

ASSESSMENT AND PREDICTION OF ASTHMA AND ITS SEVERITY IN THE PEDIATRIC COMMUNITY

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PEREIRA, J. C. R. et al. Assessment and prediction of asthma and its severity in the pediatric community. Rev. Saúde públ., S. Paulo, 24: 437-44, 1990.

ABSTRACT: Seventy four asthmatic children aged 7 to 11 years were examined along with controls matched by age and sex. Clinical and laboratory investigations preceded a 28-day follow-up where data about morning and evening peak expiratory flow rate (PEF), symptoms and treatment were recorded. The coefficient of variation of PEF was found to be an objective measurement of asthma severity that has statistically significant correlation with both symptoms ($r_s = .36$) and treatment ($r_s = .60$). Moreover, it separates mild and severe asthmatics, as confirmed by statistically significant differences ($p = .008$ or less) in symptoms, treatment, skin allergy and airways response to exercise. Skin allergy and airways responsiveness to exercise were found to be predictors of both disease and severity. By means of logistic regression analysis it was possible to establish the probabilities for both asthma and severe asthma when children presenting and not presenting these characteristics are compared. One single positive skin test represent a probability of 88% for the development of asthma and a probability of 70% for severe disease. A PEF reduction of 10% after an exercise test implies a probability of 73% for disease and a probability of 64% for severe disease. Increases in these variables imply geometrically increased risks and their presence together have a multiplicative effect in the final risk.

KEYWORDS: Asthma, epidemiology. Predictive value of tests. Risk.

INTRODUCTION

Epidemiological studies of asthma have been proposed as a means of narrowing the gap between current scientific knowledge and medical practice⁴. Indeed, the increasing trends in mortality and morbidity from asthma call for an adjustment of ongoing research in this field to the requirements for better management of this disease. Epidemiological studies should help the assessment of the ill-health process and the identification of factors related to the disease. Such studies should suggest the pathophysiology of the disease and the controlling activities that are most likely to be successful.

The present study endeavours to identify an objective measurement of the asthmatic phenomenon which could allow assessment of disease severity. Moreover, it seeks the identification of asthma correlates that can help in the prediction of the disease and its severity even when direct measurements are not available.

SUBJECTS AND METHODS

From a community survey of 1,671 schoolchildren of the Avon county (England), asthmatic children were identified according to the judgement of a physician (FC). Seventy-four of these children, aged 7 to 11 years, were examined along with controls matched by age and sex. Clinical history was obtained and tests for airways responsiveness to exercise and skin allergy were performed. In a 28-day follow-up, all children were asked to record their morning and evening peak expiratory flow rate (PEF) with a mini-Wright peak flow meter, as well as to fill in a diary card where symptoms and medication being taken should be registered.

The airways response to exercise was tested by having the children run on a treadmill set at age-related slopes and speeds that produced a mean (SD) pulse rate of 165(12)bpm in asthmatics and of 167(11.6)bpm in controls. PEF was measured before exercise and 1, 4, 10, 15 and 20 minutes after exer-

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cise with a Wright peak flow meter. The difference between the lowest PEF after exercise and initial PEF was expressed as a percentage of the latter to produce a maximum percentage fall. Results were classified as negative if PEF reductions were less than 10% and three increasing degrees of positivity were established for PEF reductions greater than 10%: 1st degree, reductions between 10 and 20%; 2nd degree, reductions between 20 and 30%; and 3rd degree, reductions greater than 30%. Medication was held up for at least 8 hours prior to the testing session.

Skin allergy was ascertained by prick-testing the children to house dust mite, cat dander, timothy grass and cow's milk (Bencard UK Ltd, Great West Rd, Brentford, Middlesex TW8 9BE). Positive and negative controls were provided by carbol-saline and histamine 1% solutions. All testing solutions were numbered and their nature was not known to the operator. The largest diameter of the weals produced were measured, positive control values were subtracted from allergen values and if the result was greater than 3mm, allergy was considered positive.

Daily symptoms were expressed by a score ranging from 0 to 11 established according to the presence and intensity of symptoms as shown in Table 1. Asthmatic children were classified in seven different groups of increasing severity according to the treatment required to control the disease, as shown in Table 2.

Measurements of PEF were adjusted for height and sex and expressed as percentage of predicted

according to the formula proposed by Polgar and Weng¹⁶. The coefficient of variation of PEF over the 28-day follow-up period was calculated as a proposed measurement of asthma and its severity. This took into consideration that the coefficient of the variation of PEF, being directly proportional to the variations of PEF and inversely proportional to the mean PEF, should be a measurement adequate to meet the most accepted definition of asthma which says that asthma is a narrowing of the airways which varies over time either spontaneously or as a result of the inhalation of bronchodilators².

Analysis of the frequency distributions of coefficient of variation of PEF (COV) among asthmatics and controls was used to establish two groups of severity to be theoretically regarded as severe and not-severe asthmatics. The 95th centile of a normal curve fitted to the controls' distribution was taken as the cut-off point so that not-severe asthmatics have COVs that are similar to those presented by non-diseased children and severe asthmatics have COV values which are unlikely to be observed among non-asthmatic children. The reliability of COV as a measurement of severity was assessed by checking its degree of correlation, among asthmatics, with symptom score, and type of treatment required to control disease (Spearman's correlation coefficient). Furthermore, the mean values of these variables were compared in the two groups of severity established by COV and the statistical significance of the differences assessed (Mann-Whitney U Probability Test).

Correlates of asthma and its severity were verified by checking the statistical significance of their differences in each group (Mann-Whitney U Probability Test). Their ability to predict either asthma or its severity was analysed by logistic regression analysis with backwise deletion of variables not achieving statistical significance at a level of $p < .05$. As a result, prediction could be expressed as risks for disease or for severe disease. According to this method¹⁰, risks can be expressed by odds ratios, which represent how much greater is the probability of subjects affected by a risk factor becoming sick (or severely diseased) than are subjects not affected by such a risk factor. Alternatively, odds ratios can be transformed to probabilities for disease (or severe disease). Odds ratios are the approximate measure of the absolute relative risk observed in the population.

RESULTS

Asthma correlates and their predictive value

In each of the asthmatic and control groups there were 43 boys and 31 girls. The mean (SD) age was 9.70 (1.18) in the asthmatic group and 9.74 (1.15) in the control. The maximum difference in age within each asthmatic/control pair was usu-

TABLE 1

Scores for ascertainment of respiratory symptoms

Symptoms	Score
By night	
Good night	0
Bad night - because slightly wheeze	1
- because awoke 2-3 times with wheeze	2
- because awake most of the time with wheeze	3
- for other reasons	0
By day	
Wheeze: None	0
Little	1
Moderately bad	2
Severe	3
Activity: Quite normal	0
Could run a short distance	1
Limited to walking	2
Off school or indoors due to chest problems	3
Cough: None	0
Occasional	1
Frequent	2

TABLE 2
Classification of type of treatment required by asthmatic children to control symptoms

Type of treatment	Severity group
No medicaments required during the follow-up	0
One single non-steroid drug sometimes needed to relieve symptoms	1
A non-steroid drug association sometimes needed to relieve symptoms	2
One single non-steroid drug used as regular prophylaxis	3
A non-steroid drug association used as regular prophylaxis	4
Inhaled corticosteroid used alone as regular prophylaxis	5
Inhaled corticosteroid associated with another drug as regular prophylaxis	6

ally less than 6 months, but in one case a greater difference, 10 months, was allowed.

Comparison of the values of the variables (1) airways response to exercise, (2) number of positive skin-tests, (3) proportion of atopic first degree relatives and (4) proportion of asthmatic first degree relatives enabled better understanding of the differences between asthmatic and non-asthmatic subjects. In Figure 1 each of these variables was transformed to a percentage difference from the overall mean to ease comparison and to allow common graphic representation.

All these variables had statistically significant differences between the two groups; their effect on the risk for the presence of asthma was

evaluated by means of logistic regression analysis. The results are shown in Table 3. The last column presents the same information conveyed by the odds ratio, but expresses it as the probability for being asthmatic.

Taking into consideration that weather conditions could have influenced airways responses to exercise, information about relative humidity and temperature was forced in the logistic regression equation. This provided an adjustment of the odds ratios of all variables for temperature and humidity. The adjusted odds ratio for airways response to exercise was found to be 2.89 (95% CI = 1.38 - 6.07), a figure very close to the original (compare with information in Table 3).

COV as an indicator of asthma severity

Figure 2 shows the frequency distribution of COV for asthmatics and controls as two stacked areas. COV among asthmatic children presents a bimodal distribution that distinguishes two different groups of asthmatics. The first of these groups overlaps the controls distribution. The 95th centile of a normal curve adjusted to the control's COV distribution was taken as a cut-off point for severity. This interprets the asthmatics' bimodal distribution as a natural separation of mild and severe patients. Indeed, the first group has significantly fewer symptoms and treatment requirements than the second one (Fig. 3).

Among the asthmatic children, COV was also found to have a fair correlation with the mean symptom score over the follow-up period ($r_s = .37$; $p < .001$) and a stronger correlation with the treatment needs of these children ($r_s = .60$; $p < .0001$).

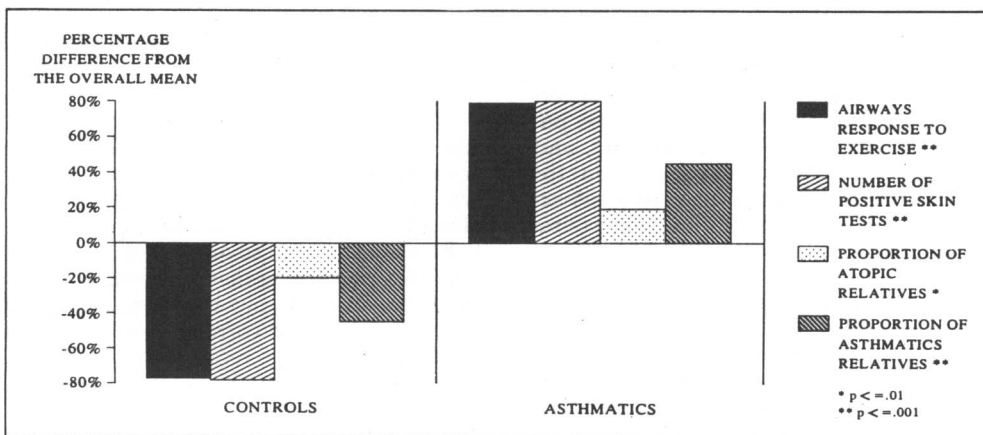


Fig. 1- Comparison of the mean values of the listed variables among asthmatics and controls

TABLE 3
Results of logistic regression analysis of asthma

Predictor Variable	Variable Unit	Regression Coefficient	Odds ratio	95% C.I.	Probability
Allergy	1 positive skin test	2.03822	7.67	3.45 - 17.07	88%
Airways Response to Exercise	reduction of 10% in PEF	1.03742	2.82	1.35 - 5.89	73%
Proportion of Atopic Relatives	100% of atopic relatives	1.82204	6.18	1.30 - 29.26	86%

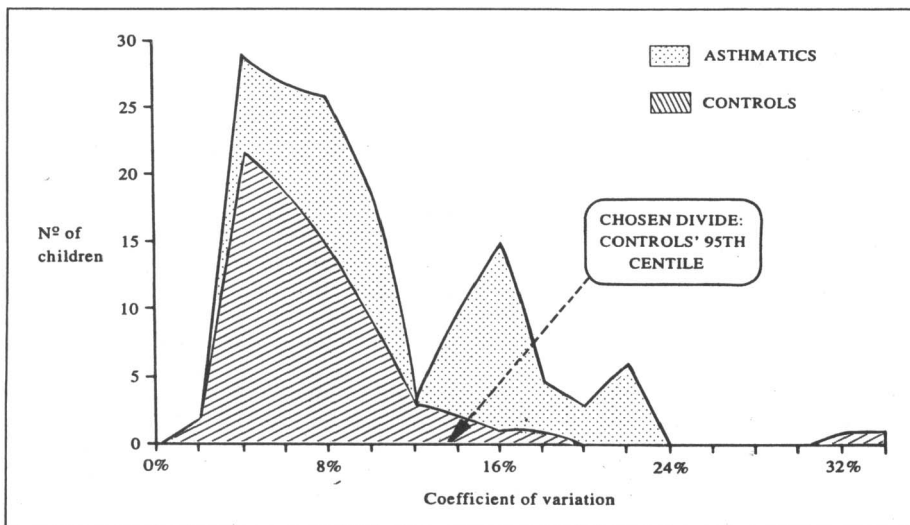


Fig. 2 - Frequency distribution of the coefficient of variation of PEF among asthmatics and controls

Although the correlation of COV with subjective assessments of severity was studied to evaluate its adequacy as a measurement of severity, it seems important to bear in mind the differences in nature that lie between subjective and objective measurements. The two subjective indices of severity herein considered should represent the patient's evaluation (symptoms) on one hand, and the physician's evaluation (treatment) on the other. The correlation between these two subjective measurements was found to be even poorer than that observed with COV: $r_s = .31$; $p < .007$.

Severity correlates and their predictive value

The group of mild asthmatics comprised 47 (63% of the total) children and the group of severe asthmatics included the remaining 27 (37% of the total). There was no significant difference in sex but severe asthmatics were significantly ($p < .001$) younger than mild asthmatics. The same varia-

bles checked before in the comparison of asthmatics and non-asthmatics were examined again, in the same fashion, for the comparison of severe and not-severe asthmatics. The results are depicted in Figure 4.

The number of positive skin tests and the response to exercise were found to be associated with severity of asthma and their predictive value was ascertained by logistic regression analysis along with age, which had been previously found to be associated with severity. Results are shown in Table 4. Considering that treatment could exert influence over COV and therefore change the predictive value of the correlate variables, it was entered in the logistic regression analysis to check its effect on the odds ratios. The adjusted odds ratios for allergy and age did not change very much: 2.20 (95% CI= 1.21 - 4.01) and 0.40 (95% CI= .22 - .73), respectively. Nevertheless, the adjusted odds ratio for airway response to exercise lost its

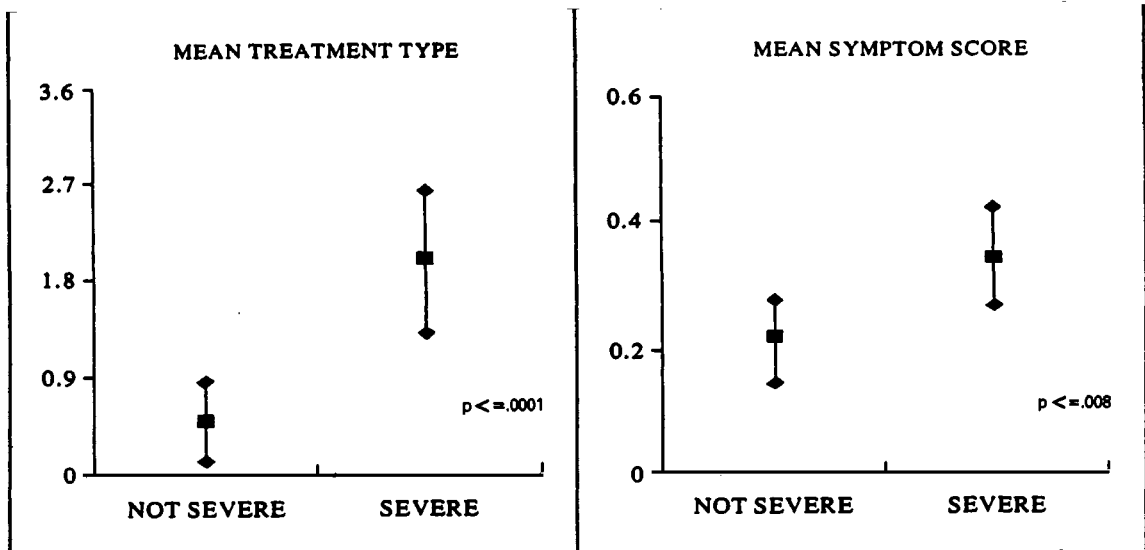


Fig. 3 - Mean values of subjective measurements of severity in mild and severe asthmatics

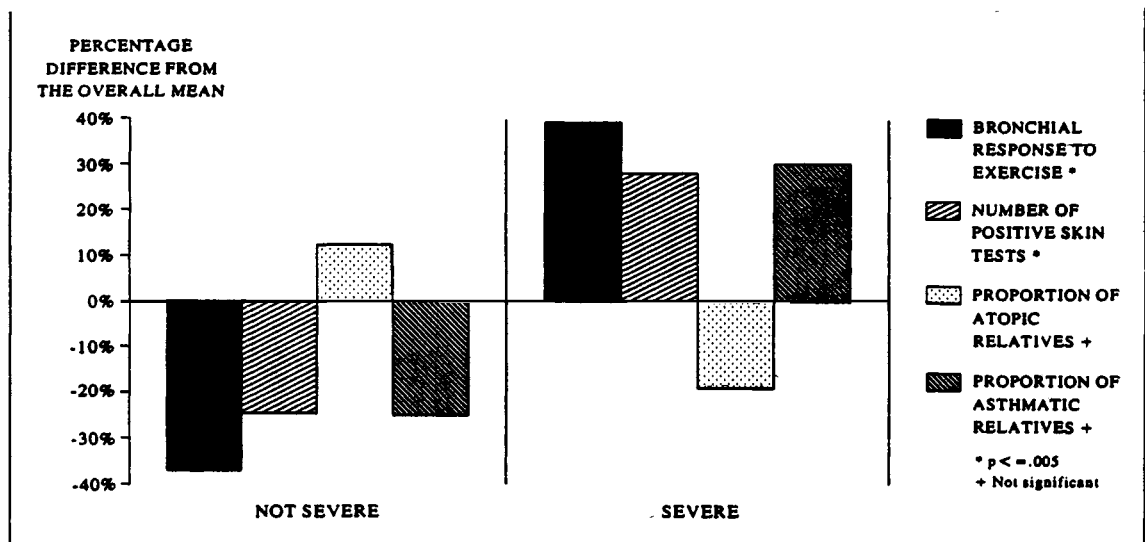


Fig. 4 - Comparison of the mean values of the listed variables in the two severity groups

TABLE 4

Results of logistic regression analysis of severity asthma

Predictor Variable	Variable Unit	Regression Coefficient	Odds Ratio	95% C.I.	Probability
Allergy	1 positive skin test	.84658	2.33	1.30 - 4.15	70%
Airways Response to Exercise	reduction of 10% in PEF	.59148	1.80	1.10 - 2.95	64%
Age	1 year	-.87426	0.42	0.24 - 0.73	29%

original level of significance and its 95% confidence interval came to include values close to one, which means an equal chance of being severely or not severely diseased: odds ratio = 1.62; 95% CI = .94 - 2.81.

DISCUSSION AND CONCLUSIONS

In the present study, it was found that the coefficient of variation of PEF (COV) had a bimodal distribution suggesting two clusterings of asthmatics, the first mild enough to overlap non-asthmatics and the second with COV values unlikely to be seen among non-asthmatic children. Therefore, COV seems to be a proper approach for the assessment of asthma severity even though it might not be a good instrument for the identification of asthmatics.

The reliability of COV as a measurement of the severity of asthma is reinforced by its ability to separate two groups of asthmatics with distinct degrees of symptoms and treatment requirements (Fig. 3). Indeed, the comparison of two groups of distinct clinical importance seems to be more adequate than the pursuit of linear correlation between subjective and objective measurements, chiefly because subjective measurements may be found, as in the present study, to have very little internal agreement.

Serial records of PEF have frequently been recommended as a means to monitor severity of asthma. The variability of PEF was demonstrated to be related to events of respiratory arrest and death^{9,21} and decreases in PEF are found to precede asthma attacks⁸. Nevertheless, an objective measurement of variations of PEF should overcome the potential bias of individual interpretation of serial records.

In the present study, the analysis of asthma correlates have consistently pointed out the importance of atopy, as measured by skin prick-tests, and airways hyperreactivity, as measured by hyperresponsiveness to exercise. Their association with both the disease and its severity suggests that they may have an incremental effect on asthma, which suggests a possible causal relationship. This thesis of an etiological role of atopy and airways hyperreactivity in the development of asthma agrees with the current knowledge of the mechanisms of the disease. Indeed, extrinsic asthma is commonly accepted as allergic in origin and inflammatory in nature.

The association between atopy and the presence and severity of asthma has already been reported by various authors^{7,12,13} but much less agreement has been achieved so far in relation to the genetic factors of asthma. Contrary to some evidence reported in the literature^{6,19,20} suggesting that asthma and other atopic diseases have dif-

ferent modes of inheritance, in the present study the proportion of non-asthmatic atopic first degree relatives was found to be associated with the presence of asthma, while the proportion of asthmatic relatives itself did not correlate with asthma in the children. On the other hand, the logistic regression analysis results suggest that the correlation of atopic relatives and the presence of asthma is very weak. Indeed, it will only be relevant for a proportion of atopic relatives greater than 85%, for only from this point onwards does the confidence interval of the odds ratio not include the value of one, which would mean that the chances of disease would be the same in the presence or absence of atopic relatives. Such a high proportion of atopic relatives (>85%) was observed in only 10 of the children studied, six of whom were asthmatics.

Although airways hyperresponsiveness to non-specific stimulation has been often referred to in the literature as a correlate of asthma severity^{11,17,18}, the specific relationship between exercise induced bronchoconstriction (EIB) and severity has not received so much attention. Nevertheless, there is evidence that, although airways hyperresponsiveness to chemical stimuli involves different mechanisms, airways responses to exercise and to either histamine or methacholine seem to have a close relationship^{1,3,5,14}, which would suggest that asthma severity should be expected to correlate with EIB as it does with other non-specific stimuli.

To better appreciate the importance of age as a correlate of asthma severity, the risks for severity may be transformed in two risks for non-severity so that instead of a risk of .4 for being severely diseased one could say a risk of 2.5 for NOT being severely diseased. In 1986, Park et al.¹⁵, studying data provided by the British National Cohort, found that fifty per cent of the children labelled asthmatics by the age of five were free of symptoms when they were ten. This gives support to the empirical impression that children tend to outgrow their asthma, and the present finding that severity of asthma abates as the children grow older might be related to such a tendency, as a child would have to be severely diseased to go through this attenuating period without overcoming the disease. For a thorough exploration of this point it would be interesting to have the relationship between age and the presence of asthma confirmed and expressed as relative risks, which could not be done in the present study as cases and controls were matched by age.

The logistic regression analysis¹⁰ provides odds ratios adjusted for all variables entering the model, so that each regressor variable is an independent predictor of asthma and its severity. Increases in these variables imply geometrical increases of risks and the presence of two variables together

has a multiplicative effect on the overall risk. In the present study, the test of possible confounding variables, as climatic conditions and treatment, confirmed the pertinency of the correlation between the regressor variables and the risks for disease and severity of disease. Airways response to exercise seems to lose its predictive value for severity of asthma when its odds ratio is adjusted for the type of treatment required, for its confidence interval comes to include values close to one. Therefore, it should not be considered in the pre-

diction of severity of asthma in children undergoing treatment.

In conclusion, the present study provided evidence that severity of asthma can be objectively assessed by the coefficient of variation of PEF and that both asthma and its severity can be predicted by the presence of their correlates. Moreover, prediction can be quantitatively expressed either by relative risk or its equivalent probability.

PEREIRA, J. C. R. et al. Avaliação e predição da asma e sua gravidade na comunidade pediátrica. Rev. Saúde públ., S. Paulo, 24: 437-44, 1990.

RESUMO: Foram submetidas a exames, juntamente com grupos controle segundo idade e sexo, 74 crianças asmáticas, com idade de 7 a 11 anos. Exames clínicos e laboratoriais precederam um acompanhamento de 28 dias, quando foram registrados dados sobre a taxa de pico do fluxo respiratório (PEF), sintomas e tratamento. Observou-se que o coeficiente de variação do PEF é uma medida objetiva do grau de gravidade da asma, que tem uma correlação estatística significativa, tanto com os sintomas ($r_s = .036$), quanto com o tratamento ($r_t = .60$). Além disso, separa os asmáticos graves e leves, como foi confirmado pelas diferenças estatisticamente significantes ($p = 008$ ou menos) nos sintomas, tratamentos, alergias da pele e resposta das vias aéreas ao exercício. Estas duas últimas foram consideradas elementos prognosticadores tanto da doença como do grau de gravidade. Pela regressão logística foi possível estabelecer a probabilidade para a asma grave quando as crianças, apresentando ou não essas características, foram comparadas. Um único teste de pele positivo representa uma probabilidade de 88% para o desenvolvimento de asma, e de 70% para doença grave. A redução do PEF de 10%, depois de um teste de exercício, leva a uma probabilidade de 73% de doença e de 64% para doença grave. Aumentos nessas variáveis implicam riscos aumentados geometricamente, cuja presença conjunta tem efeito multiplicativo no risco final.

DESCRITORES: Asma, epidemiologia. Valor de predição dos testes. Risco.

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Received in 15/2/1990

Accepted in 17/4/1990