

Association Between Allergy and Asthma from Childhood to Middle Adulthood in an Australian Cohort Study

RORY WOLFE, JOHN B. CARLIN, HELMUT OSWALD, ANTHONY OLINSKY, PETER D. PHELAN,
and COLIN F. ROBERTSON

Clinical Epidemiology and Biostatistics Unit, Murdoch Children's Research Institute; Department of Respiratory Medicine, Royal Children's Hospital; and Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia

A cohort of 378 asthmatic children was studied from 7 to 35 yr of age at 7-yr intervals. On selection for inclusion in the study sample, the children had a wide range of severity of wheezing. At each 7-yr review, asthma severity, the presence of eczema or hay fever, and skin test reactivity to house dust mite or rye grass were recorded by questionnaire or clinical interview. We report on the course of asthma and these atopic conditions over the study period and discuss associations between the two phenomena. The presence of an atopic condition in childhood was found to increase the odds of more severe asthma in later life (odds ratio [OR] = 1.66, 95% confidence interval [CI]: 1.17 to 2.36 in the case of eczema; OR = 1.39, 95% CI: 1.00 to 1.92 for hay fever; and OR = 2.25, 95% CI: 1.49 to 3.39 for skin test reactivity). Additionally, the odds of eczema and hay fever in later life increased with severity of asthma in childhood. The findings of this study provide substantially new quantitative information on the extent of association between asthma and atopic conditions from childhood into middle adulthood.

Longitudinal studies of the outcome of childhood asthma have shown atopy to be a major risk factor for asthma persisting into adult life (1–3), although this association has not always been consistent (4). A similar association has been shown for the childhood outcome of wheezing in infancy (5). These studies classified asthma as a dichotomous variable, without regard to the spectrum of severity of clinically expressed asthma at either recruitment or at outcome. In the studies, the definition of atopy varied, including a history of clinical symptoms, positive skin tests, or measured levels of IgE.

As children progress into adulthood, it is less clear whether the outcome of childhood allergy is influenced by the presence of childhood asthma. One study of a hospital clinic-based population showed that asthma severity in childhood was not associated with the presence of allergy in adulthood, but the study sample may not have been representative (6).

The prevalence of asthma has increased in most developed countries (7), and there are suggestions that allergen exposure may be a factor in causing this increase. Therefore, it is important to examine the relationship between parameters of allergy and asthma over a prolonged period, in the hope that this may lead to a better understanding of the influence of allergy on the course of asthma.

The present report describes a community-based study of children followed prospectively from the ages of 7 to 35 yr (8–12). The children were selected in such a way that the entire

spectrum of asthma severity was represented, and throughout this report, asthma is discussed according to the pattern of its symptoms and its severity, rather than simply on the basis of the presence or absence of symptoms. Information was also collected on the presence of eczema and hay fever and on skin test reactivity to common environmental allergens.

The aims of this report are to examine whether the presence of allergic features in childhood is a predictor of the subsequent course of asthma, and conversely to relate the pattern of wheezing in childhood to the course of allergic features through adulthood.

METHODS

Data and Sample

A sample of 401 children, stratified by severity of wheezing was recruited in 1964 from a 7-yr-old (school Grade 2) cohort in Melbourne, Australia (8). Wheezing status was determined initially by parental response to a questionnaire and was confirmed by clinical examination and classified into the four categories of: (1) no wheezing, (2) mild wheezy bronchitis, (3) wheezy bronchitis, and (4) asthma. The numbers of children recruited in each group were 106, 75, 107, and 113, respectively. Those in Group 1 (no wheezing) were a representative group of control children who were not included in any analysis in this paper. The 401 children in the study sample were surveyed again at age 10 yr, at which time 83 further children from the same birth cohort (then in grade 5 at school), who fulfilled criteria for a fifth category of wheezing status, severe asthma, were recruited (13). In this report, the term "childhood wheezing" refers to the category of wheezing of participants (excluding controls) when they entered the study (Table 1).

The cohort of 378 children described in Table 1 was reviewed at the approximate ages of 14, 21, 28, and 35 yr. The survey conducted at each of these reviews consisted of two parts: a questionnaire and a clinical examination. Asthma status was recorded at each review on an ordinal scale as (1) no recent asthma, (2) infrequent asthmatic attacks, (3) frequent asthmatic attacks, and (4) persistent asthma. No recent asthma was defined as no wheezing in the 3 yr prior to review, those subjects who had wheezed in the 3 yr prior to review but had not wheezed in the previous 3 mo were classified as having infrequent asthmatic attacks; the frequent asthmatic attack category covered subjects who had wheezed in the previous 3 mo but less than once a week. Participants who had wheezed at least once a week in the previous 3 mo were classified as having persistent asthma. There were slight variations in these definitions at age 14 yr (14).

Among the data recorded at entry into the study and at each review were details of the hay fever, eczema, and skin test reactivity included as atopic conditions in the study. Hay fever was defined from questionnaire responses as episodes of itching or irritation of nasal mucus membranes, with sneezing that was either seasonal or provoked by exposure to specific allergens. Eczema was defined from questionnaire responses as scaly, red, itchy lesions, usually in the flexural folds of the limbs, face, or trunk. For a positive response, eczema or hay fever had to be present within 12 mo of review. Skin test reactivity was defined as an allergic reaction to either house dust mite or rye grass. A scratch technique was used for subjects between the ages of 7 and 14 yr, and a skin prick test was used at ages 21, 28, and 35 yr. A positive response to a particular challenge was defined as a wheal with a diameter at least

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Correspondence and requests for reprints should be addressed to Dr. Rory Wolfe, Department of Epidemiology and Preventive Medicine, Monash Medical School, Alfred Hospital, Prahran, Victoria 3181, Australia.

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TABLE 1
DEFINITION OF CHILDHOOD WHEEZING CLASSIFICATIONS

Category	No. Recruited	Description
Mild wheezy bronchitis	75	Children with fewer than five episodes of wheezing always associated with bronchitis or apparent respiratory infection.
Wheezy bronchitis	107	Children with at least five episodes of wheezing with bronchitis associated with an apparent respiratory infection.
Asthma	113	Children with wheezing unassociated with respiratory infection.
Severe asthma	83	Onset of symptoms of asthma before 3 yr of age and persistence of symptoms at 10 yr of age.
Total	378	

Sampling at age 7 yr was stratified according to these groups except for the severe asthma group, which was selected at age 10 yr.

3 mm greater than the diameter of a wheal from a saline control. A further outcome, called "any atopy," was defined as existing if hay fever, eczema, or skin test reactivity was present.

Modeling of Asthma Progression

Asthma severity was conceptualized as a continuous variable that was smoothly distributed in the population but measured on a scale having four ordered categories. We further assumed that risk factors such as childhood atopy acted by shifting the distribution of asthma severity along the continuous scale on which it was measured (by an amount, b , for example, as in the left panels of Figure 1). Such an underlying effect or shift would manifest itself in changes in the observed distribution of proportions across the four ordered categories (right panels of Figure 1). We chose the logistic curve as the shape of the distribution, which meant that the underlying effect on a multiplicative scale, e^b , could be interpreted as the odds ratio (OR) for the population-averaged risk of being above (rather than below) any of the cutpoints when comparing subjects with the risk factor with those lacking it (15). This model is known as an ordinal logistic regression model (16).

Separate ordinal logistic regression models were fitted to predict the severity of asthma in later life (i.e., ages 14 to 35 yr) from each of the atopies of eczema, hay fever, and skin test reactivity in childhood. Each model included adjustment for sex, age, and childhood wheezing since these were all considered to be potentially important confounding factors. It was especially important to adjust for childhood wheezing category since this was the basis of the stratified sampling used for recruitment of the cohort. The possibility that effects changed with age was investigated by including age-by-atopy-effect interaction terms in the regression model. The statistical significance of these and other possible effects was assessed with Wald tests. In or-

der to allow for the correlation between repeated responses of individual subjects over time, the model was fitted by the method of generalized estimating equations (GEE), using an independence working correlation matrix (17).

Modeling of Atopy Indicators

To examine the course of atopy through the age range from 14 to 35 yr, we reversed the analysis in that we considered the atopy variables (eczema, hay fever, and skin test reactivity, in turn) as outcomes and modeled each separately in terms of childhood wheezing. Because all three atopy variables were binary (atopic positive/negative), logistic regression models were fitted to the relevant data. These models were also estimated with the GEE method (18) to allow for the fact that repeated observations were made over time within subjects, and in this case we used an unstructured working correlation matrix. The models included adjustments for sex, age, childhood atopy status, and childhood wheezing. The statistical significance of further candidate effects, including two-way interactions, was assessed with Wald tests.

When missing data were of concern, we used response-propensity stratification (19) in which the estimation of the model of interest was weighted for the propensity of observations to be missing. In this procedure, observations that are most representative of those that are missing are given relatively more weight in the analysis to compensate for missing data. Weights were calculated as follows: for each time-point, we defined an indicator of whether the response variable was observed or missing and fitted to this indicator a logistic regression model including age, sex, childhood atopy, and childhood wheezing as explanatory variables. The fitted probabilities from this model were grouped into quartiles, representing increasing propensity for a participant's response to be missing at the time of its intended recording. The weights were obtained as the inverse of the proportion of observed responses within these quartiles.

RESULTS

Sample

Of the 378 participants originally selected, 327 (87%) were interviewed by the investigators at least once between the ages of 14 and 35 yr. The distribution of childhood wheezing in these 327 participants was 20% in those with mild wheezy bronchitis, 27% in those with wheezy bronchitis, 31% in those with asthma, and 22% in those with severe asthma, which was almost identical to the distribution in the originally selected sample of 378 children (Table 1). Figure 2 shows the observed distribution of asthma severity at each review after childhood, and the transitions between categories of asthma severity at consecutive reviews. Overall, the cohort drifted from central to extreme categories of asthma severity. The transitions in Figure 2 indicate that this drift was a result of two processes: first, individuals at either extreme (i.e., having persistent or no recent asthma) had a greater than even chance of being in the same category at the time of subsequent follow-up; second, individuals who were observed to have infrequent or frequent asthmatic attacks had a less than even chance of being in the same category at the next review.

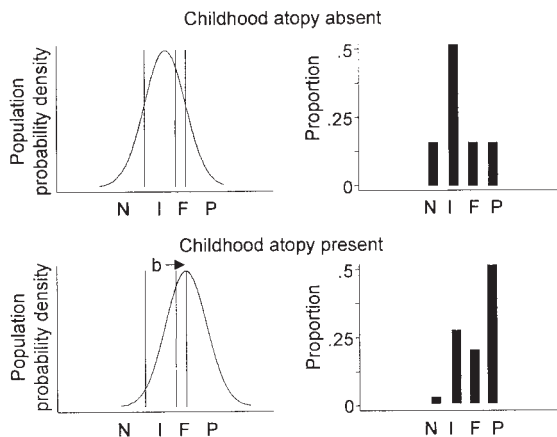


Figure 1. A model for changes in asthma severity on a continuous scale and caused by the presence or absence of a risk factor (e.g., childhood atopy) that underlies changes in observed proportions (N = no recent asthma, I = infrequent asthmatic attacks, F = frequent asthmatic attacks, P = persistent asthma). A shift of b units on the underlying continuous severity scale corresponds to an odds ratio (OR) of e^b for comparing proportions above and below each cutpoint of the ordinal scale.

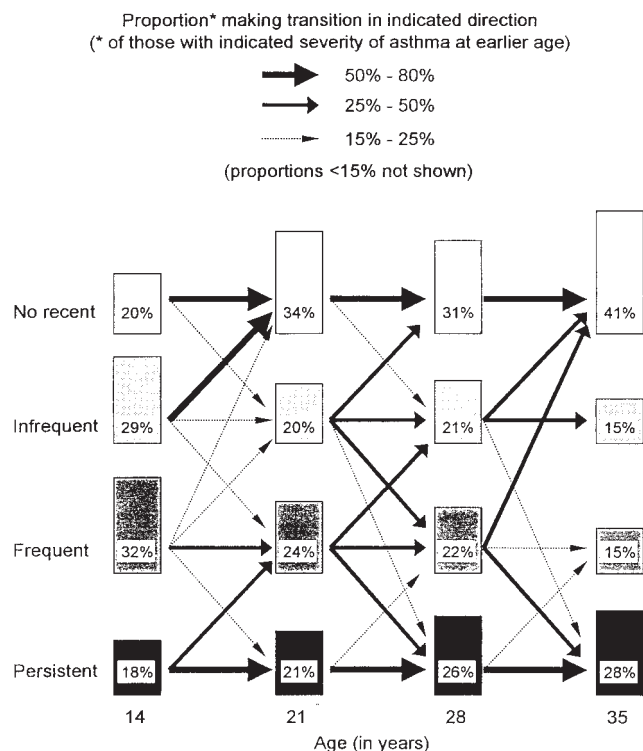


Figure 2. Distribution of asthma severity at each review, with relative frequency of transitions between each severity category.

There was a high prevalence of eczema in the study cohort during childhood (55%), but this decreased in later years (to approximately 20% for ages 21 to 35 yr). Conversely, the prevalence of hay fever was higher in adolescence and adulthood (approximately 60%) than in childhood (46%). The change in prevalence of skin test reactivity was difficult to ascertain, given the large proportions of missing data that were particularly evident at later reviews (5% missing in childhood, rising to approximately 30% missing at ages 28 and 35 yr). More than 65% of participants were positive for at least one atopic condition at each review.

Missing Data

The proportions of missing asthma responses for the 327 participants at ages 14, 21, 28, and 35 yr were 19%, 5%, 9%, and 3%, respectively. These proportions suggest that, unusually for a longitudinal study, attrition was not an important reason for lack of response. Ninety participants who had at least one missing asthma response were identified and compared with those participants (237) whose asthma response was observed at all ages. There were no significant differences between these two groups in any of the childhood variables included in our analyses. These considerations formed the basis for our assumption that data were missing completely at random (20) in the analysis of the course of asthma. This assumption was also made, on the same grounds, for the analysis of eczema and hay fever progression.

For skin test reactivity, an assumption of data missing completely at random manner did not seem reasonable. There were 17 participants (5%) with missing childhood skin tests, and of these, nine were males with severe asthma in childhood. There was attrition in later reviews (30% responses missing at 28 and 35 yr), which reflected: (1) an increased dependence on telephone-interview implementation of the questionnaire part

TABLE 2

SHIFTS IN THE DISTRIBUTION OF ASTHMA SEVERITY IN LATER LIFE ASSOCIATED WITH THE PRESENCE OF ATOPIC CONDITIONS IN CHILDHOOD EXPRESSED AS ODDS RATIOS WITH 95% CONFIDENCE INTERVALS FROM ORDINAL LOGISTIC REGRESSION MODELS*

Childhood Condition	n [†]	n [‡]	OR	95% CI
Eczema	319	1,158	1.66	(1.17, 2.36)
Hay fever	318	1,158	1.39	(1.00, 1.92)
Skin test reactivity	296	931	2.25	(1.49, 3.39)
Any atopy	319	1,166	1.66	(1.09, 2.52)

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

* Estimates from four separate models, each fitted with generalized estimating equations using independence working correlation. The linear combination of variables in each model had the form: Atopic condition in childhood + sex + childhood wheezing (categorical) + I(age > 14 yr) × childhood wheezing (linear) where × denotes interaction and I(·) is a 0/1 indicator of the specified condition.

[†] Number of participants included in the analysis.

[‡] Number of observations.

of the survey and (2) the choice of participants (e.g., women who were pregnant) to decline testing. These considerations led us to use response-propensity stratification in estimating the logistic regression model for the course of skin test reactivity.

Modeling of Asthma Progression

An ordinal logistic regression model was fitted to describe the difference in distribution of asthma severity in later life for subjects with and without eczema in childhood. Table 2 shows that after adjustment for other effects, the presence of eczema in childhood was associated with an upward shift of the distribution of asthma severity by an amount that translated to an OR of 1.66 (95% confidence interval [CI]: 1.17 to 2.36). The other ORs in Table 2 show similar shifts of the distribution of asthma severity that were associated with the presence of hay fever, skin test reactivity, and any atopy in childhood.

Of the effects for which adjustments were made in the models in Table 2, the association between childhood wheezing and the distribution of asthma severity in later life was the most important in terms of confounding. Not surprisingly, more severe categories of childhood wheezing were associated with larger upward shifts of the asthma severity distribution in later life. An interaction term of age (dichotomized as 14 yr/older than 14 yr) with childhood wheezing was included in the models to allow for a diminished association between childhood wheezing category and later asthma severity after 14 yr of age.

Modeling of Atopy Indicators

We next considered each atopic measure, in turn, as an outcome variable. We fitted separate logistic regression models to each measure in later life to determine the strength of its association with childhood wheezing. Preliminary analysis indicated that the effect of childhood wheezing on eczema and hay fever was linear (in the logit scale) across the four categories used at enrollment of the cohort. For the skin test reactivity outcome, there was evidence of a threshold effect at the severe asthma category. Because of this and other differences, the models for eczema and hay fever are presented in Table 3, and the model for skin test reactivity is presented in Table 4.

Severity of childhood wheezing was predictive of both eczema and hay fever in later life. For both outcomes, Table 3 gives the OR associated with an increase of one category of childhood wheezing severity. The most extreme comparison, between individuals with mild wheezy bronchitis and those with severe asthma in childhood, resulted in an increased odds

TABLE 3

ODDS RATIOS WITH 95% CONFIDENCE INTERVALS FROM LOGISTIC REGRESSION MODELS* OF ECZEMA AND HAY FEVER PREVALENCE ADJUSTED FOR THE PREDICTOR VARIABLES SHOWN AS WELL AS FOR AGE

	Atopic Condition			
	Eczema		Hay Fever	
No. Participants	319		318	
No. Observations	1,158		1,158	
Childhood wheezing [†]	1.40	(1.09, 1.80)	1.23	(1.02, 1.48)
Presence of atopic condition in childhood				
Effect at age 14 yr	22.4	(8.49, 59.3)	1.04	(27.6, 3.95)
Effect at age 21 yr	8.93	(4.07, 19.6)	3.33	(2.02, 5.48)
Effect at age 28 yr	3.60	(1.95, 6.67)	3.31	(1.98, 5.54)
Effect at age 35 yr	4.01	(2.17, 7.40)	2.77	(1.65, 4.63)
Sex (females relative to males)	2.16	(1.35, 3.48)	1.15	(0.79, 1.67)

* Fitted according to the generalized estimating equations (GEE) method with unstructured intrasubject correlation matrix.

[†] Odds ratio for an increase of one category in childhood wheezing.

of eczema in later life of $(1.40)^3 = 2.8$ (95% CI: 1.3 to 5.8) and of hay fever in later life of $(1.23)^3 = 1.9$ (95% CI: 1.1 to 3.2).

The models in Table 3 included adjustments for sex, age, and the relevant atopic status in childhood. An interaction effect of the latter two variables was included and described how the strong association of atopy in childhood and in later life became attenuated with age (although still significant at age 35 yr). For hay fever, this change in the relationship between current and childhood symptoms was marked between the ages of 14 and 21 yr whereas for eczema the weakening of the association appeared more gradual over time. Additionally, eczema was found to be significantly more prevalent in females than in males.

The analysis of skin test reactivity was affected by problems of data sparsity since at age 35 yr only 28 participants (6%) had a negative skin test. Only one of the participants with severe asthma in childhood had a negative skin test at age 35 yr. For this reason the analysis of skin test reactivity was restricted to the outcomes at ages 14, 21, and 28 yr.

In exploratory modeling we found evidence that the association between childhood wheezing and skin test reactivity in later life was different for participants whose childhood skin test was positive than for those for whom it was negative. This interaction effect was included in the model whose estimates are presented in Table 4, and complicates interpretation of these data.

The presence of severe asthma in childhood was associated with increased odds of skin test reactivity in later life of 4.68 (95% CI: 2.28 to 9.60) in those participants whose childhood skin test was negative. For participants whose childhood skin test was positive, there was no evidence of an association between severe asthma in childhood and skin test reactivity in later life (OR = 1.29; 95% CI: 0.57 to 2.96).

As expected, a positive childhood skin test was strongly associated with skin test reactivity at age 14 yr. This association was stronger for those participants who did not have severe asthma in childhood than for those who did. The association between childhood and contemporary skin test reactivity diminished with increasing age (and the rate was independent of childhood asthma status).

DISCUSSION

The extremely high prevalence of atopic conditions that we report reflects the close association of asthma and atopy found in previous phases of our longitudinal study (8–11). It is prob-

TABLE 4

ODDS RATIOS WITH 95% CONFIDENCE INTERVALS FROM A LOGISTIC REGRESSION MODEL* OF SKIN TEST REACTIVITY IN LATER LIFE[†]

Explanatory Variable	Odds Ratios (with 95% CI)	
Severe (versus not severe) asthma in childhood		
In the presence of positive childhood skin test	4.68	(2.28, 9.60)
In the presence of a positive childhood skin test [‡]	1.29	(0.57, 2.96)
Positive (versus negative) childhood skin test (effects for those without severe asthma in childhood [§])		
Effect at age 14 yr	15.2	(8.09, 28.5)
Effect at age 21 yr	11.1	(4.02, 30.8)
Effect at age 28 yr	6.52	(2.93, 14.5)
Sex (females relative to males)	0.81	(0.47, 1.37)

Definition of abbreviation: CI = confidence interval.

* Weighted for response-propensity stratification and fitted with generalized estimating equations with independence working correlation. The linear combination of variables in the model was: Sex + childhood skin test × (childhood asthma + age), where × denotes interaction. Estimates are presented as contrasts of interest (age main effects are not shown).

[†] Number of subjects = 295, number of observations = 715.

[‡] Interaction term = $1.29/4.68 = 0.28$ (95% CI: 0.10, 0.81), *p* value = 0.02.

[§] Odds ratios for effect of a positive childhood skin test in subjects with severe asthma in childhood were obtained by multiplying these values by the interaction term (§).

able that the majority of subjects in this study had asthma rather than wheezing associated with acute respiratory infection, which occurs mainly before the age of 3 yr (5, 21).

A number of studies have followed children with asthma through childhood and adolescence into adulthood, and several extensive reviews of the course of asthma have recently appeared (22–25). The conclusion from our analysis of the severity of asthma in adulthood is that for children with wheezing (similar to those in this sample), the presence of an atopic condition in childhood shifts the risk of asthma in later life upward toward more severe outcomes. This is consistent with other findings (26, 27).

Although our results for asthma outcome agree broadly with those in other studies, our data are richer and our analyses differ in two important ways. First, we analyzed asthma in terms of severity rather than simply of the presence or absence of symptoms. Also, our study of asthmatic children is unique in having used repeated follow-up observations in adulthood. Typically, other studies have measured the severity of asthma symptoms in adulthood at the approximate ages of 27 to 31 yr (4, 26, 27). Repeated follow-up sessions are important because of the large number of transitions in asthma severity that we observed between consecutive sessions at 7-yr intervals. Our data show that the long-term prognosis for asthmatic children is still not clearly established at 28 yr of age. Despite this instability of asthma severity in adulthood, we found that on average, the association between childhood atopy and adult asthma severity was independent of age. Therefore, although an individual is predicted to have a certain increased risk of asthma as an adult if they have a childhood history of atopy, one should still expect variation in the course of the individual's disease through adulthood.

Our models for asthma severity assumed that on the underlying continuous scale that we postulated, the action of explanatory variables or risk factors was to shift the distribution by a constant amount (Figure 1). This assumption seemed reasonable for all variables except age, for which there was strong evidence that the spread, as well as the location of the distribution changed. Individuals tended to move toward one or the other extreme of asthma severity with increasing age (Figure 2), whereas the model assumption implies a shift of these pro-

portions in one direction only. This phenomenon can be incorporated in a scaling ordinal logistic regression model (15), which we fitted to these data, with results for the effects of interest that were consistent with those reported here. The more complex model was not reported because the coefficients do not have a simple OR interpretation.

Few previous studies have examined whether severity of asthma in childhood predicts later development of atopic conditions such as eczema and hay fever. In our study cohort, the patterns of association between atopy as a later-life outcome and severity of childhood wheezing as a risk factor were similar for eczema and hay fever, but more complex for skin test reactivity. Of the former two atopic conditions, childhood wheezing was found to be predictive of atopy in adulthood. For skin test reactivity, this was true only for those participants whose childhood skin test was negative. In contrast, a previous study reported no association between skin test reactivity in adulthood and childhood wheezing (6).

By focusing on the association between observations made in childhood and the outcome of either asthma or atopic features in adulthood, the present study gave results that improve the clinician's ability to predict probable long-term outcomes for children with asthmatic symptoms. The study showed that in asthmatic children, the course of asthma in adulthood will not be clearly determined by 35 yr of age. We conclude that increasingly severe asthma, as well as the presence of hay fever, eczema, or skin test reactivity (to house dust mite or rye grass), all indicate an increased risk of more severe asthma in adulthood. The study also indicates that the more severe a child's asthma, the greater are the odds that the individual will experience eczema or hay fever in later life.

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