

Family size, atopic disorders in parents, asthma in children, and ethnicity

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Background: Several studies have reported an association between family size and atopic conditions, but few have found an association between asthma and family size.

Objective: This study was designed to assess the effect of familial aggregation and sibling number on asthma in children.

Methods: Children from 5 to 11 years of age in England and Scotland participated in a study in 1990 or 1991 in which responses to questions on asthma and wheezing in children and atopic conditions in parents were ascertained. Data on 11,924 complete family sets of child, mother, and father in three samples (the "representative" samples of England and Scotland and the English "inner city" sample) were analyzed.

Results: The following factors were highly associated with child's asthma or wheezing: mother's or father's asthma or wheezing (with the same odds ratio [OR], 2.4; 95% confidence interval [CI], 2.0 to 2.9), other atopic condition in mothers and fathers (OR, 1.5; 95% CI, 1.3 to 1.8 and OR, 1.4; 95% CI, 1.2 to 1.7, respectively), and three or more siblings compared with no siblings (OR, 0.5; 95% CI, 0.4 to 0.6).

Conclusion: The negative relation between family size and wheezing or asthma indicates a protective effect of number of children sharing an environment at a young age. The level of association of asthma or wheezing in the parents and the child and the association between the child's asthma or wheezing and other atopic conditions in parents suggest that a general susceptibility and a lung-specific susceptibility are important in the etiology of asthma. (*J Allergy Clin Immunol* 1997;99:454-60.)

Key words: Asthma, wheezing, atopic conditions, family size, familial aggregation

Familial aggregation of the phenotypes associated with asthma and atopic conditions has been described in several studies.¹⁻³ However, this on its own does not imply a genetic mechanism because families also share environment to a greater extent than the community at large. Recent advances in the genetics of asthma have been almost entirely restricted to serologic correlates of asthma and bronchial hyperresponsiveness in which linkage analyses have demonstrated regions of chromo-

Abbreviation used

OR: Odds ratio

some 11q to be linked to IgE receptor and regions of chromosome 5q to be linked to several genes that regulate IgE production and bronchial hyperresponsiveness.^{4,5} Some further advances related to T-cell receptor proteins have suggested a link between the T-cell receptor- $\alpha\gamma$ in chromosome 14 and specific IgE response.⁶

Although all the above-mentioned advances are clues as to the etiology of asthma, they indicate only predisposition to asthma. There is good evidence that the prevalence of asthma has been increasing in several westernized countries^{7,8}; and this in itself suggests that the environment also plays an important role in the etiology of asthma. It has been suggested that at least in part this may be due to demographic changes toward smaller families because a negative correlation between number of children in the family and skin test reactivity or asthma has been shown.^{9,10} Several environmental factors have been found to be associated with asthma, such as exposure to allergens, infant feeding, air pollutants, infection, and diet¹¹; but the evidence is inconsistent and applies to some groups and not others.

In the last 40 years several ethnic groups have immigrated into Britain. Differences in the prevalence of asthma between ethnic groups in children have been reported previously.^{12,13} There are doubts as to whether these are genuine differences caused by ethnicity, ethnic group characteristics associated with asthma, or differences related to the cultural perception of asthma. One possible avenue, which has not been explored, is assessment, with the same methods, of the level of association of asthma and atopic conditions in parents and their children in a multiethnic society. In this respect, it is also important to assess the association of number of children and birth order of the participating child with asthma because this association is related to a characteristic of the environment. It has been argued that the higher prevalence of atopy in small families could be due to relative isolation from other children before school age.¹⁴ This could retard the age when common childhood infections affect children in small sibships.

The National Study of Health and Growth collected information on respiratory symptoms in children and atopic conditions in parents in 1990 and 1991. This study

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TABLE I. Prevalence of atopic conditions in either the father or the mother by ethnic group and each in total*

	Prevalence in either father or mother							
	Representative sample		Inner city sample				Total	
	England	Scotland	White	Afro-Caribbean	Indian Subcontinent	Other groups	Fathers	Mothers
Total in sample	6463	4165	2183	1124	2696	1046	17677	17677
Total complete family sets	4809	3238	1202	388	1699	588	11924	11924
Symptoms in parents [n (%)]								
Asthma	595 (12.4)	311 (9.6)	121 (10.1)	57 (14.7)	156 (9.2)	33 (5.6)	641 (5.4)	679 (5.7)
Hay fever	1171 (27.2)	742 (22.9)	237 (19.7)	121 (31.2)	211 (12.4)	113 (19.2)	1277 (10.7)	1719 (14.4)
Wheeze	631 (13.1)	413 (12.7)	172 (14.3)	49 (12.6)	87 (5.1)	38 (6.5)	730 (6.1)	792 (6.6)
Rhinitis	403 (8.4)	232 (7.2)	76 (6.3)	16 (4.1)	90 (5.3)	26 (4.4)	371 (3.1)	554 (4.6)
Eczema	713 (14.8)	306 (9.4)	138 (11.4)	49 (12.6)	50 (2.9)	31 (5.3)	449 (3.8)	924 (7.7)

*A family set has information on the child, the natural mother, and the natural father.

reports on the level of familial aggregation of asthma and atopic conditions and the relation between asthma and family size and sibling order in several ethnic groups in England and Scotland, adjusting for sociodemographic factors and smoking status of the parents.

METHODS

The National Study of Health and Growth was a health surveillance system of primary school children. Information was obtained from English and Scottish samples on the basis of stratified random sampling of employment exchange areas with proportionally more study areas from poorer background and an English "inner city sample" selected by characteristics of deprivation and ethnic composition.¹⁵ The selection of the "inner city sample" was based on Small Area Statistics Census information from 1911 electoral wards in the English County and London Boroughs in terms percentage of economically active men unemployed; number of households per 1000 with exclusive use of all basic amenities; number of households per 1000 with more than 1.5 persons per room; percentage of persons born in New Commonwealth, continent of America; percentage of persons born in New Commonwealth, continent of Asia. The five wards with the highest percentage of Afro-Caribbean persons and the five wards with highest percentage of Asians originating from the Indian subcontinent were selected. Most of these wards had a very high level of overcrowding. The remaining 10 wards were chosen to have high values of at least two of the factors (unemployment, overcrowding, or lack of exclusive use of amenities). The samples, based on stratified random sampling, were similar in characteristics to a sample of children from the general population.¹⁶ Both are referred to as "representative" samples in this study. The few families from ethnic minorities in these samples were excluded from the analysis. The inner city sample was multiethnic. The English representative sample was surveyed in 1990, the Scottish representative sample in 1990 and 1991, and the inner city sample in 1991.

Information on respiratory illness in the children and atopic conditions in each parent was obtained in a self-administered questionnaire usually completed by the child's mother. In the English inner city sample questionnaires were available in English-Urdu, English-Gujarati, or English-Punjabi as appropriate. Data were collected as to whether the child had experi-

enced attacks of asthma or bronchitis during the last 12 months in separate questions, whether he or she usually coughed first thing in the morning or coughed at any other time, whether the child's "colds usually go to his or her chest," whether his or her chest ever sounded wheezy or whistling and if so whether these symptoms were present on most days or nights. The reported atopic conditions of each natural parent were also collected as shown in Table I.

In the analysis we only included families with complete information on the atopic conditions in both parents and at least one question completed on the child's respiratory symptoms. However, the results on family size, in which data were available for most children, were repeated to assess consistency in the total sample. The ethnic groups were classified according to the language spoken at home and by the field worker's subjective assessment of the child's ethnic group. In the inner city sample there were four groups: white, Afro-Caribbean, children from families originating from the Indian subcontinent, and a heterogeneous group including those that we were unable to classify in the other three groups. This classification has been used in our study since 1983. We also used, in the analysis, information on child's sex and age, number of children in the family, order of the child in the sibship, smoking status of each parent, and social class of the father.

Children were divided into four nonoverlapping groups according to information reported by the parents as to whether the child had experienced attacks of asthma or bronchitis during the last 12 months, whether he or she usually coughs first thing in the morning or coughed at any time, whether his or her chest ever sounded wheezy or whistling and if so whether these symptoms were present on most days and nights. Group I included children who did not have a respiratory symptom or condition. Group II included children with any reported symptoms or conditions (those with cough, bronchitis, and "colds [that] usually go to the child's chest") except wheezing or asthma attacks. Group III included children with occasional wheezing but no persistent wheezing or asthma. Group IV included children with persistent wheezing, asthma attacks, or both.

In the main analysis a logistic regression was carried out in which the dependent variable was dichotomized into groups III and IV and the other groups I and II. The independent variables in the model were child's age and sex, ethnic group,

TABLE II. Prevalence of at least one atopic condition in parents by group of respiratory symptoms in children and ethnic groups*

	Prevalence in parents						
	Representative sample		Inner city sample				Total
	England	Scotland	White inner city	Afro-Caribbean	Indian subcontinent	Other groups	Total† boys Total† girls
Symptoms in children [n (%)]							
Group I	1309 (39.1)	784 (33.9)	222 (32.5)	87 (41.4)	227 (19.0)	99 (25.5)	1328 (33.1) 1395 (33.9)
Group II	334 (43.9)	153 (30.3)	110 (35.4)	54 (44.6)	100 (30.5)	39 (29.3)	383 (34.9) 404 (38.3)
Group III	176 (57.7)	96 (51.9)	39 (51.3)	7 (38.9)	16 (41.0)	9 (40.9)	190 (49.6) 153 (58.4)
Group IV	241 (60.9)	134 (57.0)	74 (56.1)	22 (56.4)	40 (28.8)	16 (35.6)	335 (53.9) 190 (52.6)

See text for definitions of groups.

*Data based on complete family sets.

†Twenty-four missing values for sex.

number of children in the family, birth order, number of parents with asthma or wheezing, number of parents with another atopic condition (eczema, rhinitis, and hay fever), father's social class, maternal and paternal smoking status, and study areas. There were 55 study areas: 21 in the English representative sample, 14 in the Scottish sample, and 20 in the inner city areas. The analysis was repeated excluding children in groups II and III, thus making the contrast sharper. We also carried out the analysis contrasting group IV with all the other groups. In all the logistic analyses the main results were similar and only differed in details. In the analyses, variables that were not associated with the dependent variable at the 0.05 level were eliminated from the final model, with the exception of study area.

RESULTS

The total sample included 17,677 children; but of those, 11,924 (67%) had information on the family set (i.e., two parents and the child). Three thousand eight hundred forty-seven families were excluded from this analysis because of the lack of information for at least one atopic condition in both parents; 1373 families were excluded because of lack of information for at least one atopic condition in the father only; and 533 families were excluded because of lack of information on at least one atopic condition in the mother only. Exclusions were higher in the inner city sample than in the representative samples and were highest among Afro-Caribbeans because information on one of the parents, usually the father, was frequently missing.

Table I gives the frequency of at least one parent with an atopic condition in the family by ethnic group and in the total distribution by sex of the parent. If the heterogeneous group of other ethnic groups was excluded, parents originating from the Indian subcontinent consistently had a lower frequency for each atopic condition, except for rhinitis. Hay fever was more frequently reported by Afro-Caribbeans and eczema by whites in the representative sample. For each atopic condition the frequency was higher in mothers than fathers, but the differences were minimal for asthma and wheezing in comparison with the other conditions.

The prevalence of at least one atopic condition in the parents was high in all ethnic groups (Table II). The frequencies were usually the highest in group IV (persistent wheezing and/or asthma attacks) and lowest in children in group I (no respiratory symptoms). In the three samples of white children, there was an increase in atopic conditions in the parent by level of certainty of asthma in the child. This association is less clear in those originating from the Indian subcontinent and the Afro-Caribbeans, but this may be due to the small size of groups III and IV among the ethnic minorities. We also looked at the relation of respiratory symptoms in children and asthma or wheezing in the parents by ethnicity (Table III). Children in groups III and IV had a higher frequency of parents with asthma or wheezing than those in groups I and II in every ethnic group, but the contrast was less clear in the heterogeneous "other" ethnic group.

The prevalence of asthma or wheezing was associated with the number of children in the family in all ethnic groups, except those originating from the Indian subcontinent (Table IV). Children with no siblings had a higher prevalence of asthma or wheezing, and those in a family of four or more had a lower prevalence of asthma or wheezing. This analysis was repeated for 14,686 children with information on asthma or wheezing and family size, regardless of the availability of parents' information. The trend was still apparent for the total and for each of the representative samples but was unclear for most of the ethnic groups in the inner city sample, including the inner city whites.

In the final model of the logistic analysis, several factors were highly associated with child's asthma or wheezing (groups III and IV). The number of parents with asthma or wheezing was highly related to the dependent variable ($p < 0.001$). A child who has one parent with asthma or wheezing is approximately 2.5 times more likely to have the condition and is four times more likely to have the condition if both parents report it. The odds ratio (OR) was the same whether the father or mother was affected. Other atopic conditions (rhinitis,

TABLE III. Prevalence of asthma or wheezing in parents by group of respiratory symptoms in children and ethnic groups*

Prevalence in parents								
Representative sample			Inner city sample				Total† boys	Total† girls
England	Scotland	White inner city	Afro- Caribbean	Indian subcontinent	Other groups			
Symptoms in children [<i>n</i> (%)]								
Group I	475 (14.2)	302 (13.1)	103 (15.1)	33 (15.7)	105 (8.8)	23 (5.9)	491 (12.2)	548 (13.3)
Group II	154 (20.3)	70 (13.9)	60 (19.3)	19 (15.8)	50 (15.2)	14 (10.5)	192 (17.5)	174 (16.5)
Group III	94 (30.8)	58 (31.3)	24 (31.6)	5 (27.8)	5 (12.8)	7 (31.8)	109 (28.5)	84 (43.5)
Group IV	145 (36.6)	86 (36.6)	46 (34.8)	14 (35.9)	29 (20.9)	7 (13.7)	200 (32.1)	126 (34.9)

See text for definition of groups.

*Only complete family sets includes.

†Twenty-four missing values for sex.

TABLE IV. Prevalence of asthma or wheezing in child by ethnic group and number of children in the family*

No. of children in the family	Representative sample		Inner city sample			
	English	Scottish	White inner city	Afro-Caribbean	Indian subcontinent	Other groups
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
1	67 (19.0)	45 (18.7)	26 (22.8)	9 (23.1)	3 (8.1)	8 (17.4)
2	366 (15.6)	197 (12.9)	71 (16.1)	30 (24.6)	26 (12.9)	16 (12.0)
3	162 (12.5)	108 (12.2)	64 (20.8)	6 (6.1)	46 (14.2)	17 (12.1)
4 or more	79 (12.3)	57 (11.8)	39 (13.8)	7 (7.1)	79 (8.4)	22 (9.8)
Not known	27 (14.7)	13 (12.5)	8 (13.6)	5 (16.7)	24 (11.9)	4 (8.9)
Total with condition	701 (14.6)	420 (13.0)	208 (17.3)	57 (14.7)	178 (10.5)	67 (11.4)
Total of children	4809	3238	1202	388	1699	588

*Only complete family sets included.

eczema, and hay fever) in the parents were also highly associated with asthma or wheezing in the child, although the ORs were approximately half the magnitude of the association of asthma or wheezing in parents and children ($p < 0.001$). Family size, but not birth order, was highly associated with asthma or persistent wheezing ($p < 0.001$). Children in larger sibships had a lower OR. Children in families with more than three children were 50% less likely to have asthma or wheezing than in families with one child. Boys had more asthma or wheezing than girls ($p < 0.001$). Parents' smoking status, order in sibship, father's social class, and ethnic group were not associated with asthma or wheezing in the child and were eliminated from the final model. The interactions of ethnic group with parental conditions, family size, and birth order on asthma or wheezing were not statistically significant. When the analysis was repeated without family size, birth order was significantly associated with child's asthma or wheezing ($p < 0.001$), but the ORs were closer to 1 than for family size (Table V). The logistic analysis was repeated, and the dependent variable was changed to contrast group IV with groups I, II, and III and to contrast group IV with group I. The final model of these alternative analyses included the same variables as presented in Table V.

DISCUSSION

This study has shown that parents' asthma or wheezing is highly associated with asthma or wheezing in their children, regardless of ethnicity. Other atopic conditions in parents such as eczema, rhinitis, and hay fever are independently associated with child's asthma; but the strength of the association was less than that for parental asthma or wheezing. These findings are consistent in all ethnic groups, except those originating from the Indian subcontinent. Prevalence of asthma or wheezing in children was highly negatively associated with number of children in the family but not with birth order, if total number of children in the family was included in the model. When family size was not included in the analysis, birth order was significantly associated with asthma or wheezing in children, but the OR was closer to 1 than for number of children in the family. Once atopic conditions in the parents, family size, and sex of the child are included in the model, the association between ethnicity and asthma or wheezing in children is slight or nonexistent.

We only included family sets with complete information on atopic conditions in the parents and at least one respiratory illness item completed in the child's section of the questionnaire. With this criterion we excluded

TABLE V. Factors associated with wheezing and/or asthma attacks in children (final model)

	Total	n (%)	OR*	OR† (95% CI)	p Value
Family size and birth order included in the analysis					
Parents' asthma or wheezing					<0.001
Neither father or mother affected	9996	1111 (11.1)	1.00	1.00	
Mother only	898	234 (26.1)	2.82	2.42 (2.03-2.87)	
Father only	864	221 (25.6)	2.75	2.41 (2.02-2.87)	
Both affected	166	65 (39.2)	5.15	3.99 (2.85-5.58)	
Parents' rhinitis, hay fever, or eczema					<0.001
Neither father or mother affected	8157	895 (11.0)	1.00	1.00	
Mother only	1954	366 (18.7)	1.87	1.52 (1.31-1.76)	
Father only	1214	214 (17.6)	1.74	1.41 (1.18-1.68)	
Both affected	599	156 (26.0)	2.86	1.98 (1.61-2.45)	
Family size					<0.001
One	827	158 (19.1)	1.00	1.00	
Two	4769	706 (14.8)	0.73	0.71 (0.58-0.86)	
Three	3044	403 (13.2)	0.64	0.62 (0.51-0.77)	
More than three	2660	283 (10.6)	0.50	0.50 (0.40-0.62)	
Unknown	624	81 (12.9)	0.63	0.65 (0.48-0.88)	
Sex					0.001
Boys	6117	1005 (16.4)	1.00	1.00	
Girls	5783	623 (10.8)	0.61	0.60 (0.54-0.67)	
Family size excluded in the analysis (only results of birth order given)					
No. of older siblings					0.001
None	4616	703 (15.2)	1.00	1.00	
One	3824	502 (13.1)	0.84	0.81 (0.71-0.92)	
Two	1371	166 (12.1)	0.76	0.76 (0.63-0.91)	
More than two	508	55 (10.8)	0.67	0.68 (0.50-0.91)	
Unknown	1605	205 (12.8)	0.81	0.85 (0.71-1.01)	

The independent variables included in the initial model were child's age and sex, ethnic group, number of children in the family, birth order, number of parents with asthma or wheezing, number of parents with another atopic condition, father's social class, maternal and paternal status, and study areas.

CI, Confidence interval.

*Unadjusted OR.

†Adjusted for other variables in final model and study areas.

more families from the inner city sample than the representative samples. The overall response rate compares favorably with response rates from other large studies when several covariates were used in the analysis. However, we cannot exclude the possibility of bias related to differences in response rate of different subgroups in the three samples. The prevalence of atopic conditions by parent may have been influenced by the informant, who in most cases was the mother, but this seems unlikely to have affected the levels of association with the dependent variable in the multiple logistic regression because each parent had a similar level of association with the outcome.

It was expected that there would be a parent-child association of asthma or wheezing. Others have reported the parent-child association of asthma,^{1-3, 17-19} and most have shown an OR similar to those reported in our study, although only a few have shown the stronger association with both asthmatic parents in the family.^{1, 20} Information bias because of the possibility that parents with asthma or wheezing are more likely to report the

same symptoms in the child or that the family doctor is more likely to diagnose the condition in the child when a parent has asthma may exaggerate the strength of the association. However, by assessing methacholine response in parents of children with asthma, there is some evidence that the level of association may be even higher than association based on questionnaires.²¹ We expected that the association of asthma between generations could have been altered by cultural characteristics in some groups or by changes of habitat over the last 20 to 30 years associated with the status of the immigrant. In the ethnic group originating in the Indian subcontinent, the association was less clear. There is a possibility that the interpretation of symptoms is different for this group than for any other homogeneous group in the study because the prevalence of atopic conditions in parents with asthma or wheezing in children was lower than that in the other groups. Alternative explanations need to satisfy the observation that the prevalence of asthma has remained relatively low in both generations. Families from the Indian subcontinent tend to be larger than

those of other groups, and the relative position has not changed over the period. Only 37 of 1699 children in families originating from the Indian subcontinent in our analysis had no siblings. In our study there was no evidence that the mother-child association of asthma was greater than that of the father-child association, as suggested by Cookson et al.²² in relation to IgE responsiveness. Burrows et al.²⁰ were also unable to reconcile their findings with the results reported by Cookson et al.²² because they showed that IgE levels and asthma in children were equally highly associated with paternal and maternal asthma. The lack of difference in the level of association in our study is even more striking, considering that the information on the child and the mother may be more accurate than the information on the father because the mother usually completed the questionnaire.

In our study we were able to dissect the association of asthma in parents and children from other atopic conditions in parents and asthma in children. Other atopic conditions in parents are associated with child's asthma independently of parental asthma. Dold et al.¹⁷ could not show the association between atopic conditions other than asthma in parents and asthma in children adjusted by parents' asthma. In their study they showed a symptom-specific association (i.e., dermatitis in parents and child, asthma in parents and child, and hay fever in both generations) or other nonspecific condition associations excluding asthma. Pepys²³ suggested that both a general atopic tendency to common allergic diseases and a lung disease susceptibility affect the expression of asthma. Our findings support Pepys' argument and are important because they add weight to the relevance of genetics in the etiology of asthma because the asthma literature, with the exception of the genetics of bronchial reactivity, is almost entirely related to the study of atopy, IgE, interleukins, and T-cell receptor proteins.

The relationship between number of children in the family and asthma has been reported by Crane et al.¹⁰ and by Stoddard and Miller.²⁴ Our results are similar in so far as number of children was associated with asthma. Birth order was not associated with asthma when adjusted for family size. It is surprising that the association between family size and asthma has not been reported in other large studies on the basis of, for example, the 1958 and 1970 birth cohorts in which the relevant information would have been available.^{25, 26} Research workers using information from those cohorts have reported an association with number of children in the family in relation to hay fever and eczema^{25, 26} and, from another study, skin test reactivity.⁹ All these studies have shown that children in large families are more protected from asthma or other atopic conditions. Contrary to our data, however, Strachan²⁶ emphasized the importance of order in the sibship over family size in relation to hay fever. Golding and Peters,²⁵ if anything, showed a stronger association of hay fever and eczema with number of children than with birth order. As a

possible explanation for the birth order findings Strachan²⁶ suggested that infections in early childhood would render the child less susceptible to allergic diseases and that early infections would be more common in those with siblings. However, with the current available data, family size may be more important than birth order in relation to associations with atopic conditions. Information on the rate of infections in early childhood according to birth order and family size would help to test Strachan's hypothesis. If family size is relevant regardless of position, alternative explanations, such as nutritional status or nutrient intake, are plausible. Both obesity and height of children have increased over time.²⁷ We looked into the possibility that inclusion in the analysis of either height or weight-for-height would remove the association between number of children and asthma, but the association was not modified. Thus if nutrition is important for explaining the sibship size effect on atopic conditions, this could be due to nutritional factors unrelated to anthropometric measurements. Although the explanations for the association between asthma and family size or birth order are weak, the level of association is high in the total sample and difficult to explain away as an artefact. We are still, however, uncertain as to whether a similar pattern occurs in the ethnic minority groups because this was not clear in the larger sample.

In conclusion our analysis, in combination with previously published evidence, reinforces the belief that a general genetic susceptibility to allergic disorders and a more specific lung susceptibility may be operating in some individuals. The strong negative association between asthma or wheezing and number of children in the family has also been reported in relation to hay fever, eczema, and skin test reactivity. This suggests that an environmental exposure related to family size is a common factor in triggering or protecting a child from the onset of an atopic condition.

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