

Antecedent features of children in whom asthma develops during the second decade of life

Russell Dodge, MD, Benjamin Burrows, MD, Michael D. Lebowitz, PhD, and Martha G. Cline, MS Tucson, Ariz.

In this report we compare 36 subjects in whom asthma was first diagnosed between the ages of 10 and 20 with 297 control subjects. All subjects were studied at age 5 to 9. Among the subjects who acquired a new diagnosis of asthma (NDA), the diagnosis was usually preceded by lower respiratory tract symptoms (31 of the 36 subjects had respiratory symptoms or a diagnosis of rhinitis or chronic bronchitis before asthma developed). Among those tested, more of those with NDA had positive allergy skin test results (56.5%) before diagnosis than control subjects (29.6%; $p < 0.05$), and the subjects with NDA had higher levels of serum IgE than control subjects (mean log serum IgE = 2.27 in subjects with NDA, 1.76 in control subjects; $p < 0.05$). Pulmonary function tests revealed no significant differences in the groups before diagnosis. Using logistic regression, we determined that wheezing, cough, a diagnosis of chronic bronchitis, and a positive allergy skin test result were independent risk factors for asthma. When combinations of variables were used, subjects with wheezing and a positive allergy skin test result, cough and a positive test result, and also those with a prior diagnosis of chronic bronchitis alone were at highest risk of a subsequent diagnosis of asthma. (J ALLERGY CLIN IMMUNOL 1993;92:744-9.)

Key words: Asthma, risk, children, allergy

In a previous article we described the prevalence and incidence of asthma among subjects enrolled in the Tucson Study of Chronic Obstructive Lung Disease.¹ After initial and three follow-up evaluations, the highest rates of new asthma occurred among children under age 10. In addition, among the subjects under age 40 with new asthma, antecedent symptoms were infrequent among the very youngest subjects (those under 3 years of age) and among the subjects aged 13 to 39 at the time of enrollment. In contrast, all of subjects who were 3 to 9 years of age on entry had antecedent respiratory symptoms, which suggested an earlier onset of disease.

Now, after 11 surveys, covering nearly 20 years, we are again examining subjects in whom asthma

Abbreviations used

ANOVA:	Analysis of variance
FEV ₁ :	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
NDA:	New diagnosis of asthma
OR:	Odds ratio
RR:	Relative risk ratio

developed after enrollment. In this report we focus on the 36 subjects who first reported asthma between the ages of 10 and 20 and were studied at ages 5 to 9. We compare their features at ages 5 to 9 with those of 297 other subjects of the same age span in whom asthma did not develop between the ages of 10 and 20, even though they were at equal risk.

METHODS

The design of the overall population study from which these data are derived has been reported previously.² It represents a stratified random cluster sample of white, non-Mexican-American households residing in Tucson from 1972 to 1973 when the study was first undertaken. New members of these households have continued to be enrolled over the years. Most of these

From the Respiratory Sciences Center, University of Arizona College of Medicine, Tucson.

Supported by a National Heart, Lung, and Blood Institute Specialized Center of Research grant (HL-14136).

Received for publication Feb. 9, 1993; revised Apr. 16, 1993; accepted for publication Apr. 22, 1993.

Reprint requests: B. Burrows, MD, Respiratory Sciences Center, Arizona Health Sciences Center, Tucson, AZ 85724.

Copyright © 1993 by Mosby-Year Book, Inc.
0091-6749/93 \$1.00 + .10 1/148113

are children born into the households since the study was undertaken, providing a much larger database for young children than was available at the time of the initial survey. With this increase in the number of subjects, the population has remained representative of the target population.³ Our complete initial questionnaire was filled out by the parents of all newly enrolled children. Follow-up pediatric questionnaires were completed by parents until the child reached age 15. After this, the adult form of the questionnaire was completed by the subjects themselves.

To be included in the present report, subjects must have had a questionnaire completed when they were 5 to 9 years of age (the baseline evaluation), completed at least one follow-up questionnaire between the ages of 10 and 20, and either reported a diagnosis of asthma or been at risk to do so for at least 4 years of the follow-up period. If more than one workup was completed while a subject was 5 to 9 years old, the earliest one was used as baseline. Children who were diagnosed as having asthma before age 10 were excluded from the study.

Three hundred and thirty-three children fulfilled the above criteria. Thirty-six of them had physician-confirmed new diagnosis of asthma (NDA) when they were 10 to 20 years of age. The diagnosis was based on a positive response to the question "Has this child seen a doctor for asthma?" or "Has this child been seen by a doctor for asthma in the past year?" on at least one of the follow-up questionnaires. A diagnosis of chronic bronchitis was based on similar questions, whereas a diagnosis of "allergic rhinitis" did not require physician confirmation. We also derived the rates of respiratory symptoms from questionnaire responses. For example, we considered a subject to have a cough if there was a "yes" response to "Does this child usually cough in bad weather?" or "Does this child ever have a cough when he or she doesn't have a cold?" Among all subjects the average age ($\pm$ SD) at the baseline evaluation was 6.72 ± 1.35 years, and the average age at the time of the last questionnaire before age 20 was 17.18 ± 1.73 years, yielding an average follow-up period of 10.46 years after the baseline evaluation. There were no significant differences in the age when the baseline questionnaire was completed, the age when the last questionnaire was completed, or the length of follow-up after baseline between those with and those without new diagnoses of asthma. Among those reporting NDA, the mean age of reporting the diagnosis was 14.00 years, an average of 7.23 years after baseline data were obtained. No new asthma diagnoses were reported at ages 18 or 19.

The methods we used for allergy skin testing, measurement of serum IgE levels, and spirometric testing are given in previous reports.⁴⁻⁶ The results of these tests on the subjects of this report are incomplete because a sizable proportion of the households moved away from Arizona during follow-up, making it impossible to perform a full range of studies on many

children. In addition, allergy skin tests were performed only on subjects who were at least 3 years old when they were seen in our research clinic for their evaluations either during the first, second, sixth, seventh, or eleventh surveys among the 11 total surveys that were completed before these analyses. The last of these surveys was completed in December of 1989. Some of the subjects were enrolled after the second survey or had moved away from Arizona before they were skin tested, so baseline allergy skin test results were available for only 222 of the 333 subjects.

The problem was even greater for serum IgE measurements because these blood tests were carried out only during the first, sixth, seventh, and eleventh surveys on subjects over the age of 6 at the time they were seen in our clinic. Baseline serum IgE levels were obtained from only 56 of the subjects in the present report.

In contrast to allergy skin test results and serum IgE levels, pulmonary function test results were obtained from all subjects aged 6 or older in every survey except the fourth. They were also obtained on "outreach" visits during which our field staff went to areas where there were clusters of out-migrant households. As a result, technically satisfactory spirometric data at ages 6 through 9 are available for 233 children: 21 of the subjects with NDA and 212 of the other subjects before age 10. Spirometric tests were performed at the time of the reported diagnosis in 16 members of the NDA group and after age 10 in 251 of the control subjects. Except for the forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) ratio, which is expressed as a percent, all other spirometric variables are reported as percent of predicted value with the use of prediction equations previously reported for this population sample.⁶ All aspects of this research have been reviewed and approved by the University of Arizona Human Subjects Committee.

The 297 subjects at risk in whom NDA did not develop are the control group in subsequent analyses. Their data are compared with data from children in the NDA group. Statistical methods include chi square analysis, relative risk ratios (RRs), odds ratios (ORs), analysis of variance (ANOVA), and multiple logistic regressions.^{7, 8} ANOVA for parametric variables was performed with SPSS software (SPSS, Inc., Chicago, Ill.). All reported *p* values are two-tailed; a *p* value of less than 0.05 was considered significant.

RESULTS

Table I shows a comparison of baseline questionnaire data in patients with NDA and control subjects. In this age group, new asthma diagnoses were equally common in boys and girls. Several respiratory symptoms and a prior diagnosis of chronic bronchitis were significantly more frequent in subjects in whom asthma was later diagnosed than in control subjects. As might be expected, the symptom most predictive of a later

TABLE I. Baseline features of 36 subjects with NDA and 297 control subjects

Questionnaire responses	Subjects with features (%)		RR of NDA for subjects with features compared with those without		
	NDA	Control	RR	95% CI	p Value
Males	50.0	50.8	0.98	(0.70-1.39)	NS
Diagnosis of allergic rhinitis	44.4	31.3	1.42	(0.95-2.12)	NS
Any wheeze	44.4	21.3	2.06	(1.35-3.15)	<0.05
Wheezing apart from colds	19.4	4.4	4.44	(1.90-10.41)	<0.05
Attacks of shortness of breath with wheeze	25.0	4.1	6.17	(2.79-13.62)	<0.001
Cough	38.9	13.9	2.82	(1.71-4.64)	<0.005
Recurrent chest illnesses	38.9	20.3	1.93	(1.26-3.07)	<0.05
Diagnosis of chronic bronchitis	30.6	7.1	4.32	(2.27-8.21)	<0.001
Any of the above symptoms or diagnoses	86.1	48.3	1.78	(1.49-2.13)	<0.001

CI, Confidence interval; NS, not significant.

TABLE II. Mean of pulmonary function results $\pm$ SD in NDA and control subjects

A. Results obtained during baseline period (ages 6-9)			
	NDA	Controls	p Value*
Number of subjects	21	212	
FEV ₁ /FVC (%)	89.35 $\pm$ 9.03	89.79 $\pm$ 8.39	NS
Predicted FEV ₁ (%)	99.64 $\pm$ 10.75	101.08 $\pm$ 12.95	NS
Predicted Vmax 50% (%)	97.14 $\pm$ 29.64	100.38 $\pm$ 27.66	NS
Predicted Vmax 75% (%)	96.21 $\pm$ 38.46	100.13 $\pm$ 39.88	NS
Predicted FEF _{25-75%} (%)	97.75 $\pm$ 29.31	100.16 $\pm$ 29.74	NS
B. Results obtained at time of diagnosis for NDA subjects and at last evaluation for controls (ages 10-19)			
	NDA	Controls	p Value
Number of subjects	16	251	
FEV ₁ /FVC (%)	81.07 $\pm$ 7.39	85.78 $\pm$ 6.95	<0.01
Predicted FEV ₁ (%)	101.31 $\pm$ 14.74	104.42 $\pm$ 11.76	NS
Predicted Vmax 50% (%)	87.93 $\pm$ 26.12	99.25 $\pm$ 22.33	<0.05
Predicted Vmax 75% (%)	81.14 $\pm$ 25.69	94.79 $\pm$ 27.51	NS
Predicted FEF _{25-75%} (%)	86.08 $\pm$ 23.08	98.51 $\pm$ 21.46	<0.05

NS, Not significant; Vmax 50%, maximum expiratory flow at 50% of the FVC; FEF_{25-75%}, forced expiratory flow between 25% and 75% of the FVC.

*Determined by ANOVA.

asthma diagnosis was attacks of shortness of breath with wheeze (RR = 6.17).

The results of allergy skin testing and serum IgE level determinations in our subjects revealed that among those tested before diagnosis, 56.5% of the subjects with NDA (13 of 23) and 29.6% of the control subjects (59 of 199) had one or more positive allergy skin test results (chi square = 5.6; $p < 0.05$). In addition, among the 56 subjects who underwent serum IgE testing, the mean serum log IgE level $\pm$ SD was 2.27 ± 0.47 (geometric

mean = 186 IU/ml) in the nine subjects with NDA and 1.76 ± 0.65 (geometric mean = 58 IU/ml) in the 47 control subjects ($p < 0.05$ by ANOVA).

In Table IIA and B, we have displayed a summary of the pulmonary function tests performed by our subjects. As shown in Table IIA, at baseline evaluation spirometric variables were consistently lower in those in whom NDA developed later, but the differences from control subjects were not statistically significant. At the time of

TABLE III. Logistic regression with NDA as dependent variable and questionnaire responses as independent variables

Risk factor	Coefficient	SE	OR	95% CI
Attacks of shortness of breath with wheeze	1.48	0.54	4.4	1.5-12.6
Cough	1.28	0.47	3.6	1.5-9.1
Diagnosis of chronic bronchitis	1.06	0.41	2.9	1.3-6.5

SE, Standard error; CI, confidence interval.

reporting NDA, as seen in Table IIB, the differences between subjects with NDA and control subjects were more marked and reached statistical significance for several variables. The lack of statistical significance for the difference in FEV₁ and the maximum expiratory flow at 75% of the FVC was a result of the small number of subjects with NDA who had spirometry results that coincided with their reporting of NDA, as well as the variability of the test results. (For example, the power to detect as real the difference in the maximum expiratory flow at 75% of the FVC seen between the subjects with NDA and control subjects was less than 0.10.)

In our final analyses we used logistic regression to determine how each of the antecedent features that we have examined independently affected the risk of asthma in our subjects. Only variables that were significantly related to NDA ($p < 0.05$) were entered into the logistic equations, and the variables were entered in stepwise fashion, according to the strength of their association with NDA. As shown in Table III, attacks of shortness of breath with wheeze, cough, and a diagnosis of chronic bronchitis were all independent predictors of NDA, as indicated by ORs and their confidence intervals.

In Table IV we have shown the results of logistic regression analyses performed on the 222 subjects who had allergy skin tests. Among this subgroup of the population, any wheeze or cough, a diagnosis of bronchitis, and a positive allergy skin test result were independent risk factors for NDA.

Lastly, we have demonstrated in Table V the risk of NDA in subjects with combinations of antecedent features. Subjects with a positive allergy skin test result and any wheeze, a positive test result and cough, and subjects who had only a diagnosis of chronic bronchitis had the highest

TABLE IV. Logistic regression with NDA as dependent variable and questionnaire responses and allergy skin test status (among the 222 subjects tested) as independent variables

Risk factor	Coefficient	SE	OR	95% CI
Any wheeze	1.13	0.52	3.09	1.12-8.6
Cough	1.42	0.57	4.13	1.4-12.7
Diagnosis of chronic bronchitis	1.89	0.60	6.6	2.0-21.5
Positive allergy skin test	1.41	0.52	4.09	1.5-11.4

SE, Standard error; CI, confidence interval.

TABLE V. Logistic regression with NDA as dependent variable and combinations of variables as independent variables

Risk factor	Coefficient	SE	OR	95% CI
Positive allergy skin test plus any wheeze	1.83	0.67	6.26	1.7-23.1
Positive allergy skin test plus cough	2.25	0.87	9.50	1.7-52.5
Diagnosis of chronic bronchitis	2.28	0.59	9.73	3.1-31.2

SE, Standard error; CI, confidence interval.

risk of NDA after combinations of any two features were investigated, as expressed by ORs. Combinations of three or more features did not produce higher risks for subjects in these comparisons.

DISCUSSION

In this report we have described 36 new cases of asthma that occurred among subjects ages 10 through 19 of the Tucson Epidemiologic Study. The disease was diagnosed an average of 7.23 years after baseline studies and was usually preceded by lower respiratory tract symptoms. As expected, we found similarities between this group of 36 NDA subjects and the group of subjects with new asthma (ages 10 to 19) of our previous report on the prevalence and incidence of asthma.¹ The incidence of disease was equal in boys and girls in both studies, and we found no new cases of asthma among subjects aged 18 or 19 in the current report or among subjects aged 15 to 19 in the previous study. Because other investigators have noted that wheezing and other symp-

toms disappear in a substantial portion of their subjects during the teen years,⁹ we believe that the late teen years are when asthma is most likely to remit and is least likely to develop *de novo*.

From our data, it appears that lower respiratory symptoms between the ages of 5 and 9 are moderately sensitive and specific in predicting a subsequent diagnosis of asthma. For example, among the 36 subjects with NDA, 24 (a sensitivity of 66.7%) reported attacks of shortness of breath with wheeze, cough, or a diagnosis of chronic bronchitis before asthma developed. Conversely, among the 297 subjects in whom NDA did not develop, 238 (a specificity of 80.7%) did not have at least one of these three antecedent features. The positive predictive value of one or more of these features in our subjects was 28.9%, and the negative predictive value of the absence of all three symptoms was 95.2%.

In addition, the development of new wheeze, persistence of wheeze, and remission of wheeze were common in our population, as a review of the first and last available questionnaires of our control subjects demonstrated. In this group of 297 subjects, only 62 children reported any wheezing between ages 5 and 9, and 21 of these children had the symptom at their last evaluation between ages 10 and 20. Forty-one of the 62 children with symptoms initially had no wheezing at the time of their last evaluation, whereas 37 of the 235 children (16%) who were originally free of wheezing reported the symptom in their last evaluation.

For this report we have focused on the status of our subjects during the years just before the diagnosis of asthma in the hope of discovering risk factors for the disease. As mentioned, lower respiratory tract complaints were frequent in our subjects, and we believe that infection, exposure to respiratory irritants, and undiagnosed asthma explain most of these symptoms.^{10, 11} Almost 40% of the subjects with NDA, for example, reported recurrent chest illnesses before diagnosis (Table I). And we suspect that attacks of shortness of breath with wheeze, which is the respiratory symptom most predictive of later asthma, probably represent cases of undiagnosed asthma rather than a risk factor for the disease.

In addition to attacks of shortness of breath with wheeze, both cough and a diagnosis of chronic bronchitis were independently predictive of NDA. These results demonstrate that among our subjects, cough and chronic bronchitis are different entities. As we reported previously, even

chronic cough, defined as a cough present for at least 3 months of the year, is not particularly associated with a diagnosis of chronic bronchitis in young Tucson subjects.¹¹ Wheezing or a history of recurrent chest illnesses is much more common than chronic cough among children with a diagnosis of chronic bronchitis.¹¹ The reasons for the frequency of symptoms other than cough among subjects with a diagnosis of chronic bronchitis is unclear, but we speculate that if clinicians believe that infection is playing a role in a child's illness, they may diagnose chronic bronchitis without regard to any formal definition of the term.¹⁰ Also, to avoid frightening parents, clinicians may be reluctant to use the term "asthma" to describe children with mild symptoms.

The results of allergy skin testing and serum IgE measurements provided evidence that a disposition to allergy heightened the risk of asthma. For example, before diagnosis, subjects with NDA were significantly more likely to have a positive allergy skin test result than were the control subjects. And among the 56 subjects tested, mean serum IgE levels were higher in the NDA group than in the control group. Furthermore, we found that a positive allergy skin test result was an independent risk factor for NDA, as demonstrated by logistic regression. And finally, subjects with both a positive allergy skin test result and either wheezing or cough at the time of their baseline evaluations were among those in our study with the highest risk of NDA, as shown in Table V.

In previous reports, we have emphasized the relationship of positive allergy skin test results (and high serum IgE levels) to asthma in the Tucson subjects.^{12, 13} In cross-sectional analyses, we have found that nearly 80% of subjects with asthma between the ages of 6 and 34 have a positive allergy skin test result and that the prevalence of asthma was closely related to the serum IgE level standardized for age and sex. In a report on subjects over the age of 60, we found more skin test reactivity and higher serum IgE levels among the subjects in whom new asthma developed than among control subjects.¹⁴ Although these analyses suggest that the serum IgE measurement correlates closely with the prevalence and incidence of asthma among adults, the present data show that the results of skin testing do provide an estimate of the risk of later asthma in children, especially in those with respiratory symptoms.

Although not shown in the above analyses, we

have also found that among the subjects with NDA after age 10, very early symptoms were not predictive of a diagnosis; that is, we saw no significant differences in the rates of respiratory symptoms at ages 1 to 2 when we compared the 22 subjects with NDA and 170 control subjects for whom data were available. At ages 3 to 4, more subjects with NDA than control subjects reported only one symptom, attacks of shortness of breath with wheeze, significantly more frequently (14.3% vs 3.8%; $p < 0.01$). That symptom probably reflected asthma, present for many years before the diagnosis was made. Because we did not include subjects in whom asthma was diagnosed before the age of 10, we cannot state that very early symptoms are not predictive of future asthma in those children, and we are currently examining them.

This study demonstrates that among the Tucson subjects the development of asthma is not an abrupt event. Rather, it appears that asthma frequently begins with mild symptoms, which worsen. At what point a clinician invokes the term asthma to describe a particular patient cannot be derived from our methods. Also, unlike other diseases that occur gradually, the onset of asthma cannot be based on permanent organ dysfunction. As shown in Table IIA and B, pulmonary function testing does not discriminate well between healthy subjects and those with asthma, especially before diagnosis. Both the wide variation in normal values for the tests and the even wider variation in results that are obtained in subjects with asthma preclude use of the tests, at least on a one-time basis, to predict later asthma or to separate subjects with early disease from others in a population study. Thus as with our report on the diagnosis of asthma in older persons,¹⁴ our study is more a description of the natural history of the disease than an estimation of the risk of developing it.

We conclude that physicians should strongly consider the diagnosis of asthma in young children with wheezing or cough in the absence of acute infection. As our results show, positive allergy skin test results and high serum IgE levels can support the impression of asthma, and we encourage physicians to do such testing in chil-

dren with persistent respiratory symptoms. An early diagnosis of asthma improves the prognosis of adults with occupational asthma,¹⁵ and we believe that it may also benefit children.

We thank the participants and their parents for their continuing commitment to the Tucson Study and Bobbe Boyer, RN, for supervising the data collection.

REFERENCES

1. Dodge RR, Burrows B. The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. *Am Rev Resp Dis* 1980;122:567-75.
2. Lebowitz MD, Knudson RJ, Burrows B. Tucson epidemiologic study of obstructive lung diseases. I. Methodology and prevalence of diseases. *Am J Epidemiol* 1975;102:137-52.
3. Lebowitz MD. Trends from cohort studies: the trends in airways obstructive disease morbidity in the Tucson epidemiologic study. *Am Rev Resp Dis* 1989;140:S35-S41.
4. Barbee RA, Lebowitz MD, Thompson HC, Burrows B. Immediate skin-test reactivity in a general population sample. *Ann Intern Med* 1976;84:129-33.
5. Barbee RA, Halonen M, Lebowitz MD, Burrows B. Distribution of IgE in a community population sample: correlations with age, sex, and allergen skin test reactivity. *J ALLERGY CLIN IMMUNOL* 1981;68:106-11.
6. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal expiratory flow-volume curve with growth and aging. *Am Rev Resp Dis* 1983;127:725-34.
7. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley & Sons, 1981:165-74.
8. Rothman KJ. Modern epidemiology. 1st ed. Boston: Little Brown, 1986:153-236.
9. Martin AJ, McLennan LA, Landau LI, Phelan PD. The natural history of childhood asthma to adult life. *Br Med J* 1980;280:1397-1400.
10. Morgan WJ, Taussig LM. The chronic bronchitis complex in children. *Ped Clin North Am* 1984;31:851-64.
11. Burrows B, Lebowitz MD. Characteristics of chronic bronchitis in a warm, dry region. *Am Rev Resp Dis* 1975;112:365-70.
12. Burrows B, Lebowitz MD, Barbee RA. Respiratory disorders and allergy skin-test reaction. *Ann Intern Med* 1976;84:134-9.
13. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE and skin-test reactivity to allergens. *N Engl J Med* 1989;320:271-7.
14. Burrows B, Lebowitz MD, Barbee RA, Cline MG. Findings before diagnoses of asthma among the elderly in a longitudinal study of a general population sample. *J ALLERGY CLIN IMMUNOL* 1991;88:870-7.
15. Chan-Yeung M, MacLean L, Paggiaro P. A follow-up of 232 patients with occupational asthma due to western red cedar. *J ALLERGY CLIN IMMUNOL* 1987;79:792-6.