# A Clinical Index to Define Risk of Asthma in Young Children with Recurrent Wheezing

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**Because most cases of asthma begin during the first years of life, identification of young children at high risk of developing the disease is an important public health priority. We used data from the Tucson Children's Respiratory Study to develop two indices for the prediction of asthma. A stringent index included frequent wheezing during the first 3 yr of life and either one major risk factor (parental history of asthma or eczema) or two of three minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis). A loose index required any wheezing during the first 3 yr of life plus the same combination of risk factors described previously. Children with a positive loose index were 2.6 to 5.5 times more likely to have active asthma between ages 6 and 13 than children with a negative loose index. Risk of having subsequent asthma increased to 4.3 to 9.8 times when a stringent index was used. We found that 59% of children with a positive loose index and 76% of those with a positive stringent index had active asthma in at least one survey during the school years. Over 95% of children with a negative stringent index never had active asthma between ages 6 and 13. We conclude that the subsequent development of asthma can be predicted with reasonable accuracy using simple, clinically based parameters.**

Recent longitudinal studies have suggested that, in a large proportion of all cases of asthma, asthmalike symptoms begin during the first years of life (1). Moreover, a long-term follow-up of children with different degrees of asthma severity enrolled in Melbourne, Australia, at the ages of 7 to 10 yr suggests that severity of asthma changes little with time (2). As a consequence, it is the children with the most severe asthma during the school years who become the most severe asthmatics during adult life and up to the age of 35. Children with mild infrequent asthma, on the other hand, have either mild symptoms in early adult life or their symptoms may remit indefinitely (2). Our own studies have also suggested that children who had wheezing lower respiratory tract illnesses during the first 3 yr of life and whose wheezing episodes persisted up to the age of 6 have significantly lower levels of lung function at age 6 compared with children whose wheezing symptoms started after the age of 3 (3). Taken as a whole, these data indicate that early initiation of asthma symptoms is associated with more significant functional deterioration and more persistence of symptoms into adult life (4–6).

The aforementioned considerations have suggested that identification of symptomatic infants and young children who will go on to develop asthma may be very important for the development of a strategy for early intervention aimed at changing the natural course of the disease (4). Unfortunately, wheezy infants who will go on to develop asthma coexist with a larger group of their peers who also wheeze in early life but whose symptoms are transient and usually subside during the preschool or early school years (7). Distinguishing these two asthmalike phenotypes during infancy and early childhood simply on the basis of their clinical presentation is problematic. There are still no reliable genetic markers available and the use of any single biochemical marker is still controversial (1). It is possible, however, that by use of both clinical data and simple, easily obtainable laboratory information, a combination of these parameters may be used to identify children at high risk of developing persistent symptoms in a clinical setting.

In the present study, we used the longitudinal data available in the Tucson Children's Respiratory Study to describe predictive indices for asthma during the school years among children having wheezing episodes during the first 3 yr of life.

## METHODS

The Tucson Children's Respiratory Study is a large, longitudinal assessment of respiratory illnesses in children (8). Eligible participants were healthy infants born to parents who planned to use the pediatricians of a large health maintenance organization in Tucson. A total of 1,246 newborns and their families (78% of those eligible) were enrolled at birth between 1980 and 1984. Detailed information about enrollment has been published elsewhere (8).

At the time of enrollment, the parents completed a questionnaire about parental (either father or mother) history of a physician diagnosis of asthma ("parental MD asthma") and prenatal maternal smoking status. Parents of enrolled children were asked to complete questionnaires regarding their child's history of respiratory conditions and health at different ages during childhood: Yr 2 survey (mean [± SD] age, 1.6 ± 0.4 yr), Yr 3 survey (age, 2.9 ± 0.5 yr), Yr 6 survey (age, 6.3 ± 0.9 yr), Yr 8 survey (age, 8.6 ± 0.7 yr), Yr 11 survey (age, 10.9 ± 0.6 yr), Yr 13 survey (age, 13.5 ± 0.6 yr).

### Asthma and Wheezing Data

At the Yr 2 and Yr 3 surveys, parents were asked whether the child's chest had ever sounded wheezy or whistling and how frequently the child had wheezed (scale: 1 to 5, from "very rarely" to "on most days"). We considered that a child was an "early wheezer" if his or her chest had ever sounded wheezy and an "early frequent wheezer" if the parents reported a value $\geq 3$ in the scale. Parents were also asked if wheezing occurred only with colds or also apart from colds. We classified a child as having "wheezing apart from colds" if this symptom was reported in at least one of these two surveys.

At the Yr 6, Yr 8, Yr 11, and Yr 13 surveys parents were asked if the child had wheezed during the previous year and about the frequency of wheezing episodes. A child was considered to have developed "active asthma" if he or she had asthma diagnosed by a physician with at least one episode of asthma during the previous year or had more than three episodes of wheezing during the previous year regardless of a diagnosis of asthma (9).

### Markers of Atopy

As part of the Yr 2 and Yr 3 surveys, parents were asked whether the child had hay fever or any other condition that made his or her nose stuffy, itchy, or runny apart from colds during the past year and whether a doctor had said that these symptoms were due to allergies. We classified children as having "MD allergic rhinitis" if this condition was present in at least one of these two surveys (10). In addition, children were considered to have "MD eczema" if a physician had di-

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**TABLE 1**

**A CLINICAL INDEX TO DEFINE ASTHMA RISK***

| Major Criteria | Minor Criteria |
|---|---|
| 1. Parental MD asthma† | 1. MD allergic rhinitis§ |
| 2. MD eczema‡ | 2. Wheezing apart from colds |
| | 3. Eosinophilia (⩾ 4%) |

* Loose index for the prediction of asthma: Early wheezer plus at least one of two major criteria or two of three minor criteria. Stringent index for the predication of asthma: Early frequent wheezer plus at least one of two major criteria or two of three minor criteria.

† History of a physician diagnosis of asthma.

‡ Physician diagnosis of atopic dermatitis as reported in questionnaires at ages 2 or 3.

§ Physician diagnosis of allergic rhinitis as reported in questionnaires at ages 2 or 3.

agnosed this condition during the previous year as reported either in the Yr 2 or Yr 3 surveys.

Blood specimens were obtained at (mean ± SD) age 10.9 ± 0.6 mo, and circulating eosinophils (as percentage of total white blood cells) were calculated. "Eosinophilia" was considered to be present if eosinophils were ⩾ 4% of the total white blood cells.

### Asthma Predictive Indices

To classify children as potentially at risk for asthma at school age, we developed two indices. For the "stringent index for the prediction of asthma", children had to be defined as an early frequent wheezer during the first 3 yr of life and meet at least one of two major criteria (parental MD asthma or MD eczema in the child) or two of three minor criteria (MD allergic rhinitis, wheezing apart from colds, or eosinophilia). For the "loose index for the prediction of asthma" the child had to be defined as an early wheezer during the first 3 yr of life and meet one of two major criteria or two of three minor criteria (as previously described) (Table 1). The variables used to develop the indices were chosen because, in univariate analysis, there were significant predictors of the subsequent development of asthma. This particular combination of major and minor criteria was chosen because it provided the highest positive predictive value and the highest specificity with respect to subsequent asthma.

### Statistical Analysis

We assessed sensitivity, specificity, positive predictive value, and negative predictive value for both asthma predictive indices with respect to active asthma at the Yr 6, Yr 8, Yr 11, and Yr 13 surveys. Sensitivity is defined as the probability that schoolchildren with active asthma had a positive asthma predictive index. Specificity is defined as the probability that schoolchildren without active asthma during the school years had a negative asthma predictive index. Positive predictive value is defined as the probability that an infant with a positive asthma predictive index had active asthma during the school years. Negative predictive value is defined as the probability that an infant with a negative asthma predictive index was not classified as having active asthma during the school years.

The chi-square test was used to compare proportions. The 95% confidence intervals (CI) for sensitivity, specificity, positive predictive value, and negative predictive value, were calculated using the binomial distribution (11). Statistical significance was defined by a two-sided alpha level of 0.05. This study was approved by the Human Subjects Committee at the University of Arizona, and informed consent was obtained from parents.

**TABLE 2**

**PREVALENCE OF POSITIVE LOOSE AND STRINGENT INDEX FOR THE PREDICTION OF ASTHMA AMONG CHILDREN INCLUDED OR NOT INCLUDED IN THE STUDY AT DIFFERENT SURVEYS**

| | Positive Loose Index for the Prediction of Asthma | | | Positive Stringent Index for the Prediction of Asthma | | |
|---|---|---|---|---|---|---|
| Survey | Included % (n) | Not Included % (n) | p Value | Included % (n) | Not Included % (n) | p Value |
| At Yr 6 | 23.4 (928) | 27.6 (58) | 0.46 | 6.3 (994) | 6.9 (58) | 0.84 |
| At Yr 8 | 23.1 (780) | 25.7 (206) | 0.43 | 4.9 (790) | 11.3 (212) | 0.0007 |
| At Yr 11 | 23.6 (867) | 23.5 (119) | 0.98 | 5.7 (881) | 10.7 (121) | 0.03 |
| At Yr 13 | 22.0 (655) | 26.9 (331) | 0.09 | 5.0 (664) | 8.9 (338) | 0.02 |

**TABLE 3**

**FREQUENCY OF DIFFERENT TRAITS USED TO DEVELOP THE ASTHMA PREDICTIVE INDICES BEFORE AGE 3, BY SEX**

| Traits | Males % (n) | Females % (n) | Total % (n) |
|---|---|---|---|
| Early wheezer | 57.0* (526) | 50.6 (551) | 53.8 (1,077) |
| Early frequent wheezer | 14.3† (526) | 7.3 (551) | 10.7 (1,077) |
| Major criteria | | | |
| Parental MD asthma | 23.1 (541) | 22.2 (553) | 22.7 (1,094) |
| MD eczema | 13.2 (523) | 10.8 (548) | 12.0 (1,071) |
| Minor criteria | | | |
| MD allergic rhinitis | 18.3 (520) | 15.6 (546) | 16.9 (1,066) |
| Wheezing apart from colds | 17.9‡ (526) | 12.1 (553) | 14.9 (1,079) |
| Eosinophilia ⩾ 4% | 9.7 (454) | 10.9 (458) | 10.3 (912) |

* $p = 0.04$, † $p = 0.0002$, ‡ $p = 0.008$ in comparison to females.

## RESULTS

Of the 1,246 children who were enrolled, 79.1% and 80.4% had complete information for a combination of major/minor criteria that allowed us to determine their loose or stringent index for the prediction of asthma, respectively. Among children with a positive loose index for the prediction of asthma, there were no differences between the percentages included in or excluded from the analysis at each survey (Table 2). In contrast, a higher proportion of children with a positive stringent index for the prediction of asthma was not included at the Yr 8, Yr 10, and Yr 13 surveys when compared with those with a negative stringent index for the prediction of asthma (Table 2).

The frequency of the different parameters used to develop the asthma predictive indices is shown in Table 3. Males were more likely than females to be early wheezers and early frequent wheezers and also were more likely to have wheezing apart from colds (Table 3).

A total of 986 children had complete information for the variables used to determine loose index for the prediction of asthma. Of these 986 children, 233 (23.6%) had a positive index, with more males than females being positive (26.5% versus 20.8%, respectively, $p = 0.036$, odds ratio [OR] = 1.4, 95% CI = 1.0 to 1.8). Of the 1002 children who had complete information for the stringent index for the prediction of asthma, 63 (6.3%) had a positive index, with more males than females being positive (8.7% versus 4.0%, respectively, $p = 0.002$, OR = 2.3, 95% CI = 1.3 to 3.9).

**TABLE 4**

**PREVALENCE (%) OF ACTIVE ASTHMA AT DIFFERENT SURVEYS AND ACTIVE ASTHMA IN AT LEAST ONE SURVEY, BY SEX**

| Active Asthma | Males % (n) | Females % (n) | OR (95% CI) | p Value |
|---|---|---|---|---|
| At yr 6 | 13.8 (492) | 8.4 (522) | 1.3 (1.1–1.7) | 0.006 |
| At yr 8 | 17.5 (401) | 10.1 (424) | 1.4 (1.1–1.8) | 0.002 |
| At yr 11 | 20.6 (461) | 11.3 (486) | 1.5 (1.2–1.8) | 0.00009 |
| At yr 13 | 19.3 (337) | 15.8 (360) | 1.1 (0.9–1.4) | 0.2 |
| In at least one survey | 39.3 (356) | 31.0 (356) | 1.2 (1.0–1.4) | 0.02 |

**TABLE 5**

**SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE, AND NEGATIVE PREDICTIVE VALUE OF THE LOOSE INDEX FOR THE PREDICTION OF ASTHMA FOR ACTIVE ASTHMA AT YR 6, YR 8, YR 11, AND YR 13 SURVEYS**

| Active Asthma | OR* (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) | Positive p Value % (95% CI) | Negative p Value % (95% CI) |
|---|---|---|---|---|---|
| At Yr 6 (n = 921) | 5.5 (3.5–8.4) | 56.6 (53.3–59.9) | 80.8 (78.3–83.3) | 26.2 (23.4–29.0) | 93.9 (92.4–95.4) |
| At Yr 8 (n = 776) | 4.4 (2.8–6.8) | 50.5 (47.0–54.0) | 81.1 (78.3–83.9) | 29.4 (26.2–32.6) | 91.3 (89.3–93.3) |
| At Yr 11 (n = 861) | 2.6 (1.8–3.8) | 40.1 (36.8–43.4) | 79.6 (76.9–82.3) | 27.1 (24.1–30.1) | 87.5 (85.3–89.7) |
| At Yr 13 (n = 644) | 3.0 (1.9–4.6) | 39.3 (35.5–43.1) | 82.1 (79.1–85.1) | 31.7 (28.1–35.3) | 86.5 (83.9–89.1) |
| In at least one survey (n = 651) | 3.9 (2.7–5.7) | 41.6 (37.8–45.4) | 84.7 (81.9–87.5) | 59.1 (55.3–62.9) | 73.2 (69.8–76.6) |

* $p < 0.00001$: between positive versus negative loose index for prediction of asthma for active asthma at each survey.

Table 4 shows the prevalence of active asthma at different surveys during the school years and in at least one survey. Prevalence of active asthma and active asthma in at least one survey were significantly higher in males than in females at all ages up to Yr 11 but not at the Yr 13 survey.

Children with a positive loose index for the prediction of asthma were 2.6 to 5.5 times more likely to have active asthma some time during the school years than children with a negative loose index for the prediction of asthma (Table 5). Risk of having subsequent active asthma increased to 4.3 to 9.8 times when the stringent index was used (Table 6).

Table 5 also shows sensitivity, specificity, positive predictive value, and negative predictive value of the loose index for active asthma at different school age surveys. As expected, sensitivity decreased with age, whereas specificity was consistently around 80%, and attained 84.7% for asthma in at least one survey. Positive predictive value was quite constant, and 59.1% of subjects with a positive predictive index had active asthma in at least one survey. Negative predictive value was consistently high, ranging from 86.5% at Yr 13 to 93.9% at Yr 6 survey. Using the stringent index sensitivity was quite low in all surveys (Table 6). However, specificity increased to over 96% consistently and positive predictive value increased to 76.6% for active asthma in at least one survey. The negative predictive value remained consistently high (Table 6).

## DISCUSSION

In this longitudinal study, we used six parameters that can easily be obtained in any clinical practice (namely, frequency of wheezing, history of eczema, parental history of asthma, eosinophilia, allergic rhinitis, and wheezing without colds), to assess the risk of subsequent development of asthma in infants and young children. As expected, a stringent index that required subjects to have wheezed more frequently in early life plus other risk factors for asthma had an acceptable positive predictive value and a very high specificity, but its sensitivity was quite low. Conversely, a more loose index, which only required infrequent wheezing episodes plus the same combination of other risk factors included in the stringent index had a much higher sensitivity but lower specificity and positive predictive values. The negative predictive value at all ages was very high for both indices, suggesting that the great majority of children who did not develop asthma during the school years had a negative predicted index during the first years of life.

The main objective of this study was to determine the accuracy with which, using simple clinical parameters, the subsequent development of asthma could be predicted in a general population sample. This exercise may have very important implications for any strategy aimed at early intervention in subjects at high risk of developing asthma. It has been postulated that early intervention with anti-inflammatory drugs could change the natural course of the disease (12). Although there is some indirect evidence supporting this hypothesis (13, 14), it is by no means conclusive. Nevertheless, it would be reasonable for clinicians treating infants and young children with recurrent wheezing to be more aggressive with those subjects expected to be less likely to undergo remission from their symptoms. As with any study of this type, our results suggest that if the criteria to select at-risk individuals are very stringent, the index is able to predict with a reasonable degree of accuracy (over 75%) which children who are wheezing in early life will have significant asthma symptoms at least once during the school years. However, many children who will go on to develop significant asthmalike symptoms later in life have only mild wheezing episodes in early life, and therefore, the sensitivity of the stringent index is quite low. Conversely, if the criteria used to include children in the at-risk group are made more loose, the proportion of children who will

**TABLE 6**

**SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE, AND NEGATIVE PREDICTIVE VALUE OF THE STRINGENT INDEX FOR THE PREDICTION OF ASTHMA FOR ACTIVE ASTHMA AT YR 6, YR 8, YR 11, AND YR 13 SURVEYS**

| Active Asthma | OR* (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) | Positive p Value % (95% CI) | Negative p Value % (95% CI) |
|---|---|---|---|---|---|
| At Yr 6 (n = 937) | 9.8 (5.6–17.2) | 27.5 (24.6–30.4) | 96.3 (95.1–97.5) | 47.5 (44.3–50.7) | 91.6 (89.8–93.4) |
| At Yr 8 (n = 775) | 5.8 (2.9–11.2) | 16.3 (13.7–18.9) | 96.7 (95.4–98.0) | 43.6 (40.1–47.1) | 88.2 (85.9–90.5) |
| At Yr 11 (n = 875) | 4.3 (2.4–7.8) | 15.0 (12.6–17.4) | 96.1 (94.8–97.4) | 42.0 (38.7–45.3) | 85.6 (83.3–87.9) |
| At Yr 13 (n = 653) | 5.7 (2.8–11.6) | 14.8 (12.1–17.5) | 97.0 (95.7–98.3) | 51.5 (47.7–55.3) | 84.2 (81.4–87.0) |
| In at least one survey (n = 659) | 7.1 (3.5–14.1) | 15.7 (12.9–18.5) | 97.4 (96.2–98.6) | 76.6 (73.4–79.8) | 68.3 (64.7–71.9) |

* $p < 0.00001$: between positive versus negative stringent index for the prediction of asthma for active asthma at each survey.

have asthma and who have a positive index (sensitivity) increases significantly, but the positive predictive value decreases. This means that a high proportion of children who will not go on to develop asthma will have a positive index. In the final analysis, a decision about which of the two indices should be applied will depend on the efficacy and potential side effects of any preventive measures to be recommended for at-risk subjects. A potential treatment with high efficacy but with significant potential side effects should probably only be used in children with a very high risk of disease, that is, those with a positive stringent index. This would avoid treating a large number of children who will not go on to develop asthma with a regimen that may be prone to generate unnecessary side effects in such a population. Conversely, for a treatment regimen of low efficacy but also with little or no side effects a loose index for the prediction of asthma would be reasonable.

It is worth noting that our stringent index had a rather low sensitivity (14.8 to 27.5%). Sensitivity increased markedly when using a looser index (39.3 to 56.6%). This suggests that, for many cases of childhood asthma, symptoms are rather mild in early life and become more severe with age. This is in agreement with our own previous reports suggesting that children who wheeze in early life and are still wheezing at age 6 have apparent deficits in lung function at age 6 compared with the levels of lung function they started with during the first months of life (3). This would suggest, that from a clinical point of view, the loose index for the prediction of asthma would be able to pick up most of the children who will have asthma in early life and whose symptoms will persist beyond that age. Interestingly, we found that, for children whose asthmalike symptoms started after the age of 3, no significant loss in lung function was observed up to the age of 11 yr, even among those whose symptoms persisted up to that age (15). It is thus likely that the loose index for the prediction of asthma will be able to detect most children at risk for developing progressive disease, that is, asthma of early onset. Still, as explained previously, over 40% of all children who have a positive loose index will never have active asthma during the school years. This compares with less than 25% of children who have a positive stringent index.

There are some potential sources of bias that need to be considered when interpreting our results. Researchers involved in this study had no participation in the day-to-day clinical management of symptomatic children. What role treatment may have in the associations under study is difficult to assess. However, it is important to point out here that until very late during the follow-up, inhaled steroids were seldom, if ever, used in the treatment of asthma in these children (data not shown). Any effects of treatment would tend to decrease the predictive power of the calculated indices. It is also possible that parents of children who had symptoms in early life may be more prone to report milder symptoms in their children later in life than parents of children with no symptoms in early life. However, we have observed a strong correlation between reported symptoms and objective indices of asthma activity at different ages (16). It is thus unlikely that this source of bias may have significantly influenced our results.

We know of only one other study that has attempted the same type of longitudinal assessment reported herein. Clough and coworkers (17) recently reported the 12-mo outcome of a smaller group of children (n = 109) enrolled at a mean age of 11 mo. All enrolled children had at least one atopic parent. Using personal and family history of atopy, and immune parameters measured in blood, they reported sensitivities that were much higher than those observed in our study, although their specificity, positive predictive values, and negative predictive values were similar to ours. However, both the design of the study, length of the follow-up, and inclusion criteria were very different in Clough and coworkers' study (17) and in ours, so results may not be directly comparable. In addition, we chose simple, easily measurable parameters that could be obtained in any clinical setting. It is possible that inclusion of more complex immune parameters in our indices may increase their predictive capacity, but we believe that this would hamper their general clinical application.

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