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Asthma and chronic bronchitis

Can family physicians predict rates of progression?

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OBJECTIVE To investigate whether the progression rate of asthma or chronic bronchitis can be predicted from a cross-sectional assessment of features that can be measured by family physicians.

DESIGN Secondary analysis of data from a 2-year randomized, controlled bronchodilator intervention study in family practice.

SETTING Twenty-nine general practices in the eastern part of The Netherlands.

PATIENTS One hundred sixty patients (101 with chronic bronchitis, 59 with asthma) from the 29 general practices.

INTERVENTIONS Predictors were related to the annual decline in lung function (the forced expiratory volume in one second) by means of multiple analysis of variance, controlling for age, sex, smoking habits, initial FEV₁ level, bronchial hyperresponsiveness, reversibility of obstruction, and medication during the study.

MAIN OUTCOME MEASURES Predictors of the annual decline in lung function (FEV₁), which is believed to be the most important measure for progression.

RESULTS Only three variables predicted the decline in lung function: having a barrel-shaped chest, experiencing wheezing, and an unusual diurnal peak-flow rate index. Wheezing was the best predictor of the annual decline in lung function. In chronic bronchitis, the decline in FEV₁ of wheezing patients was 133 mL/y compared with 62 mL/y for non-wheezing patients ($P < 0.05$). In asthma with more severe symptoms, wheezing patients had a tendency to decline 156 mL/y compared with 57 mL/y among non-wheezing patients ($P = 0.08$).

CONCLUSIONS It is nearly impossible to predict the progression rate of asthma or chronic bronchitis from symptoms, physical signs of the chest, and the PEF. Therefore, patients with a rapid progression rate can probably be detected only by monitoring progression of the disease through repeated lung function testing.

OBJECTIF Analyser si l'évaluation transversale des caractéristiques mesurables par les médecins de famille peuvent prédire le rythme de progression de l'asthme ou de la bronchite chronique.

CONCEPTION Analyse secondaire des données tirées d'une étude randomisée et contrôlée effectuée aux Pays-Bas pendant deux ans et utilisant la bronchodilatation comme intervention.

CONTEXTE Vingt-neuf pratiques générales situées dans la partie orientale des Pays-Bas.

PARTICIPANTS Cent soixante patients (101 bronchitiques chroniques, 59 asthmatiques) suivis par 29 praticiens généraux.

INTERVENTIONS Les facteurs de prédiction furent associés au taux annuel de détérioration de la fonction pulmonaire (le volume expiratoire maximum/seconde) au moyen d'analyses multiples de variance, de correction en fonction de l'âge, du sexe, des habitudes tabagiques, du VEMS initial, de l'hyperréactivité bronchique, de la réversibilité de l'obstruction et de la médication utilisée pendant l'étude.

PRINCIPALES MESURES DES RÉSULTATS Les facteurs de prédiction du taux annuel de détérioration de la fonction pulmonaire (VEMS) que l'on considère être la mesure la plus importante pour évaluer la progression de la maladie.

RÉSULTATS Seulement trois variables ont pu prédire la détérioration de la fonction pulmonaire: thorax en tonneau, présence de sibilances (wheezing) et indice inhabituel du débit de pointe diurne. Parmi ces variables, le wheezing s'est avéré le meilleur facteur pour prédire le taux annuel de détérioration de la fonction pulmonaire. Dans la bronchite chronique, la détérioration du VEMS des patients présentant des sibilances fut de 133 mL/année comparativement à 62 mL/année pour les patients dépourvus de sibilances ($p < 0,05$). Chez les asthmatiques présentant des symptômes plus sévères, la détérioration des patients sibilants fut de 156 mL/année comparativement à 57 mL/année chez les non-sibilants ($p = 0,08$).

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CONCLUSIONS Il est presque impossible de prédire le rythme de progression de l'asthme ou de la bronchite chronique à partir des symptômes, des signes physiques pulmonaires et de la mesure du débit expiratoire de pointe. Le seul moyen probablement capable de détecter une détérioration rapide de la maladie consiste à en surveiller la progression par des tests répétés de la fonction respiratoire.

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ASTHMA AND CHRONIC BRONCHITIS are chronic and progressive diseases of the airways.¹⁻³ The annual decline in lung function is much higher among patients¹⁻³ than in random samples of the population.⁴ At an advanced stage of the disease, daily life becomes severely limited as a consequence of poor lung function.⁵ Patients with a rapid decline in lung function are particularly at risk of early disability or death from chronic airway obstruction.⁶

Morbidity and mortality due to asthma and chronic bronchitis seem to be rising in several countries.^{7,8} Because most patients with asthma and chronic bronchitis are treated in family practice,⁹ it is possible that underdiagnosis and undertreatment contributes to this worldwide trend. Effective treatment of asthma and chronic bronchitis in the form of inhaled corticosteroids is now available.¹⁰⁻¹² Therefore, early detection (and early treatment) of patients at risk (with a fast progression rate) is important.¹³

It is unclear how this can be carried out easily and effectively by family physicians. Family physicians are limited in their ability to diagnose the severity of asthma and chronic bronchitis objectively. In general they are able to assess bronchial symptoms, physical signs of the chest, and the peak expiratory flow rate (PEFR).

This study aimed to assess whether the progression rate of asthma or chronic bronchitis can be predicted from a cross-sectional assessment of bronchial symptoms, physical signs of the chest, PEFR, and diurnal (DI-PEFR) or week-to-week (CV-PEFR) variation in the PEFR. These indices were related to the rate of progression (annual decline in lung function) for 59 patients with asthma and

101 patients with chronic bronchitis. These patients had participated in a 2-year bronchodilator trial.¹⁴ Data from this study were used for this secondary analysis.

METHODS

Patients

One hundred sixty patients (101 with chronic bronchitis, 59 with asthma) participated in a 2-year randomized, controlled bronchodilator intervention study in family practice.¹⁴ At the start of the study, 29 family physicians selected all their patients 30 years and older with symptoms of asthma or chronic bronchitis. Only patients who showed moderate airflow obstruction (FEV_1 or FEV_1 divided by the expiratory vital capacity had to be 2 SD below their predicted value, but more than 50% of predicted value)¹⁵ or bronchial hyperresponsiveness to histamine (provocative concentration of histamine producing a 20% fall in FEV_1) were included ($PC_{20} \leq 8$ mg/mL). Exclusion criteria were dependence on corticosteroids, chronic heart failure, malignant disorders, or other severe life-threatening diseases.

The criteria for diagnosis of asthma or chronic bronchitis were based on the standards of the American Thoracic Society.^{5,14} All patients gave informed consent. The study was approved by the Ethics Committee of the University of Nijmegen.

During the 2-year study period, patients received only monotherapy with inhaled bronchodilators (salbutamol or ipratropium bromide). No corticosteroids were permitted, except during exacerbations. All exacerbations were treated in a standard way by family physicians: a broad-spectrum antibiotic and a 10-day tapering course

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with 5-mg tablets of oral prednisolone (5-5-4-4-3-3-2-2-1-1).

Measurements

Respiratory symptoms. Respiratory symptoms were assessed at the start of the study with the Medical Research Council's questionnaire and added for a score of 0 to 8.¹⁶

Physical examination. Physical examination of the chest by standardized procedure took place during an exacerbation-free period. All medication was discontinued for at least 8 hours before examination. The

examination consisted of inspection and auscultation during unforced deep breathing with open mouth¹⁷ and was performed while patients were upright. Presence or absence of the following items was noted:

- barrel-shaped chest,
- decreased expiratory breath sounds,
- prolonged expiratory phase,
- wheezing,
- inspiratory sounds audible without using a stethoscope,
- fine crackles, or
- coarse crackles.

Patients measured their PEFR weekly (on the same day and at the same time of the day) during 6 weeks, using an Assess Peak Flow Meter (Health Products Inc, USA).¹⁸ The highest values of a triple measurement in the morning and in the evening were used for three parameters: the mean of the morning PEFR during 6 weeks; the DI-PEFR (the difference between the morning and evening PEFR, expressed as a percentage of the maximum value of that day); and the CV-PEFR (the standard deviation expressed as a percentage of the mean morning PEFR of 6 weeks).

The FEV₁ was measured at 6-month intervals and after 1 and 13 months of study by means of the Microspiro HI-298 (seven assessments).¹⁹ The best of three FEV₁ measurements, with the highest sum of the forced vital capacity (FVC) and the FEV₁, was used for data analysis.

Analysis

For each patient, the annual decline in FEV₁ was estimated by linear regression of seven assessments of FEV₁ over time.¹⁴ The independent variables (bronchial symptoms, mean morning PEFR, DI-PEFR, CV-PEFR, and physical signs of the chest) were related to the annual decline in FEV₁ by means of multiple analysis of variance (MANOVA). The possibly confounding influence of several variables (age, sex, height, smoking history, number of packs smoked daily per

Table 1. Demographic characteristics of patients with chronic bronchitis and asthma

VARIABLE	PATIENTS WITH CHRONIC BRONCHITIS OR ASTHMA (N = 160) %	PATIENTS WITH CHRONIC BRONCHITIS (N = 101) %	PATIENTS WITH ASTHMA (N = 59) %
Sex (male)	55	61	47
Allergy	28	19*	44
Smoking	55	62†	42

*P < 0.005.
†P < 0.05.

Table 2. Clinical characteristics of patients with chronic bronchitis and asthma

VARIABLE	PATIENTS WITH CHRONIC BRONCHITIS OR ASTHMA N (SD)	PATIENTS WITH CHRONIC BRONCHITIS N (SD)	PATIENTS WITH ASTHMA N (SD)
Age (y)	51 (12)	52 (12)	49 (12)
Number of packs smoked daily per year	16 (16)	18 (16)*	12 (15)
Symptoms score	4 (1)	4 (1)	4 (1)
FEV ₁ (%)	76 (19)	78 (17)*	72 (21)
CV-PEFR	7.4 (4.8)	6.5 (4.0)†	9.2 (5.0)
DI-PEFR	9.3 (6.3)	7.7 (5.0)†	12.0 (6.0)

*P < 0.05.
†P < 0.001.

year, bronchodilator therapy during the study, FEV₁ as a percentage of the predicted value, PC₂₀, and reversibility of airflow obstruction) was investigated and, if necessary, controlled for.

The separate and combined effects of bronchial symptoms and the variation in PEFR on the annual decline in lung function were further quantified by dichotomizing the symptom score and the peak flow variability on the basis of rounded mean values (\leq mean \div $>$ mean).

RESULTS

Patient characteristics are shown in *Tables 1 and 2*. Patients with chronic bronchitis more often were smokers, had smoked more in the past, were less often allergic, and had a lower DI-PEFR and CV-PEFR than patients with asthma.

Correlation coefficients between symptoms, peak flow variability, and physical signs on the one hand and the annual rate of decline in FEV₁ on the other are shown in *Table 3*. Crackles were not present in asthma; therefore,

no correlation coefficient could be calculated. Correlation coefficients were low, both in asthma ($r < 0.15$) and in chronic bronchitis ($r < 0.21$). Only wheezing sounds in chronic bronchitis correlated significantly with lung function decline ($r = 0.21$, $P < 0.05$).

Table 4 shows estimates of the annual decline in lung function in the multivariate linear regression model. Only three significant relationships were found. In chronic bronchitis, a barrel-shaped chest and a high DI-PEFR were related to greater decline in lung function (estimate -166 and -8 mL/y, respectively). In the group as a whole, wheezing was accompanied by greater decline in lung function (estimate -70 mL/y). The percentage of the variance explained by the model was 43% in asthma, 27% in chronic bronchitis, and 22% in the group as a whole.

Figure 1 shows the separate and combined effects of bronchial symptoms with the week-to-week or diurnal variation of the PEFR on the annual rate of decline. All figures in *Figure 1* were adjusted for confounding variables. Wheezing sounds were present

Table 3. Correlation coefficients between symptoms, physical signs of the chest, (variability in) PEFR, and annual decline in lung function in asthma and chronic bronchitis (univariate analysis):

Pearson's correlation coefficient is used for continuous variables, Spearman's correlation coefficient for other variables.

VARIABLE	PATIENTS WITH CHRONIC BRONCHITIS OR ASTHMA	PATIENTS WITH CHRONIC BRONCHITIS	PATIENTS WITH ASTHMA
Symptom score	0.027	-0.012	0.123
PEFR	-0.085	-0.137	0.029
DI-PEFR	0.034	-0.054	0.131
CV-PEFR	0.134	0.179	0.042
Barrel-shaped chest (+/-)	0.073	0.182	-0.123
Decreased expiratory sounds (+/-)	0.058	0.084	0.047
Prolonged expiration (+/-)	0.037	0.013	0.114
Wheezing sounds (+/-)	0.151	0.214*	0.084
Noisy inspiration (+/-)	-0.017	-0.011	-0.001
Fine crackles (+/-)	-0.006	-0.013	—
Coarse crackles (+/-)	-0.037	-0.049	—

* $P < 0.05$.

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in 18 patients with asthma and 22 patients with chronic bronchitis. In chronic bronchitis patients with wheezing, the annual decline in FEV₁ was -133 mL/y versus -62 mL/y in non-wheezing patients ($P < 0.05$). This difference was caused by patients who had more severe symptoms (-142 mL/y versus -58 mL/y). In asthma, wheezing also tended to predict decline in lung function, but only among patients with more severe symptoms (-156 versus -57 mL/y, $P = 0.08$).

We also investigated whether the mean morning peak flow rate as percentage of predicted values was related to lung function decline as a separate factor or in combination with symptoms. Patients who had a peak flow of more than 70% had no greater decline in lung function than patients with a peak flow below 70%. The same holds for 50% or 60%. There was no difference between chronic bronchitis and asthma in this respect.

DISCUSSION

Family physicians managing asthma and chronic bronchitis are often confronted with patients whose disease has already worsened too much. Evidence suggests that asthma and chronic bronchitis are diagnosed too late.^{13,20,21} Morbidity and mortality due to asthma and chronic bronchitis are still rising.^{7,8} Therefore, early detection and early treatment of patients at risk (with rapidly progressing disease) is important.¹³

Our study showed that it is nearly impossible to predict the progression rate of asthma or chronic bronchitis from a cross-sectional assessment of symptoms, separate physical signs of the chest, the morning PEFr, and the DI-PEFR or CV-PEFR. In the multivariate model, only 22% to 43% of the variance in lung function decline could be explained by all variables investigated. This means that our ability to

Table 4. Multivariate linear regression of the relationship between symptoms, physical signs of the chest, (variability in) PEFr, and annual decline in lung function: All figures were corrected for possibly confounding variables.

VARIABLE	PATIENTS WITH CHRONIC BRONCHITIS OR ASTHMA ESTIMATED mL/y (SE)	PATIENTS WITH CHRONIC BRONCHITIS ESTIMATED mL/y (SE)	PATIENTS WITH ASTHMA ESTIMATED mL/y (SE)
Symptom score	8 (9)	2 (9)	7 (12)
PEFR	0 (0)	0 (0)	0 (0)
DI-PEFR	-2 (0)	-8 (4)*	3 (4)
CV-PEFR	0 (3)	3 (5)	1 (5)
Barrel-shaped chest (+/-)	-108 (79)	-166 (81)*	346 (184)
Decreased expiratory sounds	-28 (35)	-46 (43)	22 (65)
Prolonged expiration (+/-)	4 (40)	32 (46)	-27 (68)
Wheezing sounds (+/-)	-70 (33)*	-78 (40)	-102 (60)
Noisy inspiration (+/-)	33 (48)	68 (57)	29 (94)
Fine crackles (+/-)	-57 (45)	-58 (43)	—
Coarse crackles (+/-)	110 (116)	23 (107)	—
Percentage explained variance	22	27	43

* $P < 0.05$.

predict lung function decline is very limited and that patients with a fast progression cannot be detected from an assessment of symptoms, physical signs of the chest, and PEFR. Therefore, probably the only way to detect these patients is to monitor the course of disease by measuring lung function.

Introducing spirometry in family practice could be an important step forward in the long-term management of asthma and chronic bronchitis.²² Reliable and portable spirometers are available, although still rather expensive.¹⁹

Early detection is useful only when early intervention is available and effective. Evidence shows the efficacy of inhaled corticosteroids for asthma during several months²³⁻²⁵ and during 1 or more years.^{11,12,26-28} Several guidelines on the treatment of asthma have advised introducing inhaled corticosteroids at an early stage of the disease and avoiding regular use of bronchodilators.^{10,29,30} There is also some evidence for the efficacy of inhaled steroids among patients with chronic bronchitis.^{11,12} After our study, we performed a 2-year trial with inhaled beclomethasone (800 µg daily) for the 56 patients with a rapid progression rate.¹² We observed that rapid progression among these patients was decelerated by the use of the inhaled steroid for both asthma and chronic bronchitis. Therefore, early intervention with inhaled steroids appeared to be effective for these patients at risk.

The only parameters that could to some extent predict a rapid decline in lung function were a barrel-shaped chest, the presence of wheezing, and the DI-PEFR. The correlation between wheezing and the decline in lung function is interesting. Although wheezing is assumed to be a typical feature of asthma, it is also a sign of chronic bronchitis.⁵ Cross-sectional assessments have shown that wheezing correlates with airflow obstruction only in patients with chronic bronchitis.^{17,31} Wheezing was more likely to be present in asthma but did not signify the presence or absence of airflow

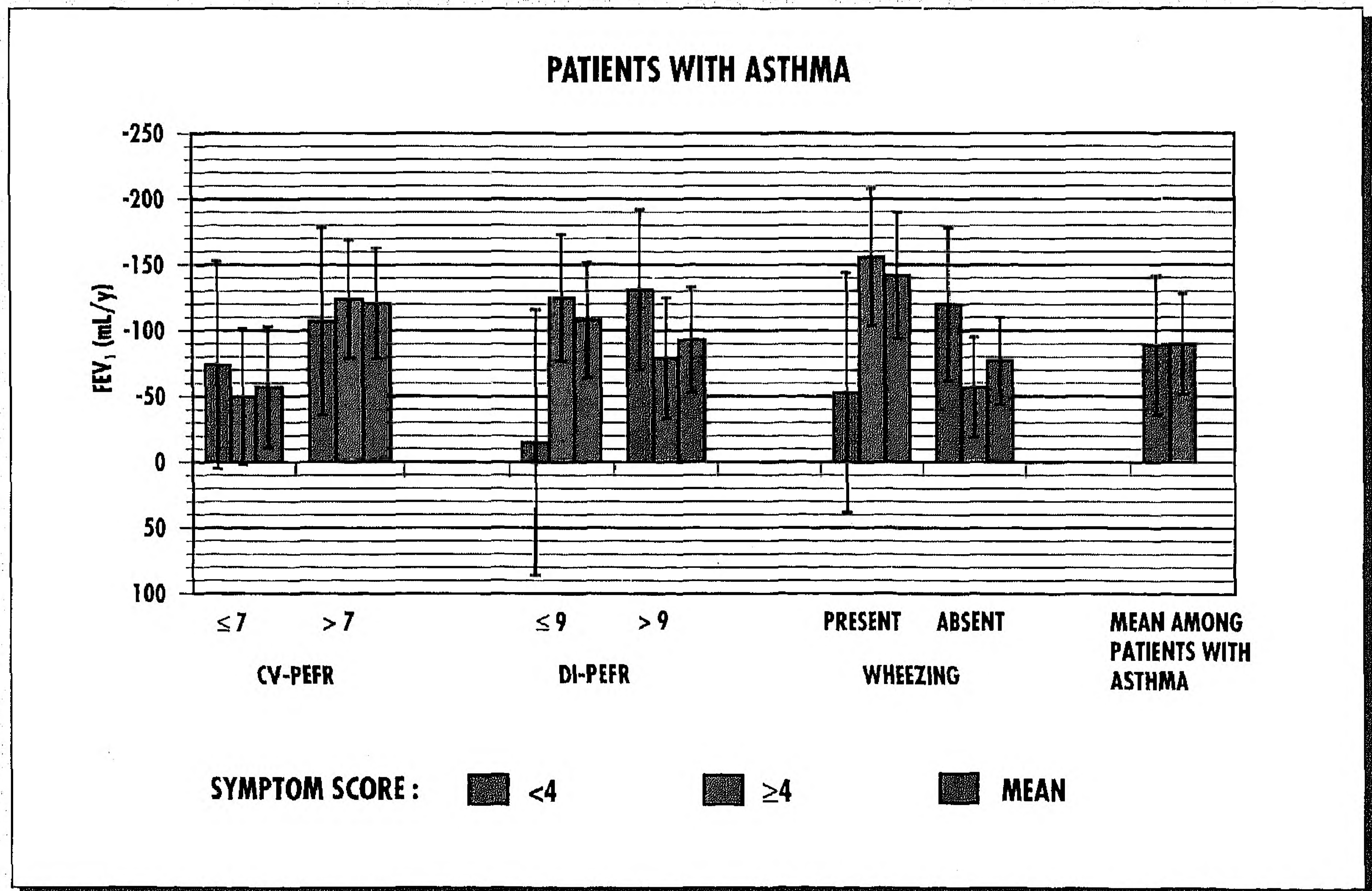
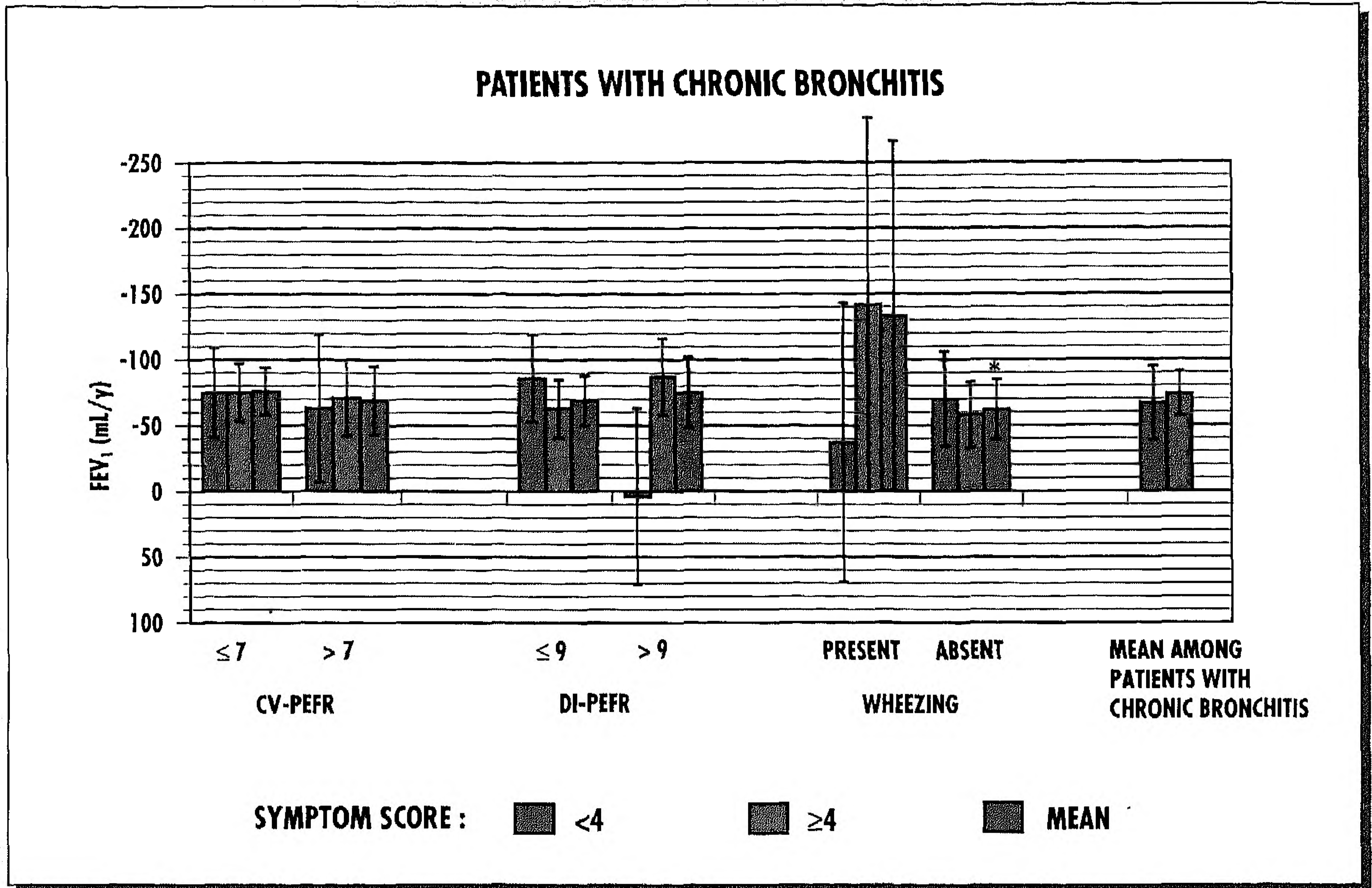
obstruction.¹⁷ In this study, the presence of wheezing was mainly related to an increased annual decline in lung function among patients with chronic bronchitis.

The presence of a barrel-shaped chest is supposed to be typical for hyperinflation and could indicate some degree of emphysematous changes.⁵ Burrows and co-workers³² demonstrated that patients with a diagnosis of emphysema had a substantial annual decline in lung function exceeding that of patients with other types of chronic obstructive airways disease. Emphysema was not excluded in our study, and it is therefore possible that some bronchitis subjects in this study already had some emphysematous changes. This probably explains the correlation between a barrel-shaped chest and a rapid decline in lung function.

These findings together suggest that physical signs of the chest, at least the signs of barrel-shaped chest and wheezing, to some extent reflect the presence of airflow obstruction^{17,31} and also have some predictive value for the course of airflow obstruction. It was interesting that a prolonged expiratory phase, which is widely accepted as the most direct sign of airflow obstruction,³¹ was in no way related to a pronounced decline in lung function.

The DI-PEFR showed a significant correlation with the annual rate of decline among patients with chronic bronchitis. Although the variability of the peak flow (both diurnal and week-to-week) was much higher in asthma than in chronic bronchitis, this variability did not predict lung function decline better in asthma. The variability in peak flow (and airway obstruction) is related to the airway responsiveness to bronchoconstrictive and bronchodilating stimuli, as they all probably express instability of the airways.³³ This particularly is the case in asthma. Inflammation is an underlying mechanism of airway instability. It has been shown before that instability of the airways in asthma, as assessed by means of the bronchial responsiveness

Figure 1. Separate and combined effects of the bronchial symptom score with CV-PEFR, DI-PEFR, and wheezing on annual rate of decline measured in FEV₁ (mL/y): Differences were tested with Student's *t* test. Figures were adjusted for possibly confounding variables.



**P* < 0.05.

to histamine, predicts a rapid annual decline in lung function.³

The mean morning PEFr was not a good predictor for the annual rate of decline in lung function in this study, though it is an effective and essential tool for managing chronic persistent asthma²⁹ and acute severe asthma,³⁴ and for self-management plans of asthma.³⁵ Burrows et al³⁶ investigated the predictive value of screening spirometry for the annual decline in FEV₁ in a sample from the general population. They also observed that one assessment of spirometry was not reliable enough to detect the patients at risk, particularly among women. More measurements of lung function over time will probably make detecting patients with asthma and chronic bronchitis more reliable.

A disadvantage of a reanalysis is that results are used from a study not originally set up for this purpose and, therefore, can serve only as an observational study. No natural course of the disease was studied, as the patients used in this study were treated with bronchodilators. However, all figures were controlled for bronchodilator use. We saw no significant influence of medication. With this limitation in mind, we observed that it is nearly impossible to predict the progression rate of asthma or chronic bronchitis from an assessment of symptoms, physical signs of the chest, and variability in PEFr. Patients at risk for rapid progression of their asthma or chronic bronchitis can probably be detected only by monitoring the course of disease by assessing lung function. ■

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