Lung function in healthy never smoking adults: reference values and lower limits of normal of a Swiss population

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Abstract

Background – Reference values and definitions of “normal” are prerequisites for population screening and classification of lung diseases. The aim of this study was to calculate reference values for never smoking Caucasian adults.

Methods – In the SAPALDIA cross sectional study respiratory health was assessed in a random sample of 9651 subjects, aged 18–60 years, from eight areas of Switzerland. Lung function was measured according to ATS criteria including quality control. In 3157 healthy never smoking adults without respiratory symptoms the mean values and fifth percentiles of lung function variables were calculated. For each sex, logarithms of lung function were regressed against age, age squared, and the logarithm of height. Residuals were used to estimate fifth percentiles across the age range using a technique not requiring normality or homoscedasticity of residuals.

Results – Most lung function variables were non-linear with age and showed an increase in early adulthood and an accelerated decline thereafter. The reference values for forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁) were higher than those of the European Community for Coal and Steel and those from North America. The prediction equations for lower fifth percentile values defined a stable proportion of subjects outside this limit whereas alternative methods for estimating the fifth percentile showed a loss of sensitivity with age.

Conclusions – The reference equations for mean values of spirometric indices and their lower fifth percentiles gave an improved and unbiased lower limit of normal. The higher mean values may in part be due to the strictly selected population, quality control procedures, cohort effects, and altitude, and are not explained by the statistical model used.

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with differently by clinicians interested in variation due to disease, in surveillance programmes in respiratory, occupational and sports medicine, or in public health screening. In all these circumstances, however, the comparison with normal values may influence decisions which have important implications both on the individual and on the health care system.

Several sets of normal values have been published over the last decades and “normality” for a given age and height may vary considerably across these data. Such variations may be explained by selection criteria of “normal” populations, measurement techniques and devices, biological variability across populations, and statistical modelling.^{1,2} Furthermore, as for other anthropometric measures such as height, birth cohort effects have been described – that is, mean values within each age group increased over time. For example, Glindmeyer³ used normal reference values from 18 cross sectional studies conducted over 130 years to estimate a 55 ml cohort increase per decade among 25 year old men of average height (173 cm). Based on Dutch data⁴ the cohort effect might be even twice as large. These effects may be explained by the change in the total burden of environmental conditions over time⁵ and/or by the technological progress of testing equipment and measurement techniques. Standardisation procedures have been improved⁶ and new equipment, as used in this study, is computer based allowing for ad hoc decisions with regard to acceptability and reproducibility of spirometric manoeuvres.⁷ Given the use of normal values in decision making, cohort effects should be considered a major argument for updating reference values on a regular basis otherwise normal values gradually lose their sensitivity in the detection of abnormal conditions among younger cohorts.

The prediction equations most widely used in Europe are based on different study populations, including smokers, studied in the years 1954 to 1980.^{8,9} Recent recommendations on equipment and standardisation of procedures propose reference values based on cross sectional studies of lifetime non-smokers.^{2,6,9}

In this paper we provide results from a recent cross sectional study within a Central European population.¹⁰ We present reference values based on a well defined selection of the SAPALDIA random population sample. Furthermore, we present fifth percentiles as lower limits of the normal range which account for changes in the distribution of lung function with age. Implications of this approach will be discussed in

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The interpretation of results of lung function tests usually relies on comparison with reference values derived from a “normal” population. The concept of normality may be dealt

Table 1 Inclusion criteria for study population in the SAPALDIA trial

	Men (n = 4743)	Women (n = 4908)	Total (n = 9651)
Acceptable and reproducible pulmonary function tests	4294 (90.5)	4588 (93.5)	8882 (92.0)
Health criteria satisfied	3471 (73.2)	3770 (76.8)	7241 (75.0)
Never smokers	1693 (35.7)	2536 (51.7)	4229 (43.8)
All criteria satisfied	1267 (26.7)	1890 (38.5)	3157 (32.7)

Values in parentheses are percentages.

comparison with the ECCS (European Community Coal and Steel) reference values.

Methods

The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) is an interdisciplinary multicentre study to evaluate the relationship between environmental factors and respiratory diseases.¹⁰ The eight areas chosen (Aarau, Basel, Davos, Genève, Lugano, Montana, Payerne, Wald) represent the wide spectrum of living conditions in Switzerland with different degrees of urbanisation, altitude (200–1600 m above sea level), air pollution, and climatic conditions. A random sample of adults aged 18–60 years who had lived for at least three years in the respective areas was drawn from the local registry of residents in 1991. A total of 17 300 subjects were invited for participation in the study of whom 9651 (59%) agreed to participate.

The cross sectional health assessment included an extended version of the European Community Respiratory Health Survey questionnaire,¹¹ spirometric tests, methacholine bronchial challenge, blood and skin allergy tests, and end expiratory carbon monoxide measurement. Non-participants, extensively studied in Payerne, were more frequently of a lower social and educational level, they reported wheezing in the last 12 months less frequently, and had higher end expiratory carbon monoxide tensions. In all other respects they did not differ significantly from the study participants.¹²

REFERENCE POPULATION

A total of 3157 participants were included in the reported data on normal values for spirometric parameters (table 1). Subjects were excluded if they had at least one of the following criteria: (1) smoked 20 or more packs of cigarettes or 360 g or more tobacco during their life time; (2) health criteria such as a positive history of wheezing in the last 12 months, shortness of breath at rest, nocturnal attacks of shortness of breath or attacks of asthma, current asthma medication, or history of cough or phlegm on most days of at least three months of the year; and (3) spirometric values that did not satisfy the quality criteria for acceptance or reproducibility.

SPIROMETRY

Spirometric tests were performed in a sitting position with nose clips. Participants performed

at least three and up to eight forced expiratory lung function manoeuvres in order to obtain a minimum of two acceptable and reproducible values.⁹ Each centre was equipped with an identical computerised spirometer (Sensor-medics 2200 SP, Bilthoven, The Netherlands) which uses the successfully evaluated and accepted mass flow anemometer technology. The sensor is based on two wires electrically heated to different temperatures and centred in the air stream. The measurement of molecule flow is independent of pressure or temperature. Integrated volumes are BTPS corrected.^{6,13}

Immediate on-screen error codes indicating the major acceptability (including start, duration and end of test) and reproducibility criteria supported the technicians' attempt for standardised procedures. Calibration with a three litre syringe was performed at least once each day.

The three best results for forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), peak expiratory flow (PEF), expiratory flow at 75%, 50%, 25% of FVC (MEF₇₅, MEF₅₀, MEF₂₅), forced mid expiratory flow (MEF₂₅₋₇₅), forced expiratory time (FET 100), and the five-digit error code for ATS criteria were stored on a hard disk and printed on paper, including flow-volume charts for further documentation. The highest values for FVC and FEV₁ of any accepted trial were chosen. Expiratory flow measures were taken from the flow-volume curve with the highest sum of FVC and FEV₁.

The height of the participants was measured standing up with their back to the wall and shoes off. The time of day of the examination was also recorded.

Twenty three technicians were hired for the study and underwent two months of full time training before the start of the study. During the study the technicians were supervised by regular visits of an expert of the central team and the locally responsible pneumologist. A quality control study showed no significant differences between individual technicians or teams.¹⁴

STATISTICAL METHODS

In a first step we estimated prediction equations for the mean. Equations for the fifth percentiles, which were our primary focus of interest as lower limits of the normal range, were then estimated from the residuals of the models for the mean. In this second step we used the method proposed by Goldstein and Pan^{15,16} which does not require any assumptions on the distribution of residuals and thus also works if residuals are not normally distributed and/or if their dispersion varies with age. All regression models were stratified by sex.

Prediction equations for the mean

To estimate equations for the mean the natural logarithms of lung function variables were regressed against ln(height), a quadratic function of age, and dummy variables for the study areas,

Table 2 Mean (SD) characteristics of reference sample

	Men (n = 1267)	Women (n = 1890)
Height (cm)	176.4 (6.7)	163.5 (6.5)
Weight (kg)	74.8 (10.3)	62.0 (10.6)
Age (years)	36.8 (12.1)	41.6 (12.4)
<30 years	34.6%	21.8%
30–40 years	24.4%	21.4%
40–50 years	24.3%	25.9%
>50 years	16.7%	30.9%

taking into consideration a random technician effect.

The rationale for considering lung function variables on the logarithmic scale was the assumption that the dependency of average lung function (LF) on height (H) and age (A) is suitably described by a function of the form^{17,18}:

$$LF = H^c f(A)$$

Whereas estimating the exponent c from the untransformed data requires the solution of a non-linear regression problem, the logarithmic transformation of the equation turns the regression problem for c into a linear one.

The quadratic function in age was originally conceived to consist of two parts, one for the age interval 18–25 years and one for the interval >25–60 years. The two quadratic polynomials were treated parametrically in such a way as to agree in y value and slope at the common boundary point of 25 years. The choice of these two intervals was suggested by the ECCS reference equations and corresponds to the

profile of declining pulmonary function over age.^{8,19} The piecewise quadratic model was only retained if its fit was significantly better than the one of a simple quadratic model defined over the entire interval 18–60 years. If such a simplified model proved to be sufficiently adequate, it was also tested whether or not the quadratic age term was statistically significant.

Individual intercept variables for the study areas – that is, area dummy variables – were introduced in order to guard against potential confounding of the regression estimates due to differences in lung function between study areas unrelated to age and height. To obtain a single intercept term at the end we computed a weighted mean of the area intercepts, choosing weights proportional to the numbers of observations.

Prediction equations for fifth percentiles

The next step was to compute fifth percentiles in consecutive age groups of residuals each containing 100 observations. These percentiles were then regressed against the age means of the respective groups and their squared values.¹⁵ Since the percentage of observations defined as being below normal by these percentile equations ought to be close to 5% in different categories of age and height, we tested the goodness of fit of our equations for the fifth percentiles by comparing the numbers of sub-normal observations in the four quartile classes of age and height, respectively, with the cor-

Figure 1 Age dependency of the distribution of FVC in (A) men and (B) women and of FEV₁ in (C) men and (D) women in the SAPALDIA reference sample. Each subject of the respective sample is represented by a dot. The solid lines represent estimates of the age relationship of mean FVC and FEV₁, respectively, obtained using the supersmoother algorithm.^{20,28}

Table 3 Prediction equations for the means of lung function variables

		SD*	R ² †
Men:			
FVC (l)	= exp (−10.321 + 2.1685 ln(H) + 0.0655A − 0.001325A ²) (A ≤ 25)	0.62	0.40
	= exp (−9.540 + 2.1685 ln(H) + 0.0030A − 0.000075A ²) (A > 25)		
FEV ₁ (l)	= exp (−9.280 + 1.9095 ln(H) + 0.0795A − 0.001698A ²) (A ≤ 25)	0.51	0.44
	= exp (−8.240 + 1.9095 ln(H) − 0.0037A − 0.000033A ²) (A > 25)		
PEF (l/s)	= exp (−6.189 + 1.2965 ln(H) + 0.1379A − 0.002731A ²) (A ≤ 25)	2.23	0.05
	= exp (−4.548 + 1.2965 ln(H) + 0.0066A − 0.000106A ²) (A > 25)		
MEF ₂₅₋₇₅ (l/s)	= exp (−3.205 + 0.9457 ln(H) − 0.0025A − 0.000137A ²)	1.12	0.27
MEF ₇₅ (l/s)	= exp (−4.440 + 0.9869 ln(H) + 0.1188A − 0.002404A ²) (A ≤ 25)	1.91	0.03
	= exp (−2.968 + 0.9869 ln(H) + 0.0011A − 0.000050A ²) (A > 25)		
MEF ₅₀ (l/s)	= exp (−2.510 + 0.8156 ln(H) + 0.0012A − 0.000119A ²)	1.39	0.12
MEF ₂₅ (l/s)	= exp (−4.474 + 1.1258 ln(H) − 0.0165A − 0.000120A ²)	0.73	0.42
FEV ₁ /FVC	= exp (1.526 − 0.3144 ln(H) − 0.0033A)	0.07	0.18
Women:			
FVC (l)	= exp (−9.457 + 2.0966 ln(H) + 0.0091A − 0.000152A ²)	0.50	0.38
FEV ₁ (l)	= exp (−8.217 + 1.8475 ln(H) + 0.0035A − 0.000130A ²)	0.41	0.47
PEF (l/s)	= exp (−5.790 + 1.4902 ln(H) + 0.0042A − 0.000082A ²)	1.53	0.09
MEF ₂₅₋₇₅ (l/s)	= exp (−3.247 + 0.9020 ln(H) + 0.0044A − 0.000240A ²)	0.81	0.33
MEF ₇₅ (l/s)	= exp (−4.048 + 1.1453 ln(H) + 0.0020A − 0.000068A ²)	1.39	0.08
MEF ₅₀ (l/s)	= exp (−2.332 + 0.7376 ln(H) + 0.0045A − 0.000166A ²)	0.98	0.17
MEF ₂₅ (l/s)	= exp (−4.757 + 1.1220 ln(H) − 0.0035A − 0.000319A ²)	0.54	0.44
FEV ₁ /FVC	= exp (1.283 − 0.2640 ln(H) − 0.0037A)	0.06	0.25

A = age (years); H = height (cm); exp(x) = e^x.

* Standard deviation of residuals; † fraction of explained variance.

For instance, for a man of 20 years and 180 cm the predicted value of FEV₁ is computed as follows:

$$FEV_1 = e^{(-9.280 + 1.9095 \times \ln(180) + 0.0795 \times 20 - 0.001698 \times 400)} = e^{1.547} = 4.696$$

responding expected numbers using χ^2 tests of three degrees of freedom. Graphically, the goodness of fit was checked by computing separate logistic regression models for the percentage of subnormal observations with age and ln(height), respectively, as predictor variables and plotting the corresponding percentage estimates against age and ln(height), respectively (see fig 2A and 2B for the goodness of fit with respect to age).

Results

The study population drawn from a random sample of the Swiss population aged 18–60 years is shown in table 1. Results for each lung function variable refer to participants who performed the tests according to ATS quality criteria.

Demographic data of the 3157 subjects show an overrepresentation of women over 50 years of age (table 2) because women were more likely to have never smoked than men of the same age group.

Figure 1A–D shows the age dependency of the distributions of FVC and FEV₁ among men

and women of our reference sample. In each of these plots, dots represent individual subjects whereas the solid line represents an estimate of the relationship between average lung function and age. These curves are non-parametric in nature – that is, not based on a parametric model – and were obtained using the super-smoother algorithm.²⁰ They all show some degree of curvature, either over the entire age range (women) or in the lower age range (men).

The prediction equations for the mean of the lung function variables are displayed in table 3 as $LF = \exp(a + b \ln(\text{height}) + c_1 \text{ age} + c_2 \text{ age}^2)$, where LF represents any of the lung function variables measured (FVC, FEV₁, PEF, MEF₂₅₋₇₅, MEF₇₅, MEF₅₀, MEF₂₅, and FEV₁/FVC) and exp(x) stands for e^x. This equation is equivalent to $\ln(LF) = a + b \ln(\text{height}) + c_1 \text{ age} + c_2 \text{ age}^2$. Separate equations for men younger than 25 years for FVC, FEV₁, PEF, and MEF₇₅, respectively, fitted our data significantly better than a single equation. A linear polynomial in age was found adequately to describe the age dependency of ln(FEV₁/FVC). For all other lung function variables (except MEF₂₅ in women) the quadratic age term was statistically significant.

The equations for the fifth percentiles, which we recommend as a lower limit of the normal range, are displayed in table 4 and are of the same form as those for the mean. In fig 2 the equations for the fifth percentiles of FEV₁ in men and women are graphically validated. A comparison with the European Community for Coal and Steel (ECCS),⁹ earlier Swiss values,²¹ and more recent North American reference values^{22,23} is shown in figs 3A–D for the mean of FVC and FEV₁ in relation to age.

Discussion

The reference values for FVC and FEV₁ obtained from healthy never smoking adults aged 18–60 years participating in our cross sectional epidemiological study are higher than those obtained from other published equations.^{9,21–23} The relevance of higher reference values is best

Table 4 Prediction equations for the fifth percentiles of lung function variables

Men:			
FVC (l)	= exp (−10.496 + 2.1685 ln(H) + 0.0655A − 0.001343A ²) (A ≤ 25)		
	= exp (−9.714 + 2.1685 ln(H) + 0.0030A − 0.000093A ²) (A > 25)		
FEV ₁ (l)	= exp (−9.281 + 1.9095 ln(H) + 0.0695A − 0.001586A ²) (A ≤ 25)		
	= exp (−8.241 + 1.9095 ln(H) − 0.0138A + 0.000079A ²) (A > 25)		
PEF (l/s)	= exp (−6.321 + 1.2965 ln(H) + 0.1250A − 0.002602A ²) (A ≤ 25)		
	= exp (−4.681 + 1.2965 ln(H) − 0.0062A + 0.000023A ²) (A > 25)		
MEF ₂₅₋₇₅ (l/s)	= exp (−3.285 + 0.9457 ln(H) − 0.0195A − 0.000003A ²)		
MEF ₇₅ (l/s)	= exp (−4.559 + 0.9869 ln(H) + 0.1048A − 0.002272A ²) (A ≤ 25)		
	= exp (−3.087 + 0.9869 ln(H) − 0.0129A + 0.000082A ²) (A > 25)		
MEF ₅₀ (l/s)	= exp (−2.710 + 0.8156 ln(H) − 0.0095A − 0.000045A ²)		
MEF ₂₅ (l/s)	= exp (−4.710 + 1.1258 ln(H) − 0.0281A − 0.000093A ²)		
FEV ₁ /FVC	= exp (1.393 − 0.3144 ln(H) − 0.0038A)		
Women:			
FVC (l)	= exp (−9.711 + 2.0966 ln(H) + 0.0111A − 0.000191A ²)		
FEV ₁ (l)	= exp (−8.398 + 1.8475 ln(H) + 0.0022A − 0.000132A ²)		
PEF (l/s)	= exp (−5.831 + 1.4902 ln(H) − 0.0127A + 0.000084A ²)		
MEF ₂₅₋₇₅ (l/s)	= exp (−3.431 + 0.9020 ln(H) − 0.0047A − 0.000193A ²)		
MEF ₇₅ (l/s)	= exp (−4.149 + 1.1453 ln(H) − 0.0107A + 0.000041A ²)		
MEF ₅₀ (l/s)	= exp (−2.471 + 0.7376 ln(H) − 0.0048A − 0.000131A ²)		
MEF ₂₅ (l/s)	= exp (−5.120 + 1.1220 ln(H) − 0.0101A − 0.000334A ²)		
FEV ₁ /FVC	= exp (1.174 − 0.2640 ln(H) − 0.0042A)		

A = age (years); H = height (cm); exp(x) = e^x.

For instance, for a man of 40 years and 180 cm the predicted fifth percentile of FVC is computed as follows:

$$FVC = e^{(-9.714 + 2.1685 \times \ln(180) + 0.003 \times 40 - 0.000093 \times 1600)} = e^{1.518} = 4.56$$

Figure 2 SAPALDIA fifth percentiles for FEV₁ (according to the prediction equations of table 4) are more accurate than traditional percentile estimates. They define a stable percentage of subnormal subjects in the reference population. In contrast, percentages of subnormal subjects in the reference population defined by the fifth percentiles according to the ECCS, Dockery, and Crapo decrease with age, indicating a loss of sensitivity. A = male reference population; B = female reference population.

Figure 3 Age dependency of mean values of (A) FVC and (B) FEV₁ in men (175 cm) and (C) FVC and (D) FEV₁ in women (165 cm) in comparison with published reference values. E = ECCS (1983, summary equations, established with different equipment up to three decades ago by graphical comparison of data in the literature); D = Dockery et al (1985, 2551 participants of the US six city study tested 1974-7 with water seal spirometers); A = Amrein et al²¹ (1969, occupation-based sample of 1200 subjects from Basel including smokers, tested with a pneumotachograph, only FEV₁); and C = Crapo et al²² (1981, 251 never smoking mormons tested at 1400 m above sea level with a water-sealed spirometer in 1980).

demonstrated at the estimated lower limit of normal. SAPALDIA fifth percentiles classify a larger percentage of our reference population as abnormal than other published reference equations (fig 2A and B). This clinically relevant difference may have different causes including differences in the populations, technical factors, altitude, or cohort effects. As far as percentile estimates are concerned, statistical modelling may partly explain the differences (see later).

STUDY POPULATION

The observed differences compared with other reference values, especially the ECCS,⁹ may be due to stricter selection criteria for our reference population, which only included asymptomatic never smokers.

The exclusion of smokers and ex-smokers is justified by epidemiological and clinical experience which has shown an accelerated decline of lung function in smokers.²⁴ Women were overrepresented, particularly in the higher age groups, because they were more likely never to have smoked than men.

Reference values are given for never smokers without respiratory symptoms (table 2). Exclusions were based on the questionnaire results only. No clinical or chest radiographic examinations were performed. This might result in the inclusion of some patients with asymptomatic lung disease of the restrictive type. The potential bias toward lower values and increased variability in higher age groups should be regarded as negligible given the low prevalence of restrictive lung disease among asymptomatic adults.

A potential selection bias can be seen in the participation rate of 59% in the SAPALDIA

study. A separate analysis of non-participants was conducted in one SAPALDIA area and showed an overrepresentation of subjects of lower social class and lower educational level and a lower prevalence of symptoms of wheezing in the non-participants.¹² Given our selection of asymptomatic subjects, this participation pattern might bias lung function toward higher values.

TECHNICAL FACTORS

Equipment has changed since the years 1954 to 1980 when the lung function tests in the other reference populations were performed. On-line feedback about acceptability of spirometric performance was not available decades ago. We argue that immediate feedback tends to yield higher values in measures that depend on cooperation of the subject – for example, on-screen information about the ATS end of test criteria gives a direct incentive for the technicians to achieve full expiration. Repetitive maximal performance is enhanced by an on-line check of reproducibility. Strict fulfillment of the manoeuvre for start criteria – for example, back extrapolation of less than 5% or less than 100 ml of FVC – is readily checked by computer devices and thus likely to optimise FEV₁. Based on these arguments one would expect attenuated differences for flow measures that are independent of effort. In fact, the most striking difference in our reference values compared with those of the ECCS relate to FVC and FEV₁. For PEF the differences were much smaller, further supporting our argument for the importance of on-line quality criteria. No quality criteria have been defined for PEF by the ATS² and no such criteria were used in our software. The lack of such criteria must be considered as a major reason for the increased variability in PEF measurements.

We used a computerised open spirometer with a mass flow sensor based on a hot wire system which fulfilled ATS performance criteria.⁶ Strictly standardised technique, regular supervision, and separate spirometric quality control studies were used to minimise variability between devices, teams, and technicians.¹⁴ These quality controls, based on repetitive measurements on volunteers, showed no systematic differences between the 23 technicians or the eight teams. To confirm the validity of the hot wire open systems a closed system (water-sealed spirometer, Sensormedics 2400) was included in our spirometer comparison test¹⁴ and the results obtained with the two different systems were in good agreement. Thus, our use of a mass flow sensor does not explain the observed higher values.

It might be argued that choosing the best values for FVC and FEV₁ from different curves according to ATS criteria tends to provide higher values. Wise *et al*²⁵ found that the largest single value from all manoeuvres showed the least short term variability for both FEV₁ and FVC and concluded that there is no reason to change the currently recommended ATS selection method.

ALTITUDE

The potential effect of altitude (83% of the participants lived 200–1200 m above sea level and none lived above 1600 m) was not tested separately. Theoretically, and based on measurements on healthy African adults, altitude can have a variable effect of up to 263 ml/1000 m on FVC in men.^{26,27} Statistical analysis of our data would support a small bias toward higher values at altitude which might have influenced our results for FVC and FEV₁ by 0.5% in men and 1% in women at most. This bias might be slightly larger (up to 1.1% in men and 1.6% in women) for the flow parameters. However, these differences are small compared with those between our predicted values and previously established reference values.

STATISTICAL MODEL

When lung function variables are considered on the logarithmic scale their age dependency showed a significant amount of curvature in the interval 18–60 years with one exception (Tiffeneau) which required a quadratic age term in all these models. For FVC, FEV₁, PEF, and MEF₇₅ in men a piecewise quadratic function in age with a break point at 25 years provided a significant improvement of fit over a simple quadratic function defined over the entire interval. The non-linearity of the logarithmic transformation implies that a linear relationship between untransformed data is no longer linear after data have been logarithmised. This leads to the seemingly paradoxical situation that, to model a linear relationship between untransformed lung function data and age, a quadratic polynomial in age is necessary in the logarithmic representation of lung function values.

Our rationale for modelling lung function variables on the logarithmic scale has been outlined in the method section. Since the use of the logarithmic transformation in this context has been debated, we decided also to compute a variant of Cole's proportional model for FVC and FEV₁.¹⁷ This model was of the form:

$$LF = \text{height}^c (b_0 + b_1 \text{ age} + b_2 \text{ age}^2).$$

Reference curves for the mean obtained from this model were almost identical to those obtained from our model, which shows that the particular choice of the scale on which the lung function variables are considered has only a minor impact on the final results.

COHORT EFFECTS

Our higher reference values are in part also explained by cohort effects. Lung function depends on a variety of individual, behavioural, and environmental factors. If the lifetime profile of all these factors changes over decades, cross sectional lung function might increase by up to 5 ml/year for FVC and FEV₁.³ Our subjects studied in 1991 probably experienced different lifetime exposures in terms of nutrition, exercise, air quality, occupational hazards, and environmental tobacco smoke than earlier ref-

erence populations. We assume that the level of all these factors has changed in the population resulting in higher lung function values than 2–3 decades ago. It is likely that changes in height only partly explain the observed changes in lung function. It will be of interest to see whether the results of the European Community Respiratory Health Survey¹¹ will confirm this pattern.

WHAT IS THE LOWER LIMIT OF NORMAL?

Because our lung function data showed changes in variability with age and some indication of non-normality of the distribution of residuals, we decided to derive direct estimates of the fifth percentiles. This approach provides more accurate estimates than the traditional one assuming a constant difference (1.645 standard deviations) between the mean and fifth percentiles (fig 2).¹⁸

It must be emphasised that cutoff points defined for "normal" by other widely used reference values lose sensitivity with increasing age within our reference sample – for example, in fig 2 the most extreme case is given for FEV₁ among women based on Crapo's reference values; older women of our reference population are far less likely to be defined as "below normal" than younger ones. In other cases the discrepancies are less pronounced but follow the same pattern. We strongly recommend a concept for "lower limits of normal" with a stable alpha error – that is, the probability of declaring a healthy person as being "below normal" should be independent of age. Normal values published so far have apparently given less priority to this goal.

If the SAPALDIA lower limits of normal were used instead of those of the ECCS up to three times as many subjects of our reference population would be considered abnormal for FVC and FEV₁. This has direct implications in the definition of disease and disease incidence, and may influence indirectly the cost of medical care as well as disability compensation. Sensitivity and specificity of widely used reference values should be tested.

LIMITATIONS AND USEFULNESS

Our reference values should only be used for the age group studied (18–60 years). Extensions beyond these age limits are not warranted. The reference values are "optimal" rather than "normal" and pertain to healthy subjects who have never smoked. They are of particular use in screening healthy subjects and in detecting early changes in lung function due to smoking or other environmental agents.

Despite these caveats we suggest the use of our reference values in comparable European populations.

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