Problems and possibilities in understanding the natural history of asthma

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In early life, asthma symptoms can occur intermittently or may not be severe enough to limit normal activities, which makes it difficult for the clinician to make reliable predictions and administer therapy with some precision. In the case of pediatric asthma, the identification of children who will experience the development of a clinically important illness that will impair their quality of life can be a complex process. The usual methods for describing this information include the prognostic statistics of sensitivity, specificity, likelihood ratio, and positive predictive value. The sensitivity, specificity, and likelihood ratio of various early markers of asthma have been calculated from several cohort studies. (J Allergy Clin Immunol 2000;106:S144-52.)

Key words: *Long-term cohort studies, sensitivity, specificity, positive predictive value, likelihood ratio, true positive, false positive, airway hyperresponsiveness, atopy*

It is important for the clinician to be able to predict how a child's respiratory symptoms could progress or resolve later in life. To make reliable predictions and administer appropriate therapy with some precision, the clinician needs to know what factors indicate the development of persistent asthma or the remission of symptoms. Otherwise, it is difficult to predict which symptomatic children will benefit from preventive interventions or which children will have an illness that will resolve of its own accord. This is a particular problem because asthma symptoms in early life may occur only intermittently or may not be severe enough to limit normal activities. Consequently, helpful interventions may not be made, and a child could go on to experience the development of severe asthma.

Only long-term cohort studies can provide information about the natural history of asthma and provide evidence of whether asthma onset in later life has a better prognosis than asthma onset in early life. Unfortunately, cohort studies are the most expensive and the most difficult types of investigations to conduct because major resources are required to keep the cohort together over a long period of time.

Abbreviations used
AHR: Airway hyperresponsiveness
PPV: Positive predictive value

The aim of this article is to summarize and compare the best evidence available about the natural history of asthma, with the use of the most rigorous cohort studies that have been conducted to date, and to present the results in such a way that the most appropriate predictive statistics can be calculated and compared. This approach is particularly relevant for the design of future primary, secondary, and tertiary intervention studies that will evaluate methods of preventing early asthma onset that persists into adult life.

PROGNOSTIC VALUE OF STATISTICS

Several wheezing phenotypes have been described within the spectrum of conditions manifested in childhood asthma.[1,2] Clinical experience shows that many infants who have wheeze and other atopic signs will experience the development of clinically important asthma, whereas infants who wheeze without atopy often improve, and their condition may remit with time.[3] Thus, some children with wheeze are, in fact, exhibiting their first symptoms of ongoing asthma, whereas other children's airway-narrowing may result from an intercurrent infection or from being born with small caliber airways, and they will not experience persistent illness later in life.[4,5] The question is, how can these children be identified? Answering this question could help clinicians effectively manage children with respiratory illness. In the case of pediatric asthma, identifying children who will experience the development of a clinically important illness that will impair their quality of life can be a complex process.

The usual methods for describing this information include the prognostic statistics of sensitivity, specificity, likelihood ratio, and positive predictive value. *Sensitivity* is the rate at which a clinical marker identifies "true positive" cases. Sensitivity, then, describes that proportion of adults with asthma who, as children, had particular signs or symptoms. *Specificity*, on the other hand, is the rate at which the absence of a clinical marker identifies "true negative" cases, that is, describes that proportion of adults who do not have asthma and who were symptom-free during childhood. The advantage of the use of sta-

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tistics of sensitivity and specificity is that they are not influenced by the prevalence of asthma in childhood or in adulthood; therefore, despite the variable prevalence of asthma from one study to another, results can be compared among international cohort studies. A major disadvantage is that sensitivity and specificity are deductive, not inductive. These statistics look back on, but cannot predict, future events.[6] In both research and clinical situations, for example, it would be more useful to predict the probability that children who have early signs of clinical atopy will experience persistent asthma later in life. The statistic to determine this would be positive predictive value (PPV), which would describe the proportion of children who show early signs of atopy or symptoms and who subsequently have asthma later in life. An advantage of the PPV is that it describes the prognostic value of signs and symptoms in a way that is useful for clinical practice. A major disadvantage is that PPV is influenced by the prevalence of the outcome in the population. Estimates of PPV can rarely be compared from study to study nor can they be extrapolated from a study to a clinician's practice.

The most helpful statistic, then, would be both inductive and able to make comparisons among studies possible, with helpful results for clinicians and patients. One statistic that can predict the probability of future asthma, although not being influenced by prevalence, is the *likelihood ratio*.[6] As an overall measure of the evidence provided by the test results that incorporate both sensitivity and specificity, the likelihood ratio may be either positive or negative[7] and is calculated as the sensitivity divided by 100-specificity, or *the true positive rate as a proportion of the false positive rate*. The major value of the likelihood ratio is that it converts the pretest estimate of a child's development of future illness into a posttest estimate, thereby providing a more effective predictor of future illness than the PPV. This Bayesian approach can be used as a measure of the evidential strength of the association between early symptoms and later asthma.[8] This statistic, combined with the evidence from cohort studies and prior knowledge of the disease frequency,[9] is a good estimate of the probability that children will develop asthma.

In the assessment of early identifiers of asthma, it is important to balance their sensitivity against their specificity. Ideally, a good test would have a very high sensitivity (most adults with persistent asthma would have the marker in childhood) and a very low specificity (adults without persistent asthma would not have the marker in childhood). A test that has these characteristics would therefore result in a high rate of true positive results and a low rate of false positive results and have a high likelihood ratio as well.

We have calculated the sensitivity, specificity, and likelihood ratio of various early markers of asthma from cohort studies whose design and reporting of results lend themselves to this approach. With this information, we can compare the usefulness of various early markers for predicting whether a child will experience the development of asthma that will persist into later life and assess whether some clinical indicators are better predictors than others. We can also determine whether asthma indicators identified during early childhood can better predict asthma that persists into adulthood than asthma indicators measured in later childhood.

COHORT STUDY SELECTION

Theoretically, cohort studies that enroll children in early life should provide the most reliable estimates of prognosis. From a methodologic viewpoint, cohort studies that provide the most reliable information for prognostic statistics fulfill certain strict criteria. Children should be enrolled at an early age; poor parental recall of early childhood symptoms will thereby be much less likely to unfavorably bias estimates of prognosis.[10] Also, the follow-up period should be long enough to allow time for respiratory symptoms to either become persistent or to resolve.

The cohort studies that are most helpful in the identification of future asthma and applicable to the general population should therefore have the following characteristics:

1. A random population sample was enrolled.
2. An inception cohort was enrolled in early childhood.
3. The follow-up period was longer than 5 years.
4. The outcome data were collected prospectively by interview with parent or patient.
5. Objective outcome measurements were included.
6. The entire cohort, including both symptomatic and asymptomatic subjects, was studied at follow-up.

In reviewing the evidence of asthma's natural history, we identified several rigorous cohort studies that fulfill the majority of these criteria. These studies, which began in the 1970s and 1980s and continued to follow their subjects over a long period of time, are listed in Table I. Except for the Japanese study, which was conducted in a rural region, all the studies were conducted in cities. We have not included cohort studies that excluded asymptomatic children from the data analyses[11] or studies that only enrolled or reported data from selected groups of children.[12-15] We have also excluded the many studies that enrolled only subjects with established asthma or case-control studies of asthmatics and selected normal control subjects. These studies cannot be used to accurately estimate sensitivity and specificity, and their results cannot be compared with those of other studies. Then, too, estimates from such studies would be significantly biased because the children most likely to fall into the false-positive or false-negative predictive groups would be effectively eliminated by the selection criteria.[16]

PREDICTIVE VALUE OF RESPIRATORY SYMPTOMS IN CHILDHOOD

Fig 1 shows the sensitivity of symptoms in early life as a predictor of later airway hyperresponsiveness (AHR), asthma, or wheeze from the studies in which

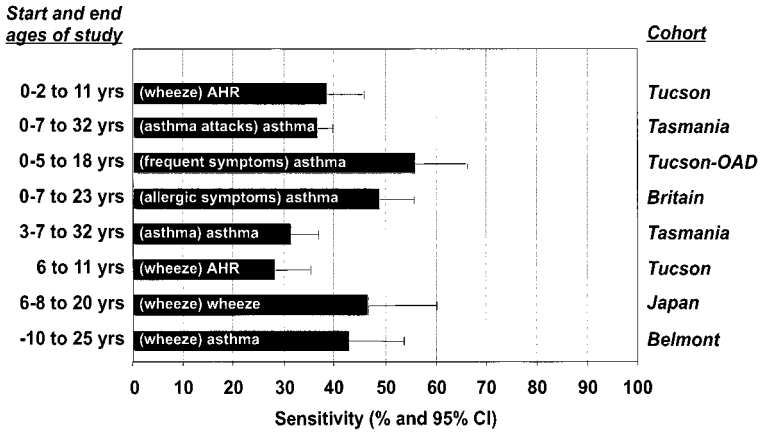


FIG 1. Sensitivity of symptoms in early life as a predictor of later AHR, asthma, or wheeze from the studies in which these statistics can be calculated. The *bars* indicate that only 30% to 50% of patients who had asthma markers later in life experienced symptoms during childhood. The labels on the bars show the condition measured at the initial study (in brackets) and at the final study. *CI*, Confidence interval.

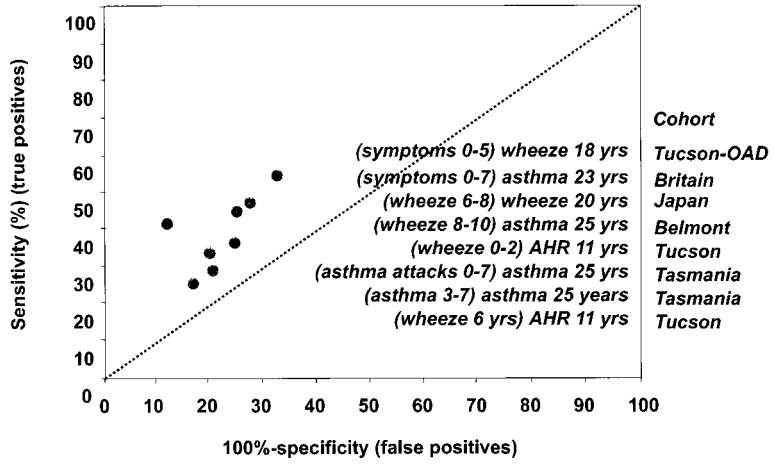


FIG 2. True positive results plotted against false positive results. At the *top left-hand corner*, the rate of true positive results is maximized, and the rate of false positive results is minimized. For a test to be useful, the point must be as far above or below the line of identity as possible.

TABLE I. Cohort studies for tracking the natural history of asthma

Country	Location	Authors	Age at inception (y)	Years of follow-up	Response rate (%)	Final sample size (n)
United States	Tucson	Martinez et al[4]	Birth	11	32	397
	Tucson-AOD	Burrows et al[44]	<5	3-11	35	273
	Boston	Carey et al[45]	0-9	12-18	No information	281
		Sherrill et al[46]			16.9	133
New Zealand	Tasmania	Jenkins et al[36]	7	25	75	1494
	Dunnedin	Burrows et al[44]	9	6	55	670
	Belmont	Peat et al (unpublished)	8	16	57	406
United Kingdom	Britain	Anderson et al[47]	7	16	50	7225
Europe	Denmark	Ulrik and Backer[48]	7-17	6	61	383
	Rome	Forastiere et al[49]	7-11	3	74	892
Japan	Awara-machi	Kagamimori et al[50]	6-8	12	33	498

AOD, Tucson study of airways obstructive disease.

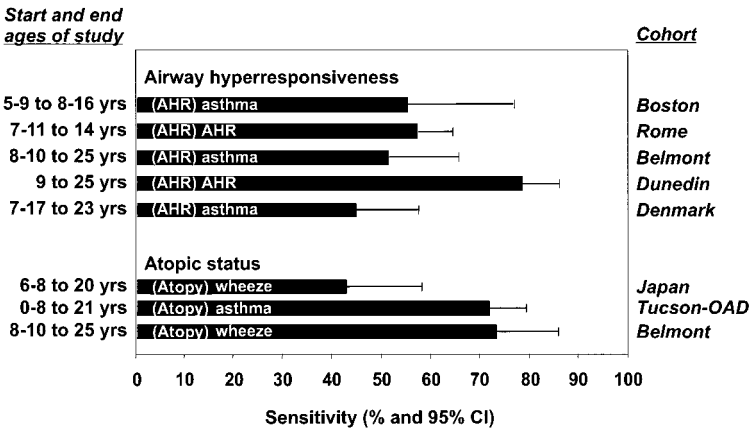


FIG 3. Sensitivity of objective markers of asthma measured mainly in mid childhood. The labels on the bars show the condition measured at the initial study (in brackets) and at the final study. *CI*, Confidence interval.

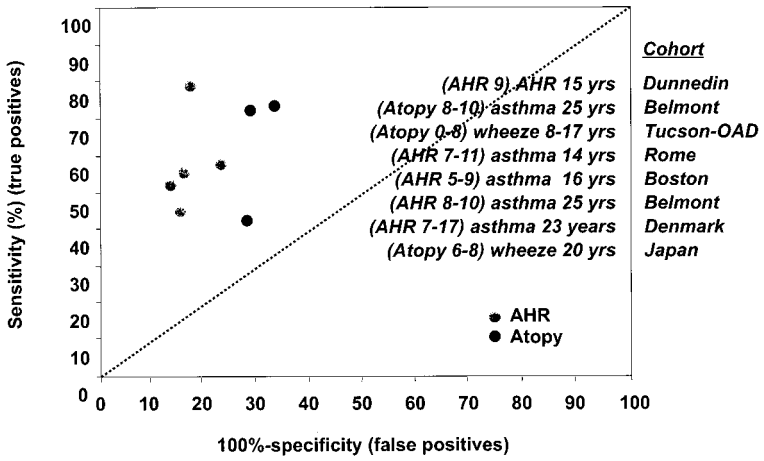


FIG 4. Sensitivity of objective markers plotted against their rates of specificity.

TABLE II. Relative value of positive predictive value

	Subjects identified (n)	True positive tests* (n)	False positive tests† (n)	False negative tests‡ (n)
Atopy	320	90	230	60
AHR	100	45	55	105
Wheeze	150	65	85	85
Atopy or AHR or wheeze	360	100	260	50

Data were calculated with the positive predictive value collected at the final follow-up of the Belmont cohort, 1995-1997; 1000 children were screened, with 150 children aged 8 to 10 years identified as those who will have frequent asthma symptoms at age 25 years.
*Will have asthma as adults.
†Will not experience the development of asthma.
‡Could not identify by the test whether these children will have asthma as an adult.

these statistics can be calculated. The data have been plotted in ascending order of the age at which predictive markers were first measured. The data indicate that, in general, only 30% to 50% of patients who had markers of asthma in later life experienced symptoms during childhood. Moreover, there does not seem to be a clear trend for sensitivity to change with the increasing age at which the childhood markers of asthma were measured or for markers of asthma in early life to be consistently more sensitive or more specific than the presence of wheeze.

Fig 2 shows the estimates of true positive tests against false positive tests. Obviously, a helpful test would be one in which the rate of true positive tests is maximized and the rate of false positive tests is minimized (the top left-hand corner of this figure). For a test to be useful, the point

TABLE III. Predictive statistics calculated for each cohort study listed in Table I*

Indicator	Location	Clinical indicator at initial study	Definition of persistent asthma at final study	Sensitivity	Specificity	Likelihood ratio for positive test
Symptoms	Tucson	Wheeze, age 0-3 y	AHR (methacholine), age 11 y	36.8	63.4	1.0
		Recent wheeze, age 6 y		27.0	81.0	1.4
	Tucson-AOD	Frequent wheeze or cough, age 1-2 y	Diagnosed asthma, age 3-11 y	53.6	64.8	1.5
	Tasmania	First attack of asthma, age 3-7 y	Self-reported current asthma, age 25 y	30.2	77.2	1.3
		> 10 asthma attacks, age 0-7 y		34.5	77.8	1.6
	Britain	Asthma, wheezy bronchitis, or allergic symptoms, age 0-7 y	Attack, asthma, or wheeze, age 17-23 y	46.9	72.5	1.7
	Japan	Wheeze with colds, age 6-8 y	Wheeze with colds, age 18-20 y	42.1	72.1	1.5
	Belmont	Recent wheeze, age 8-10 y	Active asthma, age 25-29 y	41.7	86.7	3.1
Atopy	Japan	Atopy to HDM	Wheeze with colds, age 18-20 y	44.7	72.6	1.6
	Tucson-AOD	Atopy (spts) before age 8 y	Shortness of breath/wheeze after age 8 y	72.0	71.4	2.5
		Atopy (spts) after age 8 y		44.0	72.5	1.5
	Belmont	Atopy (spts*), age 8-10 y	Active asthma, age 25-29 y	73.4	66.7	2.2
AHR	Boston	AHR (cold air), age 5-9 y	Active asthma, age 14-16 y	55.3	83.9	3.4
	Rome	AHR (methacholine), age 7-11 y	AHR (methacholine), age 10-14 y	57.2	77.0	2.5
	Belmont	AHR (histamine), age 8-10 y	Active asthma, age 25-29 y	51.5	86.6	3.8
	Dunnedin	AHR (methacholine) age, 9 y	AHR (methacholine) age, 15 y	78.5	82.7	4.5
	Denmark	AHR (exercise), age 7-17 y	Recent asthma symptoms, age 13-24 y	44.8	89.8	4.4

OAD, Tucson study of obstructive airways disease; *HDM*, house dust mite; *spts*, battery of 12 skin prick tests.
*The posttest prevalence of asthma has been calculated assuming an arbitrary population prevalence of 10% of asthma that persists.

must be as far above or below the line of identity as possible. Any test that falls below this line would have a higher false-positive rate than a true-positive rate; in other words, the proportion of asthmatic patients who did not have symptoms in earlier life would be higher than the proportion of asthmatic patients who did.

In those studies for which the rate of true positive tests is high (Tucson and Britain cohorts) and in which the marker would be having symptoms during very early life (that is, up through age 7 years), the rate of false positive tests is also higher than in the other studies. Conversely, the rate of true positive tests is lower in studies for which the rate of false positive tests is lower (Tasmanian and Tucson cohorts) and in which the marker is having symptoms slightly later in childhood (that is, between the ages of 3 and 7 years). Although it is commonly believed that asthma is easier to recognize in older children,[17] the data shown in Figs 1 and 2 do not support a hypothesis that symptoms at any particular age have a better predictive value.

PREDICTIVE VALUE OF AHR AND ATOPY IN CHILDHOOD

Fig 3 shows the sensitivity of objective markers of asthma (such as AHR) and allergy (skin prick tests) measured mainly in mid childhood. These tests have a higher true-positive rate as markers of persistent asthma than the symptom measurements shown in Fig 1; the sensitivity is generally higher at approximately 50% to 70% of tests. Fig 4 shows these estimates plotted against their rates of specificity. The rates of false positive tests are also generally lower than for the symptom reporting shown in Fig 2. This figure suggests that tests of AHR, which cannot be measured until children are old enough to perform lung function testing on their own, tend to have a lower rate of false positive tests than does atopy identified at the same age. That measurements of AHR have a lower rate of false positive test results than measurements of atopy do is to be expected. Atopy tests identify a higher proportion of the population than do AHR tests, and many atopic children do not experience the development of asthma. Again, there is no suggestion that atopy or AHR tests become better predictive tests if they are measured at an earlier or later age.

When children are being enrolled in studies that test strategies for the primary prevention of asthma, the ideal would be to screen a population of children and enroll those patients who have a marker that reliably predicts future ill-

Posttest prevalence for positive test	Likelihood ratio for negative test	Postttest prevalence for negative test
10.0	1.0	90.0
13.3	0.9	89.0
14.1	0.7	86.3
12.5	0.9	89.0
15.0	0.8	87.8
15.8	0.7	86.3
14.2	0.8	87.8
25.6	0.4	78.3
15.0	0.8	87.8
21.7	0.4	78.3
14.3	0.8	87.8
19.5	0.4	78.3
27.2	0.5	81.8
21.6	0.6	84.3
29.5	0.6	84.3
33.1	0.3	73.0
32.6	0.7	86.3

ness. Table II shows the number of children who will experience persistent asthma as adults, identified by recent wheeze, AHR, or atopy in childhood. We calculated these figures from estimates of prognostic statistics from our cohort study in Belmont; therefore, these numbers apply only to this Australian setting. We calculated that if a population sample of 1000 children was screened, then 320 children would be identified as being atopic, but only 90 of the children in this group would go on to have persistent asthma in adulthood. If atopy were used as a screening test to identify children at risk who should undergo a preventive intervention, then 90 children would be identified who would have asthma as adults and who might benefit from preventive strategies. In any case, we would also need to treat 230 children who would not experience asthma. Another 60 children would experience adult asthma but would not be identified by the atopy test and therefore would not receive the preventive intervention. Symptoms of recent wheeze and a positive AHR test identify a much smaller number of children than do atopy tests, but they also identify a smaller number of children who will go on to have asthma. Thus, these tests miss a larger number of future asthmatic patients than atopy screening.

If the children who are atopic, have recent wheeze, or have AHR are considered together, then obviously a larger number would be identified than if each test is used separately. In addition, 100 children who will have persistent adult asthma are identified, but a larger group of 260 children would be identified as not going on to have adult asthma. It is interesting that one third of asthmatic adults would not be identified by any of these tests in childhood because signs or symptoms that predict the development of asthma in this group have not been identified.

Table III shows the predictive statistics calculated for each cohort study listed in Table I. For symptoms of wheeze or asthma, the likelihood ratio for a positive test is surprisingly low for most studies, which shows that the expected posttest prevalence in children who have symptoms is not largely greater than the arbitrary pretest prevalence of 10% in the population. The likelihood ratios are higher for atopy, however, and higher still for AHR.

EFFECTS OF MEASUREMENT ERROR

Measurement error may occur as a result of recall bias or differences in the methods used to collect the information over time. In the studies shown in Table I, the measurement error is likely to have been unbiased or nonsystematic (ie, random, in that it would have occurred in both directions and in all study groups) and therefore to have reduced all of the estimates of prognostic statistics. In childhood, the presence of respiratory symptoms is measured by surrogate reports, usually from a parent, until the patient reaches adolescence. Thus, we do not know whether the extent to which symptoms in patients with asthma in childhood[18] decline in adolescence is caused by measurement error or is in fact due to a sudden increase in airway size.[19]

In the comparisons shown by the figures, only the assessments at the first and last studies of the cohort are used. Therefore, measurement error around each of these assessments will compound to reduce the estimates of both the sensitivity and specificity. An approach to the calculation of more accurate prognostic estimates would be to define asthma status with the use of the follow-up data collected for the interim studies in addition to the information at the beginning and the end of a cohort study. Because remission and relapse of asthma is common at all ages,[10] more accurate methods for the classification of these characteristics are urgently needed. The use of more accurate classifications of severity groups should be considered, thus improving our knowledge and understanding of asthma's natural history. International workshops that develop new methods of longitudinal data analysis for cohort studies have been successful[20] but have mainly addressed the statistical and practical problems of modeling lung function decline and AHR changes in adults.

RISK FACTORS

The most important risk factors that identify children at high risk for asthma include family history, ethnicity, socioeconomic status, and gender.[21-24] Many factors that

provide insights into the mechanisms of asthma have been identified, such as early infections that result from exposure to other children or siblings[22,25,26] and premature birth or low birth weight.[27] Potentially preventable environmental factors for childhood asthma include exposure to allergens,[28,29] parental smoking,[30] lack of or short-term breast-feeding,[31,32] and several dietary factors including antioxidants, omega fatty acids, and sodium.[33-35]

Nevertheless, despite a significant knowledge of the risk factors associated with asthma in early childhood, factors that determine whether children with atopy, AHR, or wheeze will progress to asthma in adulthood or remit have been poorly investigated. Some evidence suggests that children whose symptoms persist are more likely to be female[36] or to have asthmatic parents.[4,36] Without a family history of asthma, or in those instances when asthma develops in the absence of atopy, AHR, or symptoms during childhood, no potentially preventable risk factors for the continuation or remission of asthma have been identified. We also have no evidence of what factors can protect most atopic and symptomatic children from the development of adult asthma.

PREVENTING ASTHMA

Obviously, we need a more detailed knowledge of the risk factors that can predict progression or remission of asthma so that more effective primary, secondary, and tertiary preventive strategies can be developed. Failure to recognize and act on the early markers of persistent adult asthma may have an important impact on prognosis. One of the most important outcomes of persistent symptoms in childhood is entering adult life with significantly reduced lung function.[12,37] In addition, it may be that the inappropriate use of medication in children who have all the markers that predict ongoing asthma may allow the development of inflammatory processes in the airways to continue unabated[17]; this hypothesis, however, has not been tested in clinical trials.

RECOMMENDATIONS

It is difficult for a clinician to use the clinical signs of wheeze, atopy, and AHR in children to predict asthma that persists into adulthood. Practical and useful information about the natural history of asthma, however, could be obtained from the existing cohort data through the use of more standardized definitions and reporting methods. For improving short-term knowledge, it is not feasible to begin a new generation of standardized cohort studies because the results would not be available for at least another generation. Instead, our knowledge could be greatly advanced through a standardized, coordinated reporting of the data from the cohort studies that have been conducted already. Because relatively few cohort studies have used standardized methods for tracking the natural history of asthma, it would be ideal if the maximum information could be obtained from these invaluable studies. This approach would lead to data from existing studies that could be compared more reliably, thus obtaining more informative estimates of prognosis.

A restriction in some studies has been that the control group's data have not been included in analyses. Other problems also occur when potentially important early markers of asthma, such as atopic status, are reported as outcome variables rather than as predictive factors. The selection and follow-up criteria may be optimal in some studies, but the results are not easily compared when different definitions are used to classify groups. This wide heterogeneity of reporting methods significantly increases the variability of the results, limits comparability, and prevents metaregression being used to improve precision.[38]

INTERNATIONAL COLLABORATIONS

Although genetic markers of asthma may become available in the future, it is essential that the value of phenotypic markers be assessed and compared among existing cohorts. The cohort studies conducted to date represent a major achievement in terms of tracking the natural history of asthma over long periods, sometimes from early childhood into adulthood; but inconsistency in reporting prevents the use of this information to the fullest advantage. An international collaboration may be the best approach to resolving the present dilemma of wanting to know what factors predict persistent asthma and having relevant data currently held by various epidemiologic units around the world.

Two international collaborations that have made landmark advances in documenting the prevalence of asthma are the International Study of Asthma and Allergies in Childhood and the European Community Respiratory Health Survey.[39,40] These collaborations initiated a new generation of standardized studies and provided encouraging evidence of the substantial benefits of this collaborative approach. Unlike the International Study of Asthma and Allergies in Childhood and European Community Respiratory Health Survey collaborations, however, an international cohort consortium could achieve major advances in the knowledge of asthma prognosis simply by facilitating standardized reporting from available sets of cohort study data. This type of consortium would also be ideal for the establishment of comparable methods for data collection in both future cohort studies and future follow-up studies of existing cohorts.

For example, an international consortium could be responsible for the establishment of standardized methods for existing cohorts by

1. Ensuring the inclusion of control groups in the data analyses,
2. Developing standardized definitions of various markers of the severity and frequency of asthma in both early and later life,
3. Recommending the reporting of the prognostic value of respiratory symptoms, atopy, lung function, and AHR measured in childhood on asthma in later life,
4. Sharing expertise and making recommendations about statistical methods for future longitudinal analyses, and

5. Recommending methods to be used in ongoing follow-up studies of existing cohorts.

This type of collaborative approach could lead to the release of invaluable information for the design of a new generation of research studies that would test the effectiveness of preventive treatment and environmental interventions.

FUTURE DIRECTIONS IN PREVENTING ASTHMA

Can the course of asthma be changed by interventions in early life such as preventive treatment regimens, alterations in diet, or allergen avoidance procedures? The few studies of environmental interventions to date have produced extremely encouraging early results.[41-43] In these studies, which have enrolled children at high risk of the development of asthma, the incidence of early asthma symptoms has been reduced in active intervention groups. Nevertheless, asthma has developed in some children in these groups.

It is possible that a serial approach of administering antiinflammatory medications to children who have not benefited from early environmental interventions may be the most effective approach to prevention or that combining treatment and environmental interventions will have a multiplicative effect. Only rigorous, well-controlled trials will provide the required comprehensive information before effective and alternative methods of the prevention of asthma become available. Further information from cohort studies of those children most likely to benefit in the long term will be invaluable for the design of such studies. Until this information is available, research studies will have to continue to enroll population samples of young children, many of whom will not go on to experience asthma and who will not need to have treatment or environmental interventions to improve their prognosis.

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