 0.23 0.15 0.36 0.16 0.15 0.20

where P = probability that SPT result is positive,

$x_1 = 1$ if subject was from the towns with high-density housing

0 if otherwise,

$x_2 = 1$ if exposure to environmental allergens was low

0 if otherwise,

$x_3 = 1$ if subject had history of any of rhinitis, asthma or atopic eczema

0 if otherwise

$x_4 = 1$ if boy

0 if girl,

$x_5 = 1$ if subject was breast-fed at any time

0 if otherwise.

The χ^2 values given above are from a model that included both dummy variables needed to categorize housing and environmental conditions into three classes. Only the statistically significant ones are reported, the others had $P > 0.2$ in both cases, but they must be included in the model because of non-independence. The χ^2 for the history of rhinitis, etc., was very high because the variable was created during the analysis to maximize the χ^2 and must therefore be treated with caution. The equation of the model above does not include any other variables, i.e. the non-significant variables were dropped.

Discussion

The study was carefully designed and run: much pertinent information was recorded about each subject to enable some of the most important problems in the causes of allergy to be addressed.

It has often been claimed that genetics influences allergic disease [1]. Previous studies have looked at the family history of allergy and apparently shown that people with allergy in the family, particularly parents, are more likely to be atopic themselves [31]. There was no evidence for this in this study.

The other major influence is thought to be environment. There was a clear difference between the high-density industrial towns and the less dense, less industrial areas. This was not due to town and investigator confounding as all the visits were by the same research task force. All clinical trials and surveys with voluntary entry are, of necessity, biased in their inclusion of subjects. This problem is usually ignored and the acceptance rate not reported, and in comparative studies it is not a major problem. In clinical trials randomization ensures that non-treatment-related biases are minimized, and in surveys there is usually no evidence that the reasons for acceptance are related to the condition under study. This is likely to be true in this study. However the parents of children with allergy were more likely to agree to their children taking part, which may have increased the incidence of atopy. A definition of atopy needing larger or more weals would have reduced the proportion of subjects classed as atopic.

The low incidence of SPT-positive results among subjects assessed to have a low exposure to environmental allergens matches expectations.

A subject's allergy history should relate to the current SPT sensitivity. Of the thirteen symptoms considered to be probably due to allergy only three, rhinitis, asthma and atopic eczema, were found to be associated with SPT results. It is known that allergies caused by consumed products are not well represented by SPT, therefore the lack of association between SPT results and gastrointestinal or food and drug symptoms is not surprising. Bronchitis, urticaria and angio-oedema, the only other major symptoms, may be due to a wide variety of non-allergenic diseases.

The study confirmed the higher incidence of atopy among males.

The results for breast-feeding contradict the claimed protection role for it [8-11]. The result may be due to the subjects' self selection. It may be that mothers who breast-feed are more concerned about their child's welfare than those who do not, and are therefore more likely to allow the child to enter the study if it is atopic. Breast-feeding may be a partial measure of the selection bias in this study, as in other retrospective studies [28-30].

The SPT results were unaffected by the subject's age; his social class, as defined by his father's occupation, conflicting with previous statements [4]; or the subject's history of vaccinations, infectious diseases or operations.

From the final model we can see that the exposure to environmental allergens and history of rhinitis, asthma or atopic eczema have the greatest, about equal, effect. The residential area is slightly less important and sex and breast-feeding of minor, approximately equal, importance.

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