

Asthma and wheezy bronchitis in children

Skin test reactivity in cases, their parents and siblings. A controlled population study of sex differences

J. B. DAVIS

Lister House, Group Practice Centre, Harlow, Essex

Summary

Twice as many boys as girls are prone to wheeze (15.3% compared with 7%). This study examines the possible immunological basis for this phenomenon. There were 1064 children in this survey. The family of each wheezy child was indexed, and a control sample of families was selected. At least 85% of the study population were skin tested for Type 1 allergic reactions. An interval survey of values for FEV₁, FVC and PEFR against height was completed.

Of 118 wheezy subjects there were 83/542 boys and 35/522 girls. Single and multiple sensitivity, the capacity to react to two or more major allergens, is examined. Of the child asthmatics, significant differences from controls emerge for pollens, foods and the house dust mite. These differences are borne out with multiple sensitivity. ($P > 0.001$.) Of the brothers and sisters of asthmatics, only the sisters show differences from controls. This is true for grass pollen, cow's milk and the house dust mite, and also to a highly significant degree for multiple sensitivity ($P > 0.001$). When the incidence of multiple sensitivity is expressed for all children in the asthma group, that is, cases and their siblings, the sex difference is not demonstrable. The mothers ($P > 0.05$) and fathers ($P > 0.01$), of asthmatics also differ from control parents in respect of skin sensitivity.

If multiple sensitivity is equated with atopy, it may not be the main determinant of the capacity to wheeze, and thus of the sex difference.

The mean curve for interval PEFR for asthmatic children was significantly lower than that of control children and of the brothers and sisters of asthmatics.

Introduction

Sex differences in the incidence of asthma and wheezy bronchitis in children are well established. Most authors record a male/female ratio of 2:1. This does not apply to bronchitis without wheezing.

This study was designed to clarify whether this sex difference is reflected in the immunological status of the individuals concerned. The question is of particular

interest as McNichol & Williams (1969, 1973) have shown that even mild wheezy bronchitics differ from controls in immunological reactivity.

The author sought also to demonstrate whether the first degree relatives of wheezy subjects show similar differences. Such differences might be reflected in a measurable morbidity on other counts. A survey of interval values for FEV₁, FVC and PEFR against height have therefore been included.

Methods and materials

The population under scrutiny comprised 2,750 individuals, 1,064 of whom were under the age of 16. A family index was compiled. Out of 600 families, 450 had one or more children in the household. A questionnaire was sent to each of these families to ascertain the prevalence of wheezing. Each wheezy individual was also identified carefully by reference to the medical record. A strict criterion for inclusion was employed, namely, the occurrence of wheezing on two or more occasions in two or more years. An asthma group of families was created by listing those families with one or more wheezy children.

The residual population was by definition deemed to be the control population. Thirty families were removed from this group on the basis that although no child had wheezed, one or other parent had established asthma. A control group for the purposes of this study was then obtained by taking a 1:3 sample from the listed control population of families.

A survey of Type 1 allergic skin reactions was then carried out. A batch of twenty standard allergens was used employing the method described by Pepys (1972).

The results were then examined on the following basis: for individual sensitivities and for multiple sensitivity (the ability to react to a member of two or more major groups of allergen).

It is thus possible to display the allergic responses of: (1) boy and girl asthmatics compared with controls; (2) brothers and sisters of asthmatics compared with controls; (3) mothers and fathers of asthmatics compared with controls.

Each of these groupings is also examined for sex differences, given the prior difference in prevalence.

In addition to the above survey individual readings of FEV₁, and FVC were recorded at a screening clinic. Height and weight were also measured. As a separate exercise each family was loaned a peak expiratory flow meter and daily readings were taken for 1 week. This was a deliberate survey of the interval values of FEV₁, FVC and PEFR. The maximum values were established for each child.

Results

Ascertainment

Ninety per cent of the families replied to the questionnaire and 118 wheezy subjects were identified. They derived from 111 families. A control sample of 111 families was drawn. Of the families selected, 86.5% attended the screening clinic. Of those attending 92.7% of individuals were screened.

Prevalence

Of the male child population eighty-three out of 542 (15.3%) had a history of wheezing

as defined, and of the girls thirty-five out of 522 (7.0%) were identified. A sex ratio in the incidence of wheezing of 2:1 is thus manifest.

Age and sex distribution

Figure 1 shows the distribution of asthma cases by age and sex. Figure 2 shows the asthma cases by rank and sex. The sex distribution holds for all ranks. Figure 3 shows

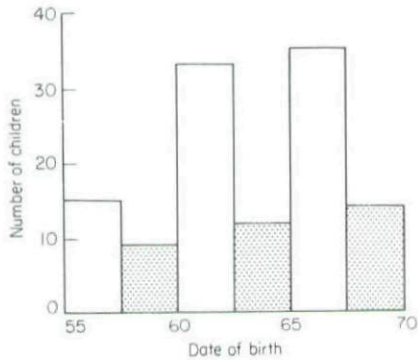


Fig. 1. Asthma cases by age and sex. □, Male; ■, female.

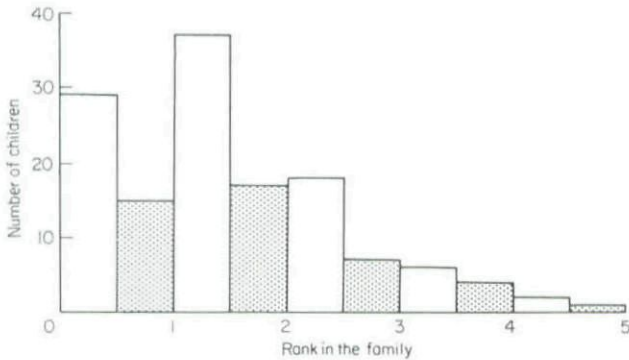


Fig. 2. Asthma cases by rank and sex. □, Male; ■, female.

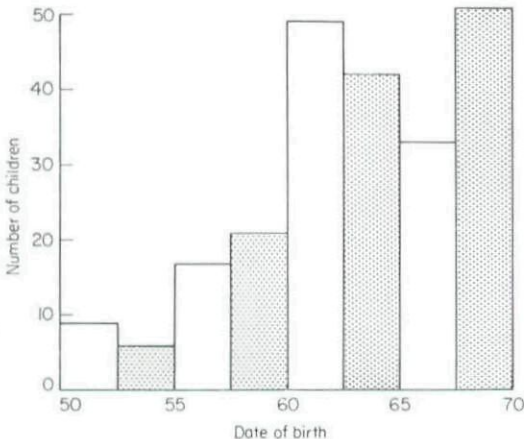


Fig. 3. Control children by age and sex. □, Male; ■, female.

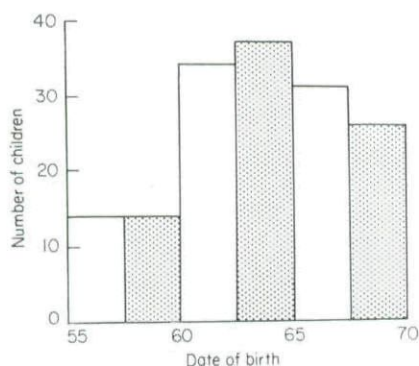


Fig. 4. Asthma siblings by age and sex. □, Male; ■, female.

the control children by age and sex. Figure 4 shows the age range of the brothers and sisters of asthmatics. The age range of the mothers and fathers of asthmatics and the mothers and fathers of controls lay between 25 and 40 years.

Individual sensitivities and multiple sensitivity

Boy and girl asthmatics compared with controls.

Individual sensitivities. Tables 1 and 2 give the results of individual sensitivity to separate allergens for boys and girls. Significant differences are demonstrated between children with asthma and control children for pollens, foods, and the house dust mite.

Multiple sensitivity. Tables 3 and 4 give the results for multiple sensitivity. Both boys and girls show highly significant differences from control children.

Brothers and sisters of asthmatics compared with controls.

Individual sensitivities. Tables 1 and 2 below also show that the sisters but not the brothers of asthmatic children, show significant differences from controls in their sensitivity to grass and shrub pollen to cow's milk and to the house dust mite.

Table 1. Individual sensitivities to skin tests in boys

	Asthma cases (79)				Control (101)		Brothers of asthmatics (75)			
	Absolute	%	χ^2	P	Absolute	%	Absolute	%	χ^2	P
Total moulds	11	13.9	2.4	0.12	6	5.9	—	—		
Pollen 1 grass	44	55.7	35.8	<0.001	13	12.9	15	20	1.15	0.3
Pollen 2 shrub	14	17.7	11.7	<0.001	2	2.0	1	1.3		
Pollen 3 tree	11	13.9	6.9	0.008	3	3.0	3	4.0		
Food 1 milk	17	21.5	10.9	0.001	4	4.0	2	2.6		
Food 2 fish	7	8.9	4.74	0.028	1	1.0	1	1.3		
Food 3 egg	4	5.0			—	—	—	—		
Food 4 wheat	6	7.6			—	—	—	—		
Food 5 nuts	5	6.3			—	—	—	—		
House dust mite	45	57.0	39.6	<0.001	12	11.9	9	12		
Control + ve	1	1.3			—	—	1	1.3		

Table 2. Individual sensitivities to skin tests in girls

	Asthma cases (35)				Control (126)		Sisters of asthmatics (76)			
	Absolute	%	χ^2	P	Absolute	%	Absolute	%	χ^2	P
Total moulds	—	—			—	—	2	2.6		
Pollen 1 grass	19	54.3	50.8	<0.001	5	3.9	16	21	18	<0.001
Pollen 2 shrub	4	11.4	7.1	0.007	1	0.8	7	9.2	6.75	0.009
Pollen 3 tree	3	8.6			—	—	7	9.2		
Food 1 milk	4	11.4	4.9	0.025	2	1.6	7	9.2	4.8	0.025
Food 2 fish	—	—			1	0.8	3	3.9		
Food 3 egg	1	2.8			—	—	—	—		
Food 4 wheat	—	—			—	—	—	—		
Food 5 nuts	1	2.8			—	—	2	2.6		
House dust mite	14	40	25.7	0.001	7	5.5	9	11.8	7.45	0.006
Control +ve	—	—			2	1.6	1	1.3		

Table 3. Multiple sensitivity to skin tests in boys

	Asthma cases				Controls		Brothers of asthmatics			
	Absolute	%	χ^2	P	Absolute	%	Absolute	%	χ^2	P
0	24				90		61			
1	22	27.8	9.9	0.002	9	8.9	14	18.6	11	0.001
2	39	49.4	32	<0.001	10	9.9	6	8.0		
	85 (79)				109 (101)		81 (75)			

0, None positive, 1, single positive, 2, multiple positive (2 or more).

Figures in parentheses represent numbers actually tested.

Table 4. Multiple sensitivity to skin tests in girls

	Asthma cases				Controls		Sisters of asthmatics			
	Absolute	%	χ^2	P	Absolute	%	Absolute	%	χ^2	P
0	13				125		62			
1	10	28.6	14.8	<0.001	6	4.7	6	7.9		
2	15	42.9	34.6	<0.001	5	4.0	14	18.4	11.5	<0.001
	38 (35)				136 (126)		82 (76)			

0, None positive; 1, single positive; 2, multiple positive (2 or more).

Figures in parentheses represent numbers actually tested.

Multiple sensitivity. Tables 3 and 4 above confirm that the sisters of asthmatics differ from controls in their capacity to react to two or more major allergens. This is not shown for the brothers of asthmatics.

Asthmatic children and their non-asthmatic siblings. The incidence of multiple

Table 5. Individual sensitivities to skin tests in parents

	Fathers						Mothers					
	Control		Asthma				Control		Asthma			
	(89)		(89)				(94)		(92)			
	Absolute	%	Absolute	%	χ^2	P	Absolute	%	Absolute	%	χ^2	P
Total moulds	2	2.2	8	8.8	2.64	0.1	7	7.4	20	21.7	6.5	0.01
Pollen 1 grass	10	11	20	22	3.7	0.05	14	14.9	25	27.2	3.5	0.05
Pollen 2 shrub	3	3.3	7	7.7	0.95	0.35	6	6.4	7	7.6		N.S.
Pollen 3 tree	4	4.4	9	9.9	1.33	0.25	5	5.3	9	9.8	0.77	0.4
Food 1 milk	3	3.3	7	7.7	0.95	0.35	4	4.3	8	8.7	0.87	0.4
Food 2 fish	—	—	2	2.2			1	1.0	5	5.4		
Food 3 egg	—	—	—	—			1	1.0	4	4.3		
Food 4 wheat	—	—	1	1.1			1	1.0	3	3.3		
Food 5 nuts	—	—	1	1.1			1	1.0	3	3.3		
House dust mite	13	14.6	20	22	1.34	0.25	14	14.9	20	21.7	3.5	0.05
Control +ve	4	4.4	5	5.5			10	10.6	3	3.3		

Table 6. Multiple sensitivity to skin tests in parents

	Fathers								Mothers			
	Control		Asthma				Control		Asthma			
	Absolute	%	Absolute	%	χ^2	P	Absolute	%	Absolute	%	χ^2	P
0	75		69				77		61			
1	16	18	9	10			16	17	18	19.6		
2	5	5.6	18	20.2	7.2	0.006	8	8.5	20	21.7	5.4	0.02
	96 (89)		96 (89)				101 (94)		99 (92)			

0, None positive; 1, single positive; 2, multiple positive (2 or more).

Figures in parentheses represent numbers actually tested.

sensitivity may also be expressed for asthmatic children and their siblings as a single group. The value for boys is forty-five out of 154 (29.2%) and for girls is twenty-nine out of 111 (26.1%). This difference is not significant.

Mothers and fathers of asthmatics compared with the mothers and fathers of controls

Individual sensitivities. Table 5 shows that differences are marginal. That is with the exception of grass pollen in the fathers and mothers, and the house dust mite in mothers only.

Multiple sensitivity. Table 6 shows that the fathers and mothers of asthmatics differ significantly from controls.

Interval survey of values for FEV₁, FVC and PEFR

The mean curve for PEFR for the boy and girl asthmatics was significantly lower than

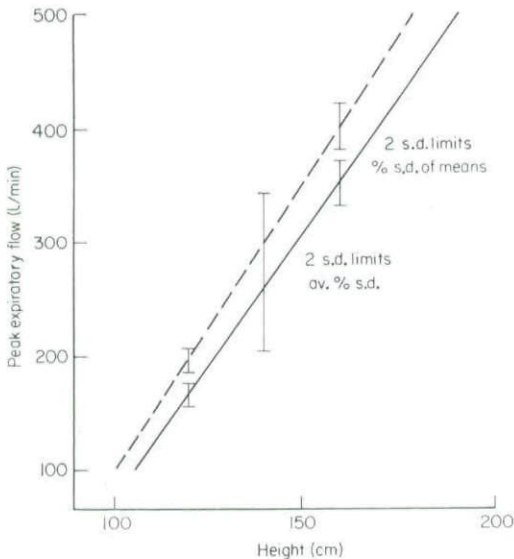


Fig. 5. Peak expiratory flow rate/height (graph) for control boys and girls (---) and asthma boys and girls (—).

that of the control group of children of either sex. No difference was demonstrated between the brothers and sisters of asthmatics and control children.

A simple straight line graph may be constructed for the values of peak flow in l/min against height in cm, Fig. 5. The detail of the co-ordinates is now given, control children PEFR 100 l/min against a height of 102 cm to 450 l/min against 170 cm. Asthmatic children 100 l/min against 106 cm to 400 l/min against 170 cm.

The control mean curve falls within the 2 s.d. limits of means for all authors described by Polgar & Promadaht (1971). The mean curve for asthma boys and girls may be described as significantly low because its 2 s.d. limits lie outside those defined for the control group. The standard deviation of the mean for PEFR is 2.9%.

Figure 5 also displays the scatter of normal values for PEFR expressed in terms of the average percentage standard deviation ($2 \times 12.8\%$, approximately 25%).

Using the same technique, no differences were demonstrable for values of FEV_1 or FVC between asthmatic children and control children, or between the brothers or sisters of asthmatics and controls of the same sex.

Discussion

In comparing this work with that of previous authors it is found that Horn & Gregg (1973) demonstrated an overall prevalence of wheezing of 14.3% in a population of 991 children. They found positive skin tests in about 60% of 131 wheezy subjects. Blair (1974), in a general practice population study, showed a prevalence of 7.4% over a wide age range. Multiple sensitivity was present in 47% of asthma cases. Morrison Smith, Harding & Cumming (1971) found 9.9% of 21,000 schoolchildren to be wheezy subjects. He found that only 5% of asthmatics over the age of 5 failed to give positive skin tests.

In reviewing the immunopathology of lung disease Pepys (1973) emphasized the

importance of the immunological reactivity of the individual. The term atopic, he suggested, could be used of individuals who have a facility to produce IgE in response to common allergens. The work of Stenius *et al.* (1971), in particular, has demonstrated correlations between Type 1 skin prick test reactions, serum IgE levels and the clinical history.

That such considerations might apply to wheezy bronchitis as well as asthma is of considerable interest. Indeed, McNichol & Williams (1973) have dropped the distinction and call for the concept of a spectrum of severity always linked to the presence of an immunological disorder.

For the purpose of argument it is assumed that the author's category of multiple sensitivity may be used as an objective index of atopy. What then are the implications of this study?

The asthmatic child and his family are distinct from control individuals and families. In particular, the child, his parents, and non-asthmatic female siblings differ from controls. These observations apply to each category as a group although there are non-atopic subjects in each group. It is appropriate, therefore, to examine each category of individual and assess the findings.

Five times as many wheezy children are atopic compared with controls. This level may be regarded as a mean for a wider range of differences, concealing the spectrum of severity in asthma. Other authors find a high correlation between severe asthma and the degree of allergic disturbance (see McNichol & Williams, 1973). The importance of the Type 1 allergic response and IgE mediated disturbance in wheezy subjects is thus emphatic. Some individuals wheeze without being atopic. However, when they are considered as members of a group, atopy distinguishes them from controls.

The brothers of asthmatics do not differ from controls and have a one in ten chance of being atopic. The sisters of asthmatics have a one in five chance of being atopic, four times the control expectation. It is thus clear that a significant number of girls are atopic but are not wheezy subjects. This may at least have some genetic importance. As mothers they may carry a risk of atopy.

It is clear that there is a sex difference in the prevalence of wheezing. Wheezy children of either sex have a comparable immune status given the sex difference. It has been shown above that the non-wheezy sisters of asthmatics have a significant incidence of atopy. However, when the incidence of atopy is expressed for the asthmatics and their siblings as a single group, a sex difference is not demonstrable. Thus, 28% of the children in these families are atopic whatever the sex and whether or not they wheeze.

It is therefore suggested that although atopy is a major characteristic in wheezy subjects, that this may not be the main determinant of the capacity to wheeze, and thus of the sex difference.

One in five of both the mothers and fathers of asthmatic children is atopic. For a given child the parents could assort in various ways. That is, neither atopic, father only atopic, mother only atopic, or both mother and father atopic. This assortment may well determine the severity of the child's asthma, but has not been explored in this study. It also has implications, both genetic and in expected morbidity, for the individuals concerned.

In concluding this section it is relevant to point to the interest of studying the pattern of atopy for a population of same age asthmatics, over a range of severity grades.

Leigh & Marley (1967) studied the prevalence of asthma in the first and second

degree relatives of asthma subjects. They found that 18% of the first degree relatives of asthma individuals had asthma. They did not document any objective measure of allergic status. Schwarz (1952) studied the incidence of allergic disorders in the relatives of asthmatic subjects and found significant differences in the incidence of asthma over control individuals. He found that 19.2% of the healthy relatives of asthma subjects gave positive responses to one or more scratch allergens. He did not test an adequate sample of control individuals and was unable to identify an allergic group of asthmatics clinically.

The author's study shows differences of the same order in the incidence of atopy in the first degree relatives of asthmatic children. An examination of the sex differences highlights the interesting distribution of atopy between girl asthmatics and their non-asthmatic sisters. The usefulness of recording multiple sensitivity as an index of atopy, especially in the study of sex differences is therefore arguable.

The mean value for interval PEFr for wheezy subjects is significantly low. The number of severe asthmatics in the sample is small and not likely to have weighted the result. Holland *et al.* (1969) found differences in interval PEFr but could not link this to any one of three factors including area of residence, social class and frequency of respiratory illness. Of respiratory illness only a past history of pneumonia, bronchitis or asthma is associated with reduced levels. Whether these exerted independent effects was not shown. The factors under consideration only accounted for 10–15% of the total variation. The author's study points to an indirect association with atopic status. That this should apply to wheezy bronchitics as well as asthmatics is of some interest. Atopic status may not however, be the main determinant of the capacity to wheeze.

Conclusions

The cumulative prevalence of the asthma/wheezy bronchitis syndrome in a population of 1064 individuals of 15 years and under, was 15.3% of males, and 7% of females.

Of control individuals 5–10% demonstrate multiple sensitivity (the capacity to react to two or more major allergens).

Of the asthmatic individuals (of a range of ages and severity) 49% of males and 42% of females demonstrate multiple sensitivity.

Twenty-one per cent of the parents and sisters, but not the brothers, of asthmatic individuals, show the same capacity.

When the incidence of atopy amongst asthmatics and their siblings is aggregated no sex difference is demonstrable. Mean value, 28%.

When atopy is equated with multiple sensitivity it may not emerge as the main determinant of the capacity to wheeze.

The mean curve for interval PEFr for this group of asthmatic children was significantly lower than that of control children.

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