

Parental asthma as a risk factor for the development of early skin test sensitization in children

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Background: Recent epidemiologic evidence has challenged the paradigm suggesting a direct causal relationship between allergic sensitization and asthma.

Objective: We sought to investigate the role of a familial predisposition for asthma in the development of atopy in children.

Methods: Subjects were participants in the Tucson Children's Respiratory Study. Skin tests to aeroallergens were performed in parents and in children at ages 6, 11, and 16 years. Parents were considered asthmatic if they reported physician-confirmed asthma. Parents were divided into 4 phenotypes on the basis of skin sensitization (Skt+ or Skt-) and asthma status (As+ or As-): Skt-/As-, Skt-/As+, Skt+/As-, and Skt+/As+. **Results:** Children's allergic sensitization differed among parental phenotypes at all ages ($P < .0001$). Children in the Skt+/As- and Skt+/As+ groups were significantly more likely to be allergic than children in the Skt-/As- group at all ages. Among children with allergic parents, those with at least one parent with asthma were significantly more likely to have positive skin test responses than those with nonasthmatic parents at age 6 years (52.4% vs 37.4%, $P < .005$) and 11 years (70.1% vs 55.6%, $P < .005$) but not at age 16 years (82.3% vs 75.1%, $P = .180$). Results were independent of wheezing in the child and of the characteristics of atopy in parents. The Skt-/As+ group had too few subjects for meaningful comparisons.

Conclusion: Among children of atopic parents, parental asthma is a risk factor for allergic sensitization in early childhood. The strong association between allergic sensitization and asthma is at least in part explained by an increased susceptibility to allergen sensitization in subjects predisposed to asthma. (*J Allergy Clin Immunol* 2004;113:284-90.)

Key words: Asthma, skin test sensitization, wheezing, IgE, eosinophils

It is widely recognized that atopy and asthma are strongly linked. Several studies have provided evidence that atopic sensitization is related to an increased prevalence of asthma, bronchial hyperresponsiveness, and a greater severity of respiratory symptoms.¹⁻³

Abbreviations used

As: Asthma status

Skt: Skin sensitization status

The close association between allergic sensitization and asthma has suggested that a causal association might exist between these 2 entities. The postulated mechanism is that allergen exposure results in sensitization and that continued exposure in sensitized individuals leads to clinical manifestations of asthma by causing bronchial responsiveness and airway inflammation.

This interpretation has been recently challenged on the basis of increasing evidence that a more complex relationship might be involved. First, in population-based studies it has been observed that less than one half of asthma cases are attributable to atopy.⁴ When comparing the prevalence of asthma and atopy worldwide, it has also been noted that although there are countries that show similar trends for the prevalence of asthma and atopy,⁵⁻⁷ areas with a high prevalence of atopy but an unexpectedly low rate of asthma can be found.⁸⁻¹⁰ In addition, longitudinal studies have demonstrated that sensitization to asthma-related allergens that occurs early in life is much more strongly associated with asthma risk than late-onset sensitization.^{11,12} These findings are not consistent with a simple, straightforward, causal relationship between allergic sensitization and asthma.

It has been recently postulated that the asthmatic condition itself might play a role in determining a specific pattern of atopic sensitization.^{13,14} More specifically, it is possible that a genetic predisposition to asthma might increase the subject's susceptibility to become sensitized to local aeroallergens.¹⁵ In this scenario the process of becoming sensitized to aeroallergens would parallel, but not necessarily cause, the development of asthma.

On the basis of this hypothesis, we postulated that parental asthma might be a risk factor independent of parental skin test reactivity for the development of skin test sensitization in children.

METHODS

Study population

Subjects included in this analysis are participants in the Tucson Children's Respiratory Study, a large birth-cohort study of the risk factors for the development of asthma in childhood. A total of 1246 healthy infants were enrolled between May 1980 and October 1984. Parents planning to use a large health maintenance organization in

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Tucson, Arizona, were contacted shortly after their child's birth, and informed consent was obtained. The study was approved by the Institutional Review Board of the University of Arizona.

Questionnaires

At the time of enrollment, parents completed a questionnaire about their history of respiratory illnesses and other personal characteristics. Parents were considered to have asthma, allergic rhinitis, or both if they had ever had a physician-confirmed diagnosis of asthma, allergic rhinitis, or both. Information regarding breast-feeding was obtained from a questionnaire completed by parents at the time of the year-2 survey. Data on physician-diagnosed lower respiratory infections were collected during the first 3 years of life.

Multiple questionnaires ascertaining the child's respiratory health were completed by the parents at different ages. Data for this study come from the year-6 survey (6.3 ± 0.9 years), the year-11 survey (10.9 ± 0.6 years), and the year-16 survey (16.5 ± 0.5 years).

Frequent wheezing in children was defined as at least 3 wheezing episodes in the previous year. Children were considered to have allergic rhinitis if a physician diagnosis was present and the child had used medications in the past year.

Skin prick tests

At the time of the year-6 survey, skin prick tests to common allergens in the Tucson area were performed in 760 children, 802 mothers, and 653 fathers. Skin tests were repeated at the year-11 and year-16 surveys on 709 and 483 children, respectively. Only those allergens that were consistently tested over time were considered in this study, specifically Bermuda grass, olive tree, careless weed, *Alternaria alternata*, mesquite tree, and mulberry tree (all allergens obtained from Hollister-Stier laboratories, Everett, Wash).

The sum of 2 perpendicular diameters was computed for each wheal after 20 minutes. Wheal sizes of 3 mm or greater, after subtraction of the control, were considered positive, and a positive skin test response (atopy) was defined as a positive reaction to one or more allergens.

IgE and eosinophil levels

Total serum IgE levels were measured in 719 mothers and 550 fathers with the paper radioimmunoassorbent test (Pharmacia Diagnostics, Piscataway, NJ) at the time of the year-6 survey. All samples were assayed in duplicates, and the means were computed; the lower limit of detection in this assay is 0.1 IU/mL. The number of eosinophils per cubic millimeter of peripheral blood was determined in 784 mothers and 606 fathers at the time of the year-6 survey.

Study design

To study the role of a positive parental history of asthma, atopy, or both on the development of allergic sensitization in the child during the first 16 years of life, parents were divided into 4 mutually exclusive phenotypes on the basis of the presence or absence of at least 1 parent with physician-diagnosed asthma and at least 1 parent with a positive skin test response. The groups were defined as follows: Skt-/As-, negative skin test response/negative for asthma; Skt-/As+, negative skin test response/positive for asthma; Skt+/As-, positive skin test response/negative for asthma; and Skt+/As+, positive skin test response/positive for asthma. In most families the latter group was made up of mothers or fathers who had both positive skin test responses and asthma. However, in 18.9% of cases, one parent had a positive skin test response with no asthma, and the other had asthma but had a negative skin test response. Because this group had consistently similar results to those of asthmatic parents with positive skin test responses, they were pooled into a single category.

Among parents with positive skin test responses, the following characteristics of allergy were considered: number of positive skin test responses, maximum wheal size, number of atopic parents (one or both), total serum IgE level (z scores), and eosinophil count. Tertiles of maximum wheal size, number of positive skin test responses, total serum IgE level, and eosinophil count were calculated, and parents were categorized into 3 groups according to these values. Odds ratios for the association between parental asthma and skin test sensitization in the child were computed for all parents with positive skin test responses and for each group separately. When combining paternal and maternal information, data regarding the parent with a positive skin test response were selected, or in the case of 2 atopic parents, the highest value was chosen.

As part of the study design, data were analyzed at 3 different points in time (year 6, year 11, and year 16). At each survey, only children who underwent skin prick testing and for whom we had data on both parental asthma and parental skin test responses were included.

Statistical methods

The relationship of parental phenotype to skin test sensitization in the child was assessed in contingency tables, with the χ^2 test used to determine statistical significance. The Mantel Haenszel test for homogeneity was used to compute odds ratios and 95% CIs for skin test sensitization in the child associated with parental asthma after stratification by severity of allergic markers in the parents. The unpaired Student *t* test and the nonparametric Mann-Whitney test were used depending on the variable's distribution to compare continuous variables.

Statistical analyses for total serum IgE levels were performed by using log-transformed values. IgE levels differed between mothers and fathers and correlated with age. Sex- and age-standardized z scores were therefore computed on the basis of the following age categories: 29 years or less, 30 to 39 years, and 40 years or greater.

Generalized estimating equations, with skin test sensitization in the child as a dependent variable, were used in the multivariate analyses to adjust for potential confounding and for the serial correlation within subjects (multiple observations in the same subjects). Linear contrasts were performed to test the association between asthma in parents and skin test reactivity in the child at each survey. The best fitted covariance pattern was selected by using the Quasilikelihood Information Criterion.¹⁶ As compared with traditional parametric tests and logistic regression models, generalized estimating equations offer the advantage of relaxing the independence assumption, modeling the serial correlation between observations (by fitting a covariance pattern model), and being less sensitive to missing values (assuming that they are missing at random).

Statistical significance was defined by a 2-sided α level of .05 for all tests. When multiple comparisons were performed, the Bonferroni correction was applied.

RESULTS

Of the 1246 children originally enrolled in the Tucson Children's Respiratory Study, 741 children met the inclusion criteria at age 6 years, 691 at age 11 years, and 462 at age 16 years. No significant differences were found between subjects included at any survey and those excluded with respect to ethnicity, maternal smoking during pregnancy, breast-feeding, maternal asthma, paternal asthma, or lower respiratory tract infection in the first 3 years of life. However, participants at the year-6 and year-16 surveys were more likely to have mothers with higher education than those who did not participate in these surveys, whereas participants in the year-11 sur-

TABLE I. Characteristics of the study population

	CRS enrollees (n = 1246) [†]	Participants at year-6 survey* (n = 741) [†]	Participants at year-11 survey* (n = 691) [†]	Participants at year-16 survey* (n = 462) [†]
Ethnicity (% white)	67.2	65.6	64.7	66.8
Maternal education (% ≤12 y)	32.1	29.3 [‡]	30.9	24.7 [‡]
Maternal smoking during pregnancy (%)	16.0	14.9	15.0	14.1
Breast-feeding (%)	83.3	83.3	82.2	84.3
Maternal asthma (%)	12.2	11.8	12.1	10.2
Paternal asthma (%)	13.4	14.6	14.4	11.9
Maternal allergen sensitization (%)	60.5	61.7	62.3 [‡]	63.1
Paternal allergen sensitization (%)	64.8	65.3	64.7	66.8
LRI in the first 3 y of life (%)	54.5	55.9	55.8	54.4

CRS, Children's Respiratory Study; LRI, lower respiratory tract infection.

*For this analysis, only children with skin prick test results and data on parental asthma and parental skin test responses were included at each survey.

[†]Not all subjects had data for all characteristics because of missing values.[‡]Differed significantly from children who did not participate ($P < .05$).

TABLE II. Atopy in children at each survey by parental phenotype

Parental phenotype	Children with positive skin test responses at year 6, % (n)	Children with positive skin test responses at year 11, % (n)	Children with positive skin test responses at year 16, % (n)
Total	37.9 (741)	55.1 (691)	71.6 (462)
Negative skin test response/ negative for asthma (Skt-/As-)	24.4 (131)	38.2 (123)	48.8 (82)
Negative skin test response/ positive for asthma (Skt-/As+)	33.3 (21)	42.9 (14)	75.0 (4)
Positive skin test response/ negative for asthma (Skt+/As-)	37.4* (446)	55.6§ (417)	75.1 [†] (297)
Positive skin test response/ positive for asthma (Skt+/As+)	52.4 [‡] (143)	70.1 [‡] (137)	82.3 [†] (79)
Overall P value	<.0001	<.0001	<.0001

*Significantly different ($P < .05$) compared with the Skt-/As- parental phenotype.[†]Significantly different ($P < .0001$) compared with Skt-/As- parental phenotype.[‡]Significantly different ($P < .005$) compared with Skt+/As- parental phenotype.§Significantly different ($P < .005$) compared with Skt-/As- parental phenotype.

vey were more likely to have mothers with positive skin test responses (Table I).

In the group as a whole, 37.9% of the children had positive skin test responses at the time of the year-6 survey, 55.1% at the time of the year-11 survey, and 71.6% at the time of the year-16 survey. Results were similar when limited to 433 children for whom complete data were available at all 3 surveys (43.4%, 58.4%, and 72.5%, respectively).

The percentage of children with positive skin test responses differed among parental phenotypes at all 3 surveys (Table II). Specifically, children of parents with positive skin test responses, either with or without asthma, were significantly more likely to have positive skin test responses than children of Skt-/As- parents at all ages. The proportion of children with positive skin test responses in the Skt+/As+ parental phenotype was significantly higher than that in the Skt+/As- group at both the year-6 and year-11 surveys ($P < .005$, still significant after the Bonferroni correction was applied) but not at the year-16 survey. Because of the limited number of children in the Skt-/As+ parental phenotype, no meaningful comparison was possible with respect to this specific group of chil-

dren. No differences were found when analyses were performed for mothers and fathers separately.

We tested the hypothesis that the higher prevalence of children with positive skin test responses observed in the Skt+/As+ group when compared with the Skt+/As- group could be attributed to different skin test response characteristics in these 2 groups of parents. Skt+/As+ parents did show significantly higher values of maximum wheal size, IgE z scores, and number of eosinophils per cubic millimeter of blood, as well as a significantly higher proportion of subjects with more than 3 positive skin test responses when compared with the Skt+/As- group (data not shown). Parents were categorized into 3 groups according to tertile values of maximum wheal size, number of positive skin test responses, IgE z scores, and number of eosinophils per cubic millimeter to test whether such differences could account for the different proportion of children's skin test sensitization between Skt+/As- and Skt+/As+ phenotypes. The odds ratios for the association between asthma in the parents and skin test sensitization in the children did not differ significantly across all these strata by using the χ^2 Mantel Haenszel test for homogeneity of odds ratios (Fig 1).

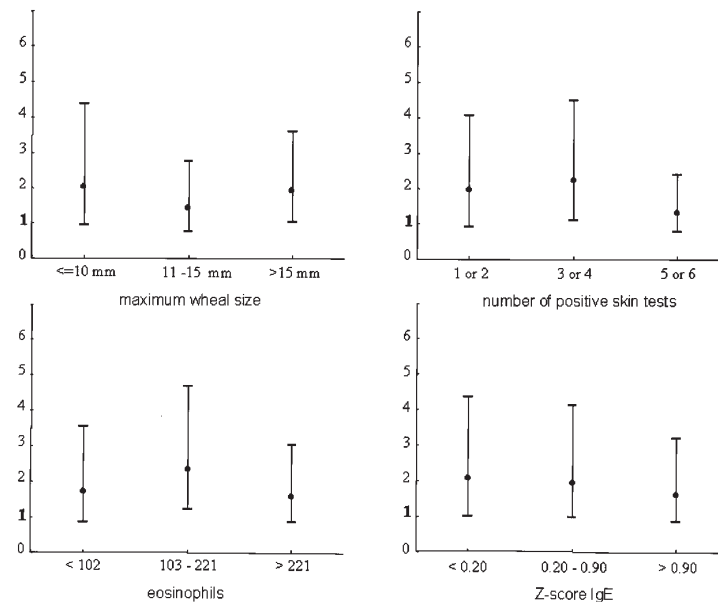


FIG 1. Odds ratios for skin test sensitization in children associated with parental asthma after stratification for the characteristics of atopy in parents. Only children of Skt+/As- and Skt+/As+ parents were included in this analysis.

TABLE III. Frequent wheezing and allergic rhinitis in children at each survey by parental phenotype

Parental phenotype	Children at year 6, % (n)		Children at year 11, % (n)		Children at year 16, % (n)	
	Frequent wheezing	Allergic rhinitis	Frequent wheezing	Allergic rhinitis	Frequent wheezing	Allergic rhinitis
Negative skin test response/negative for asthma (Skt-/As-)	5.3 (150)	21.7 (143)	4.3 (138)	19.0 (137)	5.7 (105)	22.6 (115)
Positive skin test response/negative for asthma (Skt+/As-)	6.8 (485)	31.4 (475)	9.7 (466)	32.3 (465)	7.0 (374)	31.7 (385)
Positive skin test response/positive for asthma (Skt+/As+)	13.9 (158)	46.9 (147)	18.3 (153)	48.3 (149)	13.1 (107)	39.5 (119)
P value	<.01	<.01	<.01	<.001	<.05	.115

P value for the comparison between the Skt+/As- and Skt+/As+ parental phenotypes.

This suggests that the association is specific to parental asthma rather than to a stronger allergic predisposition among asthmatic parents with positive skin test responses. Children of Skt+/As+ parents were not only more likely to have positive skin test responses than children of Skt+/As- parents, but they were also more likely to have frequent wheezing at all ages and to have allergic rhinitis at age 6 and 11 years (Table III).

Multivariate analyses (generalized estimating equations) were performed to further investigate the independent role of asthma in parents with positive skin test responses on the development of children's sensitization, with skin test reactivity in the child as the dependent variable and child's wheezing, parental asthma, parental allergic rhinitis, and characteristics of allergy in parents as independent variables. All of the following variables were tested in the model: frequent wheezing for the children and physician-diagnosed asthma, physician-diagnosed allergic rhinitis, maximum wheal size, number of positive skin test responses, log IgE, number of eosinophils, and number of parents with positive skin test responses for the parents. Only those variables that

maintained a significant association with skin test reactivity in the children are shown (Table IV). Although most characteristics tested were significantly associated with skin test sensitization in the children in univariate analysis, only wheezing in the children, parental asthma, parental IgE levels, and the number of atopic parents remained significant in the multivariate analysis. As indicated in Table IV, parental asthma was a significant risk factor for allergic sensitization in the children independent of the other variables included in the model. Of note, the effect of parental asthma on the development of skin test sensitization in the children was independent of the children's wheezing status. When the effect of parental asthma on skin test reactivity in children was tested at each survey, adjusted odds ratios were significant at age 6 years (1.82; 95% CI, 1.21-2.73) and at age 11 years (1.78; 95% CI, 1.15-2.76) but not at age 16 years (1.28; 95% CI, 0.70-2.35).

Our findings held true also after restricting our analysis only to those children for whom data regarding asthma and skin test sensitization were available for both parents (data not shown).

TABLE IV. Odds ratios (95% CIs) from generalized estimating equations with skin test reactivity in children at different ages as the dependent variable and parental asthma,* child's wheezing, and characteristics of allergy† in parents as independent variables

Parental variables included	OR	95% CI	P value
Parental asthma	1.50	1.07-2.11	.019
Child's wheezing	1.93	1.33-2.79	.001
z Score log IgE in parents	1.31	1.09-1.58	.004
No. of parents with positive skin test responses	1.45	1.08-1.95	.014

OR, Odds ratio.

*Only parents with positive skin test responses were included.

†The following variables were tested: number of positive skin test responses in parents, maximum wheal size in parents, parental z score log IgE, parental eosinophils, number of parents with positive skin test response (1 or 2), and physician-diagnosed allergic rhinitis in parents. Only those variables that showed significant association with skin test reactivity in the child are shown in the model.

DISCUSSION

The main finding of our study was that among children of parents with positive skin test responses, parental asthma is an independent risk factor for the development of skin test sensitization early in life. This association holds true regardless of the characteristics of parental skin test reactivity that could themselves explain the greater prevalence of skin test sensitization in the offspring. When we adjusted for such characteristics—namely maximum wheal size, number of positive skin test responses, and IgE and eosinophil levels—parental asthma was still a significant determinant of allergic sensitization in the children. Our findings thus suggest that parental asthma might predispose not only to the development of the asthmatic condition, as has already been shown,¹⁷ but also to allergic sensitization and that parallel, rather than sequential, mechanisms might be involved.

The concept of an influence of family history for asthma on the development of skin test sensitization in the offspring is not new. Burrows et al¹⁸ found that the presence of asthma in the mother or father was, as expected, a highly significant determinant of asthma in the child but that it was also a strong predictor of the child's serum IgE levels. Our results and those of Burrows et al, suggest that there is probably a far more complex relationship between allergic sensitization and the susceptibility to asthma than has been previously postulated.

This is also supported by the findings of Lau et al.¹⁹ In a prospective birth-cohort study they showed that although allergen exposure was related to skin test sensitization and sensitization was itself positively associated with asthma, there was no association between the level of allergen exposure early in life and the subsequent development of asthma. These results suggest that the factors determining the development of skin test reactivity appear to be substantially different than those associated with the development of childhood asthma. Perhaps the strong association between sensitization and asthma reflects the susceptibility of individuals with asthma to become sensitized to those perennial allergens that are most prevalent in the environment in which they live rather than an increased risk of asthma development among individuals exposed to those allergens.

When we investigated the role of a familial susceptibility for asthma on the development of skin test reactivity in the first 16 years of life, we found that individuals with a parental history of asthma were more likely to have allergic sensitization earlier in life than those without such a history. The effect of a familial predisposition for asthma was in fact evident at both 6 and 11 years of age but became nonsignificant at 16 years of age, a time at which it is plausible to surmise that factors other than parental asthma might play a major role in the development of allergic sensitization. These findings hold particular interest because early sensitization has been previously associated with an increased risk of persistent asthma and bronchial hyperresponsiveness and with a greater loss in lung function.^{12,20}

We propose that there might be different genetic mechanisms underlying the pattern of sensitization developing at different ages. Our hypothesis is that the pattern of allergic sensitization that is associated with a genetic predisposition for asthma is manifested early in life and requires very low levels of allergen exposure. On the basis of this and other studies, we speculate that a genetic background for asthma might be the link between early sensitization and the subsequent development of persistent asthma, bronchial hyperresponsiveness, and decrease in lung function.

The mechanisms determining an increased susceptibility to becoming sensitized early in life among subjects with a family history for asthma remain unknown. Nevertheless, in the same population we have previously shown that markedly reduced IFN- γ responses by PBMCs in the first year of life are associated with a greater subsequent risk of development of allergic sensitization.²¹ One possible explanation for the link between early allergic sensitization and asthma is that this sensitization is the result of an underlying immunologic deviation. Asthma susceptibility might be related to a tendency to develop T_H2-mediated reactions locally in the lung and airways. These reactions, on the one hand, might promote sensitization to inhaled allergens, whereas on the other hand, they might give rise to local alterations of the airways that can affect the normal process of airway growth, especially in the first few years of life. In support of this contention, it has been shown that mediators

involved in T_H2 -type reactions, such as leukotrienes²² and ILs (IL-13,^{23,24} IL-4,^{25,26} and IL-5²⁷), have the capacity to exert direct effects on airway components, causing hypertrophy, hyperplasia, or both of fibroblasts and smooth muscle cells.

Alternatively, it has been postulated that the abnormalities in the bronchial epithelium associated with the development of asthma create an inflammatory state that might predispose the airway to local sensitization. Once allergen sensitization is established, it would have direct enhancing effects on local inflammatory and remodeling responses.²⁸ However, when we included a child's frequent wheezing in a multivariate model, we found that the association of parental asthma with skin test reactivity in the children was independent of the child's wheezing status. This suggests that a genetic predisposition for asthma plays a role in the development of skin test sensitization in the child independent of the development of clinical manifestations of asthma.

There are some limitations in our study that need to be considered. To avoid possible recall bias, we defined both asthma and allergic rhinitis in parents on the basis of a questionnaire completed by them at the time of enrollment before any outcome in the child could potentially bias their responses. Moreover, although all information was obtained from questionnaires, we used a physician diagnosis of asthma to minimize the risk of classifying as asthmatic those individuals whose respiratory symptoms were attributable to other causes. However, we cannot rule out the possibility that some asthmatic subjects might indeed have been misclassified as nonasthmatic because they were not given a diagnosis by a physician.

In our study we included children for whom data regarding skin test reactivity, asthma, or both in either parent were available. This could have led to a misclassification of children in regard to their parental phenotype because of inclusion of children for whom data for one parent were unavailable. However, when we restricted our analyses only to those children for whom complete data about asthma and skin test sensitization in both parents were available, our findings remained substantially unchanged (data not shown).

In conclusion, there is emerging evidence supporting the existence of a complex relationship between asthma and allergic sensitization. Individuals with a family history of asthma and atopy are more likely to become sensitized to local aeroallergens than those who only have a family history of atopy. This suggests that the asthmatic condition might not only be the consequence of atopic status but might provide one or more heritable factors for allergen sensitization that occurs by mechanisms that remain to be elucidated.

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