Vol. 96 (2002) 444–449

The FEV_1/FEV_6 predicts lung function decline in adult smokers

P. L. ENRIGHT*, J. E. CONNETT† AND W. C. BAILEY‡

*The University of Arizona, Tucson, Arizona, †University of Minnesota, Minneapolis, Minnesota and ‡UAB Lung Health Center, Birmingham, Alabama, U.S.A.

Abstract The use of FEV_1/FEV_6 in place of the traditional FEV_1/FVC to detect airways obstruction during spirometry testing performed by primary care providers would reduce time and patient effort. We hypothesized that the FEV_1/FEV_6, would predict the subsequent decline in FEV_1 in adult cigarette smokers who enrolled in the multicenter Lung Health Study. Ten clinical centers in the U.S. and Canada recruited 5887 male and female smokers, aged 35–60 years, with borderline to mild airways obstruction by spirometry. Those who successfully stopped smoking during the 5-yr study (usually as the result of the smoking cessation intervention) were excluded from this analysis. In those continuing to smoke, the relative strength of spirometric predictors of the change in FEV_1 during 5 years of follow-up ($DFEV_1$) was determined using a linear regression model. The following covariates were significant independent predictors of $DFEV_1$: the baseline degree of airways obstruction, age, gender, cigarettes per day, years of education, and bronchial hyperresponsiveness. The FEV_1/FEV_6 was nearly as strong an independent predictor as was the FEV_1/FVC (a traditional index of airways obstruction). The degree of airways obstruction, as determined by the FEV_1/FEV_6 from spirometry, is an independent predictor of subsequent decline in lung function; and therefore, may be used to detect smokers at higher risk of developing COPD.

doi:10.1053/rmed.2001.1270, available online at http://www.idealibrary.com on IDEAL®

Keywords spirometry; COPD; smoking.

INTRODUCTION

The availability of easy-to-use lung function tests would help in developing the case for more widespread lung function testing in both primary care and sub-specialty settings. Barriers to the more widespread use of office spirometry include the expense of the equipment, the difficulty of administering and performing the test, and the perception that there is inadequate evidence that doing the test affects patient outcomes.

Ample information presently exists that spirometry results detect the adult cigarette smokers who are likely to develop clinically significant COPD. The FEV_1 is also an excellent predictor of morbidity and mortality (1,2). Due to this large evidence base, the National Lung Health Education Program recommends that primary care providers (PCPs) use office spirometry to detect airways obstruction in all adult cigarette smokers seen in their outpatient clinics, and then to use the results to promote smoking cessation (3).

Many patients have difficulty exhaling until current 'end-of-test' standards for accurately measuring FVC are met (4). Shortening each forced exhalation maneuver to 6 sec (resulting in the FEV_6) would reduce both patient and technician effort and fatigue, and testing time, possibly making spirometry more appealing to both primary care and subspecialty providers. A shorter maneuver duration would also make it easier for office spirometers to accurately measure low flows at the end of the maneuvers, making office spirometers less expensive.

In the subgroup of continuing smokers in the multicenter Lung Health Study (LHS), several variables were independent predictors of the subsequent fall in FEV_1 over the 5-yr follow-up, including FEV_1/FVC, age, cigarettes smoked per day, bronchodilator response, and methacholine responsiveness (5). These results provided additional evidence that the FEV_1/FVC predicts decline in lung function in adult smokers, and therefore, may be used to define 'early COPD'.

Predicted reference values and lower limits of the normal range for the FEV_6 and the FEV_1/FEV_6 from a large population-based sample were recently published (6). The FEV_1/FEV_6 was found to be an accurate and reliable alternative for the FEV_1/FVC for diagnosing airways obstruction in a large group of patients referred to a pulmonary function laboratory (7). The purpose of this analysis of LHS data is to provide further evidence

Correspondence should be addressed to: Dr. Paul Enright, The University of Arizona, 1501 N Campbell Ave, Rm 2342, Tucson, AZ 85724. Fax: +1 520 626 6970; E-mail: lungguy@aol.com

validating the substitution of FEV_1/FEV_6 for the traditional FEV_1/FVC when detecting early COPD in adult cigarette smokers.

METHODS

Design and recruitment

The Lung Health Study was a randomized multicenter clinical trial, carried out from October 1986 to April 1994, designed to test the effectiveness of intervention—smoking cessation and bronchodilator administration—in smokers thought to be in the early stages of COPD. Detailed descriptions of the design and recruitment have been published (8,9). Entry criteria were chosen to identify otherwise healthy current smokers, aged 35–65 years, who had airways obstruction and who did not have conditions that would compromise follow-up or interpretation of lung function. For the purpose of study eligibility, airways obstruction was defined as an FEV_1/FVC of 70% or less and an FEV_1 between 55 and 90% of predicted. Candidates for the study were excluded if they reported factors that might interfere with follow-up (such as more than 25 alcoholic drinks per week), or if they regularly used physician-prescribed bronchodilators, beta-blockers, nitrates for angina, corticosteroids, or insulin. The study design was approved by the Human Studies Review Boards of each participating institution, and informed consent was obtained from all study participants.

Volunteers for the study were recruited in a variety of ways, including media publicity, mass mailings, and worksite and public screening. Exclusionary criteria were examined at the second screening visit. Current smokers who qualified then attended a third screening (S3) visit at which time a detailed history of respiratory symptoms, pre-existing diseases, smoking status was asked (and verified by salivary cotinine and exhaled carbon monoxide levels), and spirometry and methacholine challenge tests were performed (10,11). Participants were then randomized to one of three study groups: SIA, special intervention with an intensive smoking cessation program, plus a prescription for an ipratropium bromide inhaler to be taken four times per day; SIP, special intervention with an intensive smoking cessation program, and a placebo inhaler; or UC, no cessation program and no inhaled medication (usual care).

Interventions

The smoking cessation program was the same for all 10 clinical centers as previously described in detail (12). At the time of randomization, all SIA and SIP participants were interviewed by a physician who strongly recommended that they stop smoking, explaining in detail that they were at very high risk for symptomatic COPD. Group smoking cessation sessions met 12 times in 10 weeks with an early quit day, behavior modification techniques, and aggressive replacement therapy using nicotine gum, provided at no cost (13). Those who quit entered a maintenance program aimed at preventing relapse. The SIA group were prescribed daily inhaled ipratropium bromide while the SIP group were given placebo inhalers.

Spirometry testing

Details of the pre and post-bronchodilator spirometry procedures have previously been published (10). A methacholine challenge test (MCT) was performed about 3 weeks after the baseline spirometry testing (11). During five annual follow-up examinations, spirometry was repeated and smoking status determined (self-reported and biochemically validated) (12).

Analyses

Only the subset of LHS participants who continued to smoke cigarettes during the 5-yr follow-up were analyzed for this report. The baseline to 5-yr follow-up change in FEV_1 ($DFEV_1$, in $ml\,yr^{-1}$) was the dependent variable in linear regression models. We determined which of several measures of baseline airways obstruction best predicted subsequent FEV_1 decline, when correcting for age, gender, cigarettes per day, years of education, treatment group, BD response, and MCT slope. Candidate obstruction variables included raw FEV_1, %predicted FEV_1, FEV_1/FVC, and FEV_1/FEV_6 (26). It was determined *a priori* that the R^2 of each model would be the criterion for comparing the five models. SAS version 6 (Cary, NC) was used for statistical analyses.

RESULTS

Selected baseline characteristics of the 1767 men and 1060 women who were classified as continuing smokers are shown in Table 1. Male and female participants had similar average values for FEV_1 percent of predicted (75%), FEV_1/FEV_3 (76%), FEV_1/FEV_6 (69%), and FEV_1/FVC (63%). Men had significantly larger mean values for most of the other baseline variables in Table 1, including the reported number of cigarettes smoked per day, pack-years of smoking, years of education, body mass index (BMI), and the absolute pulmonary function measures FEV_1, FEV_3, FEV_6, and FVC. Women were more likely to react to methacholine, while men had a slightly lower (and non-significant) mean percent response to the bronchodilator. Ninety four percent of the participants performed spirometry testing at the fifth year of follow-up.

The spirometry variables were highly correlated. The correlation coefficients were FVC *vs*. $FEV_1 = 0{\cdot}902$; FVC

Table 1. Baseline characteristics of Lung Health Study participants who were classified as continuing smokers through 5 yrs of follow-up

	Men (n=1767)			Women (n=1060)		
Baseline Variable	Mean	SD	SE	Mean	SD	SE
Age, years	48·1	6·9	0·2	48·1	6·6	0·2
BMI, kg m^{-2}	26·1	3·7	0·1	24·1	3·9	0·1
Education, years	13·6	2·9	0·1	13·0	2·5	0·1
Cigarettes day^{-1}	33·2	13·2	0·3	29·9	12·0	0·4
Pack-yrs	42·7	19·7	0·5	36·0	16·6	0·5
FEV_1, liters	2·95	0·48	0·01	2·09	0·36	0·01
FEV_3, liters	3·91	0·61	0·01	2·74	0·45	0·01
FEV_6, liters	4·31	0·65	0·02	3·02	0·48	0·01
FV_C, liters	4·72	0·70	0·02	3·30	0·50	0·02
FEV_1/FEV_3, %	75·6	4·3	0·1	76·5	3·9	0·1
FEV_1/FEV_6, %	68·5	5·2	0·1	69·3	4·8	0·1
FEV_1/ FVC, %	62·7	6·1	0·1	63·5	5·6	0·2
FEV_1 % predicted	74·8	9·5	0·2	74·9	9·3	0·3
BD response, %	4·03	4·93	0·12	4·25	5·30	0·16
PC-20 $\leq$10 mg ml^{-1}, %ppts	45·1	49·8	1·1	73·6	44·1	1·4
MCTslope	−8·60	17·3	0·4	−16·7	26·1	0·8
Mean annual $DFEV_1$, ml yr^{-1}	−60·6	54·0	1·3	−52·9	39·6	1·2

ppts; study participants; SD: standard deviation; SE: standard error; MCTslope: the degree of bronchial responsiveness from the baseline methacholine challenge test.

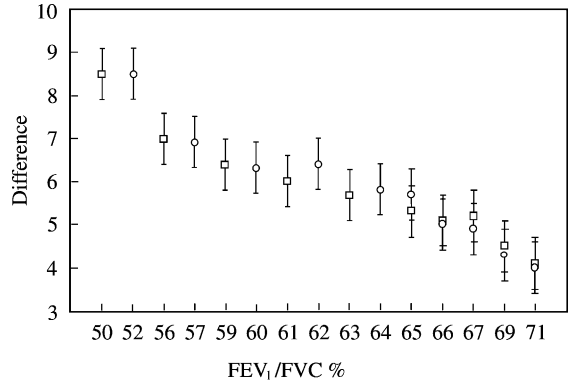

Fig. 1. The mean difference between two indices of airway obstruction, the new FEV_1/FEV_6 and the traditional FEV_1/FVC, as a function of the degree of airways obstruction, in deciles of FEV_1/FVC on the horizontal axis, for men and for women. The vertical bars approximate +/−2 standard errors. The two indices are highly correlated, but the FEV_1/FEV_6 is higher than the FEV_1/FVC (by 6–9%) in smokers with moderate airways obstruction (a ratio of 50–60%). □: Men; ○: Women.

vs. FEV_3 = 0·964; and FVC *vs*. FEV_6 = 0·981. On average, the FEV_6 was 112 ml smaller than the FVC. Figure 1 compares the new index of airways obstruction—the FEV_1/FEV_6—with the traditional FEV_1/FVC over the range of severity of airways obstruction. The difference between these two variables was 6–9% larger in those smokers with more severe airways obstruction.

Table 2. Rates of decline in FEV_1 (ml per yr) by deciles of FEV_1/FEV_6, stratified by gender

	Men (n=1767)	Women (n=1060)
FEV_1/FEV_6	Mean (SD)	Mean (SD)
Lowest decile	−93·2 (71·5)	−78·2 (47·0)
2nd decile	−74·3 (57·1)	−68·3 (47·4)
3rd decile	−65·0 (55·7)	−60·0 (43·3)
4th decile	−66·1 (57·5)	−51·6 (38·0)
5th decile	−57·8 (48·6)	−56·6 (40·1)
6th decile	−51·2 (48·6)	−41·3 (31·9)
7th decile	−48·1 (44·2)	−50·5 (31·9)
8th decile	−54·9 (43·6)	−44·1 (32·1)
9th decile	−50·9 (44·9)	−40·8 (30·0)
Highest decile	−44·5 (45·4)	−37·7 (30·7)

Participants with the lowest decile of FEV_1/FEV_6 had the most severe degree of baseline airways obstruction, and the largest subsequent mean declines in lung function (indicating faster progression of COPD).

The mean declines in FEV_1 among continuing smokers were 61 ml yr^{-1} in men and 53 ml yr^{-1} in women. Table 2 shows the bivariate association of the degree of baseline airway obstruction (as measured by the FEV_1/FEV_6, in deciles) and the subsequent mean rates of decline in FEV_1 in men and women. Those with the most severe

degree of airways obstruction at the baseline exam (the lowest decile of FEV_1/FEV_6) lost more than twice as much lung function over the next 5 yrs when compared to those with the least baseline airways obstruction (for instance, FEV_1 fell 93·2 ml yr^{-1} *vs.* 44·5 ml yr^{-1} for men).

Table 3 shows the results of the linear regression analysis used to determine the independent predictors of the annual change in FEV_1 from baseline to Year 5, for continuing smokers. A negative coefficient for a given variable implies that an increase in that variable is associated with a faster rate of decline in FEV_1. Thus, since age has coefficient of minus 0·47, an increase of 10 yrs in age predicts 4·7 ml yr^{-1} additional loss of FEV_1. Men had faster rates of decline than women (probably an effect of larger body size). Most of the baseline variables entered in this analysis were significant predictors of subsequent changes in FEV_1. Higher baseline values for age, baseline cigarettes per day, bronchodilator response, and greater methacholine reactivity were associated with larger rates of decline in FEV_1, while being in treatment group SIA (*vs.* UC) and having a higher baseline FEV_1/FEV_6 % were associated with slower rates of FEV_1 decline.

The overall R^2 for the regression model that included FEV_1/FEV_6 was 11·3%. This means that the model predicts about 11% of the variance in subsequent change in lung function. Unmeasured factors (perhaps genetic) account for most of the variation in lung function decline. Table 4 indicates the R^2 values for regression models done separately in men and women, in which one of the following baseline spirometry variables was entered: FEV_1 %predicted, FEV_1/FEV_6, or FEV_1/FVC. The 'best' models, in the sense of having the largest R^2, were those which included FEV_1/FVC, but the difference in R^2 between these models and those in which FEV_1/FEV_6 was entered was not significant. On the other hand, FEV_1 percent predicted was clearly a significantly weaker predictor of subsequent decline in FEV_1.

DISCUSSION

Our results confirm the 'horse-racing effect' first described by Fletcher *et al*. (14): the baseline degree of airways obstruction is a predictor of the subsequent worsening in airways obstruction (decline of FEV1) in adult cigarette smokers. Burrows *et al*. found that one can reasonably predict a relatively rapid decline in lung function by finding low lung function (a low FEV_1/FVC) in male (but not female) current cigarette smokers (15). The analogy is that if you glance at horses midway through a race, those horses which are ahead probably got there by running faster during the first half of the race, and they are more likely to finish ahead of the other horses. Burrows concluded that 'there appears to be overwhelming evidence supporting the value of early detection of obstructive airways disease to allow the institution of vigorous antismoking efforts among those with early airway obstruction.'

Our results also confirm those of Fletcher's and extend them to include female smokers. Burrows' study included 141 male and 152 female smokers, with a mean of 5·4 FEV_1 measurements over 10 yrs (15), while we studied approximately 10 times as many continuing male and female smokers with six FEV_1 measurements over 5 yrs, giving us considerably more power to detect an effect in

Table 4. Comparison of the strength (linear model R^2×100%) of various baseline (S3 visit) spirometric measures of airways obstruction in predicting mean change in FEV_1 in continuing smokers. The model includes age, cigarettes smoked per day, education level, study treatment group, BD response, and methacholine responsiveness

	Men	Women
FEV1 %pred	6·9	8·6
FEV1/FEV6	10·7	14·0
FEV1/FVC	11·4	14·0

Table 3. Linear regression model predicting mean change in FEV_1 (ml yr^{-1}) in continuing smokers over 5 yrs of follow-up

Predictor	Estimate	T Statistic	*P* value	SE
Gender (men *vs.* women)	−6·71	−3·58	0·0003	1·87
Age	−0·47	−3·64	0·0003	0·13
Cigarettes day^{-1} (baseline)	−0·33	−4·72	0·0001	0·07
BD response %	−0·95	−5·32	0·0001	0·18
MCT slope	0·23	5·32	0·0001	0·04
FEV_1/FEV_6 % (baseline)	2·24	12·52	0·0001	0·18
Education (yrs)	−0·05	−0·15	NS	0·32
Treatment group (SIA *vs.* UC)	6·60	3·12	0·0018	2·12
Treatment group (SIP *vs.* UC)	0·12	0·06	NS	2·12

R^2: 11·3%; *n*: 1767 men and 1060 women; NS: not significant ($P > 0·05$)

women as well as in men. Both studies excluded those with very low baseline FEV_1 and those with known asthma. Burrows' study also found that the FEV_1/FVC ratio was the best spirometric predictor of subsequent change in FEV_1.

Airways obstruction in smokers, in addition to predicting subsequent rapid decline in lung function, was also a strong independent predictor of morbidity and mortality from cardiovascular disease and COPD (and all-cause mortality) in several large longitudinal studies (1,2,16–18). Based on such evidence, one group of investigators suggested over 10 yrs ago that 'perhaps it is time that this test (spirometry) was more generally applied' (17).

Many factors are associated with an increase in the risk of a cigarette smoker developing COPD (objectively measured as reduced lung function). These include heredity and genetic factors (19), childhood respiratory infections (20), the age of onset, intensity, and duration of smoking (21), environmental particulate exposures (22), and the presence of airway hyper-responsiveness (11). It is difficult to accurately measure all of these factors in a given patient. The smoking history is subject to recall bias. Occupational and environmental exposures are rarely measured for a single patient, and methacholine challenge testing is time consuming and often unavailable in smaller communities. Measurement of spirometry, on the other hand, is relatively quick and easy to perform in the outpatient setting, and an objective predictor of the patient developing COPD.

Currently available diagnostic spirometers usually cost more than (U.S.) $2000, inhibiting their widespread purchase by primary care physicians (PCPs). One of the factors keeping the cost high is the need for relatively expensive flow sensors to measure the very low flows that occur towards the end of FVC maneuvers. Forced expiratory maneuvers in patients with airway obstruction often last for 10–20 sec before a plateau is reached (23) in order to meet current ATS spirometry specifications for an acceptable end-of-test (25). This makes the spirometry test session more difficult for the patient and the technician, and more time-consuming, further inhibiting its widespread use by PCPs for detecting COPD in adult smokers. Shorter duration maneuvers make spirometry easier and faster. The use of the FEV_6 instead of the FVC for the detection of airflow limitation allows all the maneuvers to be shortened to only 6 sec. This study demonstrates that the use of the FEV_1/FEV_6 is a good substitute for the FEV_1/FVC when screening smokers for the presence of airways obstruction and predicting an abnormal rate of decline in lung function (which would eventually become clinical COPD).

In order to use the FEV_1/FEV_6 ratio to detect airways obstruction in middle-aged smokers, and minimize the false positive and false negative rates, the results from a given patient must be compared to an age, gender, and race adjusted predicted value (and lower limit of the normal range) for the FEV_1/FEV_6 (25). Studies providing spirometry reference equations which are currently used in North America have not published predicted values for the FEV_1/FEV_6. However, recently published spirometry reference equations from the third National Health and Nutrition Examination Survey (NHANES III), a sample of the general United States population, includes FEV_1/FEV_6 reference equations for both men and women aged 8–80, and three major race/ethnic groups (6). The lower limit of the normal range for the FEV_1/FEV_6 for 40–60-year-old smokers is about 73% (range 70–76%). The exact value depends on age, gender, and race. When spirometer manufacturers change the prediction equations and automated interpretations to utilize the FEV_1/FEV_6, most clinicians will probably not notice because these internal functions are like a 'black box'.

Characteristics of our study may affect generalization of our results to all patients seen in the outpatient practices of PCPs. We used spirometry technicians who were highly trained and motivated to obtain maximal and reproducible results, which may not be the case in some primary care settings. We used very accurate diagnostic-quality volume-sensing spirometers with customized automated maneuver quality checks, and flow–volume curves were superimposed on a large computer monitor. These features may not be available in lower cost office spirometers. Our cohort consisted largely of middle-class, middle-aged Caucasian smokers, in contrast to the majority of patients seen in many inner-city clinics. Nevertheless, manufacturers are developing relatively low cost, yet accurate office spirometers, with automated quality checks, which incorporate the new FEV_1/FEV_6 reference equations. These new instruments should then allow primary care providers to easily detect mild airways obstruction in cigarette smokers, with acceptable positive and negative predictive power, in order to determine their risk of developing COPD.

Acknowledgements

We thank the LHS pulmonary function technicians for providing excellent quality spirometry tests and Dr Sonia Buist and others for thoughtful reviews and suggestions for improving the manuscript. This study was supported by National Heart, Lung and Blood Institute contract number HR 46002.

REFERENCES

1. Ebi-Kryston KL. Respiratory symptoms and pulmonary function as predictors of 10-year mortality from respiratory disease, cardiovascular disease, and all causes in the Whitehall Study. *J Clin Epidemiol* 1988; **41:** 251–260.

2. Sorlie PD, Kannel WB, O'Connor G. Mortality associated with respiratory function and symptoms in advanced age: the Framingham Study. *Am Rev Respir Dis* 1989; **140:** 379–384.
3. Ferguson G, Enright PL, Buist AS, Higgins M. Office spirometry for lung health assessment in adults. An consensus statement from the National Lung Health Education Program. *Chest* 2000; **117:** 1146–1161.
4. Eaton T, Withy S, Garrett JE, *et al*. Spirometry in primary care practice. The importance of quality assurance and the impact of spirometry workshops. *Chest* 1999; **116:** 416–423.
5. Anthonisen NR, Connett JE, Kiley JP, *et al*. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1: The Lung Health Study. *JAMA* 1994; **272:** 1497–1505
6. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference equations from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; **159:** 179–187.
7. Swanney M, Jensen RL, Crichton DA, *et al*. FEV_6 is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. *Am J Respir Crit Care Med* 2000.
8. Connett JE, Kusek JW, Bailey WC, O'Hara P, Wu M. Design of the Lung Health Study: A randomized trial of early intervention for chronic obstructive pulmonary disease. *Controlled Clin Trials* 1993; **14:** 3S–19S.
9. Durkin DA, Kjelsberg MO, Buist AS, *et al*. Recruitment of participants in the Lung Health Study: Description of Methods. *Controlled Clin Trials* 1993; **14:** 20S–37S.
10. Enright PL, LR Johnson, JE Connett, H Voelker, AS Buist. Spirometry in the Lung Health Study: methods and quality control. *Am Rev Respir Dis* 1991; **143:** 1215–1223.
11. Tashkin DP, Altose MD, Connett JE, *et al*. The Lung Health Study: Airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. *Am Rev Respir Dis* 1992; **145:** 301–310.
12. O'Hara P, Grill J, Rigdon MA, *et al*. Design and results of the initial intervention program for the Lung Health Study. *Prev Med* 1993; **22:** 304–315.
13. Bjornson W, Rand C, Connett JE, *et al.* Gender differences in smoking cessation after 3 years in the Lung Health Study. *Am J Public Health* 1995; **85:** 223–230.
14. Fletcher C, Peto R. The natural history of chronic airflow limitation. *Br Med J* 1977; **1:** 1645–1648.
15. Burrows B, Knudson RJ, Camilli AE, Lyle SK, Lebowitz MD. The 'horse-racing effect' and predicting decline in FEV_1 from screening spirometry. *Am Rev Respir Dis* 1987; **135:** 788–793.
16. Traver GA, Cline MG, Burrows B. Predictions of mortality in COPD: a 15-year follow-up study. *Am Rev Respir Dis* 1979; **119:** 895–902.
17. Tockman MS, Comstock GW. Respiratory risk factors and mortality: longitudinal studies in Washington County Maryland. *Am Rev Respir Dis* 1989; **140:** S56–S63.
18. Lange P, Nyobe J, Jensen G, Schnohr P, Appleyard M. Ventilatory function impairment and risk of cardiovascular death and of fatal or non-fatal myocardial infarction. *Eur Respir J* 1991; **4:** 1080–1087.
19. Feld RD. Heterozygosity of alpha-1-antitrypsin: a health risk? *Crit Rev Clin Lab Sci* 1989; **27:** 461–481.
20. Samet JM, Tager IB, Speizer FE. The relationship between respiratory illness in childhood and chronic airflow limitation in adulthood. *Am Rev Respir Dis* 1983; **127:** 508–523.
21. Xu X, Dockery DW, Ware JH, Speizer FEF, Ferris BG. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. *Am Rev Respir Dis* 1992; **146:** 1345–1346.
22. Tashkin DP, Detels R, Simmons M, Liu H, Coulson SAH, Sayre J, Rokaw S. The UCLA population studies of COPD: impact of air pollution and smoking on annual change in FEV_1. *Am J Respir Crit Care Med* 1994; **149:** 1209–1217.
23. Stoller JK, Basheda S, Laskowski D, Goormastic M, McCarthy K. Trial of standard versus modified expiration to achieve end-of-test spirometry criteria. *Am Rev Respir Dis* 1993; **148:** 275–280.
24. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; **152:** 1107–1136.
25. American Thoracic Society. Lung function testing: Selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991; **144:** 1202–1218.