

Parental History and the Risk for Childhood Asthma

Does Mother Confer More Risk than Father?

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Although heredity plays a major role in asthma and in other allergic diseases, mechanisms underlying the inheritance of these disorders are poorly understood, as is the relative contribution of maternal and paternal conditions to risk of disease. We investigated doctor-diagnosed maternal and paternal asthma, eczema, and hay fever as cross-sectional predictors of childhood asthma and allergic disease in 306 children with a median age of 3.5 yr from families in which at least one parent had a history of either asthma or other allergic conditions. For both childhood asthma and eczema, the strongest parental predictors were the same conditions in the parents. For asthma in particular, maternal asthma was most strongly associated with asthma in the child over all ages in both univariate (OR = 3.2, 95% CI = 1.5 to 6.7) and multivariable (OR = 4.1, 95% CI = 1.7 to 10.1) models. Paternal asthma was weakly associated with childhood asthma in the univariate model (OR = 1.4, 95% CI = 0.6 to 3.2), but this association increased in magnitude in the multivariable model (OR = 2.7, 95% CI = 1.0 to 7.2). Among the children < 5 yr of age, the risk for childhood asthma associated with maternal asthma (OR = 5.0, 95% CI = 1.7 to 14.9) was greater than the risk associated with paternal asthma (OR = 1.6, 95% CI = 0.5 to 5.9), whereas both maternal asthma and paternal asthma were associated with similar risks among children ≥ 5 yr of age (OR = 4.6, 95% CI = 1.1 to 19.0 and OR = 4.1, 95% CI = 1.0 to 16.0, respectively). The odds of having a child with asthma were three times greater in families with one asthmatic parent and six times greater in families with two asthmatic parents than in families where only one parent had inhalant allergy without asthma; furthermore, inhalant allergy in one parent also conferred additional risk in the presence of asthma in the other parent. Further investigation is needed into the relative importance of genetic factors and *in utero* and post-natal exposures in determining the differential effects of maternal and paternal asthma on the development of childhood asthma. Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma: does mother confer more risk than father?

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Asthma is one of the most common chronic diseases worldwide, and its prevalence is known to be increasing, particularly among children (1, 2). Interactions between hereditary and changing environmental factors may be responsible for the increased prevalence of asthma. Asthma is known to be associated with atopy, as measured by serum IgE levels or skin test reactivity to allergens (3-5). Children of atopic parents are at greater risk for atopy and asthma than are children of non-atopic parents. However, the mode of inheritance of asthma and allergic diseases has not been fully elucidated. It appears

that the inheritance of these disorders does not follow classic Mendelian patterns characteristic of single-gene disorders; rather, there may be a number of genes that predispose to the development of these complex traits (6).

A recent study showed that a maternal history of atopic disease was a stronger predictor of newborn IgE levels than was a paternal history of atopic disease (7); the implication of this finding for the relationships between parental history of atopic disease and childhood asthma has not been clearly defined. In contrast, a cross-sectional German study of children 9 to 11 yr of age found that paternal asthma was associated with a greater risk for childhood asthma than was maternal asthma (8). The relative importance of maternal versus paternal history in the development of childhood asthma may be age-associated and may be related as much to differentially acquired environmental risk factors as to differentially acquired genetic factors.

In this cross-sectional study, we examined the relative contributions of maternal and paternal doctor-diagnosed asthma, eczema, and hay fever to the risk of doctor-diagnosed childhood asthma and other allergic conditions in a cohort at risk for developing these conditions.

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METHODS

Population and Study Sample

The Epidemiology of Home Allergens and Asthma Study is an ongoing longitudinal family and birth-cohort study the primary aim of which is to examine the role of indoor home allergen exposure in the development of asthma/whoeeze and allergic sensitization in early childhood among children whose parents have a doctor's diagnosis of asthma or other allergic conditions. This cross-sectional analysis, which was restricted to the siblings of the index children who were biologically related to both parents, comprised 217 of 499 families from the Boston metropolitan area. The 499 families were recruited between September 1994 and June 1996, Monday through Friday, within 48 h of the birth of the index child at a tertiary hospital in Boston (the Brigham and Women's Hospital). Inclusion criteria were: (1) a maternal age ≥ 18 yr; (2) no intention to move during the next 12 mo; (3) a residence considered safe by the mother to visit during daytime hours; (4) maternal ability to speak either English or Spanish; (5) residence inside Route 128 (a major highway that encircles the greater Boston area). Families were excluded if the index child presented with one of the following: prematurity (< 36 wk), major congenital abnormalities, or hospitalization in the neonatal intensive care unit. Eligible mothers were asked the following. (1) Have you ever had a doctor's diagnosis of asthma, hay fever, or allergies? (2) Has the biologic father of your child ever had a doctor's diagnosis of asthma, hay fever, or allergies? If either or both parents had a history of any of these diagnoses, a screening questionnaire was then administered. This questionnaire included information on the parental histories of smoking and asthma, hay fever, or allergies; stability of residence; and willingness to participate in the study.

A home visit was conducted 2 to 3 mo after the birth of the index child. At this visit a trained research assistant administered a detailed home characteristics questionnaire to the primary caregiver. Included were questions about the presence or absence of doctor-diagnosed asthma, hay fever, eczema, and other allergies in all siblings of the index child. Biologic relationships between the siblings and each parent were ascertained via a follow-up telephone interview when the index child was 16 mo old.

Because paternal asthma and allergy status was ascertained through maternal interviews, reporting or misclassification bias was a concern. To estimate the amount of reporting bias in our study, fathers were mailed a brief questionnaire in January 1997 with the same questions regarding a doctor's diagnosis of asthma and allergies that had been asked of the mothers in the screening questionnaire.

Definitons

Parental histories of asthma and allergies were obtained from the screening questionnaire administered to the mothers. Maternal asthma was defined as ever having had doctor-diagnosed asthma, as indicated by the answer to the question "Has a doctor ever said that you had asthma?" Doctor's diagnoses of hay fever, eczema, and allergies were ascertained in like fashion. Paternal doctor-diagnosed asthma and allergies were ascertained from maternal responses to the same questions. Participants who responded affirmatively with regard to a doctor's diagnosis of allergies were asked whether they were allergic to milk products, foods other than milk, antibiotics or other medicines, house dust or house-dust mites, cockroaches, pollens, animals, insect bites, mold, or things that come in contact with the skin. The condition "inhalant allergy" for each parent was defined as a doctor's diagnosis of hay fever or allergies to either house dust or house-dust mites, cockroaches, pollens, animals, or mold. Exclusive categories of joint maternal and paternal asthma and inhalant allergies were then created as follows: (1) two asthmatic parents with or without inhalant allergies; (2) one parent with asthma, the other without asthma but with inhalant allergies; (3) one parent with asthma, the other with neither asthma nor inhalant allergies; (4) neither parent with asthma, both parents with inhalant allergies; (5) neither parent with asthma, and only one parent with inhalant allergies.

For the children, doctor's diagnoses of asthma, hay fever, and eczema were determined from responses to questions in the home characteristics questionnaire that were identical to those asked about the same conditions in the parents. The race of the child was determined

from responses of the mother when asked in which ethnic or racial group(s) she would place herself and which group(s) she would place her child's father. Information on socioeconomic factors was taken from responses to the questionnaire. Information was available about current and past smoking habits of the mother, and a variable was created for perinatal smoking to designate active smoking by the mother during the year before or the year after the birth of each child in this analysis.

Statistical Analysis

Outcomes for this study were doctors' diagnoses of asthma, hay fever, and eczema for the total cohort of children. The proportion of missing values regarding these diagnoses in the children and their parents was low and ranged from no missing values to 14 records (4.7%) with missing values for paternal hay fever.

To account for correlations between children from the same household, methods developed by Zeger and Liang (9), using generalized estimating equations for the logistic case, were used to evaluate the relationships between the dependent and independent variables. Models with only one independent variable were first examined to evaluate the crude relationships between the predictors and the dependent variables of interest. Maternal and paternal histories were then examined for each of the three dependent variables with the creation of indicator variables for each maternal and paternal history of asthma and other allergic condition. Joint maternal and paternal history was further examined through the creation of indicator variables for the exclusive categories of combinations of asthma and inhalant allergy, with the category "neither parent with asthma, and only one parent with inhalant allergies" as the reference group. All analyses were performed with the SAS statistical software package (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics of the Cohort

Of the 499 families in the cohort, 307 had children other than the index child at the time of the first home visit, for a total of 439 children. Among these children, 31 were missing information on biologic relationships to the index child's parents, seven were not biologically related to both parents, 52 were not biologically related to the father of the index child, and 43 were not biologically related to the mother of the index child, leaving 306 children from 217 families for this analysis who were biologically related to both parents: 151 families (69.6%) had one child in addition to the index child, 52 (24.0%) had two additional children, 11 (5.1%) had three additional children, and three (1.5%) had four or more additional children. The proportions of children, mothers, and fathers who had either asthma, eczema, or hay fever are shown in Table 1. Among the children, 26 (8.5%) had asthma only, 50 (16.3%) had eczema only, and nine (2.9%) had hay fever only. Three children (1.0%) had asthma, eczema, and hay fever, seven (2.3%) had both asthma and eczema, and three (1.0%) had both eczema and hay fever. Two-hundred eight of the children (68.0%) had none of the three diagnoses.

TABLE 1
PROPORTIONS OF ASTHMA, ECZEMA, AND HAY FEVER AMONG CHILDREN AND THEIR PARENTS IN THE STUDY COHORT

Group	n	Asthma (%)	Eczema (%)	Hay Fever (%)
Children				
< 5 yr	220	8.2	19.5	1.4
5–10 yr	67	17.9	22.4	11.9
> 10 yr	19	31.6	26.3	21.1
Mothers	217	29.5	23.0	41.5
Fathers	217	23.5	15.2	38.2

TABLE 2

UNIVARIATE* AND MULTIVARIABLE† ODDS RATIOS FOR THE RELATIONSHIP OF PARENTAL HISTORY TO CHILDREN'S ASTHMA

Parental Condition‡	Children (n)	Percentage with Asthma	Asthma	
			Univariate OR (95% CI)	Multivariable OR (95% CI)
Maternal				
Asthma, n = 64	84	20.2	3.2 (1.5–6.7)	4.1 (1.7–10.1)
Eczema, n = 50	73	8.2	0.7 (0.3–1.7)	0.5 (0.2–1.4)
Hay fever, n = 90	124	15.3	1.6 (0.8–3.5)	1.8 (0.8–4.0)
Paternal				
Asthma, n = 51	81	14.8	1.4 (0.6–3.2)	2.7 (1.0–7.2)
Eczema, n = 33	45	8.9	0.7 (0.2–2.2)	0.9 (0.3–2.8)
Hay fever, n = 83	118	10.2	0.7 (0.3–1.7)	0.9 (0.4–2.2)

* Simple logistic regression for dependent outcomes using generalized estimating equations.

† Multiple logistic regression for dependent outcomes using generalized estimating equations; covariates included all maternal and paternal conditions listed in the table.

‡ n = number of parents.

The median age of the children in the cohort was 3.5 yr (range, 1.1 to 23.9 yr). Among children < 5 yr of age, the proportion with asthma was 8.2%. Among children ≥ 5 yr of age, this proportion was greater: 17.9% among children between 5 and 10 yr of age and 31.6% among children > 10 yr of age. Similarly, the proportions with eczema and hay fever increased in the older age groups.

The proportions of asthma and other allergic conditions were higher among mothers than among fathers (Table 1). Of the 217 families, three (1.4%) had both parents with asthma, 109 (50.3%) had 1 parent with asthma, 28 (12.9%) had both parents with inhalant allergies and neither with asthma, and 77 (35.5%) had only one parent with inhalant allergy and the other parent with neither allergy nor asthma.

Differential Effects of Maternal and Paternal History

The relationship between a parental history of asthma, eczema, and hay fever and the presence of asthma in children is presented in Table 2. Maternal asthma had the strongest associations with childhood asthma in both the univariate and multivariable models (OR = 3.2, 95% CI = 1.5 to 6.7 and OR = 4.1, 95% CI = 1.7 to 10.1, respectively). Although paternal asthma was weakly associated with childhood asthma in the univariate model (OR = 1.4, 95% CI = 0.6 to 3.2), this association was strengthened after controlling for other maternal and paternal conditions (OR = 2.7, 95% CI = 1.0 to 7.2). Further controlling for maternal perinatal smoking, children's age, sex, race, and family income did not significantly change the estimates for the associations between parental asthma and childhood asthma.

Interactions of maternal asthma and of paternal asthma with children's age categories were included in a model together with the main effects of maternal and paternal asthma and children's age categories (Table 3). Among children < 5 yr of age, the risk associated with maternal asthma was more than three times greater than the risk associated with paternal asthma (OR = 5.0, 95% CI = 1.7 to 14.9 versus OR = 1.6, 95% CI = 0.5 to 5.9, respectively; $p = 0.08$ for difference) in this age group. The risks associated with both maternal and paternal asthma were similar among the children ≥ 5 yr of age. These results were unchanged when controlled for other maternal and paternal conditions.

The analyses presented above were performed on the whole cohort of siblings of the index child, which included

TABLE 3

JOINT EFFECTS OF PARENTAL CONDITIONS AND CHILDREN'S AGE ON CHILDREN'S ASTHMA RISK

Parental Asthma	Children's Age (yr)	OR (95% CI)*
Referent (neither parent with asthma)	< 5	1.0
Maternal asthma	< 5	5.0 (1.7–14.9)
	≥ 5	4.6 (1.1–19.0)
Paternal asthma	< 5	1.6 (0.5–5.9)
	≥ 5	4.1 (1.0–16.0)

* From a generalized estimating equations model with main effects and interaction terms between maternal/paternal asthma and children's age categories.

those who were not biologically related to either one or both of the parents. These analyses produced very similar risk estimates as the analyses presented so far, but with greater precision. For childhood asthma, maternal asthma (OR = 3.0, 95% CI = 1.6 to 5.6 and OR = 3.6, 95% CI = 1.9 to 7.1 for univariate and multivariable models, respectively) remained a stronger risk than paternal asthma (OR = 1.1, 95% CI = 0.5 to 2.2 and OR = 2.1, 95% CI = 0.9 to 4.6 for univariate and multivariable models, respectively). The association of maternal asthma and asthma in the children < 5 yr of age was significantly different from the association between paternal asthma and asthma in this age group: OR = 5.9, 95% CI = 2.3 to 14.8 for maternal asthma versus OR = 1.4, 95% CI = 0.5 to 4.3 for paternal asthma; $p = 0.02$ for difference. The effects of maternal and paternal asthma in the children ≥ 5 yr of age remained similar to each other: OR = 2.5, 95% CI = 0.9 to 7.3 for maternal asthma and OR = 2.5, 95% CI = 1.0 to 6.4 for paternal asthma.

As was the case for childhood asthma, the greatest risk associated with childhood eczema was conferred by the mother in analyses on the cohort of children who were biologically related to both parents (Table 4): maternal eczema was associated most strongly with childhood eczema in both univariate and multivariable models than the other maternal and paternal conditions. Paternal eczema also had significant associations with childhood eczema, but this association was weaker than the maternal eczema-childhood eczema relationship. In models with interaction terms between maternal and paternal

TABLE 4

UNIVARIATE* AND MULTIVARIABLE† ODDS RATIOS FOR THE RELATIONSHIP OF PARENTAL HISTORY TO CHILDREN'S ECZEMA

Parental Condition‡	Children (n)	Percentage with Eczema	Eczema	
			Univariate OR (95% CI)	Multivariable OR (95% CI)
Maternal				
Asthma, n = 64	84	20.2	0.8 (0.4, 1.6)	0.7 (0.3, 1.5)
Eczema, n = 50	73	34.3	3.3 (1.7, 6.5)	3.7 (1.8, 7.3)
Hay fever, n = 90	124	26.6	1.8 (0.9, 3.3)	1.9 (0.9, 3.7)
Paternal				
Asthma, n = 51	81	21.0	0.9 (0.4, 2.0)	1.0 (0.4, 2.4)
Eczema, n = 33	45	37.8	2.7 (1.3, 5.9)	3.2 (1.3, 7.7)
Hay fever, n = 83	118	17.8	0.8 (0.4, 1.5)	0.9 (0.4, 1.7)

* Simple logistic regression for dependent outcomes using generalized estimating equations.

† Multiple logistic regression for dependent outcomes using generalized estimating equations; covariates included all maternal and paternal conditions listed in the table.

‡ n = number of parents.

eczema and children's age groups, maternal eczema was again more strongly associated with childhood eczema than paternal eczema in the children < 5 yr of age: OR = 4.4, 95% CI = 2.1 to 9.3 for maternal eczema and OR = 2.8, 95% CI = 1.1 to 7.1 for paternal eczema. For children ≥ 5 yr of age, paternal eczema was found to have a stronger association with childhood eczema than was maternal eczema: OR = 4.3, 95% CI = 1.2 to 15.7 for paternal eczema and OR = 1.7, 95% CI = 0.5 to 5.4 for maternal eczema. None of the parental history variables was significantly associated with childhood hay fever, but relatively few children had hay fever at the young age of our cohort.

To estimate the frequency of misclassification of paternal conditions, we analyzed the responses to the questionnaire that had been mailed to the fathers. The response rate from the fathers was 62.1%. Performing analyses on the whole cohort, we compared the sensitivity (number of fathers correctly classified as having the condition divided by the total number of fathers with the condition) and specificity (number of fathers correctly classified as not having the condition divided by the total number of fathers without the condition) of maternal report of paternal condition (asthma or eczema) in families with at least one child with the condition of interest (asthma or eczema), with the sensitivity and specificity of maternal report in families without affected children. In the case of paternal asthma, the sensitivity and specificity of maternal report among families without an asthmatic child were 0.72 (31 of 43) and 0.94 (94 of 100), respectively; the corresponding values were 0.83 (five of six) and 0.89 (16 of 18), respectively, among families with at least one asthmatic child. These values were not significantly different from each other. A model using the direct paternal response for asthma revealed an association with childhood asthma (OR = 1.0, 95% CI = 0.4 to 2.7) that was similar to the original association (OR = 1.4, 95% CI = 0.6 to 3.2) (Table 2).

Among homes without childhood eczema, the sensitivity and specificity of maternal report of paternal eczema were 0.58 (14 of 24) and 0.97 (102 of 105), respectively; for families with at least one child with eczema, the sensitivity and specificity were 0.82 (nine of 11) and 0.93 (25 of 27), respectively. A model using the direct paternal response for eczema showed an OR of 1.9 (95% CI = 0.9 to 4.2), reflecting an association weaker than (but in the same direction as) the association seen in Table 4 (OR = 2.7, 95% CI = 1.3 to 5.9). Thus, differential misclassification may have biased our estimates toward

a stronger association between paternal and childhood eczema than actually exists.

Additive Effect of Maternal and Paternal History on Childhood Asthma

The results of modeling the risk for childhood asthma in relation to exclusive combinations of parental asthma and inhalant allergies are presented in Table 5. Compared with a baseline value for families with one parent with inhalant allergy and the other parent with neither inhalant allergy nor asthma, the risk for childhood asthma rose about threefold when one parent had a history of asthma, and the other parent had only inhalant allergy. In addition, the risk for childhood asthma rose more than sixfold from baseline when both parents had a history of asthma. The risk associated with the presence of inhalant allergies in both parents was not different from the baseline of only one parent having inhalant allergy. However, the presence of inhalant allergy in one parent increased the risk for childhood asthma further when the other parent also had asthma. The pattern was similar after adjustments for children's age, sex, family income, race, and maternal smoking in the perinatal period.

DISCUSSION

In our cohort, the risk for childhood asthma and eczema was increased by the presence of the same conditions in the parents. Our results suggest that maternal influences have a stronger association with childhood asthma and eczema, particularly in children < 5 yr of age. The risk for childhood asthma also increased (from a baseline of no parental history of asthma) with the number of parents with asthma; this risk was also increased further by a parental history of inhalant allergy other than asthma, in the presence of asthma in the other parent.

A strong familial aggregation of asthma and allergic diseases has been established (6, 10). Parental asthma has been shown in several studies to be a strong predictor of asthma in the child. In a community-based sample of 770 children 5 to 9 yr of age from East Boston, Massachusetts, Sherman and co-workers (11) showed that the relative risk for asthma in the index child was 1.95 (95% CI = 1.29 to 2.95) when at least one parent had asthma. The risk for childhood asthma was also increased (RR = 1.61, 95% CI = 1.03 to 2.50) when one of the parents had atopy (defined as either eczema or hay fever), but parental atopy was not as strong a predictor as was parental

TABLE 5
UNIVARIATE* AND MULTIVARIABLE† ODDS RATIOS FOR THE RELATIONSHIP OF PARENTAL HISTORY OF ASTHMA AND INHALANT ALLERGY TO CHILDHOOD ASTHMA

Parental History of Asthma and Inhalant Allergy‡	Children (n)	Percentage of Children with Asthma	Univariate	Multivariable
			OR (95% CI)	OR (95% CI)
Neither parent with asthma, one with inhalant allergy, n = 77	131	9.2	1.0	1.0
Neither parent with asthma, both with inhalant allergy, n = 28	44	6.8	0.9 (0.2, 4.7)	1.2 (0.2, 7.0)
One parent with asthma, other without inhalant allergy, n = 75	149	16.8	3.1 (1.1, 8.3)	2.6 (0.8, 8.0)
One parent with asthma, other with inhalant allergy, n = 34	61	19.7	4.9 (1.6, 15.3)	6.8 (1.9, 24.8)
Two asthmatic parents, n = 3	8	37.5	6.3 (0.5, 81.9)	14.1 (0.9, 221.5)

* Simple logistic regression for dependent outcomes using generalized estimating equations.

† Multiple logistic regression for dependent outcomes using generalized estimating equations; covariates included children's age, family income, race, sex, and maternal perinatal smoking.

‡ n = number of parent pairs.

asthma. The study of Sherman and coworkers did not attempt to quantify the separate contributions of maternal and paternal asthma to the risk for asthma in the child. In a study of 6,665 families of 9- to 11-yr-old children in Munich and Southern Bavaria, Dold and coworkers (8) similarly found that the risk for asthma in the child was increased when one parent had asthma (OR = 2.6, 95% CI = 1.7 to 4.0). However, the risk related to maternal asthma (OR = 1.5, 95% CI = 0.7 to 2.7) was not as great as that related to paternal asthma (OR = 4.4, 95% CI = 2.5 to 7.8). A parent with either atopic dermatitis or allergic rhinitis did not increase the risk for asthma in these children. In another study of 6- to 14-yr-old schoolchildren in the United Arab Emirates (UAE) (12), the risk for asthma conferred by a maternal history of asthma (RR = 2.67, 95% CI = 1.65 to 4.35) was about the same as that conferred by a paternal history of asthma (RR = 2.85, 95% CI = 1.81 to 4.49). In addition, both maternal allergic rhinitis and eczema also significantly increased the risk for childhood asthma, whereas a paternal history of these conditions were not related to childhood asthma.

The studies cited above also found that the strongest associations involved the presence of the same condition in the parent and in his or her child. In the study of Dold and coworkers (8) of German schoolchildren, the presence of allergic rhinitis in one parent was the strongest risk factor for allergic rhinitis in the children (OR = 3.6, 95% CI = 2.9 to 4.6), whereas parental asthma (OR = 2.5, 95% CI = 1.6 to 4.0) and parental atopic dermatitis (OR = 1.7, 95% CI = 1.1 to 2.5) conferred lower risks. Similarly, for childhood atopic dermatitis, parental atopic dermatitis conferred the highest risk (OR = 3.4, 95% CI = 2.6 to 4.4), whereas parental asthma (OR = 1.5, 95% CI = 1.0 to 2.2) and parental allergic rhinitis (OR = 1.4, 95% CI = 1.1 to 1.8) conferred lower risks. Furthermore, in a subsequent analysis of these schoolchildren, a family history of asthma, but not of hay fever or atopic dermatitis, was a significant determinant for the presence of asthma in the child, after controlling for skin test reactivity, bronchial hyperresponsiveness, and sex (13).

In assessing these individual risks, however, these studies did not control for the presence of other allergic conditions in the parents. After controlling for these other allergic conditions, we found similar associations: the strongest risk factor for childhood asthma in the child was parental asthma, and the strongest risk factor for childhood eczema was parental eczema. It should be pointed out, however, that in our study the effect estimate associated with paternal asthma changed significantly when other maternal and paternal conditions were controlled. The presence of inhalant allergy in one parent increased the risk for childhood asthma only in the presence of asthma in the other parent. These findings support the idea that there may be different inheritance mechanisms for asthma and the other allergic conditions, but that these mechanisms may be interrelated with one another to varying degrees. In particular, asthma and inhalant allergies are thought to share similar pathogenic mechanisms (14, 15) and thus may be inherited in similar ways. Future studies investigating the inheritance of asthma and allergic diseases will need to account for the different phenotypes present in both parents.

The children in our study were younger on average than those in the previously mentioned studies of German and UAE schoolchildren, and this age difference may explain why we found a stronger effect of maternal than of paternal asthma. Indeed, among children < 5 yr of age, maternal asthma conferred a significantly increased risk for childhood asthma, whereas no significant effect was detected for paternal asthma (Table 3). In addition, the risk associated with maternal

asthma was more than three times greater than the risk associated with paternal asthma in this age group. Issues related to statistical power limited the confidence with which maternal and paternal asthma as risk factors could be compared, but the data suggested that this difference was significant. In the older age group (≥ 5 yr of age), the risks conferred by maternal and paternal asthma were similar to each other. Our results are consistent with the hypothesis that there may be preferential inheritance of allergic diseases through the maternal line and suggest that this phenomenon is manifested early in the life of the child. Ruiz and colleagues (16) studied 39 newborns with only one atopic parent (20 atopic mothers and 19 atopic fathers) based on skin testing results. They found that infants were at significantly greater risk of developing atopic dermatitis when their mothers were atopic than when their fathers were atopic (RR = 4.7, 95% CI = 2.5 to 9.0) and that the infants of atopic mothers had an earlier onset of atopic dermatitis. Several studies have also shown that maternal atopy and serum IgE levels were stronger predictors of cord-blood IgE levels than were paternal atopy and serum IgE levels (7, 17). In another study of 21 infants whose fathers had rhinoconjunctivitis and/or bronchial asthma and whose mothers had no symptoms of atopic disease, no effect of paternal IgE on cord-blood IgE was detected (18). Our results, in conjunction with the results of the studies cited above, lead us to speculate that perhaps the maternal condition exerts a stronger effect early in the life of the child, whereas the paternal condition may be involved in the development of asthma in later life.

Cookson and colleagues (19) suggested preferential inheritance of atopy through the maternal line by showing excess sharing of the maternal 11q13 allele among affected sibling pairs. Other investigators, however, have been unable to demonstrate differences in the sharing of paternal and maternal alleles at 11q13 (20–22). Genetic mechanisms such as paternal genomic imprinting (23) and the Carter effect (7, 24), which have been shown to operate in other diseases, have been proposed to explain the preferential inheritance through the maternal line, but thus far no evidence indicates that these mechanisms are operative in asthma or in other allergic diseases.

In addition to genetic inheritance, mechanisms for conferring early-life risk preferentially through the maternal line may include transplacental transfer of antigens, maternal antibodies, or maternally derived cytokines (23), leading to the reported association between maternal history of allergy and high neonatal serum IgE levels (7, 17). Therefore, factors that modulate the maternal immune system during pregnancy are thought to be active in the development of allergic disease in the offspring (25). These mechanisms exert their greatest effect early in life and may lead to earlier onset of allergic disease. Furthermore, inheritance by either genetic or environmental mechanisms may vary not only by age but also by type of atopic disease. Because of the cross-sectional design of this analysis, the lack of biologic markers, and the lack of information regarding maternal exposures during pregnancy, we are unable to draw definite conclusions about the reasons for the differential effects of maternal and paternal asthma on childhood asthma. Furthermore, since we had no information about the age of onset of asthma in the children we studied, any conclusions about the effects of maternal and paternal asthma on childhood asthma at different ages must be deferred pending future prospective analyses.

We obtained similar results when we performed the same analyses on the whole cohort of 439 siblings. In these analyses, the association between maternal asthma and childhood asthma remained stronger than the association between paternal asthma and childhood asthma, particularly among the

children < 5 yr of age. This leads us to consider that, in addition to the possible genetic/biologic mechanisms enumerated above, exposure to shared environments between a biologic or nonbiologic parent and a very young child may also play a significant role in the development of asthma and other allergic conditions in the children.

Both a selection bias and a reporting bias may have affected our results. Because mothers were the initial contact for entry into the cohort, it was possible that asthmatic mothers may have been more likely to agree to join the cohort than were nonasthmatic mothers. A review of the screening information, however, showed that the proportion of mothers with asthma in the cohort (154 of 499, 30.9%) was lower than the proportion of asthmatic mothers among those not in the cohort (357 of 906, 39.4%). Likewise, the proportion of asthmatic fathers was lower in the cohort than the proportion in those excluded (117 of 499, 23.4% versus 267 of 906, 29.5%). In addition, the proportions of eczema and hay fever were similar among the mothers and fathers in the two groups. This information suggests that selection bias was not a significant factor operating in the recruitment of our cohort.

Because paternal asthma and allergy status was ascertained through maternal interviews, reporting or misclassification bias was a concern. Our validation study, although not based on a random sample, nevertheless gave us some idea about the magnitude of the potential bias. Our findings suggest that for maternal report of paternal asthma, some nondifferential misclassification was present, but this bias did not appear to be large and did not significantly affect our results for asthma. The case for paternal eczema, however, appears to be different. Our results suggest that mothers were more likely to classify fathers correctly if a child had eczema than if none of their children had eczema; this bias may partly explain the strength of association between paternal and childhood eczema in our cohort. These findings are not surprising. We would expect that a mother would be able to classify her child's father's asthmatic condition with reasonable accuracy, especially if he were symptomatic or taking medications. We would expect less accurate classification of the father's eczema condition independent of the child's eczema since eczema is generally a less debilitating and symptomatic condition than is asthma.

In summary, although asthma and other allergic conditions often go together, children are more likely to develop atopic diseases similar to those of their parents. The explanation may be different inheritance patterns for asthma and the other atopic diseases. Furthermore, our study adds to the evidence for preferential inheritance of early-childhood asthma along maternal lines. Whether this effect is due to genetic factors, placental transfer of maternal factors, and/or exposure to environmental influences is not known and will need to be studied further. Ongoing follow-up and study of our cohort should provide further insight into the complex relationships that affect the development of asthma and atopic disease in children.

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