

Parental history of atopic disease: Disease pattern and risk of pediatric atopy in offspring

Sharon Hensley Alford, MPH,^a Edward Zoratti, MD,^a Edward L. Peterson, PhD,^a Mary Maliarik, PhD,^a Dennis R. Ownby, MD,^b and Christine Cole Johnson, PhD^a

Detroit, Mich, and Augusta, Ga

Background: Family history is an important risk factor for atopic disease. However, most studies assess only limited information on family history. Because atopic disease can exhibit transient or persistent patterns, it may be useful to assess information on patterns of disease within families. This approach has been applied in other diseases, such as cancer, to discriminate between predominately inherited versus environmentally caused (sporadic) cases.

Objective: In a cohort of children who were followed from birth until age 6 to 7 years, we examined the relationship between parental onset (ie, childhood and adulthood) and duration of atopic disease (ie, persistent disease) and the risk of pediatric atopic disease. Our hypothesis was that different parental disease patterns would be important to pediatric risk of disease.

Methods: Data from 476 families in the ongoing Childhood Allergy Study in Detroit, Mich, were analyzed by using logistic regression. We examined the association between parental patterns of disease and disease onset in their children.

Results: Father's disease history, particularly asthma history, was more strongly related to pediatric outcomes than mother's history. Asthma status in the fathers, whether it was childhood-only, adulthood-only, or persistent, was associated with current asthma in the children. Childhood-only and persistent asthma in fathers conferred a higher risk of atopy in the study children, whereas adulthood-only disease did not. There was also a significant relationship between persistent allergy in the father and atopy in the study children.

Conclusion: Our data support the hypothesis that there are complex inheritance patterns for allergy and asthma. Therefore, a detailed family history of atopy, including childhood and adulthood experiences, is critical to identifying and classifying risk and disease phenotypes. (*J Allergy Clin Immunol* 2004;114:1046-50.)

Key words: Allergy, asthma, pediatric, family history

Abbreviation used

aOR: Adjusted odds ratio

Family history is an important risk factor for atopic disease, including atopic dermatitis, allergic rhinitis, and atopic asthma.¹ The strong positive association between family history and risk of atopy is persistent across studies of adults and children regardless of study design (cross-sectional, longitudinal) or study location. The current standard for reporting family history of atopic disease (ie, hay fever, asthma, atopic dermatitis) is by self-report or with 1 family member reporting for the entire family. Commonly used questionnaires (ie, American Thoracic Society's Children's questionnaire and the International Study of Asthma and Allergy in Children questionnaire) inquire only about the presence of current or ever doctor-diagnosed disease among parents. Presumably, such an imprecise classification of parental history makes it more difficult to dissect associations between the patterns of atopic disease of a parent and child.

As new research emerges suggesting that atopic disease may exhibit transient or persistent patterns,²⁻⁵ it stands to reason that methods for assessing family history should be altered to incorporate information on patterns of disease within families. Such detail would enhance efforts to identify genetic polymorphisms associated with particular disease patterns. Two important factors in assessing disease patterns in families are age of disease onset and disease persistence. For example, in breast cancer, the risk of developing breast cancer is higher if a woman has a first-degree relative who developed the disease in her 30s versus her 70s. We hypothesized that these types of family history patterns may also be relevant to atopic disease inheritance and clues to the different phenotypes of atopy seen within clinical practice. To our knowledge, no one has looked at these factors in an analysis of atopic disease family history.

In the Detroit area Childhood Allergy Study, a cohort of children who were followed from birth until age 6 to 7 years, we examined the relationship between parental disease histories and the risk of pediatric atopic disease. For this analysis, atopic disease is defined as allergy and asthma. In particular, we examined whether the children of parents reported to have asthma or allergies during both childhood and adulthood (persistent disease) were at higher risk for atopic disease by age 7 years.

From ^athe Henry Ford Health System, Detroit, and ^bthe Medical College of Georgia.

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Reprint requests: Sharon Hensley Alford, MPH, Henry Ford Health System, One Ford Place, 5C, Detroit, MI 48202.

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METHODS

Study population

The data used in this analysis were collected as part of an ongoing study to evaluate the environmental determinants of allergic diseases in a population of children followed from birth. The selection of children for the study has previously been described.⁶ Briefly, all pregnant women living in an area of northern, suburban Detroit defined by contiguous zip codes, and belonging to the Health Alliance Plan, a health maintenance organization, were eligible for recruitment if their babies were due between April 15, 1987, and August 31, 1989. Women meeting eligibility criteria for the study were invited during prenatal visits to participate. If a woman agreed, written informed consent was obtained, and a study nurse collected demographic, health, and lifestyle-related information from her. Parents were contacted at least annually for an extensive interview.

The sixth annual questionnaire contained a question about family history of allergy and asthma that had not been asked in previous interviews. The respondent was asked to report the asthma and allergy status for first-degree (mother, father, and siblings) relatives of the study child. Asthma and allergy status was reported as yes/no for childhood (defined as <21 years of age) and adulthood for each relative. The association between parental history and the study child's disease status was explored.

When study children were between 6 and 7 years old, they were clinically evaluated for asthma and allergies. If the family agreed and the child was brought to the clinic for the evaluation, written consent was obtained from the parent, and verbal consent was obtained from the study child. The child or the parent had the right at any time to discontinue the examination. The clinical evaluation included a medical history, physical examination, blood draw, spirometry, methacholine challenge, and skin prick tests by using the allergens *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, ragweed (*Ambrosia artemisiifolia*), cat, dog, and bluegrass (*Poa pratensis*) (extracts from Bayer Biologics, Spokane, Wash). Both positive (histamine 1 mg/ml) and negative controls (glycerosaline) were used. Tests were applied by the puncture method by using a lancet (Bayer Biologics). Skin tests were considered positive if the product of perpendicular wheal diameters was ≥ 4 mm to any of the allergens tested when there was no reaction to glycerosaline. Atopy was defined as a positive skin test to any of the 6 allergens tested.

Blood samples were analyzed for allergen-specific IgE antibodies by using a commercial assay (AlaSTAT; Diagnostic Products Corp, Los Angeles, Calif) for the same allergens used in skin testing. Specific IgE levels were expressed in international units per milliliter (1 IU/mL corresponds to 2.4 $\mu\text{g/L}$), and values of ≥ 0.35 IU/mL were considered positive in accordance with the manufacturer's recommendation. Seroatopy was defined as any positive test for allergen-specific IgE.

During the medical history questionnaire, the respondent, usually the subject's mother, was asked whether the study child had ever been diagnosed by a doctor as having asthma, whether the child had asthma symptoms in the last 12 months, and whether the child was currently taking asthma medications. For the purposes of this analysis, we used defined current asthma as symptoms reported in the last 12 months and currently using asthma medications. In addition, we used 2 variables for determining allergy status: atopy was defined as having any positive skin prick test, and seroatopy was defined as having any positive serum allergen specific-IgE.

The Henry Ford Health System Institutional Review Board approved all aspects of this study.

Statistical analysis

The baseline characteristics of those included in the study compared to those excluded were examined by using χ^2 tests. This

was also the methodology used to compare the mother's and father's prevalence of asthma (or allergy) in childhood or adulthood.

Logistic regression was used to calculate odds ratios and 95% CIs for the outcome variable against parental history of disease for the study child. We were able to adjust for several potential confounding variables including sex of the child, parental education, parental smoking status, multiple pet ownership, first born status, and presence of atopic disease in the other parent. Parental education was defined as either parent having a college degree versus neither. Parental smoking status was collected every year during the annual contact with the family. To adjust for the child's environmental tobacco smoke exposure, we defined a dichotomous variable for ever versus never exposed, where ever exposure occurred when either parent reported smoking during any of the annual questionnaires. Previous work by our group has shown pet ownership to be an important mediating variable in the development of allergy.⁷ To control for this potential confounder of family history, we adjusted for ownership of 2 or more cats or dogs in the first year of the child's life versus fewer than 2 pets or no ownership of pets in the first year of life. We adjusted for the presence of disease in the other parent by each disease category. For example, childhood asthma in the father was adjusted for childhood asthma in the mother.

RESULTS

A total of 1194 pregnant women were eligible for the Childhood Allergy Study, and 953 consented to their child participating. Of these, the 835 children with a valid cord blood IgE measurement were enrolled. A total of 488 children (58.4% of the enrolled cohort) underwent the clinical examination at age 6 to 7 years. The baseline characteristics of children undergoing the examination were not significantly different from those not followed up for all evaluated variables (data not shown).

Our analyses were limited to those subjects ($n = 476$; 57% of the original cohort) with family history data. Families for whom this information was not available did not differ from those included with respect to sex of the child, child's atopy or asthma status, parental education, and parents' smoking behavior. For each subject, 1 parental respondent reported on the entire family's history. For 98% of the 476 families, the respondent was the mother.

Table I reports for mothers and fathers the percentage who had no asthma or allergies (never category), disease only in childhood, disease only in adulthood, or disease in both childhood and adulthood (persistent). In most cases, mothers were reported to have more disease than fathers in both childhood and adulthood. There was a statistically significant difference between mothers and fathers for adult onset of asthma ($P = .01$) and allergies ($P = .025$). Table II shows more detail on the reported experience of parents by providing the breakdown with regard to the child's status.

We conducted the conventional analysis of family history by looking at the risk of our atopic outcomes by any history of disease reported in parents. Table III provides adjusted odds ratios (aORs) for each outcome for the study child by any history of asthma in either parent, any history of allergy in either parent, and any history of

TABLE I. Reported experience of parental allergies and asthma

	Father		Mother	
	Asthma n (%)	Allergy n (%)	Asthma n (%)	Allergy n (%)
Never	437 (92)	293 (64)	412 (86)	259 (55)
Childhood only	13 (03)	7 (01)	12 (03)	14 (03)
Adulthood only	11 (02)	68 (15)	28 (06)	96 (20)
Persistent (both periods)	14 (03)	100 (21)	25 (05)	106 (22)

TABLE II. Reported experience of parental allergies and asthma by atopic outcome in the study child

	Paternal history of disease		Maternal history of disease	
	Asthma % (n/total*)	Allergy % (n/total)	Asthma % (n/total)	Allergy % (n/total)
	Never		Never	
Current asthma	6.0 (26/437)	5.1 (15/293)	7.0 (29/412)	6.6 (17/259)
Atopy	29.4 (128/435)	26.4 (77/292)	30.7 (126/411)	29.5 (76/258)
Seroatopy†	35.1 (135/385)	34.0 (87/256)	38.1 (139/365)	38.0 (89/234)
	Childhood only		Childhood only	
Current asthma	15.4 (2/13)	14.3 (1/7)	0 (0/12)	7.1 (1/14)
Atopy	66.7 (8/12)	42.9 (3/7)	33.3 (4/12)	7.1 (1/14)
Seroatopy	83.3 (10/12)	66.7 (4/6)	27.3 (3/11)	15.4 (2/13)
	Adulthood only		Adulthood only	
Current asthma	18.2 (2/11)	11.8 (8/68)	7.1 (2/28)	8.3 (8/96)
Atopy	18.2 (2/11)	33.8 (23/68)	33.3 (9/27)	39.0 (37/95)
Seroatopy	44.4 (4/9)	31.8 (20/63)	39.1 (9/23)	46.3 (38/82)
	Persistent		Persistent	
Current asthma	21.4 (3/14)	9.0 (9/100)	12.0 (3/25)	6.6 (7/106)
Atopy	50.0 (7/14)	39.8 (39/98)	29.2 (7/24)	30.2 (32/106)
Seroatopy	61.5 (8/13)	48.3 (42/87)	31.8 (7/22)	31.1 (28/90)

*“Don’t know” responses were excluded, resulting in slight variation in the denominators.

†Not all children provided blood for the IgE measures used to determine seroatopy.

asthma and/or allergy in either parent. The results indicate, as expected, that a family history increases the risk of atopy. However, these results mask the patterns noted in the stratified analysis presented in Table IV that include disease onset pattern information.

Table IV shows a difference in pattern between asthma and allergy history, between maternal and paternal history, and between childhood-only, adulthood-only, and persistent disease. Table IV reports the odds of current asthma, atopy, and seroatopy for the study child relative to mother or father’s disease experience with adjustment for sex, parental education, parental smoking status, multiple pet ownership, first-born status, and disease status in other parent, with disease in the study child. For this analysis, as in Table III, the referent group is children whose parents were reported to never have had asthma or allergies.

Notable in Table IV is that the results suggest little or no relationship between maternal history of disease and childhood outcomes, whereas the results are much more notable between paternal history and childhood disease. For paternal history of allergy, all of the aORs are greater than 1.00, with persistent disease in fathers significantly associated with atopy in the study child (aOR = 2.03; $P < .05$).

Asthma status in the fathers, whether it was childhood-only, adulthood-only, or persistent, was associated with current asthma in the children. The aORs for current asthma in the children with respect to asthma status of the fathers are notable for their consistency in magnitude (range, 4.39-7.36). From our data, we estimate that children whose fathers had asthma only in childhood had a 4-fold increased risk of current asthma (aOR = 4.39) compared with children whose fathers never had asthma, although this is not statistically significant. Higher risk estimates, which were statistically significant, were observed in our data for adulthood-only and persistent asthma in fathers for current asthma in the study children with aORs of 6.00 ($P < .05$) and 7.36 ($P < .01$), respectively.

The relationships between paternal history of childhood asthma and atopy and seroatopy in the study child are each statistically significant, with aORs of 5.93 ($P < .05$) for atopy and 8.35 ($P < .01$) for seroatopy. A consistent relationship is also seen between paternal history of persistent asthma and atopy and seroatopy, with relatively close estimated aORs of 2.29 (atopy) and 2.93 (seroatopy), but these are not statistically significant. However, paternal adulthood asthma is inconsistently associated with atopy and seroatopy with aORs on either side of 1.

TABLE III. Odds ratios for asthma and allergy in study children with parental history of asthma or allergy in either parent*

	Any history of asthma in either parent	Any history of allergy in either parent	Any history of asthma and/or allergy in either parent
	aOR† (95% CI)	aOR† (95% CI)	aOR† (95% CI)
Current asthma	2.72 (1.19-6.18)‡	1.38 (0.59-3.26)	1.47 (0.60-3.58)
Atopy	1.54 (0.94-2.54)	1.84 (1.16-2.94)‡	1.93 (1.19-3.13)§
Seroatopy	1.60 (0.96-2.65)	1.33 (0.84-2.09)	1.51 (0.94-2.40)

*Associations reported as aORs and 95% CIs. Referent group is children with no family history of asthma or allergy.

†Adjusted for sex, parental education, parental smoking, multiple pet ownership, and first-born status.

‡P value < .05.

§P value < .01.

TABLE IV. Odds ratios for asthma and allergy in study children with parental history of asthma or allergy compared with children of parents with no asthma or allergy*

	Paternal history of disease		Maternal history of disease	
	Asthma aOR† (95% CI)	Allergy aOR† (95% CI)	Asthma aOR† (95% CI)	Allergy aOR† (95% CI)
Childhood only				
Current asthma	4.39 (0.85-22.64)	—‡	—	—
Atopy	5.93 (1.48-23.82)§	1.02 (0.08-13.01)	1.50 (0.41-5.40)	0.52 (0.06-4.90)
Seroatopy	8.35 (1.75-39.96)¶	1.41 (0.08-25.46)	0.76 (0.19-3.07)	—
Adulthood only				
Current asthma	6.00 (1.06-33.93)§	1.60 (0.40-6.37)	1.06 (0.13-8.62)	0.99 (0.28-3.47)
Atopy	0.57 (0.12-2.80)	1.75 (0.84-3.64)	1.59 (0.64-3.99)	1.71 (0.91-3.22)
Seroatopy	1.84 (0.43-7.83)	1.05 (0.49-2.23)	1.33 (0.52-3.40)	1.30 (0.67-2.51)
Persistent				
Current asthma	7.36 (1.73-31.35)¶	1.14 (0.38-3.46)	2.96 (0.78-11.22)	0.71 (0.22-2.32)
Atopy	2.29 (0.71-7.40)	2.03 (1.12-3.69)§	0.95 (0.36-2.55)	0.94 (0.51-1.73)
Seroatopy	2.93 (0.83-10.42)	1.60 (0.87-2.95)	0.79 (0.29-2.13)	0.70 (0.37-1.32)

*Associations reported as aORs and 95% CIs.

†Adjusted for sex of the study child, parental education, parental smoking, multiple pet ownership, first-born status, and history of disease in other parent.

‡Cell size, with adjustment, too small to produce an estimate.

§P < .05.

¶P < .01.

Because the onset pattern may differ between boys and girls and we suspected a possible sex-by-sex interaction between parents and children, we ran the analyses reported in Table IV with an interaction term for sex of the study child for each category of parental history and outcome. None of the interaction terms were statistically significant.

DISCUSSION

The results of our analysis are notable because, to our knowledge, this is the first analysis to assess the contribution of the parental pattern of atopic disease by condition, onset, and persistence to the risk of pediatric atopy. An additional strength of our study is that the data are from a birth cohort in which clinical evaluations were conducted. We hypothesized that the disease pattern in parents would be associated with the risk of disease in their children. Particularly, we were interested to test whether childhood-only disease and childhood disease that persisted into adulthood (ie, disease with a potentially stronger

inherited component) conveyed a higher risk for atopic disease in the study child at 6 to 7 years of age than disease that developed in adulthood (ie, sporadic disease).

Although it is well accepted that any family history of atopic disease is a risk factor for asthma and allergy, our data suggest a stronger relationship between paternal history of disease, particularly for asthma, and disease risk in the study children. There is inconsistency among previous articles regarding the role of maternal and paternal history of disease and associated risk in their offspring. A review of these findings in birth cohort studies^{2,3,8-17} brings to light a further complication in the interpretation of the cumulative literature, which is the variation in the time of disease assessment in the child. For example, in the Isle of Wight cohort (n = 1215), paternal history was reported to be insignificant in analyses from the 2-year assessment of allergic disease (defined as allergic symptoms, positive skin prick test, asthma, eczema, rhinitis, or food intolerance); however, paternal history was significant at the 4-year assessment.^{10,11} It is likely that our own analysis is subject to the same temporal bias, because the results are based on the experience of the study

child at 6 to 7 years of age and therefore do not capture all of childhood. Our study is currently funded to assess the study children at 17 to 18 years of age. As a result, we may be able to contribute more information in the near future.

Another important consideration of our study is that because mothers reported on both maternal and paternal history, it is possible that more noteworthy, and therefore more severe disease, was reported for the fathers. This is supported by the fact that there was significantly more disease reported in mothers than in fathers. It could be the case that the relationships observed among the fathers represent disease associated with more definitive or severe disease rather than differences in risk by the sex of the parent.

In addition, it is not clear whether *allergy* was interpreted as allergic rhinitis, as intended, or whether the respondent was considering a broader definition of the term. There was a significant finding between persistent allergy (again, a more notable condition) in the fathers and atopy in the study children (aOR = 2.03; $P < .05$).

Therefore, because of the nature of our data collection, we believe that paternal asthma onset patterns were most accurately captured. Reviewing this risk category, assuming that it most closely represents true risk relationships, we see that the asthma-to-atopy relationship is like cancer, with childhood or early-onset disease conferring higher risk to the study children than adulthood or late-onset disease. The asthma-to-asthma relationship is more consistent across paternal history categories, suggesting that although heredity is important, environmental factors have a relatively stronger influence on timing of disease onset.

It should be noted that the timing of the data collection is important because atopic disease in a child has been shown by Kulig et al¹⁸ to influence reporting of disease in the parent. Our detailed family history, including information on childhood and adulthood experience, which is central to our analysis, was not collected until year 6. However, limited data regarding maternal and paternal allergy and asthma status were collected at enrollment. We tested for agreement between these reports and found the κ statistics to range between .48 and .66. This is good agreement, considering that new cases of allergy and asthma may have developed in the parents between enrollment and the 6-year assessment. A total of 20 mothers and 18 fathers were classified as having a history of allergy at baseline without reported allergy at 6 years. For asthma, there were 5 mothers and 4 fathers with discrepant histories. We reran the Table IV analysis, excluding the discrepant cases, but this did not materially change our results.

Finally, because 92% of the mothers in our study self-reported as being non-Hispanic white subjects, our analyses could not include stratification by race or ethnicity. However, we were able to adjust for socioeconomic status by using parental education as a surrogate.

In conclusion, distinction of the patterns of atopic disease, including features such as age of onset, disease persistence through adulthood, and disease severity, will likely contribute to our deciphering the different risk

categories and clarifying the appropriate means of identification and classification of atopic disease. Future studies are needed to explore further the association between parental disease history patterns and their children's disease experience.

This manuscript is dedicated to the memory of my brother, Domenic Vito Criscio, born November 23, 1985, and laid to rest July 20, 2004 (Ms Hensley Alford).

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