

## Occasional review

# Decline of FEV<sub>1</sub> by age and smoking status: facts, figures, and fallacies

Huib A M Kerstjens, Bert Rijcken, Jan P Schouten, Dirkje S Postma

Department of Pulmonology and Department of Epidemiology, University of Groningen, Groningen, The Netherlands  
 H A M Kerstjens  
 B Rijcken  
 J P Schouten  
 D S Postma

Correspondence to: Dr H A M Kerstjens, Department of Pulmonology, University Hospital Groningen, PO Box 30001, 9700 RB Groningen, The Netherlands.

Assessment of pulmonary function testing plays a central role in everyday practice of the pulmonary physician. New patients are diagnosed and graded in severity on the basis of results from these tests, and the course of the disease in previously diagnosed patients is judged with the help of lung function measurements. The use of pulmonary function tests for these purposes requires a concept of what constitutes both a normal level and a normal decline and, consequently, an unusually low level and accelerated decline. The concept of a normal level is perceived to be fairly straightforward and is routinely deducted from some set of reference values. The population selection of the reference equations used is taken to be sufficiently representative of the patient under study. In this review the problems associated with this assumption will be discussed and the cut off values between normal and abnormal examined. The same reference equations are often employed for the judgement of normal decline, assuming that the coefficient for age adequately represents decline in individuals. This approach, however, can be rather inadequate and this will be reviewed. Additionally, special reference will be given to estimating decline in smokers. Because of its ease of measurement and its very good reproducibility, the forced expiratory volume in one second (FEV<sub>1</sub>) is the most widely used and quoted lung function test in clinical practice

as well as in patient based research and in epidemiological studies of healthy subjects, and therefore the items discussed will be mainly centred around the FEV<sub>1</sub>.

### General course of FEV<sub>1</sub> over time

There is still considerable debate over the shape of lung function increase and decline during life. During childhood and adolescence there is naturally a rise in lung function, the exact shape of which is beyond the scope of this paper.<sup>1</sup> For the period early in adult life, different shapes have been suggested. Although some authors have taken the decline in lung function to start at 15–20 years of age,<sup>2,3</sup> others have found that the FEV<sub>1</sub> continues to rise to the age of 25 years,<sup>4–6</sup> or even into the fourth decade.<sup>17</sup> It is probably fair to say that in healthy individuals there is a plateau phase in early adulthood in which there is little or no change in FEV<sub>1</sub>.<sup>16,8</sup> The European Community for Coal and Steel stipulates that no change occurs between the ages of 18 to 25 and an age of 25 years should be entered into the regression equation for this whole age range.<sup>9</sup> After this plateau FEV<sub>1</sub> starts to decrease, with the newer studies that exclude smokers more carefully suggesting a later start in non-smokers. It has long been thought that this ensuing decrease is linear — that is, that FEV<sub>1</sub> decreases by the same number of ml each year. However, many authors have now shown that the decline accelerates with ageing.<sup>5,7,10–12</sup> As a result of these models of change in FEV<sub>1</sub>, at any given time in adulthood FEV<sub>1</sub> is determined by three factors: (1) the maximally attained level of lung function during early adulthood; (2) the onset of decline of lung function or, alternatively, the duration of the plateau phase; and (3) the rate of decline of lung function (fig 1).<sup>13</sup> In other words, from one low measurement of FEV<sub>1</sub> in an adult it is impossible to determine whether the reduced lung function is due to not having achieved a high maximum during early adulthood, to having had a shortened plateau phase, to having an accelerated rate of decline, or to any combination of these.

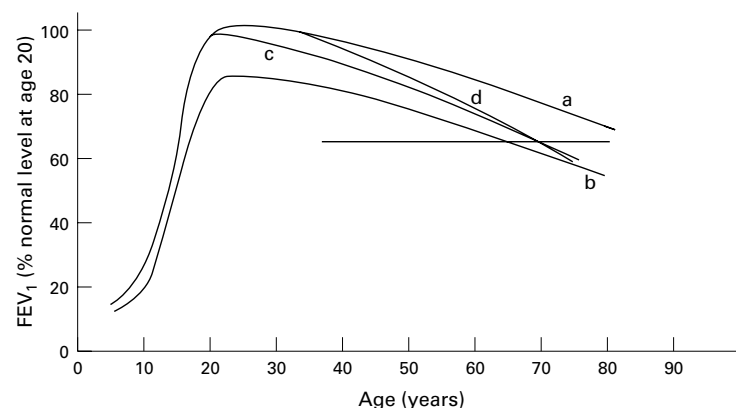


Figure 1 FEV<sub>1</sub> plotted as a percentage of maximal at age 20 years against age. Line a = healthy normal subjects, line b = submaximal growth but normal decline, line c = premature or early decline, line d = an accelerated decline in lung function compared with normal subjects (line a). In real life more than one mechanism for a low level of FEV<sub>1</sub> in adult life can be operating in any one individual. Figure reproduced with permission from Weiss and Ware.<sup>13</sup>

### Cohort and period effects: discrepancies between estimates of decline derived from cross sectional and longitudinal studies

When following individuals over time, most clinicians assume FEV<sub>1</sub> to decline by the age

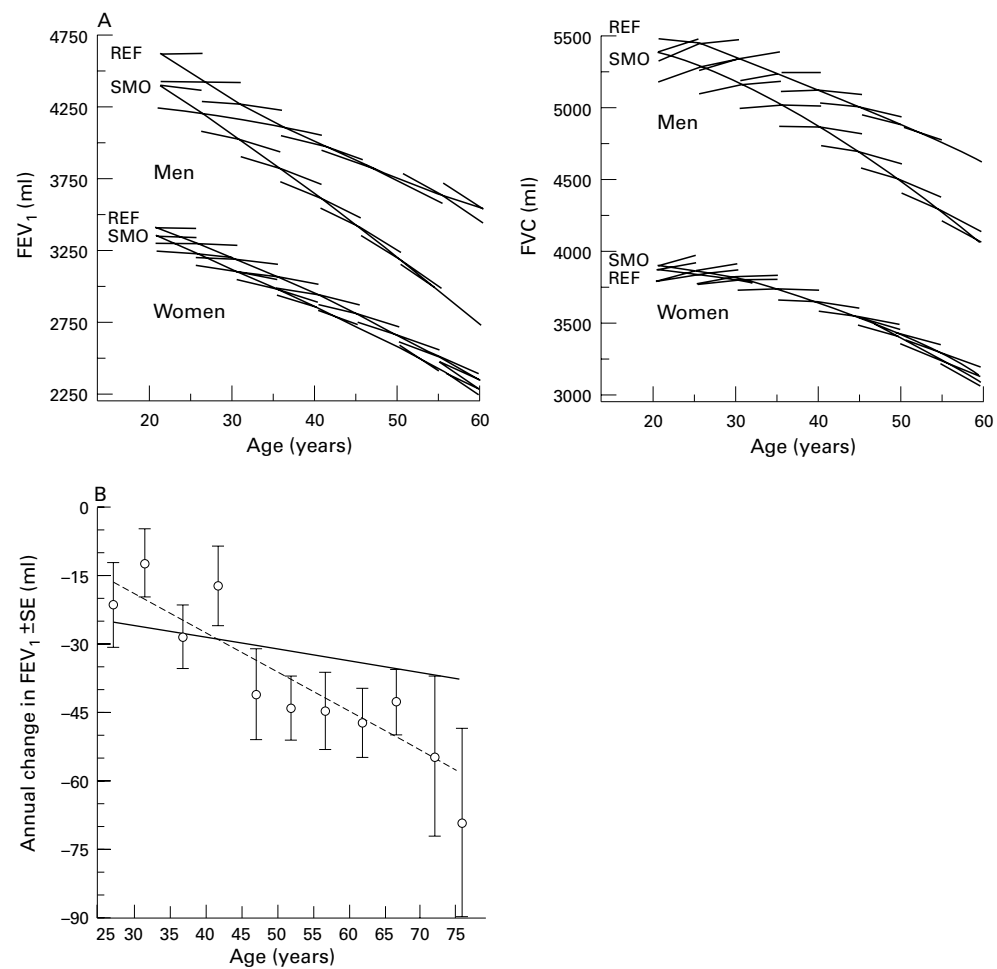


Figure 2 (A) Age dependence of FEV<sub>1</sub> and FVC cross sectionally (continuous line between 20 and 60 years) and longitudinally (short lines covering 10 year follow up) in the Vlaardingen-Vlagentwedde study. The short lines show the estimated longitudinal change between about 1974 and 1984 from selected ages halfway through the survey period (around 1979). Thus age can be considered to correspond with discrete birth cohorts – that is, 1979 minus age. SMO = smokers; REF = never smokers without symptoms. Estimates are for men and women with a standing height of 177 and 164 cm, respectively. Reproduced with permission from van Pelt et al.<sup>6</sup> (B) Comparison of predicted and observed rates of change of FEV<sub>1</sub> for male study participants in Six Cities study. The circles and error bars represent the mean (SE) of the observed annual rate of loss of FEV<sub>1</sub> for subjects grouped by five year intervals. The solid line connects the means of the predicted rates of loss calculated from the cross sectional model and the dashed line connects the predicted means from the longitudinal model. Reproduced with permission from Ware et al.<sup>11</sup>

coefficient in the reference equations that are employed in their lung function laboratory. For instance, when using the ECCS equation,<sup>9</sup> the average yearly decline from 25 years of age is assumed to be 29 ml/year for men and 25 ml/year for women. This essentially assumes that a 40 year old person will decline with the same ml/year as a 40 year old did 10 or 20 years ago when the equations were assembled. Moreover, it assumes that the equations were constructed in a longitudinal fashion – that is, actually looking at decline over time – whereas most equations used are derived from cross sectional analyses.<sup>2–4,9,11</sup> Several studies have now shown that remarkable discrepancies exist between estimates of annual decline derived from cross sectional data sets as opposed to longitudinal data sets.<sup>6,7,11,14,15</sup> In the two larger data sets<sup>6,11</sup> the decline in FEV<sub>1</sub> assessed longitudinally within individuals up to about 50 years of age has been found to be smaller than predicted from cross sectional analyses, whilst after that age the reverse is the case. In the Dutch Vlaar-

dingen-Vlagentwedde study cross sectional age coefficients derived from the first survey overestimated the decline observed over 12 years of follow up in 20 year old individuals by 35 ml/year.<sup>6</sup> By contrast, at the age of 60 the same procedure underestimated the decline by 11 ml/year (fig 2A). Similarly, in the Six Cities study the actual decline was underestimated by cross sectional estimates by 19 ml/year at the age of 75 (fig 2B).<sup>11</sup> The latter finding would be compatible with a survivor effect in cross sectional studies – that is, a selection of those having better lung function who still contribute to the data at an older age. This would cause cross sectional analyses to overestimate lung function at an older age and hence underestimate the decline. Such a survivor effect was indeed demonstrable, but Ware and colleagues show that in their study it explained only a small part of the discrepancies at older age.<sup>11</sup>

Apart from the mathematical and methodological problems in the actual production of reference equations as mentioned above, ad-

Table 1 Factors affecting the interpretation of FEV<sub>1</sub> values in individuals

Measurement of FEV <sub>1</sub>	Patient related sources of variation <sup>20</sup>	Subject (biological) variation Concurrent disease/conditions	Time of day, season, work shift, learning effect, fatigue, language, intelligence <sup>2</sup> , prior medication, prior coffee/tea/exercise, weather conditions Smoking history, environmental smoke, congestive heart failure, obesity, stress incontinence, occupational exposures, pollution, socioeconomic class Training, adherence to guidelines, patient contact
	Procedure related sources of variation	Technician  Technical Posture Measurement of height Instrument	Calibration, volume history, maximal effort, software Body posture, head tilting, nose clip Stated versus measured, <sup>85</sup> standing, shoes, stockings Water seal, dry rolling seal, pneumotachometer
Choice of reference values	Comparability of measurement techniques and conditions	Technique Healthy volunteers	Number of tests, choice of best test, temperature correction, software Non-smokers, never-smokers Environmental smoke? Lifestyle <sup>2</sup> Selected for special purpose? (workers from factory etc)
	Applicability of group selection in reference population to subject under study	Race Environment Cohort effects	Pollution, urban/rural habitat, altitude (see text)

ditional problems with defining decline may also arise from so called cohort and period effects.<sup>15</sup> Cohort effects are caused by factors such as environmental and nutritional changes and would, for example, explain why lung function in young adults is higher now than it was 40 years ago. As an example, in the Six Cities study Ware *et al* showed that part of the discrepancy between longitudinal and cross sectional data on the decline in lung function is due to age related changes in height in younger cohorts.<sup>11</sup> Additionally, in many population studies of healthy non-smoking subjects no allowance is made for environmental tobacco smoke, and this might also lead to cohort effects since smoking rates (and therefore passive smoking rates) are falling sharply in many countries.<sup>16,17</sup> Changes in genetic make up may also give rise to cohort effects, but usually occur over much longer time spans. Glindmeyer *et al* have attempted to quantify the cohort effect for vital capacity over a period of 135 years. They estimated the cumulative cohort effect in 25 year old men of 173 cm height to be close to 5 ml/year,<sup>14</sup> signifying that each former generation of 25 years earlier had a vital capacity 125 ml lower than in the subsequent generation! From the Vlaardingen-Vlagtwedde study it has been estimated that the effect might even be twice as high.<sup>15</sup>

In addition to cohort effects, period effects can exist. Period effects include factors such as changes in techniques and apparatus during the time a study is performed, and learning effects in the sense of achieving higher spirometric values with experience.<sup>11,14,18</sup> Xu and colleagues have calculated period and cohort effects separately in the 24 year follow up study of Vlaardingen-Vlagtwedde and found both to be present.<sup>15</sup> Looking at period effects in four different survey periods, they found an increase in the average level of FEV<sub>1</sub> of 250 ml for men and 219 ml for women in the last survey period (1985–1990) compared with the first survey period (1973–1978).<sup>15</sup> An overview of the intricacies of longitudinal data analysis as opposed to cross sectional analyses has recently been provided by Schouten and Tager.<sup>19</sup>

### Reference values for healthy never-smokers

Problems associated with the use of reference values have been dealt with by several

authors.<sup>9,20–25</sup> For meaningful use of reference values to interpret a manoeuvre of FEV<sub>1</sub> in a lung function laboratory, three important conditions have to be met: (1) the measurement of FEV<sub>1</sub> derived in the laboratory should be reliable and its sources of variation should be known and appreciated;<sup>20</sup> (2) the measurement techniques and conditions in the local laboratory should be comparable with those used in the study giving rise to the reference values; and (3) the population from which the reference values are derived should have characteristics encompassing those of the subject under study. Only when all three conditions have been met can a meaningful value for FEV<sub>1</sub> % predicted be found and interpreted. A list of factors involved is given in table 1.

Both the European Respiratory Society and the American Thoracic Society have produced detailed recommendations on the procedures and techniques of lung function measurements which have recently been updated.<sup>9,26,27</sup> In addition, the European guidelines provide reference equations which are a composite of earlier studies.<sup>9</sup> By contrast, the American Thoracic Society has left the choice of reference values to the clinician, stating that although biological plausibility and simplicity in the model used to develop prediction equations are important issues, neither is as important as appropriate group selection and comparable instrumentation and technique.<sup>25</sup> It is important to realise that some reference values currently in use have been put together before these recommendations were published and hence need not be the same as those currently in use in any given laboratory. This is especially true for the reference values for FEV<sub>1</sub> of the European Community for Coal and Steel which are derived from 20 unrelated studies performed between 1960 and 1980 with varying apparatus, measurement conditions, and techniques.<sup>9</sup>

Five commonly used and two new reference equations are listed in table 2. Newer equations tend to be derived by increasingly elaborate statistical techniques such as polynomial equations<sup>5,10,12</sup> and splines.<sup>8,28</sup> As a result the clinician is left with either more complex equations for which software is sometimes available<sup>5,10,12</sup> or even with no equations at all as, for instance, in the case of spline and smoothing techniques.<sup>28</sup> In the latter case predicted value data can be used only within the same study.

Table 2 Adult reference equations for FEV<sub>1</sub>; five frequently used and two new ones

Reference	Population	Age range†	Exclusion of smokers	No. studied	Cross sectional or longitudinal	Dependency of FEV <sub>1</sub> on age		Regression equations
Morris <sup>3</sup>	Two religious fractions; healthy	20–84	Not longer than 6 months	M 517 F 471	Cross sectional	Linear	M F	0.0362H – 0.032A – 1.260 0.0350H – 0.025A – 1.932
Crapo <sup>2</sup>	Healthy Mormons, altitude 1400 m	18–91	<0.5 pack years	M 125 F 126	Cross sectional	Linear (from 15 years?)	M F	0.0414H – 0.0244A – 2.190 0.0342H – 0.0255A – 1.578
Knudson <sup>4</sup>	Healthy, no respiratory symptoms	18–84	“Never regularly”	M 217 F 204	Cross sectional*	Breakpoint at 25 years (M) and at (20 and) 70 yrs for F; linear	M (A<25) M (A≥25) F (A20–70) F (A≥70)	0.0519H + 0.0636A – 6.1181 0.0665H – 0.0292A – 6.5147 0.0332H – 0.0190A – 1.8210 0.0143H – 0.0397A + 2.6539
Quanjer <sup>9,26</sup>	Reference values averaged from several studies	18–70	No	M 10 337 F 5316	Cross sectional	18–25 years as 25 years, linear from 18–70 years	M F	0.0430H – 0.029A – 2.49 0.0395H – 0.025A – 2.60
Dockery <sup>10</sup>	Healthy never smokers without respiratory symptoms	25–74	No current or ex-smokers	M 647 F 1904	Cross sectional*	Non-linear	M F	10 <sup>-4</sup> H <sup>2</sup> (1.541 – 0.00406A – 0.0000614A <sup>2</sup> ) 10 <sup>-4</sup> H <sup>2</sup> (1.541 – 0.00406A – 0.0000614A <sup>2</sup> – 0.209)
Glindmeyer <sup>12</sup>	Healthy blue collar paper manufacturing workers	18–65	No current or ex-smokers	M‡ 2844 F‡ 1224	Cross sectional	Non-linear	M M	0.0453H + 0.00895A – 0.000489A <sup>2</sup> – 3.455 0.0321H + 0.00382A – 0.000329A <sup>2</sup> – 1.853
Brändli <sup>5</sup>	Healthy Swiss never smokers, partly at higher altitude	18–60	No current or ex-smokers	M 2167 F 1890	Cross sectional	Breakpoint at 25 years for men only; non-linear	M (A≤25) M (A>25) F	e <sup>-9.280 + 1.9095ln(H) + 0.0795A – 0.001698A<sup>2</sup></sup> e <sup>-8.240 + 1.9095ln(H) – 0.0037A – 0.000033A<sup>2</sup></sup> e <sup>-8.217 + 1.8475ln(H) + 0.00375 – 0.000130A<sup>2</sup></sup>

ECCCS=European Community for Coal and Steel; H=height in cm; A=age in years; ln=natural logarithm.

\* Longitudinal data available from same study.

† Age range above 18 years.

‡ Only Caucasian presented here.

The differences between prediction equations might at first sight seem to be of little relevance. However, to demonstrate that this is by no means always the case we calculated from different reference equations for a measured FEV<sub>1</sub> the corresponding % predicted FEV<sub>1</sub>. For a 60 year old short man the measured FEV<sub>1</sub> can correspond to 65–102% predicted depending on the regression equation used (table 3). Thus, the choice of reference equations that are most suitable for the individual under study is of utmost importance. With life expectancy increasing, it is also important to realise that the current equations are less suitable for those aged above 75 years and new sets for the elderly have recently been proposed.<sup>29–31</sup> Reference equations for non-Caucasian subjects – for example, Afro-Americans – are different from those for Caucasian subjects. A discussion of these non-Caucasian equations is beyond the scope of this paper.<sup>12,25,26</sup>

### FEV<sub>1</sub> by smoking category

The reference equations commonly used to calculate the predicted FEV<sub>1</sub> value relate only to healthy individuals. Smokers are excluded from this definition as smoking affects all three factors that determine the level of FEV<sub>1</sub> at any given time – namely, the maximal FEV<sub>1</sub>

attained, the time of onset of decline, and the rate of decline.<sup>32</sup> The influence of environmental tobacco smoke begins in utero<sup>33,34</sup> and has been convincingly documented in infancy.<sup>35,36</sup> Active smoking has its effect on lung function within a few years of taking up the habit in adolescents, affecting both level and rate of growth.<sup>32,37</sup> As a consequence, due to smoking during adolescence a lower maximum or peak level of FEV<sub>1</sub> is achieved (fig 1).<sup>1,38,39</sup> Tager and colleagues estimated the FEV<sub>1</sub> to be, on average, 390 ml lower for boys who smoke and 360 ml for girls.<sup>38</sup>

Several authors have shown that smoking shortens the plateau phase of FEV<sub>1</sub>.<sup>1,6,8,32</sup> The third factor determining the FEV<sub>1</sub> at any given time point – the rate of decline after the plateau phase – is the factor that has traditionally received the most attention (table 4). Fletcher and colleagues were probably the first to look longitudinally at the effect of smoking on the level and decline of lung function in their landmark study of London workers.<sup>18</sup> They documented that smokers had a steeper decline in FEV<sub>1</sub> than did non-smokers, and also that only a small percentage of all smokers progress to develop clinically manifest obstructive lung disease with much more loss of lung function, the so-called susceptible smokers.<sup>18,40</sup> Subjects who already have some airways obstruction were found to be the ones most at risk for subsequent accelerated decline, for which they coined the term “horse racing effect”.<sup>18</sup> Soon after the publication of these findings came the Vlaarding-Vlagtwedde study and several other large epidemiological studies all documenting detrimental effects of smoking on the decline in FEV<sub>1</sub> (table 4).<sup>141–44</sup> From the data displayed in table 4 it would seem reasonable to say that moderate to heavy smoking men have, on average, a 15 ml/year larger decline than non-smokers. The effect in women was found to be only slightly lower in these studies. There are

Table 3 Measured, predicted, and % predicted FEV<sub>1</sub> for two examples using seven different regression equations

	Man, 150 cm, 60 years, FEV <sub>1</sub> 1.75 litres		Man, 180 cm, 30 years, FEV <sub>1</sub> 3.5 litres	
	Predicted FEV <sub>1</sub>	% predicted FEV <sub>1</sub>	Predicted FEV <sub>1</sub>	% predicted FEV <sub>1</sub>
Morris <sup>3</sup>	2.25	78	4.30	81
Crapo <sup>2</sup>	2.56	68	4.53	77
Knudson <sup>4</sup>	1.71*	102	4.58	76
Quanjer <sup>9</sup>	2.23	78	4.38	80
Dockery <sup>10</sup>	2.42	72	4.42	79
Glindmeyer <sup>12</sup>	2.12	83	4.53	77
Brändli <sup>5</sup>	2.68	65	4.64	75

\* Extrapolation from the height range sampled.

Table 4 Longitudinal studies of decline in FEV<sub>1</sub> in smokers compared with non-smokers

Reference	Population	Age range	No. studied	Follow up (n)	Reference decline in never smokers (ml/year)	Findings in current (persistent) smokers (ml/year)	
Fletcher <sup>18</sup>	London transport and bank workers, enriched subgroups	30-59	792	8 years (16)	M -36	M <5 cig/day -44 5-15 cig/day -46 15-25 cig/day -54 >25 cig/day -54	
Tashkin <sup>51</sup>	Four community cohorts, sampled for different pollution exposure	25-64	2401	5 years (2)	M -56 F -42	M -70 F -54	
Camilli <sup>42</sup>	General population sample	20-70	1705	10 years (7)		M 13 ml/year lower than in never smokers F 7 ml/year lower than in never smokers	
Tager <sup>1</sup>	Population sample, indexed via school children	5-55	1887	10 years (10)	M (<40) -20 (40-55) -35 F (<42) -10 (42-55) -35	M (21-32) -25 (33-43) -40 (44-55) -30 F (19-29) -20 (30-55) -30	
Lange <sup>43</sup>	Hospital catchment area sampled for cardiovascular study, enriched subgroups	20-? (at least 69)	7764	5 years (2)	M (<55) -21 (≥55) -34 F (<55) -13 (≥55) -32	M (<55) <15 cig/day -14 (≥55) -53 F (<55) 15-24 cig/day -14 (≥55) -41 ≥15 cig/day -35 -55 -30 -51	
Sherman <sup>58</sup>	Population samples from 6 US cities	25-74	3948	12 years (4)	Symptoms - M -33 F -28	+ M -34 F -31	Symptoms - M -42 F -34
Xu <sup>44</sup>	2 × 2 cohorts sampled for different pollution and urbanisation	15-54	4554	24 years (8)		Compared with never smokers <15 cig/day 15-24 cig/day ≥25 cig/day M -4 (3) -10 (3) -14 (3) F -6 (2) -11 (2) -19 (3)	

many more cross sectional studies in smokers than there are longitudinal studies. It should again be stated that the cross sectional studies by design will not be able to separate reliably the effects of smoking on the maximal level of FEV<sub>1</sub> achieved in early adulthood, on the duration of the plateau phase, or on the rate of decline.<sup>19</sup> Important observations have been reported in studies which document a dose-response relation in the effect of smoking on the rate of decline in pulmonary function, the effect being higher with more cigarettes, more years, or more pack years smoked.<sup>18,43-46</sup> There are, however, substantial areas of uncertainty as to why only a minority of smokers are susceptible, and whether or not there are safe thresholds for smoking in those subjects. It is prudent to think there is not. The early identification of the susceptible smoker could lead to more targeted smoking prevention or smoking cessation programmes.<sup>47-49</sup> Smoking cessation has been shown in many studies to result in normalisation of the decline in FEV<sub>1</sub> to the rate of never smokers<sup>42,44,46,50,51</sup> and this has recently been confirmed in a large scale intervention study.<sup>52</sup> There seems to be a small positive effect on the level of FEV<sub>1</sub> separate from its effect on declining pulmonary function.<sup>52</sup> Pipe and cigar smoking has also been found to accelerate the decline in FEV<sub>1</sub>.<sup>44,53</sup> There is, to date, little clarity on sex differences in the susceptibility to cigarette smoke, with similar numbers of studies reporting that men are more susceptible<sup>42,51,53-55</sup> and that women are more vulnerable.<sup>16,37,44,56,57</sup> It has been shown by several authors that symptomatic smokers have larger declines than non-symptomatic smokers.<sup>8,58</sup> Although weight per se does not enter as a significant factor into any of the regression equations for FEV<sub>1</sub> given in the table, a negative effect of weight gain on decline in pulmonary function has recently been reported in two studies.<sup>59,60</sup> The loss of FEV<sub>1</sub> due

to increase in weight associated with smoking cessation therefore counteracts to some degree the positive effect of smoking cessation itself on FEV<sub>1</sub>.

#### Other risk factors associated with accelerated decline of FEV<sub>1</sub>

When interpreting the results of (changes in) FEV<sub>1</sub>, it is important to realise that smoking is not the only known risk factor for accelerated decline in lung function, though it is by far the most important one both in epidemiological settings and in patients with already manifest disease. Some patients with asthma show accelerated decline in FEV<sub>1</sub>.<sup>61-65</sup> Since chronic obstructive pulmonary disease (COPD) is usually associated with smoking, and smoking is the primary risk factor for accelerated decline, it is unclear whether the disease by itself gives rise to accelerated decline. In patients with COPD and mild to moderate obstruction, cessation of smoking seems to move the decline in pulmonary function back into the normal range.<sup>32</sup> Risk factors for accelerated decline among subjects with already clinically manifest obstructive disease have also recently been reviewed;<sup>49</sup> next to smoking, increased airway hyperresponsiveness was the only factor consistently found to predict a more rapid decline.<sup>66-68</sup> Studies of general population samples (as opposed to patients with already manifest disease) have identified the following risk factors for accelerated decline which are reviewed elsewhere: airways hyperresponsiveness,<sup>69,70</sup> atopy,<sup>69</sup> childhood respiratory infections,<sup>71</sup> air pollution,<sup>72</sup> and occupational hazards.<sup>73,74</sup>

#### Is this lung function abnormal?

Measurement of lung function is subject to large variation and age, height, and sex in prediction equations only account for some

40–50% of any forced vital capacity measured.<sup>20</sup> Such data are not available for FEV<sub>1</sub> but should be comparable. It is less appreciated that the interpretation of the results of a given test result by pulmonary physicians is also subject to considerable variation; when 26 pulmonary physicians were asked to grade obstruction in 10 consecutive patients as none, mild, moderate, or severe, only 60% agreement was obtained.<sup>21</sup> Part of this confusion stems from a lack of common concept of normality.<sup>20 22–24 75–77</sup> Three methods are available to determine the lower limit of normal FEV<sub>1</sub>: (1) a fixed percentage below the predicted value; (2) a fixed point of the normal Gaussian distribution, most commonly the 5th percentile; and (3) the actual percentile curves. Unfortunately, the first method of assessing “abnormality” is still by far the most commonly used method by clinicians and 80% predicted is the commonly used limit. This method has no logical background and has, in fact, been proven to be inappropriate by many authors over the last four decades.<sup>25 9 12 25 78–81</sup> Why does the method persist? Probably for two reasons – primarily because it is the easiest method to use, and also because it has been used for such a long period both by clinicians and researchers. The reason why the fixed percentage criterion should be abandoned is that the boundary between acceptable and unusually low function in large population studies is not proportional to the mean value, but instead the distribution is homoscedastic – the loss, for instance, of 0.84 litres is just as unusual for an old as for a young man, and for a tall as for a short man. In other words, 5% of the healthy young tall population have values as low or lower than this volume below predicted, and similarly 5% of the short old population (fig 3).<sup>78</sup> The second and third methods of assessing normality have a common statistical basis. The third method, which uses percentile curves, is the best method

from a statistical perspective,<sup>5 76 80</sup> and although not in vogue in pulmonary medicine, it has been used to great advantage for many years in paediatrics for growth curves (height for age, weight for height, etc). In cases where the distribution of values around the predicted value is Gaussian across all ages and heights, the 95% percentile should be the same as 1.64 times the standard deviation of the residuals (sometimes called the residual standard deviation, RSD). This is the abovementioned second method. In the case of the European Community for Coal and Steel equations, the distribution in fact turns out to be sufficiently Gaussian to justify the use of 1.64 RSD or the 5th centile as the cut off value, representing values of 0.84 l as the cut off for men and 0.62 l for women.<sup>9</sup> This method is easier to implement in clinical practice than the use of percentile curves for different heights and sexes. The underlying assumption is that it is deemed acceptable that 5% of the normal population be classified as having an abnormally low lung function. Results of function tests should then be expressed in the number of RSDs below predicted instead of in % predicted. Only a few lung function laboratories appear so far to have taken up this statistically more logical approach, and many clinicians remain reluctant. Likewise, selection of patients for having an abnormal lung function in a research setting should preferably also be performed utilising RSD.<sup>82</sup> Fortunately, software of newer lung function devices increasingly renders the FEV<sub>1</sub> deviation from normal not only in % predicted but also in RSD below predicted. For children, in contrast to adults, the standard error of the estimate is indeed proportional to predicted mean and hence a fixed percentage of predicted can be used as the lower boundary in children.<sup>26</sup>

With regard to the assessment of a given level of FEV<sub>1</sub>, the calculation of boundaries for acceptable versus accelerated decline in lung

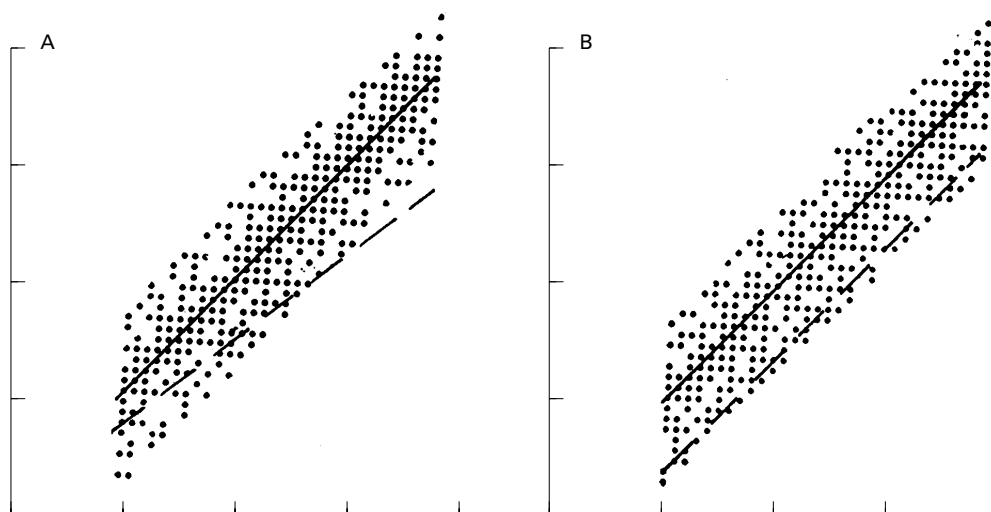


Figure 3 Set of hypothetical points relating some parameter to a physiological function. Solid line in middle of dots represents regression line for these points. Broken line represents limits of normal (A) 20% below the regression line and (B) 2 SE of the estimate below the regression line. Since the variance – that is, the scatter of points around the regression line – is uniform regardless of the point on the regression line one chooses, the degree of deviation from regression is fixed and the use of percentage as in (A) is invalid. FEV<sub>1</sub> and VC data have this characteristic of uniform variance so that the use of 2 SE is legitimate. Reproduced with permission from Sobol.<sup>78</sup>

function should be derived as 5th percentiles employing the standard error of the estimate from regression equations of decline exactly as explained above using RSD for level of FEV<sub>1</sub>. These regression equations involve quadratic terms of age.<sup>7,11,15</sup>

### Conclusions

Interpretation of a given FEV<sub>1</sub> in the light of what is an unusually low value and what is well within the common range is daily practice for the clinician. Although a clinical judgement should never be based solely on the results of a lung function test, the judgement of the physician can have large personal, social, legal, and economic consequences. However, the interpretation is not always as straightforward as it may seem at first glance.

For the proper interpretation of any measured FEV<sub>1</sub>, the sources of variation in one's own laboratory should first be appreciated. There is considerable variation due to technical and patient related sources. It is also essential that the reference equations chosen should be appropriate for the subject under investigation.

It has long been shown that smoking – both active and passive – has a negative influence on lung function, particularly cigarette smoke which influences all three determinants of an FEV<sub>1</sub> at any given time during adult life – the peak achieved during early adulthood, the duration of the ensuing early adulthood plateau phase, and the rate of subsequent decline. On average, moderate to heavy male smokers roughly have a 15 ml/year larger decline in lung function than non-smokers.

Finally, most reference values currently in use are of a cross sectional nature and are therefore not well suited for predicting decline within individuals.

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