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Family size, childhood infections and atopic diseases

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Abstract

***Background* – This study addresses the causes of the increases in childhood asthma and allergic disease. On the basis of an observed inverse relationship between family size and allergic disease or atopy, it has been proposed that a fall in common childhood infections may have been responsible for the rise in asthma. This study was undertaken to investigate the relationships between family size and reported allergic disease and to test the hypothesis that an inverse relationship between the two is a consequence of childhood infections.**

***Methods* – Data had been obtained in a 1964 cross sectional survey of a random sample of Aberdeen schoolchildren aged between 10 and 14 in that year. Records of the presence or absence of asthma, eczema, or hay fever at the time of the survey and a history of measles, pertussis, varicella, rubella, and mumps before and after the age of three years were available for 2111 subjects.**

***Results* – The risks of hay fever (odds ratio 0.2, 95% CI 0.1 to 0.8) and eczema (OR 0.3, CI 0.1 to 0.7) were inversely related to having had three or more older siblings, whilst the risk of asthma (OR 0.4, CI 0.1 to 0.9) was inversely related to having had three or more younger siblings. Increasing total numbers of siblings showed a significant trend in protection against both eczema and hay fever. A weak protective effect against asthma was found for measles after the age of three (OR 0.5, CI 0.3 to 0.9) and slight increases in the risk of eczema were associated with having had rubella or pertussis and of asthma with having had varicella. The number of infections before the age of three was associated with a significant trend in the odds ratios towards increased risk of asthma ($p = 0.025$). There were significant trends in the odds ratios towards greater risk of eczema and hay fever with increasing exposure to rubella, mumps, and varicella. These relations between infection and atopic diseases were independent of the potential confounding factors age, sex, father's social class, and total number of siblings.**

***Conclusions* – These data add to the accumulating evidence that membership of a large sibship confers some protection against atopic disease. This does not appear to be explained by the common childhood infections which show conflicting relationships with atopic disease, in that measles may have some protective effect against asthma but the more infections a child has had, the more likely he or she is to have atopic disease. The explanation of the sibship effect is likely to lie elsewhere and the fall in common childhood infections is unlikely to explain the rise in atopic disease.**

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Keywords: atopic disease, family size, childhood infections.

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It is now generally accepted that there has been a substantial increase in the prevalence of asthma and other allergic diseases among children in developed countries over the past three decades.[1 2] We have argued that this must be due to environmental changes and that the most relevant are those likely to have increased the population's overall susceptibility to precipitating factors such as allergens.[3] Two hypotheses seem plausible: (1) that this alteration in susceptibility is due to changes in the dietary intake of protective factors,[3 4] and (2) that it is due to a reduction in the frequency and/or severity of childhood infections. This latter hypothesis arose from the observation of an inverse association between family size and risk of atopy,[5 6] possibly explicable on the assumption that childhood infections are more frequent in larger families. Three studies have provided indirect support for this hypothesis: (1) children who suffered measles in Guinea-Bissau have been shown to have been less likely than those who did not to develop skin sensitivity to mites,[7] (2) Japanese children with delayed hypersensitivity to tuberculin were less likely than tuberculin negative children to have atopy or asthmatic symptoms,[8] and (3) Italian military recruits were less likely to have asthma, allergic rhinitis, or atopy if they were serologically positive to hepatitis A.[9] However, in this last study a strong effect of family size persisted even after adjusting for hepatitis A positivity.

There has been a documented reduction in the incidence of the serious childhood illnesses, measles and pertussis, since the introduction of immunisation in 1968 and 1950, respectively,[10] and this coincides with the increase in prevalence of asthma in children, although the fall in infection rates seems to have been more rapid than the apparently continuing rise in asthma. It is nevertheless reasonable to propose

that this reduction may have contributed to the increase in asthma. We have examined the relationship between sibship size, infection, and atopy in a random sample of Aberdeen schoolchildren for whom data on family structure, father's social class, history of infections, and atopic disease were already available.

Methods

This study is a retrospective analysis of data gathered in 1964 when the MRC Medical Sociology Research Unit carried out a survey of a random sample of 2743 Aberdeen school children aged 10–14 years. Interviews conducted with the parents of 2511 children contained questions on the common childhood infections, including measles, pertussis, rubella, mumps and varicella, and the age at which they occurred. Any history of hay fever, eczema, or wheezy illness and details of father's social class, sibship size, and position of the child in the family were also recorded. Children with a history of respiratory symptoms were seen by a doctor and the diagnosis of asthma, defined as "recurrent dyspnoea of an obstructive type without other demonstrable cause" determined on clinical grounds, was confirmed in 121 subjects for whom details of pulmonary function[11] and educational and social characteristics[12] were published. Infection data which were not entered into the database at the time of the 1964 study were available for 2111 subjects whose original interview schedules were accessible to us.

Social class in childhood was derived from the father's occupation recorded at the time of the 1964 interviews and coded according to the Registrar General's classification of occupations (1951): non-manual (classes I and II and the non-manual segment of III); skilled manual (remainder of class III); and semi-skilled and unskilled manual (classes IV and V).[11] For each childhood infection a variable was stratified as: never had infection before 1964 study; infection occurred up to age 3; or infection occurred after age 3. In this way the prevalence of atopic disease among subjects acquiring a particular infection in early childhood was compared with the prevalence among those who did not acquire the infection before they were surveyed at age 10–15 years. The three year cut off was chosen as the age by which atopic status will have been established in the majority of subjects. Analyses based on a one or two year cut off yielded similar results to those reported. In order to examine the effect of repeated exposure to infection, several summary measures of infection were examined. The sum of all infections occurring on or before the age of three was stratified as none, any one, two, or three or more infections. Measles and pertussis occurring up to the age of three were combined since they have an important respiratory component. The sum of the other three (rubella, mumps, and varicella) were stratified as none, any of the three, and two or more occurring on or before the age of three.

The unadjusted prevalence of asthma, eczema, and hay fever was calculated by number of older, number of younger and total number of siblings, individual childhood infections, and the sum of these infections. Logistic regression was used to assess the independent effect of sibship size and childhood infections on atopic disease after adjustment for potential confounding by age, sex, and social class of father. The χ^2 test for trend was applied where appropriate. The statistical software program Stata Release 4 (Stata Corporation, Texas, USA) was used for the analyses.

Results

Among the 2111 subjects for whom complete information on sibship size, infections and atopic disease was available, 104 were recorded as having had asthma, 73 hay fever, and 98 eczema by the age of 10–14 years. Subjects included in these analyses did not differ from those excluded in terms of age, sex, sibship size, or social class of father.

Table 1 shows the relationship of atopic disease to sibship composition. Having three or more older siblings was associated, after adjustment for age, sex, father's social class, and sum of all infections, with a significant reduction in risk of both eczema and hay fever, but not asthma. In contrast, having three or more younger siblings was independently associated with a lower risk of asthma (odds ratio 0.4, 95% confidence interval (CI) 0.1 to 0.9). The total number of siblings had a more powerful protective independent effect on atopic disease than did the number of older or younger siblings and there was a trend in the odds ratios with increasing number of siblings which was significant for eczema ($p = 0.002$) and for hay fever ($p = 0.003$).

Table 2 shows the effect of childhood infections on the prevalence of atopic disease. Subjects who had rubella, pertussis, mumps, or varicella on or before the age of three were more likely to have asthma, eczema, or hay fever than those who did not acquire these infections in childhood – that is, before the age of 10–14 years. After adjustment for age, sex, father's social class, and total number of siblings the only infection associated with a significant increase in risk was rubella which was independently related to eczema. There was little effect of early childhood measles on the prevalence of atopic disease, although the prevalence of asthma was somewhat lower in those who acquired measles before the age of three. The temporal relations of infections with atopic disease are not directly shown in this study, but may be relevant particularly to the effect of infections occurring after the age of three. Nevertheless, the data for infection after the age of three years are shown in table 2 in order to provide complete information on the frequency of infections occurring throughout childhood. Of note, the occurrence of measles after the age of three was independently associated with a reduced risk of asthma (OR 0.5, CI 0.3 to 0.9), while varicella was associated with an increased risk of asthma and pertussis with an increased risk of eczema.

Table 1 Prevalence and risk of atopic disease according to number of siblings at age 10–14 years

	Asthma			*Eczema*			*Hay fever*		
	Prevalence (%)	*OR* (95% CI) p for trend*	*OR† (5% CI) p for trend*	*Prevalence (%)*	*OR* (95% CI) p for trend*	*OR† (95% CI) p for trend*	*Prevalence (%)*	*OR* (95% CI) p for trend*	*OR† (95% CI) p for trend*
Number of older siblings									
0	33/779 (4.2%)	1.0	1.0	36/779 (4.6%)	1.0	1.0	35/779 (4.5%)	1.0	1.0
1	44/676 (6.5%)	1.6 (1.0 to 2.6)	1.5 (0.9 to 2.4)	38/674 (5.6%)	1.2 (0.8 to 2.0)	1.2 (0.7 to 1.9)	26/676 (3.9%)	0.8 (0.5 to 1.4)	0.8 (0.5 to 1.3)
2	16/344 (4.7%)	1.1 (0.6 to 2.1)	1.0 (0.6 to 1.9)	20/344 (5.8%)	1.3 (0.7 to 2.3)	1.3 (0.7 to 2.3)	9/344 (2.6%)	0.6 (0.3 to 1.3)	0.6 (0.3 to 1.2)
≥3	11/312 (3.5%)	0.8 (0.4 to 1.6) p=0.684	0.7 (0.4 to 1.5) p=0.442	4/312 (1.3%)	0.3 (0.1 to 0.8) p=0.159	0.3 (0.1 to 0.7) p=0.105	3/312 (1.0%)	0.2 (0.1 to 0.8) p=0.010	0.2 (0.1 to 0.8) p=0.006
Number of younger siblings									
0	43/840 (5.1%)	1.0	1.0	47/839 (5.6%)	1.0	1.0	32/840 (3.8%)	1.0	1.0
1	35/647 (5.4%)	1.1 (0.7 to 1.7)	1.1 (0.7 to 1.7)	30/646 (4.6%)	0.8 (0.5 to 1.3)	0.8 (0.5 to 1.3)	24/647 (3.7%)	1.0 (0.6 to 1.7)	1.0 (0.6 to 1.7)
2	21/369 (5.7%)	1.1 (0.6 to 1.9)	1.2 (0.7 to 2.0)	12/369 (3.3%)	0.6 (0.3 to 1.1)	0.6 (0.3 to 1.1)	10/369 (2.7%)	0.7 (0.4 to 1.5)	0.8 (0.4 to 1.6)
≥3	5/255 (2.0%)	0.3 (0.1 to 0.9) p=0.140	0.4 (0.1 to 0.9) p=0.193	9/255 (3.5%)	0.6 (0.3 to 1.3) p=0.056	0.6 (0.3 to 1.3) p=0.072	7/255 (2.8%)	0.8 (0.3 to 1.8) p=0.395	0.8 (0.3 to 1.8) p=0.446
Total number of siblings									
0	6/169 (3.6%)	1.0	1.0	13/169 (7.7%)	1.0	1.0	9/169 (5.3%)	1.0	1.0
1	35/611 (5.7%)	1.7 (0.7 to 4.2)	1.6 (0.7 to 4.0)	32/610 (5.3%)	0.6 (0.3 to 1.2)	0.6 (0.3 to 1.2)	31/611 (5.1%)	0.9 (0.4 to 2.0)	0.9 (0.4 to 2.0)
2	34/539 (6.3%)	2.0 (0.8 to 4.4)	1.8 (0.8 to 4.5)	27/538 (5.0%)	0.6 (0.3 to 1.2)	0.6 (0.3 to 1.1)	19/539 (3.5%)	0.7 (0.3 to 1.5)	0.6 (0.3 to 1.5)
3	17/380 (4.5%)	1.3 (0.5 to 3.4)	1.3 (0.5 to 3.3)	19/380 (5.0%)	0.6 (0.3 to 1.3)	0.6 (0.3 to 1.2)	6/380 (1.6%)	0.3 (0.1 to 0.9)	0.3 (0.1 to 0.9)
4	5/215 (2.3%)	0.6 (0.2 to 2.2)	0.6 (0.2 to 2.0)	4/215 (1.9%)	0.2 (0.1 to 0.7)	0.2 (0.1 to 0.7)	6/215 (2.8%)	0.6 (0.2 to 1.7)	0.6 (0.2 to 1.7)
≥5	7/197 (3.4%)	0.9 (0.3 to 2.9) p=0.102	0.9 (0.3 to 2.7) p=0.079	3/197 (1.5%)	0.2 (0.1 to 0.7) p=0.002	0.2 (0.05 to 0.6) p=0.002	2/197 (1.0%)	0.2 (0.05 to 1.0) p=0.004	0.2 (0.04 to 1.0) p=0.003

* Adjusted for age, sex, social class of father.
† Adjusted for age, sex, social class of father, and sum of infections before age 3.

Table 2 Risk of atopic disease according to history of infection up to age 10–14 years

	Asthma		*Eczema*		*Hay fever*	
Infection history	*Prevalence (%)*	*Adjusted OR (95% CI)**	*Prevalence (%)*	*Adjusted OR (95% CI)**	*Prevalence (%)*	*Adjusted OR (95% CI)**
Measles						
No	18/241 (7.5%)	1.0	10/214 (4.2%)	1.0	9/241 (3.7%)	1.0
≤age 3	40/737 (5.4%)	0.7 (0.4 to 1.2)	35/736 (4.8%)	1.2 (0.6 to 2.4)	24/737 (3.3%)	0.8 (0.4 to 1.9)
>age 3	46/1133 (4.1%)	0.5 (0.3 to 0.9)	53/1132 (4.7%)	1.1 (0.5 to 2.1)	40/1133 (3.5%)	0.9 (0.4 to 1.8)
Rubella						
No	63/1241 (5.1%)	1.0	58/1240 (4.7%)	1.0	43/1241 (3.5%)	1.0
≤age 3	11/123 (8.9%)	1.9 (0.9 to 3.8)	11/123 (8.9%)	2.0 (1.0 to 4.0)	7/123 (5.7%)	1.7 (0.7 to 4.0)
>age 3	30/747 (4.0%)	0.8 (0.5 to 1.3)	29/746 (3.9%)	0.8 (0.5 to 1.3)	23/747 (3.1%)	0.8 (0.5 to 1.4)
Pertussis						
No	74/1660 (4.5%)	1.0	70/1658 (4.2%)	1.0	54/1660 (3.3%)	1.0
≤age 3	17/241 (7.1%)	1.7 (0.9 to 2.9)	10/241 (4.2%)	1.0 (0.5 to 2.0)	6/241 (2.5%)	0.8 (0.3 to 1.8)
>age 3	13/210 (6.2%)	1.6 (0.8 to 2.9)	18/210 (8.6%)	2.0 (1.2 to 3.5)	13/210 (6.2%)	1.8 (0.9 to 3.4)
Mumps						
No	54/1257 (4.3%)	1.0	50/1256 (4.0%)	1.0	39/1257 (3.1%)	1.0
≤age 3	10/135 (7.4%)	1.8 (0.9 to 3.6)	8/135 (5.9%)	1.6 (0.7 to 3.4)	7/135 (5.2%)	1.6 (0.7 to 3.8)
>age 3	40/719 (5.6%)	1.3 (0.9 to 2.0)	40/718 (5.6%)	1.4 (0.9 to 2.1)	27/719 (3.8%)	1.2 (0.7 to 1.9)
Varicella						
No	22/711 (3.1%)	1.0	30/710 (4.2%)	1.0	18/711 (2.5%)	1.0
≤age 3	18/302 (6.0%)	1.8 (0.9 to 3.5)	21/302 (7.0%)	1.6 (0.9 to 2.9)	16/302 (5.3%)	1.9 (0.9 to 3.9)
>age 3	64/1098 (5.8%)	1.9 (1.1 to 3.1)	47/1098 (4.3%)	0.9 (0.6 to 1.5)	39/1098 (3.6%)	1.2 (0.7 to 2.2)

* Adjusted for age, sex, social class of father, and total number of siblings.

The unadjusted prevalence of the atopic diseases tended to be higher in subjects who had more infections before the age of three (table 3). For asthma there was a significant trend ($p = 0.025$) in the odds ratios with increasing numbers of infections even after adjustment for age, sex, father's social class, and total number of siblings. Having had measles or pertussis or both before the age of three had no influence on the prevalence of atopic disease. In contrast, the trends in the odds ratios were towards greater risk of atopic disease with increasing exposure to rubella, mumps and varicella; these trends were significant for eczema ($p=0.02$) and hay fever ($p=0.014$) and of borderline significance for asthma ($p=0.054$).

Discussion

The rise in the prevalence of asthma in advanced societies worldwide remains an extremely important public health problem. Recent data from Scotland indicate that some 15% of the 12 year old population have the disease[13 14] and our previous studies suggest that at least 60% of these will have asthma persisting into middle age.[15] When these are added to the numbers of those who will develop asthma in adult life it can be seen that the economic effects in terms of health service costs and loss of time from work, currently not far short of 1 billion annually in the UK, are likely to become very important. There can be few conditions for which there is a stronger economic argument for finding a means of prevention.

The evidence to date suggests that the increase in childhood asthma is related to an increased prevalence of atopy.[16] This appears in turn to be associated with increased Th2 lymphocyte responses and a reduced Th1 response, and there are theoretical reasons with experimental support for thinking that early infections may switch the development of T cell clones in the Th1 direction.[17 18] However, there is also evidence that in children who develop atopy the Th2 phenotype is present at birth and that interferon gamma, the main cytokine associated with the Th1 cell, is present in reduced concentrations in cord blood.[19 20] It

Table 3 Risk of atopic disease according to sum of infections before age 3

	Asthma		*Eczema*		*Hay fever*	
	Prevalence (%)	*Adjusted OR (95% CI)* p for trend*	*Prevalence (%)*	*Adjusted OR (95% CI)* p for trend*	*Prevalence (%)*	*Adjusted OR (95% CI)* p for trend*
Sum of all infections						
None	40/1030 (3.9%)	1.0	44/1029 (4.3%)	1.0	30/1030 (2.9%)	1.0
Any one	40/727 (5.5%)	1.4 (0.9 to 2.2)	35/726 (4.8%)	1.1 (0.7 to 1.8)	31/727 (4.3%)	1.5 (0.9 to 2.5)
Any two	17/271 (6.3%)	1.6 (0.9 to 3.0)	11/271 (4.1%)	1.0 (0.5 to 2.0)	9/271 (3.3%)	1.1 (0.5 to 2.4)
Three or more	7/83 (6.7%)	2.1 (0.9 to 4.9) p=0.025	8/83 (9.6%)	2.6 (1.2 to 5.9) p=0.134	3/83 (3.6%)	1.4 (0.4 to 4.9) p=0.379
Sum of measles and pertussis						
None	66/1424 (4.6%)	1.0	65/1423 (4.6%)	1.0	53/1424 (3.7%)	1.0
Either	11/194 (5.7%)	1.2 (0.6 to 2.3)	9/194 (4.6%)	1.1 (0.5 to 2.2)	4/194 (2.1%)	0.5 (0.2 to 1.5)
Both	27/493 (5.5%)	1.2 (0.7 to 1.9)	24/492 (4.9%)	1.1 (0.7 to 1.8)	16/493 (3.3%)	0.9 (0.5 to 1.6)
Sum of rubella, mumps and varicella						
None	73/1631 (4.5%)	1.0	69/1629 (4.2%)	1.0	48/1631 (2.9%)	1.0
Any of the three	24/409 (5.9%)	1.3 (0.8 to 2.1)	21/409 (5.1%)	1.2 (0.7 to 2.0)	20/409 (4.9%)	1.6 (0.9 to 2.8)
Two or more	7/71 (9.9%)	2.2 (0.9 to 5.0) p=0.054	8/71 (11.3%)	3.1 (1.4 to 6.7) p=0.020	5/71 (7.0%)	2.6 (0.9 to 6.9) p=0.014

* Adjusted for age, sex, social class of father, and total number of siblings.

thus seems likely that, if childhood infections are a determinant of atopy and asthma, they are not the only one and prenatal influences are important.

Ours is the latest of a number of studies to have demonstrated an inverse relationship between family size and risks of indices of atopic disease such as skin test positivity,[6 21 22] self-reported inhalant allergy,[23] and symptoms suggesting asthma,[24] eczema,[5] and hay fever.[5 21] While the evidence is not wholly consistent, as Shaheen has pointed out,[25] it is quite strong for hay fever and atopy, and less clear for asthma. It seems likely that there is a real measure of protection against atopy afforded by having greater numbers of siblings, and it was reasonable to propose that this might be due to increased spread of infections in the family.[5] However, there are inconsistencies here also in that, while Italian military recruits with hepatitis A positivity seem to be protected against atopy and asthma,[9] preschool nursery attendance is not apparently associated with protection.[22] In a recent study involving a cohort of adolescents, no significant relations were observed between hay fever and history of infection in the first month of life.[21] Our study is the first, however, to demonstrate direct evidence that the association of family size with atopic disease is not explicable on the basis of the common infectious diseases acquired throughout childhood, either individually or in sum. While we have had to rely on data recorded by the children's parents, we believe that, at least with respect to measles, pertussis and mumps, this information is likely to be sufficiently reliable since these illnesses were distinctive and often severe in infants at that time.

It remains possible that measles may have a weak protective effect since it alone of the common childhood infections did show a trend in the opposite direction, and this would be consistent with the Guinea-Bissau study where measles was severe.[7] However, considering our results, it is difficult to argue that the fall – at least in the common childhood infections – has been responsible for the rise in asthma and allergies in the UK, and it is necessary to seek the explanation elsewhere. Perhaps more importantly, it seems unlikely that changes in family size over the last three decades have had a sufficient influence on asthma to be responsible for the change in prevalence of the disease, and this is consistent with the findings reported from a study of two large British birth cohorts.[26] What therefore remains as a plausible explanation of this change?

If the change in atopic disease has occurred as a consequence of postnatal influences, other infections may be responsible, although it is not clear which of these have fallen substantially in incidence over the relevant period. Our data did not allow us to comment on these except insofar as the sum of common named infections may give some indication of liability to others. Similarly, we were not able to allow for a number of other factors such as parental smoking and housing conditions. It is possible that mass immunisation may have influenced the population's susceptibility to atopic disease. Our results, taken with those from Guinea-Bissau, do suggest that measles may confer some weak immunity to atopy and there is evidence that measles immunisation may act in the opposite direction by inducing a predominant Th2 response.[27] Thus, the national measles vaccination programme may in part explain the change. However, increasingly, the evidence is pointing towards intrauterine events as determinants of childhood asthma and allergies.[19 28]

It has been suggested that the natural fetal T cell phenotype is Th2, a mechanism for protection of the fetus against interferon gamma (IFNγ) produced by the mother[29] and this, if true, provides a nice evolutionary explanation for the persistence of the atopic genotype. Also in evolutionary terms, persistence of the asthma phenotype must have put young children and adults at a survival disadvantage and mechanisms are likely to have evolved to overcome this by switching to the Th1 phenotype which provides greater protection against infection. Ideally, this switch should have occurred around the time of birth when the fetus was well established and in preparation for meeting the infective threats to the air breathing mammal. If this reasoning is correct, it is necessary to consider what environmental factors

could cause such a switch in the fetus prior to or immediately after birth, and could now be operating less effectively in our environment in order to prevent such a switch occurring. The most obvious of these is the nutrition of the mother and the child.

There is some recent evidence that diet may influence airway responses in children and adults. We have found in population studies that the lowest tertiles of intake of vitamins C and E are associated both with significantly increased risks of the development of wheeze in adult life and with having increased bronchial reactivity.[30 31] Others have shown that consumption of fresh oily fish gives significant protection against having asthma in childhood and have argued that the balance of dietary fats may be important.[4 32] Could these factors act during pregnancy to alter the T cell responses of the fetus and/or to protect the child's airways from allergens after birth? There is reason to believe that the balance of omega-3 and omega-6 fatty acids and vitamin E in the diet may indeed influence T cell differentiation, while vitamin C is the major antioxidant required for protection against inflammatory airway reactions. Moreover, it is at least conceivable that changes in fetal nutrition could result from having had previous pregnancies, and thus explain the curious association between family size and atopy without having to invoke later infections. Further investigation in this area appears promising.

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