

Respiratory pathophysiologic responses

Relations of bronchial responsiveness to allergy skin test reactivity, lung function, respiratory symptoms, and diagnoses in thirteen-year-old New Zealand children

Benjamin Burrows, MD,^a Malcolm R. Sears, MB, FRACP, FRCPC,^b
Erin M. Flannery,^c G. Peter Herbison, MSc,^d and M. David Holdaway, MD,
FRACP^e Tucson, Ariz., Hamilton, Ontario, Canada, and Dunedin, New Zealand

Background: Many factors have been found to relate univariately to bronchial responsiveness (BR), but their independent relationships are often unclear because many are interrelated.

Objective: The purpose of this study was to present a multivariate analysis of the closeness of the association of various factors that are related univariately to BR, including allergy skin tests.

Methods: The results of methacholine challenge were transformed into a continuous variable (BRindex), which has a nearly Gaussian distribution. With stepwise multiple regression, the closeness of the association of the independent variables with BRindex was evaluated.

Results: Of the 11 skin tests applied, four showed independent relationships to BRindex (mite, cat, dog, and *Aspergillus* species). The sizes of these skin test reactions were correlated with BRindex, and their sum appeared to maximize the overall correlation of allergy skin tests with BRindex ($r = 0.516$). The lowness of the ratio of forced expiratory volume in 1 second to vital capacity and of percent predicted forced expiratory volume in 1 second added significantly to the skin tests in correlating with BRindex, (multiple $r = 0.621$). Adding diagnoses and symptoms increased the multiple r to 0.685.

Conclusions: The size of the reactions to the four skin tests noted above showed much closer correlations with BR than total serum IgE had shown at age 11, and the relationship was present in asthmatic and nonasthmatic subjects. (*J ALLERGY CLIN IMMUNOL* 1995;95:548-56.)

Key words: Asthma, bronchial responsiveness, allergy skin tests, lung function

From ^aRespiratory Sciences Center, University of Arizona College of Medicine, Tucson; ^bFirestone Regional Chest and Allergy Unit, St. Joseph's Hospital-McMaster University, Hamilton; and the Departments of ^cMedicine, ^dPreventive and Social Medicine, and ^ePaediatrics and Child Health, University of Otago Medical School, Dunedin, New Zealand. Data collection and processing in New Zealand were supported by grants from the Medical Research Council of New Zealand and the Otago Medical Research Foundation. Data analyses in Arizona were supported by a Specialized Center of Research Grant from the Lung Division, National Heart, Lung, and Blood Institute (HL-14136).

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Reprint requests: Benjamin Burrows, MD, Respiratory Sciences Center, University of Arizona College of Medicine, Tucson, AZ 85724.

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Extensive literature concerning factors related to bronchial responsiveness (BR) to methacholine challenge is now available. It has been shown in different populations that BR is related to baseline lung function, various respiratory symptoms and diagnoses, serum IgE level, and allergy skin test (ST) reactivity.¹⁻¹⁰ Observations in New Zealand children have shown that asthma and BR are primarily related to allergy to house dust mite and cat and have no significant independent relation to grass.¹¹

In recent reports,¹²⁻¹⁴ we have confirmed these findings and shown that hay fever is primarily related to allergy to grass and that the frequent association of asthma and hay fever is largely explained by the common occurrence of allergy to both mite or cat and grass allergens in the same

Abbreviations used

BR:	Bronchial responsiveness
BRindex:	The log (after adding 10 to eliminate negative values) of (the percent decline in FEV ₁ /log final methacholine concentration expressed as milligrams per deciliter)
FEV ₁ :	Forced expiratory volume in 1 second
%FEV ₁ :	Percent predicted FEV ₁
PC ₂₀ :	Provocative concentration causing a 20% fall in FEV ₁
RATIO:	FEV ₁ /VC expressed as a percent
ST:	Skin test
STtotal:	The sum of mite, cat, <i>Aspergillus fumigatus</i> , and dog skin test reaction sizes after subtracting the size of the negative control from each skin test reaction
VC:	Vital capacity

individual. We have also shown that the greater frequency of asthma in boys became insignificant when adjusted for allergy ST responsiveness to house dust mite and cat, that the relation of BR to these allergens was present even in children without known atopic disease, that the sizes of the mite and cat reactions were related to the frequency of BR, and that a reduction in lung function added significantly to the allergy ST results in predicting BR.

It is the purpose of this report to present a multivariate analysis of the strength of the association of the various factors related univariately to BR, including allergy ST reactivity, and to look for interactions of factors in determining BR, such as the interaction previously demonstrated between lung function and serum IgE level.¹⁵ We also examine the manner in which the ST results can be used to maximize their association with BR, the size of the ST reaction required to show a significant relationship to BR, and whether the degree of BR can be predicted even in subjects who are not responsive enough to have a measurable provocative concentration causing a 20% fall in FEV₁ (PC₂₀). To allow parametric methods and facilitate multivariate analyses, we calculated a continuous index of the FEV₁ decline during methacholine challenge. As in our previous report regarding IgE relationships at age 11,¹⁵ a different method for calculating this index appeared preferable to that previously recommended by O'Connor et al.¹⁶

METHODS

The basic population sample is described in more detail in previous reports.^{10, 17} A total of 720 New Zealand schoolchildren of European extraction were examined when they were 13 years of age in the course of a multidisciplinary longitudinal study of a cohort of children born in Dunedin, New Zealand between April 1, 1972 and March 31, 1973. These 720 children were representative of the full enrolled sample of 1037 3-year-olds and also of the entire birth cohort of 1661 children in regard to major demographic and socioeconomic variables, except that the few children of nonEuropean extraction have been excluded from this study. Of the 720 children seen, 698 (96.9%) had a battery of allergy skin tests applied, a requirement for inclusion in this study. Of these 698, 667 (95.6%) had either a validated abbreviated methacholine challenge previously described^{15, 18} or were tested for bronchodilator response to salbutamol.

Comparisons of the 667 subjects who had both STs and some type of challenge with the remaining 53 subjects who had less complete testing revealed no significant differences in sex distribution or in the frequency of reported asthma, wheeze, or history of eczema. However, a higher rate of hay fever was reported by those with incomplete data (50.9% vs 27.6%, $p < 0.001$). Of the 53 subjects with incomplete data, 49 did have simple spirometry performed. There were no significant differences in the FEV₁ or in the FEV₁ to vital capacity (FEV₁/VC) ratio in those with and without complete data. Although there may be a bias toward less willingness to have STs and bronchial challenges in those with allergic disease, the overall completion rate among those children seen at age 13 is so high that it should not markedly affect the findings in this study.

Of the 667 subjects who had both STs and challenges, however, five had such low lung function that for safety and ethical reasons, they were given only salbutamol, to which they showed a significant response. This group consisted of three boys and two girls, all of whom were reactive to house dust mite as determined by allergy STs. These five subjects are excluded from subsequent analyses. Their exclusion would be expected to have little effect on the overall findings except to minimize slightly the apparent relationships of BR to ST responses and lung function. All remaining analyses are carried out on the 662 subjects who had a methacholine challenge and a complete battery of allergy STs, as well as questionnaire information. They represent 91.9% of the 720 subjects seen at age 13.

The study was approved by the Ethics Committee of the Otago Hospital Board, and written consent for each procedure was obtained from each child's parent or guardian.

The baseline characteristics of the 662 subjects are summarized in Table I. In our previous articles, only test reactions at least 2 mm greater than the negative control were considered positive.¹¹⁻¹⁴ Because it is shown in this

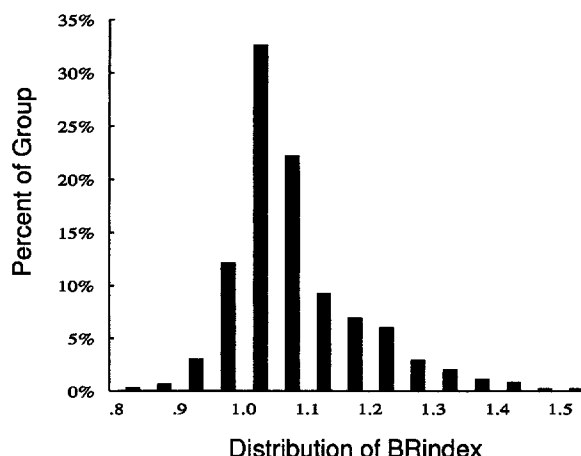


FIG. 1. The distribution of BRindex calculated as discussed in the text.

report that even very small (1 mm) ST reactions relate to other findings, the percent of test reactions larger than the control are included in Table I.

The battery of STs applied consisted of 11 allergens common to the locale of the study, and the prick test technique was used. The allergens were mixed rye grass pollen (subsequently called "grass"), cat epithelium ("cat"), dog hair ("dog"), horse hair ("horse"), kapok, wool, *Aspergillus fumigatus*, *Alternaria*, *Penicillium*, and *Cladosporium* molds (all supplied by Miles, Inc., Hollister-Stier Div., West Haven, Conn.) and *Dermatophagoides pteronyssinus* ("mite") supplied by Bencard, Brentford, U.K.

Percent predicted values for FEV₁ (%FEV₁) are based on height predicted values in each sex for those subjects in this study who denied ever having asthma and denied wheezing. The FEV₁/VC ratio is expressed as a percent and called *RATIO*.

In this article, subjects are considered "responders" if they showed a 20% or greater decline in the maximum FEV₁ at a concentration of methacholine less than 25 mg/ml (i.e., a PC₂₀ <25). Details of the testing methods have been presented in previous reports.^{15, 18}

To calculate a continuous index of methacholine responsiveness, the log of the slope of the percent decline from the baseline FEV₁ after the last dose of methacholine per unit concentration of methacholine was calculated, approximating the method of O'Conner et al.¹⁶ To eliminate negative values in those subjects whose FEV₁ increased slightly during the test, a constant of 1 was added before log transformation. The resulting distribution of slopes was almost identical to that of slopes in our previous analyses involving IgE.¹⁵ The slope calculated in this manner was markedly skewed to the right and showed a tendency to bimodality. The skewness index for this variable was 4.1. The skewness index was reduced to 2.1 when the slope was calculated instead as the percent decline in baseline FEV₁ divided by the log of the last concentration of methacholine

TABLE I. Characteristics of the study population

Total no. of subjects	662
Age (yr)	13
Percent male	51.5
Reported asthma (%)	10.6
Reported wheezing (%)	35.5
Reported hay fever (%)	27.3
Reported ever eczema (%)	33.7
Mean height $\pm$ SD (cm)	156.01 $\pm$ 7.47
Mean FEV ₁ $\pm$ SD (L)	2.80 $\pm$ 0.47
Mean % pred FEV ₁ $\pm$ SD	98.86 $\pm$ 11.16
Mean FEV ₁ /VC ratio $\pm$ SD (%)	86.98 $\pm$ 6.36
Percent positive ST reactions	
Any reaction > control	
Grass (%)	35.2
Mite (%)	32.0
Cat (%)	15.0
<i>Alternaria</i> (%)	7.6
Horse (%)	6.6
Dog (%)	6.2
<i>Cladosporium</i> (%)	5.6
<i>A. fumigatus</i> (%)	6.0
Kapok (%)	4.4
<i>Penicillium</i> (%)	5.4
Wool (%)	3.5

expressed as milligrams per deciliter. It was further reduced to 1.2 when a logarithm of that slope was taken after adding 10 to the slope to eliminate any negative values. The distribution of this final value, subsequently called the *BRindex* is shown in Fig. 1. Thus for the same reasons as in our previous report,¹⁵ we decided to use the *BRindex* as the continuous variable reflecting the degree of response to methacholine. Although it does not have a perfectly Gaussian distribution, it approximates one closely enough to use in parametric analyses. It should be emphasized that the *BRindex* is introduced only to provide a continuous and relatively normally distributed variable for use in statistical analyses. It is not intended to be a direct measure of the dose-response curve to methacholine. For this reason, some findings from our parametric analyses that use *BRindex* are displayed in terms of the percent of subjects with a PC₂₀ less than 25, whom we consider responders.

All symptoms and diagnoses are derived from administered questionnaires. Asthma, wheezing, and hay fever were considered current and used in the analyses if the conditions were stated to have been present during the last 2 years. Eczema was included if it was said to have ever been present. There were very few subjects who reported having bronchitis or intermittent cough who did not also have asthma. In the absence of asthma, these variables showed no significant relation to BR, and they are not considered further.

The data were collected, processed by computer, and analyzed initially at the University of Otago. The stored,

TABLE II. Relations to methacholine response measured by BRindex

	Mean BRindex $\pm$ SD		p Value
	With the finding	Without the finding	
Male gender	1.094 $\pm$ 0.104	1.063 $\pm$ 0.094	<0.0005
Reported asthma	1.236 $\pm$ 0.113	1.060 $\pm$ 0.080	<0.0001
Reported wheeze	1.128 $\pm$ 0.120	1.051 $\pm$ 0.075	<0.0001
Reported hay fever	1.114 $\pm$ 0.121	1.065 $\pm$ 0.088	<0.0001
Reported ever eczema	1.106 $\pm$ 0.113	1.065 $\pm$ 0.090	<0.0001
ST response			
Positive mite	1.137 $\pm$ 0.125	1.051 $\pm$ 0.071	<0.0001
Positive cat	1.171 $\pm$ 0.127	1.062 $\pm$ 0.085	<0.0001
Positive horse	1.156 $\pm$ 0.141	1.073 $\pm$ 0.094	<0.0001
Positive dog	1.181 $\pm$ 0.142	1.072 $\pm$ 0.093	<0.0001
Positive kapok	1.143 $\pm$ 0.140	1.076 $\pm$ 0.097	<0.0005
Positive grass	1.120 $\pm$ 0.120	1.056 $\pm$ 0.079	<0.0001
Positive <i>Penicillium</i>	1.088 $\pm$ 0.101	1.078 $\pm$ 0.100	NS
Positive <i>Alternaria</i>	1.137 $\pm$ 0.132	1.074 $\pm$ 0.096	<0.0001
Positive <i>Cladosporium</i>	1.117 $\pm$ 0.132	1.076 $\pm$ 0.098	<0.05
Positive <i>A. fumigatus</i>	1.138 $\pm$ 0.136	1.075 $\pm$ 0.096	<0.0005
Positive wool	1.116 $\pm$ 0.106	1.077 $\pm$ 0.100	NS
Correlation coefficients vs BRindex			
With % predicted FEV ₁	-0.291		<0.0001
With FEV ₁ /VC ratio	-0.465		<0.0001

NS, Difference not statistically significant.

computerized data were then transferred to the University of Arizona for further analysis. Statistical methods include simple and trend chi square, analysis of variance, simple correlation, and stepwise multiple regression with SPSS/PC+ software (Statistical Program for the Social Sciences, Chicago, Ill.). All reported *p* values are two-tailed, and *p* values of less than 0.05 are considered statistically significant.

RESULTS

As expected on the basis of our previous reports,¹²⁻¹⁴ highly significant univariate relationships to BRindex were found for reported asthma, wheezing, hay fever, and ever eczema, as well as inverse relationships to %FEV₁ and the FEV₁/VC ratio. There was also a significantly higher mean BRindex in boys than in girls.

Before carrying out any further analyses on the relation of STs to BRindex, we examined whether subjects with 1 mm reactions (called negative in our previous reports) had higher rates of BR than those with no reaction and whether they should be included in the analyses. In the case of grass, the most commonly positive allergen, five of 23 subjects with 1 mm reactions had a PC₂₀ of less than 25 (21.7%) compared with 33 of 429 (7.7%) of those with no grass reactivity (*p* < 0.05). The frequency of any responsiveness (defined as a PC₂₀

<25) was also significantly higher in those with 1 mm reactions to dog (*p* < 0.05) than in those with no reaction. The mean BRindex was significantly higher in those with 1 mm reactions compared with those with no reactions to dog (*p* < 0.005), cat (*p* < 0.02), and grass (*p* < 0.05). Although this tendency was also clearly present in mite and *A. fumigatus* reactions, because of the small number of 1 mm reactions, the differences between 0 and 1 mm reactions were not statistically significant for these allergens. Univariately, all allergy STs except those with *Penicillium* species and wool showed significant relationships to BRindex. These univariate relationships are shown in Table II.

On closer examination of the relationship of STs to BRindex, it became apparent that there was a highly significant relation of BRindex to the sizes of the reactions. Even after excluding all zero reactions, the sizes of the mite, cat, dog, and *A. fumigatus* reactions were each significantly correlated with BRindex. Their correlation coefficients were 0.311 (*p* < 0.001) for mite, 0.2379 (*p* < 0.01) for cat, 0.316 (*p* < 0.05) for dog, and 0.326 (*p* < 0.05) for *A. fumigatus* when zero reactions were not included.

We then examined the relation of BRindex to the size of the allergy ST reactions in a multiple stepwise regression. Only those tests that showed

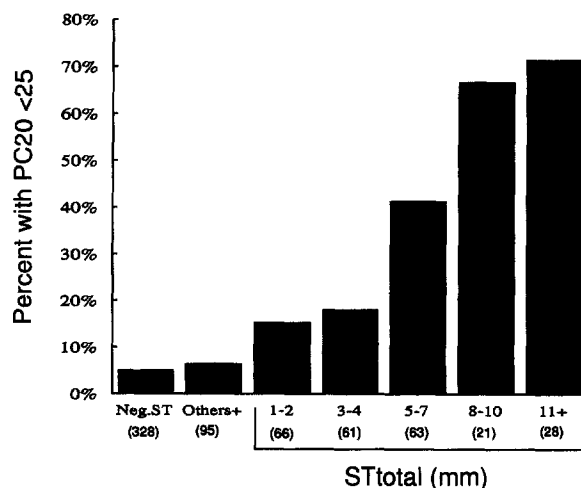


FIG. 2. The relation of ST reactivity to the percent of subjects considered responders by PC₂₀ criteria (PC₂₀ < 25 mg/ml). The first bar shows findings in subjects who have completely negative responses to all allergy STs. The second bar shows findings in subjects with positive ST responses only to allergens other than mite, cat, *A. fumigatus*, and dog. The remaining bars indicate the sum of reaction sizes to these latter four allergens (STtotal), expressed in millimeters. The numbers at risk are shown in parentheses.

significant univariate relations to BRindex were included. The results are shown in Table III. Mite entered the regression first, removing any significant remaining relationships to horse, kapok, grass, and *Cladosporium* and *Alternaria* species. Cat then entered the regression, followed by *A. fumigatus* and finally by dog. The final multiple *r* was 0.516. The fact that the number of these tests for which results were positive was not then significant suggests that there were no important interactions among them. The coefficients for mite, cat, *A. fumigatus*, and dog were very similar. Because this was the case, we tried simply adding the sizes of the mite, cat, *A. fumigatus*, and dog reactions. The resulting sum showed a correlation with BRindex of 0.516, identical to the multiple *r* derived from multiple regression including the same variables. This sum of the four STs is used subsequently to express the overall ST relation to BRindex and is called "STtotal." Its relationship to the frequency of responders measured by PC₂₀ of less than 25 is shown in Fig. 2. The rate of responders was 71.4% in subjects with STtotal values of 11 mm or more, and the trend for the rate of responders to increase with STtotal was very highly significant ($p < 0.0001$) even among subjects with a reaction to one or more of the four relevant STs. In the 592 nonasthmatic subjects in the population, BRindex

TABLE III. Multiple regressions using allergy ST sizes to predict BRindex

Variable	Coefficient $\pm$ SE in final equation	<i>p</i> Value in final equation	Multiple <i>r</i> after entry
Mite	0.0153 $\pm$ 0.00188	<0.0001	0.456
Cat	0.0159 $\pm$ 0.00363	<0.0001	0.498
<i>A. fumigatus</i>	0.0163 $\pm$ 0.00524	<0.002	0.509
Dog	0.0143 $\pm$ 0.00583	<0.02	0.516

The number of the above test results that were positive did not add to the prediction, and no other ST result showed a significant additive effect.

versus STtotal showed a correlation coefficient of 0.331 ($p < 0.0001$).

We next looked for interactions between ST reactivity and spirometric variables in predicting BRindex, converting RATIO and %FEV₁ into tertiles and converting STtotal into groups of 0, 1 to 4, and 5+ mm values. There were significant interactions of STs and each of the spirometric measures in an analysis of variance. This reflected a tendency for increasing inverse correlations between BRindex and the spirometric variables with increasing ST reactivity. For example, the correlation coefficients for RATIO versus BRindex went from -0.300 in subjects with negative ST responses to -0.449 in those with STtotals of 1 to 4 mm and to -0.536 in those with STtotals of 5+ mm.

We also looked for interactions of an asthma diagnosis with the spirometric variables and with STtotal in predicting BRindex. With analysis of variance, significant interactions were found between asthma and %FEV₁ and between asthma and STtotal in predicting BRindex. This reflected higher inverse correlations in asthmatic subjects than in nonasthmatic subjects. The correlation coefficients in nonasthmatic subjects for %FEV₁ and for STtotal versus BRindex were -0.183 and $+0.331$, respectively; in the asthmatic subjects these were -0.425 and $+0.525$. The relation of rates of asthma, with and without a PC₂₀ less than 25 mg/ml, to ST findings is shown in Fig. 3.

We calculated and examined interaction terms for all of these variables showing significant interactions, but in no case did the addition of interaction terms cause the main effects to become insignificant in a multiple regression. Furthermore, they did not meaningfully increase the multiple *r* in any of the subsequent stepwise regressions to be described. For these reasons and to simplify presentation of the data, none of the interaction terms

TABLE IV. Use of test variables to predict BRindex

Variable	Coefficient $\pm$ SE in final equation	p Value in final equation	Multiple r after entry
STtotal	0.0124 $\pm$ 0.000955	<0.0001	0.516
RATIO	-0.00477 $\pm$ 0.000545	<0.0001	0.613
% Pred FEV ₁	-0.000966 $\pm$ 0.000301	<0.005	0.621

TABLE V. Use of all variables in the study to BRindex

Variable	Coefficient $\pm$ SE in final equation	p Value in final equation	Multiple r after entry
Asthma	0.0939 $\pm$ 0.0113	<0.0001	0.540
STtotal	0.00873 $\pm$ 0.000966	<0.0001	0.625
RATIO	-0.00377 $\pm$ 0.000517	<0.0001	0.677
% Pred FEV ₁	-0.000750 $\pm$ 0.000281	<0.01	0.681
Wheeze	0.0169 $\pm$ 0.00677	<0.02	0.685

Sex, hay fever, and eczema did not enter the regression.

TABLE VI. Study of subjects nonresponsive by PC₂₀ criteria (n = 559)

Variable	Coefficient $\pm$ SE in final equation	p Value in final equation	Multiple r after entry
RATIO	-0.00259 $\pm$ 0.000423	<0.0001	0.262
Asthma	0.0634 $\pm$ 0.0123	<0.0001	0.337
STtotal	0.00319 $\pm$ 0.000958	<0.0005	0.366
Wheeze	0.0112 $\pm$ 0.00538	<0.05	0.375

Sex, %FEV₁, hay fever, and eczema did not enter the regression.

are utilized further. It is of interest, however, that the correlation of the interaction term combining STtotal and the lowness of the RATIO, that is, STtotal $\times$ (100 - RATIO), had a correlation coefficient with BRindex as high as 0.565.

The manner in which RATIO and %FEV₁ as continuous variables add to STtotal in a multiple regression is shown in Table IV. Inclusion of RATIO eliminated any significant relationship of gender to BRindex. When effects of STtotal and RATIO were examined in relationship to the frequency of any PC₂₀ value less than 25, 12 of the 13 subjects (92.3%) with an 8+ STtotal and a RATIO of less than 75% had such PC₂₀ values. In contrast, only three of 162 subjects (1.9%) with a

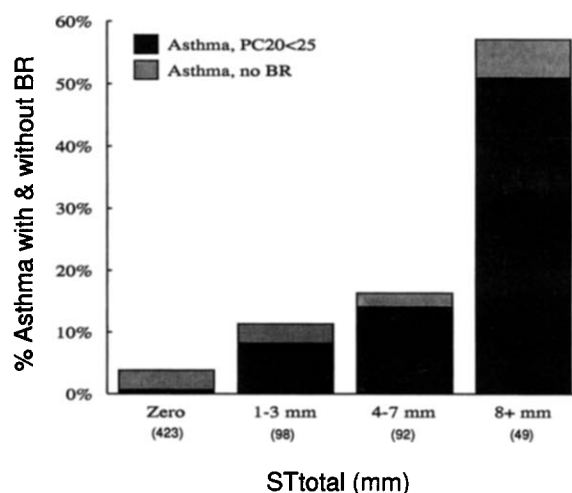


FIG. 3. The overall height of the bars indicates the total percent of subjects reporting asthma. The black portion of the bars indicates those who have a PC₂₀ less than 25 mg/ml. The shaded portion at the top indicates reported asthma without BR as determined by PC₂₀ criteria. The trend for an increasing proportion of subjects with asthma to have a PC₂₀ values less than 25 with increasing STtotal (the sum of mite, cat, *A. fumigatus*, and dog reactions) is significant at $p < 0.0001$. The numbers at risk are shown in parentheses.

RATIO greater than 90% and STtotal values of zero showed a PC₂₀ value of less than or equal to 25. In the zero STtotal group, relatively high rates of responsiveness were seen only in the few subjects with frank spirometric abnormality (an FEV₁/VC ratio < 75%). When gender was added to this model, it became insignificantly related to BRindex after RATIO entered the regression.

Stepwise multiple regressions were then carried out with BRindex as the dependent variable by using all of the variables that showed a univariate relationship to BRindex. Results are shown in Table V.

Table VI shows regressions for those subjects who did not have a calculable PC₂₀ value and would have been grouped together as "nonresponsive" by this criterion. The degree of responsiveness assessed by BRindex was significantly related to several predictor variables even in these subjects.

In general, RATIO proved to be a better predictor of responsiveness than the %FEV₁, and in all cases any significant gender relationship to responsiveness disappeared after STtotal or RATIO was controlled. The same was true for hay fever and for history of eczema. It is also of interest that asthma was related to BRindex even in subjects without a measurable PC₂₀ value, and this

relationship remained after controlling for RATIO and STtotal.

DISCUSSION

The analyses presented here generally follow along the lines of the analyses reported in 11-year-old children, which examined IgE levels as an index of allergy.¹⁵ Present data in 13-year-olds, suggest that not all types of IgE have similar relationships to BR. The specific IgE leading to grass ST sensitivity, for example, appears to show no independent relationship to BR. As shown previously, grass sensitivity relates closely to hay fever but is not independently related to asthma.¹²

There are several important limitations of this study. Although the sample of the total birth cohort first evaluated at age 3 appeared to be representative of the entire birth cohort and subsequent studies have not shown significant biases in regard to major social or demographic variables, it has become nearly impossible to assure that those subjects studied in later surveys remain completely representative of the entire original birth cohort. In this sample, there appeared to be a reluctance of subjects with hay fever to undergo allergy STs. Another problem is that the sickest subjects were sometimes given only salbutamol and not challenged with methacholine. This occurred much less frequently in 13-year-old children than in 11-year-old children, and all such 13-year-old children had positive allergy ST responses to house dust mite. Their exclusion would tend to minimize slightly the relationships of BR to allergy ST positivity.

There is also a problem in comparing the relationships of BR to serum IgE levels versus allergy ST responses because these test results were not obtained simultaneously. However, although there were more children considered too ill to be challenged with methacholine at age 11 than at age 13, those who were so tested showed almost identical values for BRindex. The mean $\pm$ SD BRindex values at ages 11 and 13 were 1.08 ± 0.11 and 1.08 ± 0.10 , respectively. The correlation coefficient for BRindex versus log serum IgE at age 11 was 0.285 compared with an r value of 0.516 for BRindex versus STtotal in this study.

The allergy test results independently related to BRindex (mite, cat, *A. fumigatus*, and dog) are the same as those previously detected by analyzing the odds ratios for responders when one considered ST results as either positive or negative.¹¹ In this report, however, the size of the test reaction was shown to be significantly related to BRindex even

in those with positive reactions. There did not appear to be any cutoff level at which the size of the ST reactions became significant predictors of BRindex. Even 1 mm reactions showed significant relations. Requiring a larger reaction to consider a test result as positive may make sense when the tests are being used to determine the important allergens in clinical practice, but one might question whether a high cutoff for positivity is reasonable in population studies. In the data presented here, the degree of BR generally increased steadily with the sizes of the reactions. The frequency of responsiveness has been reported previously to be related to the severity of ST reactions in a general population sample.¹⁹

Highly significant correlations of BRindex with various predictor variables were found even when only those subjects who would have been grouped together as nonresponders by PC₂₀ criteria were considered. It is interesting that asthma itself was an independent predictor of BRindex in these subjects, suggesting that even those patients with asthma who appear nonresponsive to methacholine by usual PC₂₀ criteria do have some increase in methacholine responsiveness. These findings again demonstrate the advantages of a continuous index of BR, not only in facilitating multivariate analyses, but in showing relationships that are lost when a large fraction of the population is grouped together in a nonresponsive category.

As in our previous study involving IgE in 11-year-old children,¹⁵ a different index of response to methacholine proved to be more normally distributed than the slope recommended by O'Connor et al.¹⁶ The more nearly Gaussian distribution makes the BRindex more suitable for parametric analyses. On the other hand, when we did use a slope approximating that suggested by O'Connor et al.,¹⁶ the results were qualitatively almost identical to those with BRindex. In fact, the overall correlation with all significant predictor variables was 0.691, slightly higher than the 0.685 found with BRindex. This slight improvement in multiple r is, however, an artifact of the more skewed distribution of the slope in the report by O'Connor et al.¹⁶ The statistical methods used in the analyses in this study are very robust and not very much affected by minor deviations of the dependent variable from a truly normal distribution. We are not necessarily recommending the BRindex used herein as the best method for creating a continuous variable for BR in any other data set. It simply proved to be the most normally distributed variable in this study and therefore should provide the most valid para-

metric estimates relating methacholine response to predictor variables. As indicated by the multiple r of 0.685, the maximal reduction in variance of BRindex (r^2) was 47%, when all independently significant predictor variables were used in the total population sample.

Spirometric test results were highly significant predictors of BR, regardless of the ST status of the subjects and among asthmatic, as well as nonasthmatic, subjects. It is unclear whether this results from lung function in children reflecting the state of inflammation of their airways, thereby reflecting the activity of the disease, which we cannot otherwise accurately assess, or whether it is a result of the geometric changes in the airways implied by a low %FEV₁ or RATIO. The relation of BR to RATIO in subjects with asthma is similar to that noted in 11 year-old children.¹⁵

The most striking difference in these analyses from those previously reported for IgE is the significant relationship between the degree of allergy measured by STs and the BR seen in asthmatic subjects. This is compatible with previous observations by others, indicating a relation of the degree of allergy with the severity of disease in childhood asthma.²⁰ No such relationship was seen between serum IgE level and BR in 11-year-old children with asthma.¹⁵ It seems likely that this results from the ability of skin testing to identify the types of IgE most relevant to BR. This possibility is compatible with the findings that grass STs (the most common positive test response in this study) did not relate to BR after mite, cat, *A. fumigatus*, and dog were taken into account; but the size of the grass-induced ST reaction was significantly correlated with the serum IgE level obtained 2 years earlier ($r = 0.344$, $p < 0.0001$) in the 294 subjects who had IgE levels at age 11 and totally negative responses to mite, cat, *A. fumigatus*, and dog at age 13.

Although serum IgE levels have the advantage of providing a continuous index of overall allergy and can identify the subjects in the population who are least "allergic," they have the disadvantage of measuring all types of IgE, not all of which appear relevant to the asthma and BR problem. Allergy STs, on the other hand, allow no assessment of the relation of BR to allergy in the 423 of 662 (63.9%) of our study population who are nonreactive to any of the four relevant STs and certainly not in the 328 of 662 (49.5%) who showed no reactions at all to any of the STs applied. Both types of testing may be needed to understand the overall role of allergy in suspected atopic diseases in epidemiologic stud-

ies. It seems possible that highly sensitive tests for specific serum IgEs might eliminate at least some of the problems in relying on positive ST reactions.

Our data in New Zealand children do not confirm the observation of Tollerud et al.²¹ in adults that serum IgE levels relate more closely to asthma than allergy ST results or the similar findings in the Tucson study.²² This may be true only in adults in whom allergy ST responses to the critical allergens may not remain positive. Even more likely is the possibility that the small batteries of allergy STs used in these studies did not contain the allergens most likely to be associated with asthma in their locales.

Those allergens that relate to BR in this study and to asthma in previous reports¹¹ are either ubiquitous or found primarily indoors. They may be involved in the pathogenesis of asthma because they are the allergens to which there is the most continuous exposure and to which newborns are likely to be exposed. They are also readily inhaled into the lower airway. The lack of an independent relation of other allergens to BR does not mean that they cannot act as triggers of acute asthmatic attacks in sensitive subjects, and if they result in late-phase reactions they may increase the airway inflammation and BR. The importance of mite and cat in this study may also reflect the high concentrations of these allergens in New Zealand homes. The risk of later asthma has been shown to relate to the magnitude of earlier exposure to allergens, at least for house dust mite.²³ Other indoor allergens, such as cockroach, may be of major importance in locales where such allergens are very prevalent.²⁴ The specific allergens relating most closely to BR in this study may be very dependent on the characteristics of the environment in New Zealand.

It seems important to emphasize that we do not mean to imply from these data that BR and asthma are simply a result of allergy to certain inhaled allergens. The pathogenetic mechanisms for asthma are undoubtedly more complex. Because symptoms of the disease often begin during the first few years of life, at which time they are usually triggered by viral respiratory infections, it seems possible that such infections have a role in its pathogenesis rather than simply identifying the susceptible child. Indeed, it is possible that the immunologic changes associated with these viral infections induce a general tendency to form IgE. We are also unable to exclude the possibility that the tendency to develop bronchial hyperresponsiveness is itself an

inherited trait, which becomes manifest when provocative factors such as infections or allergy to inhalants supervene. It does appear to us, however, that the development of allergies to environmental allergens represents a very important factor in the persistence of asthma into later childhood and that control of these allergic phenomena may be of critical importance in control of the disease.

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