ORIGINAL ARTICLE

Association of parental eczema, hayfever, and asthma with atopic dermatitis in infancy: birth cohort study

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Objective: To evaluate the association of parental history of atopic disease with childhood atopic dermatitis, and to examine the relative strength of associations with maternal and paternal disease.
Design: Mothers were recruited to the Avon longitudinal study of parents and children (ALSPAC) from the eighth week of pregnancy. Before parturition, both parents were asked, separately, to report their lifetime history of eczema, asthma, and hayfever. Parents reported symptoms of atopic dermatitis in their children at ages 6, 18, 30, and 42 months.
Results: Of 8530 children with complete information on rash at ages 6, 18, 30, and 42 months, 7969 had complete information on maternal atopic disease and 5658 on maternal and paternal atopic disease. There was a strong association between parental eczema and childhood atopic dermatitis: odds ratio 1.69 (95% confidence interval, 1.47 to 1.95) for maternal eczema only, 1.74 (1.44 to 2.09) for paternal eczema only, and 2.72 (2.09 to 3.53) for eczema in both parents. Associations with parental asthma or hayfever were attenuated after controlling for parental eczema. There was no evidence that associations with maternal atopy were stronger than with paternal.
Conclusions: Associations between parents' atopic disease and the risk of atopic dermatitis in offspring vary according to the type of atopic disease in the parents, but not according to parental sex. These results are at variance with previous studies reporting stronger associations with maternal than paternal atopy, and suggest that there is no ''parent-of-origin'' effect in atopic dermatitis. Parental eczema may be a better marker than parental asthma/hayfever in predisposing to childhood eczema.

Atopic dermatitis is an inflammatory skin disease that is characterised by itching, redness, and scaling of the skin, predominantly in the skin creases. Although the causes of atopic dermatitis are unclear, the familial aggregation of the disease is well established through many family studies of atopic dermatitis, asthma, and allergic rhinitis.[1–9] The individual association of different parental atopic diseases with the occurrence of atopic dermatitis in their offspring is less clear, requiring studies examining each condition separately. Some reports have suggested that a history of eczema in one or both parents is a much stronger risk factor for the development of atopic dermatitis in the child than a history of other atopic disease.[2 5 7] Two studies have looked at the influence of parental histories of asthma and eczema separately.[5 7] Each showed that a parental history of eczema was a strong risk factor for atopic dermatitis in the child, while a parental history of asthma showed a weaker association.

Genomic imprinting, such that a gene influencing allergic disease is silenced when transmitted from the father but expressed on the maternally derived chromosome, is thought to occur in atopy. Several studies that looked at parent-of-origin effects have suggested that atopy in a child is more strongly associated with a history of atopy in the mother than in the father.[4 5 9–14] Of 21 such studies reviewed by Moffatt and Cookson,[9] 18 showed maternal atopy to be important, whereas evidence for an influence of paternal atopy was less strong. These investigators concluded that parent-of-origin effects should be accounted for when identifying genes involved in atopic diseases. Some studies have found more atopic disease in children with a history of atopy in both parents than if only one parent had such a history.[8 15] As these issues will influence the appropriate design of association and linkage studies exploring genetic influences on atopic dermatitis, it is important to clarify the relative magnitudes of the association between childhood atopic dermatitis and different maternal and paternal atopic diseases. We evaluated these associations in a large population based prospective study, the Avon longitudinal study of parents and children (ALSPAC).

METHODS

ALSPAC is an ongoing prospective birth cohort study that enrolled 14 541 mothers from the eighth week of pregnancy. These mothers were resident in the county of Avon, with expected date of delivery between 1 April 1991 and 31 December 1992. Of a total of 14 062 children born alive, 12 411 were followed up at least once between the ages of 6 and 42 months. Data are collected through self completed questionnaires, biological samples, and clinical assessments. Before the birth of their child, fathers and mothers were asked, separately, to report their lifetime history of eczema, asthma, and hayfever as part of a large booklet questionnaire. Before embarking on the study, the social characteristics of Avon were checked against those of Britain as a whole, using data from the 1970 British birth cohort. It was found that characteristics such as living in a single room or flat, race, parental education, being a single mother, and prevalence of smoking were similar to those of the country as a whole. The distribution of atopic diseases such as eczema, wheezing, and hayfever was also similar. However, children from the county of Avon were less likely to live in rented accommodation and were also less likely to have a father in manual occupation

Abbreviation: ALSPAC, Avon longitudinal study of parents and children

than children in the rest of Britain. Details of the study design and selection of participants can be found on the ALSPAC website.[16]

Details of the ascertainment and definition of childhood atopic dermatitis are given elsewhere.[17] Briefly, questions about current rash and rash during the previous six months were asked as part of large booklet questionnaires that were sent to the mothers when the children were aged 6, 18, 30, and 42 months. These questions, which were modified from Hanifin and Rajka,[17–19] focused on itchy rash in joints and creases. At six months, mothers were also asked to report oozy and crusted rash on the face, shins, or forearms. Those children whose mothers reported such rashes in at least two follow up questionnaires were defined as having atopic dermatitis.[17] Presence or absence of a family history was therefore not included in our definition.

Data analysis

Analyses were done using Stata version 7.0 (Stata Corporation, College Station, Texas, USA). We employed logistic regression to estimate odds ratios for the association between childhood atopic dermatitis and parental atopic diseases before and after controlling for parental social class, parental education level, parity, breast feeding, and birth weight. Missing information on social class variables was coded as a separate category when these variables were included in the regression models.

RESULTS

Complete information on rash at 6, 18, 30, and 42 months was available for 8530 children, of whom 7969 had complete information on maternal atopic disease and 5658 had complete information on maternal and paternal atopic disease. Among these 5658 families, 36.7% of the fathers and 15.7% of the mothers had manual jobs, while 57.3% of the mothers and 41.5% of the fathers had educational qualifications below A level (advanced level qualification obtained at the end of secondary education and a prerequisite for university entry in most universities in the United Kingdom). Most of the mothers (82.1%) had parity of 2 or less at the time of the study pregnancy. Median maternal age was 28 years (range 14 to 45 years, interquartile range 26 to 32 years).

Table 1 shows the reported prevalence of atopic diseases in the parents. The prevalence of maternal atopic diseases for 7969 mothers who provided complete information was similar to that in the 5658 mothers for whom there was also complete information on paternal atopic disease. The most commonly reported disease was hayfever, and the least commonly reported was asthma. The proportion of fathers reporting eczema (14%) was notably smaller than the proportion of mothers (24%). The prevalence of reported asthma and hayfever was, however, similar for fathers and mothers.

Table 2 shows the association between different maternal atopic diseases and atopic dermatitis in children. Controlling for potential confounding factors made little difference to the magnitude of estimated associations, which were similar in the 7969 mother–child pairs with complete maternal and child information and in the 5698 pairs for which there was also complete paternal information. The strongest association was with maternal eczema, adjusted odds ratio 1.63 (95% confidence interval (CI), 1.47 to 1.82). The adjusted odds ratios for maternal asthma (1.30 (1.12 to 1.50)) and maternal hayfever (1.28 (1.16 to 1.42)) were similar. The adjusted odds ratio for the association between any maternal atopic disease and childhood atopic dermatitis was 1.43 (1.30 to 1.57). Table 3 shows associations between paternal atopic diseases and atopic dermatitis in the 5658 children with complete information on both maternal and paternal eczema (this number was similar to the total number of children with information on paternal eczema). Again, the strongest association was with paternal eczema. Associations with paternal atopic disease were slightly stronger than the corresponding associations with maternal atopic disease (shown in table 2).

Table 4 examines the association between a history of maternal disease, paternal disease, or both, for the three atopic diseases and for any parental atopic disease. Associations were again strongest for parental eczema, and similar for parental asthma and hayfever. The strongest associations were seen when both parents reported the disease. For the individual atopic diseases, odds ratios for paternal disease alone were generally somewhat larger than for maternal disease alone. For asthma and hayfever, the odds ratios when both parents reported the disease were greater than the product of the odds ratios for maternal and paternal disease alone.

The right hand column of table 4 shows association with individual parental atopic diseases after controlling for the other two atopic diseases. The associations with parental asthma and hayfever were markedly attenuated, although evidence of associations remained, particularly when both parents reported the disease. In contrast, associations with parental eczema were only slightly attenuated after controlling additionally for parental asthma and parental hayfever. Table 5 shows that associations between paternal atopic disease and childhood atopic dermatitis were generally similar to or stronger than the corresponding associations for maternal atopic disease. Controlling for atopic disease in the spouse made little difference to these findings.

DISCUSSION

It is important to establish the nature of inheritance of childhood atopic dermatitis, to facilitate the search for the genes that cause this disease.[12 14 20–24] Patterns of inheritance will influence both the design and the analysis of genetic linkage and association studies. Dissection of individual genetic influence will rely on a clear understanding of mode

Table 1 Number (% prevalence) of parents who reported atopic diseases

	Children with complete maternal information (n = 7969)	Children with complete maternal and paternal information (n = 5658)		
	Maternal atopic disease	Maternal atopic disease	Paternal atopic disease	Both parents
Eczema	1911 (24.0%)	1379 (24.4%)	796 (14.1%)	246 (4.4%)
Asthma	893 (11.2%)	635 (11.2%)	736 (13.0%)	91 (1.6%)
Hayfever	2495 (31.3%)	1794 (31.7%)	1746 (30.9%)	602 (10.6%)
Any atopic disease	3698 (46.4%)	2651 (46.9%)	2324 (41.1%)	1141 (20.2%)

Table 2 Relation between maternal atopy and the incidence of atopic dermatitis in 7969 children with complete information on maternal atopic disease, and 5658 children with complete information on maternal and paternal atopic disease

	Children with complete maternal information (n = 7969)			Children with complete parental information (n = 5698)
	Children with atopic dermatitis (n (%))	Crude OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)*
Maternal eczema				
No	1798/6058 (29.7)	1	1	1
Yes	784/1911 (41.0)	1.65 (1.48 to 1.83)	1.63 (1.47 to 1.82)	1.71 (1.51 to 1.94)
Maternal asthma				
No	2247/7076 (31.8)	1		1
Yes	335/893 (37.5)	1.29 (1.12 to 1.49)	1.30 (1.12 to 1.50)	1.27 (1.07 to 1.51)
Maternal hayfever				
No	1676/5474 (30.6)	1		
Yes	906/2495 (36.3)	1.29 (1.17 to 1.43)	1.28 (1.16 to 1.42)	1.30 (1.16 to 1.47)
Maternal atopic disease				
No	1224/4271 (28.7)	1	1	1
Yes	1358/3698 (36.7)	1.45 (1.32 to 1.59)	1.43 (1.3 to 1.57)	1.46 (1.30 to 1.63)

*Controlling for maternal social class, paternal social class, maternal education level, parity, breast feeding, and birth weight.
CI, confidence interval; OR, odds ratio.

of inheritance and the relation of one atopic disease to another. The results of this study suggest that associations between parents' atopic disease and the risk of atopic dermatitis in their children vary according to the type of atopic disease in the parents, but not by sex of the parent manifesting that disease. A parental history of eczema is the strongest predictor of atopic dermatitis in their children, while parental histories of asthma alone or hayfever alone had substantial associations with childhood atopic dermatitis only if both of the parents manifested the disease. Furthermore, associations with parental asthma or hayfever were markedly attenuated after controlling for parental eczema.

Two important strengths of this study are the large number of families included, and that information was collected prospectively. In particular, information on parental atopic disease was collected in questionnaires sent separately to both mothers and fathers before the birth of their child. This should minimise differences in the accuracy of reporting of parental atopic disease between mothers and fathers, and avoid recall bias. Complete information on childhood atopic dermatitis and parental atopic disease was available for 5658 families. Although this represents only 45.6% of the children who were followed at least once between 0 and 42 months, we think it is unlikely that selection biases have affected our results. First, associations with maternal atopy were little changed when we considered the 7979 (93.5%) of mother–child pairs with complete information on childhood atopic dermatitis and maternal atopic disease. Second, although the prevalence of childhood atopic dermatitis is likely to be somewhat lower in families with missing information,[17] the magnitude of the association between parental atopic disease and childhood atopic dermatitis is unlikely to be very different.

It is notable that although, as previously reported, there were no sex differences in the incidence of childhood atopic dermatitis,[17] the reported prevalence of maternal eczema was substantially higher than that of paternal eczema. Although this could reflect differences in the propensity to report the condition, no such differences were seen for asthma or hayfever and the differences did not lead to changes in the magnitude of associations between maternal and paternal

Table 3 Relation between paternal atopy and incidence of atopic dermatitis in 5658 children with complete information on maternal and paternal atopic disease

Atopic disease	Children with atopic dermatitis (n (%))	Crude OR (95% CI)	Adjusted OR (95% CI)*
Paternal eczema			
No	1566/4861 (30.8)	1	1
Yes	352/796 (44.2)	1.78 (1.52 to 2.07)	1.76 (1.50 to 2.05)
Paternal asthma			
No	1558/4922 (31.7)	1	1
Yes	293/735 (40.0)	1.43 (1.22 to 1.67)	1.46 (1.23 to 1.72)
Paternal hayfever			
No	1183/3911 (30.3)	1	1
Yes	668/1746 (38.3)	1.41 (1.27 to 1.61)	1.37 (1.22 to 1.56)
Paternal atopic disease			
No	978/3334 (29.3)	1	1
Yes	873/2323 (37.6)	1.45 (1.30 to 1.62)	1.41 (1.25 to 1.59)

*Controlling for maternal and paternal social class, maternal and paternal education level, parity, breast feeding, and birth weight.
CI, confidence interval; OR, odds ratio.

Table 4 Odds ratios for the association between parental history of eczema, hayfever, and asthma and childhood atopic dermatitis, in 5658 families with complete information on parental atopy

	Children with atopic dermatitis (n (%))	Crude OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI) controlling additionally for other parental atopic disease
Parental eczema				
No	1046/3729 (28.1)	1	1	1
Mother only	453/1133 (40.0)	1.71 (1.49 to 1.96)	1.69 (1.47 to 1.95)	1.65 (1.43 to 1.91)
Father only	224/550 (40.7)	1.76 (1.47 to 2.12)	1.74 (1.44 to 2.09)	1.60 (1.32 to 1.94)
Both parents	128/246 (52.0)	2.78 (2.14 to 3.60)	2.72 (2.09 to 3.53)	2.40 (1.83 to 3.13)
Parental asthma				
No	1366/4378 (31.2)	1	1	
Mother only	192/544 (35.3)	1.20 (0.99 to 1.45)	1.18 (0.98 to 1.43)	0.96 (0.79 to 1.18)
Father only	245/645 (38.0)	1.35 (1.14 to 1.60)	1.34 (1.12 to 1.59)	1.08 (0.89 to 1.30)
Both parents	43/91 (52.8)	2.46 (1.62 to 3.73)	2.46 (1.62 to 3.75)	1.63 (1.05 to 2.52)
Parental hayfever				
No	790/2720 (29.0)	1	1	1
Mother only	393/1192 (33.0)	1.20 (1.04 to 1.39)	1.18 (1.02 to 1.37)	1.09 (0.94 to 1.28)
Father only	398/1144 (34.8)	1.30 (1.12 to 1.51)	1.26 (1.08 to 1.46)	1.17 (1.00 to 1.37)
Both parents	270/602 (44.9)	1.99 (1.66 to 2.38)	1.92 (1.60 to 2.31)	1.60 (1.32 to 1.94)
Parental atopic disease				
No	477/1824 (26.2)	1		
Mother only	501/1510 (33.2)	1.40 (1.21 to 1.63)	1.37 (1.18 to 1.60)	NA
Father only	385/1183 (32.5)	1.36 (1.16 to 1.60)	1.32 (1.12 to 1.55)	NA
Both parents	488/1141 (42.8)	2.11 (1.80 to 2.47)	2.04 (1.74 to 2.40)	NA

*Controlling for maternal social class, paternal social class, maternal & paternal education level, parity, breast feeding; and birth weight.
CI, confidence interval; NA, not applicable; OR, odds ratio.

eczema and childhood atopic dermatitis. Some misclassification of parental atopic disease is inevitable, as it was assessed using a single self report from a questionnaire. This implies first, that the associations reported here are underestimates of the true associations, and second, that we will not have controlled perfectly for the effect of each parental atopic disease in the multivariable analyses.

Another limitation of the study was that childhood atopic dermatitis was diagnosed using self reported questionnaires only. Clinical assessment by an experienced dermatologist is regarded as the best way to diagnose atopic dermatitis,[25] although this is not practical in large epidemiological studies. In one epidemiological study there was good agreement between parental assessment of flexural dermatitis and assessment by a trained investigator.[26] The magnitude of associations with parental atopy might vary between ethnic groups or between countries; we are not able to address this issue here.

The results of this study are not in agreement with various epidemiological studies reporting stronger associations of childhood atopic disease with maternal than with paternal atopy.[4 5 9 11 13] Possible explanations for a greater associations with maternal than paternal atopy include paternal imprinting contributing to stronger maternal heritability, environmental factors more likely to be shared by mother and child than father and child, and maternal effects acting through foetal environment.

However, it is also possible that observation of a stronger maternal influence is artefactual. First, questionnaires used to assess parental atopy are usually completed by mothers and hence may misclassify paternal symptoms. This would imply that there is greater regression dilution bias in the estimated association with paternal atopy than maternal atopy. Second, reporting of paternal disease is usually less complete than reporting of maternal disease,[27] as was the case in this study. In consequence, associations of similar

Table 5 Effect of maternal atopic disease on childhood atopic dermatitis after controlling for paternal atopic disease, and effect of paternal atopic disease on childhood atopic dermatitis after controlling for maternal atopic disease

Parental atopic disease by sex	OR (95% CI)*	OR (95% CI)* after controlling for same disease in the spouse	OR (95% CI)* after controlling for other atopic diseases in the spouse
Maternal			
Eczema	1.71 (1.50 to 1.94)	1.67 (1.47 to 1.90)	1.67 (1.47 to 1.90)
Asthma	1.27 (1.07 to 1.51)	1.27 (1.07 to 1.51)	1.27 (1.07 to 1.51)
Hayfever	1.30 (1.16 to 1.47)	1.29 (1.15 to 1.45)	1.28 (1.13 to 1.44)
Any atopic disease	1.46 (1.30 to 1.63)		1.45 (1.25 to 1.57)
Paternal			
Eczema	1.75 (1.50 to 2.04)	1.70 (1.45 to 1.98)	1.69 (1.44 to 1.97)/
Asthma	1.42 (1.21 to 1.66)	1.41 (1.20 to 1.66)	1.41 (1.20 to 1.65)
Hayfever	1.39 (1.23 to 1.56)	1.38 (1.22 to 1.55)	1.38 (1.22 to 1.55)
Any atopic disease	1.42 (1.26 to 1.59)		1.40 (1.25 to 1.57)

*Controlling for maternal and paternal social class, maternal and paternal education, parity, breast feeding; and birth weight.
CI, confidence interval; OR, odds ratio.

magnitude may be statistically significant for maternal disease but not for paternal disease. Third, more attention may have been paid to studies supporting the hypothesis of stronger maternal effects than those which did not support this hypothesis.

Although our results suggest that there is no parent of origin effect in atopic dermatitis, it is possible that such effects are present for other atopic diseases. For example, in a genetic linkage study in which the probands had allergic asthma, 17% of families showed maternal inheritance of the leu181 variant of the β subunit of the high affinity IgE receptor.[14]

Various definitions of atopic phenotype in children have been used, including childhood history of different allergic diseases, raised serum IgE in cord blood, and positive skin prick tests. However, the relation between these phenotypes is unclear, which may further complicate the search for genes that are involved in individual atopic diseases.

Conclusions

Our findings support the hypothesis that atopic dermatitis has a polygenic aetiology, with genes for parental eczema more strongly associated than genes for parental asthma/hayfever. Parental eczema may also be a better marker for common environment predisposing to eczema than parental asthma/hayfever. Alternatively, the adjusted associations between childhood atopic dermatitis and parental asthma/hayfever might reflect residual confounding. Studies in which parental eczema is ascertained more accurately (for example, through doctor diagnosis) might show no association with parental asthma/hayfever after controlling for parental eczema.

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