

Effects of smoking and changes in smoking habits on the decline of FEV₁

P. Lange, S. Groth, J. Nyboe, J. Mortensen, M. Appleyard, G. Jensen, P. Schnohr

Effects of smoking and changes in smoking habits on the decline of FEV₁. P. Lange, S. Groth, J. Nyboe, J. Mortensen, M. Appleyard, G. Jensen, P. Schnohr.

ABSTRACT: The aim of this study was to examine the effects of cigarette smoking and changes in smoking habits on the decline of forced expiratory volume in the first second of expiration (FEV₁). We studied 7,764 men and women for 5 yrs. The subjects were grouped according to self-reported smoking habits during the observation period. We found that persistent cigarette smoking, in particular heavy smoking, accelerated the decline in FEV₁. In 310 subjects who quit smoking during the observation period, the decline of FEV₁ was less pronounced than the decline observed in persistent smokers. In subjects younger than 55 yrs of age, smoking reduction was associated with a less pronounced FEV₁ decline, while in the elderly subjects smoking reduction had no effect on the FEV₁ decline. An increase in the number of cigarettes smoked was generally associated with a more rapid decline of FEV₁, while the beginning of smoking during the 5 yrs of observation did not seem to influence the decline of FEV₁. We conclude that smoking cessation or reduction may lead to a demonstrable beneficial effect on the FEV₁ decline within a few years.

Eur Respir J., 1989, 2, 811-816

Copenhagen City Heart Study, Medical Dept B and Dept of Clinical Physiology and Nuclear Medicine, Rigshospitalet and Medical Dept P/Chest Clinic, Bispebjerg Hospital, Copenhagen, Denmark.

Correspondence: P. Lange, Medical Dept B 2011, Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen, Denmark.

Keywords: Epidemiology; lung diseases; lung function; smoking.

Received: January, 1989; accepted after revision June 12, 1989.

This study was supported by grants from The Danish Heart Foundation, The National Union for the Fight against Lung Diseases and Danish Medical Research Council.

Cigarette smoking is the major factor accelerating age-related decline of forced expiratory volume in the first second of expiration (FEV₁). Some longitudinal studies have failed to demonstrate beneficial effects of smoking cessation on the decline of FEV₁ [1, 2], but it is now generally accepted that quitting of smoking, within a few years results in normalization of the FEV₁ decline towards the values of never-smokers [3-10]. Although many longitudinal studies have comprised a large number of subjects, the numbers of individuals who have stopped smoking have been too small to demonstrate whether quitting has a similar effect on the loss of lung function in heavy smokers as in light smokers. Likewise, the numbers of subjects who reduced smoking, began smoking for the first time, or resumed smoking during the observation periods have in several studies been too small to warrant a separate analysis of the effects of these changes in smoking behaviour on the decline of FEV₁.

The purpose of the present investigation was to analyse the impact of changes in smoking habits on the decline of FEV₁. The main objective was to see whether smokers who stop or reduce smoking have a smaller decline of FEV₁ than smokers who do not change their smoking habits. The study was performed by analysing a large sample of the general population, including a considerable number of subjects who quit, reduced, resumed and increased smoking.

Subjects and methods

In 1976, a prospective cardiovascular epidemiological study, the Copenhagen City Heart Study, was initiated. The participants were selected among 90,000 persons living in a defined area around the University Hospital of Copenhagen, Rigshospitalet. A sample of 19,698 subjects was selected at random after age stratification: persons younger than 20 yrs of age were excluded and the sample fraction was highest (50%) for persons 40-69 yrs old. This age distribution was chosen to make a study of risk factors for ischaemic heart disease and chronic obstructive lung disease possible within a relatively short observation period.

The subjects were invited by letter to attend a health examination at Rigshospitalet on a specific date between March 1, 1976 and March 31, 1978, and again five years later between April 6, 1981, and September 7, 1983. A total of 14,223 (74% of invited) attended the first examination and a total of 12,698 (70% of invited) attended the second examination. Details of the selection procedure of the study sample and a description of the nonresponders have been given elsewhere together with an outline of the questionnaire and the complete examination programme [11, 12].

From the total sample of 11,135 subjects who attended both examinations, we excluded 344 persons with a

history of bronchial asthma because the withdrawal of antiasthmatics prior to the pulmonary examination was not standardized. Also excluded were 2,718 persons who at either examination reported consuming other kinds of tobacco than cigarettes, 139 subjects who stopped smoking less than one year prior to the second examination, and 170 subjects with incomplete data required for the analysis. This resulted in a final study group of 7,764 subjects.

Spirometry

At both examinations, the recordings of FEV_1 were made on the same electronic spirometer (Monaghan N 403, Littleton, Colorado), which was calibrated daily. As a criterion for the correct performance, a reproducibility of measurements within 95% was used. The largest volume was used in the analysis. The study design ensured that none of the subjects had been smoking tobacco for at least 45 min prior to the pulmonary function examination.

The results of asymptomatic never-smokers without bronchial asthma and diabetes mellitus, and with alcohol consumption of less than 50g per day were used to calculate prediction values for FEV_1 for normal subjects in the study sample. The prediction equations were:

$$\text{For women} \\ FEV_1(\text{ml}) = 410 - 27.6 \times \text{age}(\text{yrs}) + 21.2 \times \text{height}(\text{cm})$$

$$\text{For men} \\ FEV_1(\text{ml}) = -469 - 35.2 \times \text{age}(\text{yrs}) + 32.0 \times \text{height}(\text{cm})$$

The FEV_1 calculated using these equations was compared with reference values for normal subjects published by The Danish Lung Association [13]. The comparison showed no systematic differences, as the values for FEV_1 in all sex, age and height groups were within 200 ml of each other.

For each subject, the difference between the FEV_1 at first and at second investigation was divided by the length of the observation period for this subject to obtain the annual FEV_1 change (ΔFEV_1).

Smoking habits

According to the reported smoking habits subjects were grouped as follows:

NS-NS: Never-smokers: subjects who at both examinations claimed that they had never smoked tobacco;

EX-EX: Ex-smokers: subjects who stopped smoking prior to the first examination and remained nonsmokers during the observation period;

LS-LS: Light smokers: consistent smokers who at first and second examination smoked less than 15 cigarettes a day;

HS-HS: Heavy smokers: consistent smokers who at first

and second examination smoked more than or equal to 15 cigarettes a day;

LS-EX: Light smokers who quitted: subjects who were smoking less than 15 cigarettes a day at first examination and quitted smoking more than one year prior to the second examination;

HS-EX: Heavy smokers who quitted: subjects who were smoking more than or equal to 15 cigarettes a day at first examination and quitted smoking more than one year prior to the second examination;

HS-LS: subjects who between the two examinations reduced smoking from more than or equal to 15 cigarettes a day to less than 15 cigarettes a day;

LS-HS: subjects who between the two examinations increased cigarette smoking from less than 15 cigarettes a day to more than or equal to 15 cigarettes a day;

NS-SM: subjects who were never-smokers or ex-smokers at first examination and started or resumed smoking between the two examinations.

Statistical methods

To assess the FEV_1 decline in the different smoking groups multiple linear regression was applied with ΔFEV_1 as the dependent variable. Separate regressions were performed for men and women and for younger (age < 55 yrs) and elderly subjects (age ≥ 55 yrs). The independent variables of interest were the previously defined smoking groups which, with the exception of never-smokers (NS-NS), were included as binary variables assigned 1 for subjects belonging to a particular smoking group and 0 otherwise. It was planned to include age (yrs) and height (cm) as confounders in the analysis. However, as height did not reach the level of significance in any of the regressions it was not included in the final model.

Adjustment for the initial FEV_1 was considered, but decided against. This was done following the suggestions of VOLLMER [14] who in a recent paper concluded that when initial values differ substantially between the groups of interest adjustment of initial values may not be appropriate. The final regression model was:

$$\Delta FEV_1(\text{ml}\cdot\text{yr}^{-1}) = k_0 + k_1 \times \text{age}(\text{yrs}) + k_2 \times \text{smoking group}$$

where k 's are regression coefficients. In the regression model, the group of persistent never-smokers (NS-NS) was included in the intercept (k_0). Therefore, a significant regression coefficient for any other smoking group ($k_{2, \text{group}}$) means that this smoking group has a decline of FEV_1 which differs significantly from the decline of never-smokers. A positive sign of the regression coefficient for a smoking group, indicates a greater decline in this group than among never-smokers.

We investigated if interaction terms representing combinations of age and smoking groups significantly improved the regressions, but this was not the case.

In the analysis, we were unable to include the exact times of the changes in the smoking habits, as this information was not covered in the interview. The data presented will therefore tend to underestimate the impact of a given change in smoking habits, as the FEV₁ decline occurring before this change also contributes to Δ FEV₁.

Results

Table 1 shows the number of subjects and the mean values of age, initial FEV₁ as percentage of predicted (FEV₁ %pred), duration of smoking habit, and daily cigarette consumption according to smoking group and sex. FEV₁ %pred differed between the smoking groups,

Table 1. – General characteristics of the subjects according to sex and smoking group

	n	Age yrs	Initial FEV ₁ %pred	Duration of smoking yrs	Cigarette consumption	
					First examination	Second examination
Women						
NS-NS	1,467	54(12)	98(19)	0	0	0
EX-EX	628	53(11)	98(18)	16(11)	0	0
LS-LS	1,080	52(10)	92(18)	27(11)	8(3)	8(3)
HS-HS	820	47(9)	90(16)	26(9)	19(5)	19(5)
LS-EX	157	51(12)	94(20)	23(12)	6(4)	0
HS-EX	25	46(10)	92(16)	25(10)	19(10)	0
HS-LS	186	49(10)	88(18)	27(10)	17(2)	10(3)
LS-HS	233	46(10)	91(17)	24(10)	10(2)	16(3)
NS-SM	98	46(12)	97(18)	12(12)	0	6(2)
Men						
NS-NS	453	47(14)	100(18)	0	0	0
EX-EX	736	56(11)	99(20)	24(13)	0	0
LS-LS	506	52(11)	94(18)	33(12)	8(3)	8(3)
HS-HS	882	48(10)	90(17)	31(11)	22(7)	22(7)
LS-EX	82	50(11)	92(20)	31(13)	7(4)	0
HS-EX	46	48(10)	98(19)	30(11)	20(5)	0
HS-LS	140	53(10)	88(19)	35(11)	18(4)	10(2)
LS-HS	137	46(11)	93(17)	28(11)	10(2)	18(4)
NS-SM	79	48(12)	97(18)	22(14)	0	11(2)

Mean values with SD in parentheses. FEV₁ %pred: forced expiratory volume in the first second of expiration as percentage of the predicted value at first examination, calculated by comparing the results of each participant with the prediction equations for normal subjects in the study sample (see text). n= number NS-NS: never-smokers; EX-EX: ex-smokers; LS-LS: light smokers; HS-HS: heavy smokers; LS-EX: light smokers who quit; HS-EX: heavy smokers who quit; HS-LS: heavy smokers who changed to light smokers; LS-HS: light smokers who changed to heavy smokers; NS-SM: never-smokers or ex-smokers who began smoking. For further explanation of groups see text.

Table 2. – Unadjusted decline of FEV₁ (ml·yr⁻¹) by sex, age, and smoking group

Smoking group	Women				Men			
	<55 yrs		≥55 yrs		<55 yrs		≥55 yrs	
	n	Δ FEV ₁	n	Δ FEV ₁	n	Δ FEV ₁	n	Δ FEV ₁
NS-NS	722	13(3)	754	32(3)	302	21(7)	151	34(9)
EX-EX	321	18(5)	307	32(4)	306	27(7)	430	36(5)
LS-LS	641	17(4)	439	39(3)	279	22(6)	227	52(3)
HS-HS	624	30(4)	196	48(5)	634	42(5)	248	56(6)
LS-EX	80	15(10)	77	28(9)	51	17(16)	31	11(20)
HS-EX	17	9(10)	8	-	32	36(24)	14	43(36)
HS-LS	127	14(10)	59	49(10)	70	17(15)	70	51(11)
LS-HS	184	30(6)	49	56(11)	105	30(11)	32	53(20)
NS-SM	72	10(11)	26	52(14)	61	27(20)	18	24(22)

Mean values with SE in parentheses. Differences in groups smaller than 10 are not given. Δ FEV₁: unadjusted decline of forced expiratory volume in the first second of expiration; n: number of subjects. For other abbreviations see legend to table 1.

Table 3. - Regression analysis of ΔFEV_1 (ml·yr⁻¹) on age and smoking group for women and men

Independent variable	Women		Men	
	<55 yrs	≥55 yrs	<55 yrs	≥55 yrs
Intercept	-43	-14	-34	40
Age yrs	1.3*** (0.2)	0.7* (0.3)	1.4*** (0.3)	-0.1 (0.6)
Smoking group				
NS-NS	0	0	0	0
EX-EX	-2 (6)	0 (5)	-2 (10)	2 (9)
LS-LS	1 (5)	9* (4)	-7 (5)	19* (10)
HS-HS	17*** (5)	19*** (6)	14* (7)	21* (10)
LS-EX	3 (10)	-3 (9)	-11 (18)	-24 (19)
HS-EX	-2 (21)		9 (18)	10 (27)
HS-LS	0 (8)	18* (10)	-12 (15)	18 (14)
LS-HS	18* (7)	26** (10)	8 (13)	19 (19)
NS-SM	0 (11)	23 (15)	-1 (16)	-11 (24)

Regression coefficients with SE in parentheses. The smoking group comprising less than 10 subjects was not included in the regression analysis. Estimated significance level for testing coefficient=0: #: 0.05<p<0.1; *: 0.01<p<0.05; **: 0.001<p<0.01; ***: p<0.001. For other abbreviations see legend to table 1.

being highest in persistent never-smokers and ex-smokers and lowest in persistent heavy smokers and heavy smokers who reduced smoking. The average number of cigarettes smoked by the persistent smokers did not change during the observation period. Subjects who reduced smoking and subjects who increased smoking reported a change in daily cigarette consumption of approximately the same magnitude. Almost all of the subjects who started or restarted smoking during the observation smoked less than 15 cigarettes a day on the second examination.

In nearly all smoking groups, the average annual decline of FEV_1 was higher in men than in women and higher in the elderly than in younger subjects (table 2). Smokers, especially heavy smokers, had higher ΔFEV_1 than nonsmokers. The distributions of ΔFEV_1 in the different smoking groups were almost normal, but as in other longitudinal studies, the scatter of the results was considerable. In fact there were subjects in all smoking groups who actually experienced a gain in FEV_1 during the observation. Standard deviations ranged between 60–120 ml. They were larger in men than in women, and in quitters than in persistent never-smokers.

The mean declines presented in table 2 are not suitable for statistical comparison as they are not adjusted for the exact age of the subjects. Such adjustment was performed by means of multiple linear regression, which included the smoking groups as the variables of interest and age as the covariate (table 3). In all sex and age groups, persistent heavy smokers had a significantly higher decline of FEV_1 than never-smokers. Similar trends were observed among elderly persistent light smokers, especially men, while the younger light smokers had declines of FEV_1 not significantly different from never-smokers.

In both sexes, elderly light smokers who quitted had a smaller decline of FEV_1 than persistent light smokers. In heavy smokers, quitting had also a beneficial effect on the FEV_1 decline. However, in elderly men, the quitting effect was less pronounced among heavy smokers than among light smokers. There were too few elderly women in the HS-EX group to allow a separate analysis. Smoking reduction had a pronounced beneficial effect among the younger subjects, while it had no effect in the elderly.

An increase in the number of cigarettes smoked was associated with a higher decline of FEV_1 in all subgroups, except for elderly men. The latter observation was consistent with the finding of almost the same decline among elderly men in the LS-LS group as in the HS-HS group.

The decline of FEV_1 among persistent ex-smokers (EX-EX) and among beginners (NS-SM) was not significantly different from the decline of never-smokers.

Discussion

The results of this study confirm that smoking, especially heavy smoking, accelerates the decline of FEV_1 . The findings suggest that smoking cessation has an advantageous effect on the FEV_1 decline and that reduction of the number of cigarettes smoked also has a beneficial effect among younger subjects.

The effect of smoking resulting in a more rapid FEV_1 decline among smokers compared with never-smokers is well known and has been reported by several investigators [1–10]. As in the majority of the earlier studies, we found the association between smoking and the accelerated decline of FEV_1 to be dose-dependent and in light smokers also age-dependent.

In most previous studies in which a beneficial effect of smoking cessation on the FEV₁ decline has been observed, heavy smokers and light smokers have been considered jointly, mainly because of a small number of quitters [3–10]. As light smokers tend to stop smoking more frequently than heavy smokers, and as it can be difficult to demonstrate a significant accelerating effect of light smoking on Δ FEV₁, especially in the younger subjects (table 3), the beneficial effect of smoking cessation with regard to the lung function could have been overestimated by considering all quitters jointly. Separate analysis of heavy and light smokers who stopped smoking showed that quitting was associated with a reduction of FEV₁ decline in both groups but that this effect was most pronounced among light smokers (table 3). In general, quitting of smoking had a decelerating effect on the decline of FEV₁ among the younger as well as the elderly subjects. This is in accordance with the results of CAMILLI *et al.* [10] and warrants that quitting of smoking for preserving lung function should be recommended in all age groups. HUGHES *et al.* [15] found that smoking cessation resulted in a reduction of FEV₁ decline even in subjects with established pulmonary emphysema.

The subjects who started or resumed smoking did not experience a significantly steeper decline of FEV₁ than the nonsmokers. The relatively short observation period, the small number of beginners, and the fact that the majority of beginners smoked less than 15 cigarettes a day are the most likely explanations for this finding.

In contrast to the considerable number of studies on the effect of smoking cessation, the literature on the effects of reducing the number of cigarettes smoked is sparse. Two short term studies showed that subjects who reduced their tobacco consumption by 25% or more experienced an improvement in some of the indices of the function of the small airways [16, 17]. In the latter study, even a slight, although nonsignificant, improvement in FEV₁ was noticed [17]. Although the average change in the number of cigarettes smoked by the elderly and younger reducers was not significantly different in our study, the younger group experienced a considerable reduction of the FEV₁ decline compared to persistent heavy smokers, while the older group did not (table 3). Thus, it seems that reduction of smoking can be beneficial in the young, while no appreciable effect on FEV₁ need be found among elderly subjects. This may be due to a cumulative effect of smoking in the elderly who have been smoking for much longer than the younger subjects.

Women differ from men with regard to smoking habits: generally, they start later in life, smoke fewer cigarettes, smoke cigarettes with lower tar yields, inhale less deeply and do not smoke the cigarette as close to the end as men [18]. Although we generally found similar effects of smoking and changes in smoking in men and women, some differences were observed. Most importantly, the FEV₁ decline among the elderly light smokers differed between the sexes, being in men as high as in heavy smokers, while in women considerably lower in light smokers than in heavy smokers.

Compared to a randomized trial, an observational study like ours has several limitations. Firstly, the exact time of the change of the smoking behaviour and the lung function at that time were unknown. Secondly, the smoking status of the participants was based on self reports only. It would have been preferable if the reported changes in the smoking behaviour, especially quitting, had been objectively verified. Some newly conducted studies have shown that the amount of cigarettes smoked is likely to be under-reported and that some subjects who report to have quit smoking still smoke tobacco [19]. If under-reporting also pertains to our population, it would lead to underestimation of the effect of quitting and thus have only limited impact on our conclusions. However, if under-reporting of smoking differed between the sexes and age groups our conclusions could be less valid. Finally, although many of our comparisons of the FEV₁ decline between different smoking groups reached the level of significance, the wide interindividual variability within the smoking groups indicated that the predicted Δ FEV₁ in a single subject is very uncertain [20].

In spite of these methodological limitations we conclude that both younger and elderly subjects who quit and younger smokers who reduce within a few years are likely to experience a reduction of FEV₁ decline compared to subjects who do not change smoking behaviour.

References

1. Huhti E, Ikkala J. – A 10-year follow-up study of respiratory symptoms and ventilatory functions in a middle-aged rural population. *Eur J Respir Dis*, 1980, 61, 33–45.
2. Krzyzanowski M. – Changes of ventilatory capacity in an adult population during a five year period. *Bull Eur Physiopathol Respir*, 1980, 16, 155–170.
3. Wilhelmsen L, Orha I, Tibblin G. – Decrease in ventilatory capacity between ages of 50 and 54 in representative sample of Swedish men. *Br Med J*, 1969, 3, 553–556.
4. Comstock GW, Brownlow WJ, Stone RW, Sartwell PE. – Cigarette smoking and changes in respiratory findings. *Arch Environ Health*, 1970, 21, 50–57.
5. Sharp JT, Oglesby P, McKean H, Best WR. – A longitudinal study of bronchitic symptoms and spirometry in a middle-aged, male, industrial population. *Am Rev Respir Dis*, 1973, 108, 1066–1077.
6. Ashley F, Kannel WB, Sorlie PD, Masson R. – Pulmonary function: relation to aging, cigarette habit, and mortality. *Ann Intern Med*, 1975, 82, 739–745.
7. Fletcher CM, Peto R, Tinker C, Speizer FE. – In: The natural history of chronic bronchitis and emphysema. Oxford University Press, Oxford, 1976.
8. Kauffmann F, Drouet D, Lellouch J, Brille D. – Twelve years spirometric changes among Paris area workers. *Int J Epidemiol*, 1979, 8, 201–212.
9. Bosse R, Sparrow D, Rose CL, Weiss ST. – Longitudinal effect of age and smoking cessation on pulmonary function. *Am Rev Respir Dis*, 1981, 123, 378–381.
10. Camilli AE, Burrows B, Knudson RJ, Lyle SK, Lebowitz MD. – Longitudinal changes in forced expiratory volume in one second in adults. *Am Rev Respir Dis*, 1987, 135, 794–799.
11. Jensen G. – Epidemiology of chest pain and angina pectoris (thesis). *Acta Med Scand*, 1984, Suppl. 682.

12. Appleyard M. – The Copenhagen City Heart Study. *Scand J Soc Med*, 1989, Suppl. 41.
13. Spirometri. En rekommandation. Dansk Lungemedicinsk Selskab, 1986.
14. Vollmer WM. – Comparing change in longitudinal studies: adjusting for initial value. *J Clin Epidemiol*, 1988, 41, 651–657.
15. Hughes JA, Hutchison DCS, Bellamy D *et al.* – The influence of cigarette smoking and its withdrawal on the annual change of lung function in pulmonary emphysema. *Quart J Med*, 1982, 202, 115–124.
16. Buist AS, Sexton GJ, Nagy JM, Ross BB. – The effect of smoking cessation and modification on lung function. *Am Rev Respir Dis*, 1976, 114, 115–122.
17. McCarthy DS, Craig DB, Cherniack RM. – Effect of modification of the smoking habit on lung function. *Am Rev Respir Dis*, 1976, 114, 103–113.
18. Royal College of Physicians of London. – In: Health or smoking? Follow-up Report of the Royal College of Physicians. Pitman, London, 1983.
19. Coultas DB, Howard CA, Peake GT, Skipper BJ, Samet JM. – Discrepancies between self-reported and validated cigarette smoking in a community survey of New Mexico hispanics. *Am Rev Respir Dis*, 1988, 137, 810–814.
20. Burrows B, Lebowitz MD, Camilli AE, Knudson RJ. – Longitudinal changes in FEV₁ in adults: methodologic considerations and findings in healthy non-smokers. *Am Rev Respir Dis*, 1986, 133, 974–980.

Effets du tabagisme et des modifications des habitudes tabagiques sur la diminution du VEMS. P. Lange, S. Groth, J. Nyboe, J. Mortensen, M. Appleyard, G. Jensen, P. Schnohr.

RÉSUMÉ: Le but de cette étude était d'examiner les effets de la consommation de cigarettes et des modifications des habitudes tabagiques sur le déclin du VEMS. Nous avons étudié 7.764 hommes et femmes pendant 5 ans. Les sujets ont été regroupés selon leurs habitudes tabagiques aux taux déclarés au cours de la période d'observation. Nous avons trouvé que la persistance de la consommation de cigarettes, et en particulier les tabagismes intensifs, accéléreraient le déclin du VEMS. Chez 310 sujets qui ont arrêté de fumer pendant la période d'observation, le déclin du VEMS a été moins prononcé que celui observé chez les fumeurs persistants. Chez les sujets âgés de moins de 55 ans, la réduction du tabagisme a été associée à un déclin moins prononcé du VEMS, tandis que chez les sujets plus âgés, la réduction du tabagisme n'a pas d'effet sur le déclin du VEMS. Une augmentation du nombre de cigarettes consommées est généralement associée à un déclin plus rapide du VEMS, alors que le fait de commencer à fumer pendant les 5 années d'observation ne semble pas influencer ce déclin. Nous concluons que l'arrêt ou la réduction du tabagisme peut conduire en peu d'années à un effet bénéfique démontrable sur le déclin du VEMS.

Eur Respir J., 1989, 2, 811–816