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Spirometric reference equations for European females and males aged 65–85 yrs

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Spirometric reference equations for European females and males aged 65–85 yrs. F. García-Río, J.M. Pino, A. Dorgham, A. Alonso, J. Villamor. ©ERS Journals Ltd 2004.

ABSTRACT: The aim of this study was to describe spirometric reference equations for healthy never-smoking European adults aged 65–85 yrs and to compare the predicted values of this sample with those from other studies including middle-aged and/or older adults.

Reference equations and normal ranges for forced expiratory volume in one second (FEV1), forced vital capacity (FVC), forced expiratory volume in six seconds (FEV6), FEV1/FVC ratio and FEV1/FEV6 ratio were derived from a healthy subgroup of 458 subjects aged 65–85 yrs. Spirometry examinations followed the 1994 American Thoracic Society recommendations and the quality of the data was continuously monitored and maintained. Reference values and lower limits of normal were derived using a piecewise polynomial model with age and height as predictors.

The reference values of FEV1 and FVC from the present study were higher than those given by prediction equations from the European Community for Coal and Steel. By contrast, use of prediction equations from Caucasian-American elderly subjects (Cardiovascular Health Study) consistently overpredicted FVC and FEV1 in females by 8.5 and 2.1%, respectively. In males, equations from the Cardiovascular Health Study overpredicted FVC by 2.8%, whilst underpredicting FEV1 by 2.5%.

In conclusion, these results underscore the importance of using prediction equations appropriate to the origin, age and height characteristics of the subjects being studied.
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Spirometry is probably the most important tool used in screening for pulmonary disease and is the most frequently performed pulmonary function test. Although the average age of patients tested at pulmonary function laboratories each year is ~60 yrs old, many of the reference equations commonly used for the prediction of normal spirometric values in North America and Europe have been derived from studies that included relatively small numbers of individuals >65 yrs old [1–9]. In fact, predicted values for older individuals are often based upon few observations or extrapolations from data acquired in studies of younger adults. However, the application of prediction equations derived from primarily younger adult populations to older adults may be inappropriate because the relationship between lung function, age and height may change with age. In fact, the current international guidelines recommend that spirometry reference equations should, in general, not be extrapolated for ages or heights beyond those covered by the data that generated them [10, 11].

Valid reference values for spirometric parameters in healthy elderly Afro-Americans [12] and Japanese-American elderly males [13] have been previously reported. Only two sets of standards have been published on lifetime nonsmokers in Caucasian-American elderly subjects [14, 15]. Although significant differences between Caucasians of American and European origin have been suggested [16], no study has collected pulmonary measurements for both sexes across a large sample of elderly European subjects. ENRIGHT *et al.* [14] derived spirometric prediction equations from a reference population of healthy individuals aged 65–85 yrs. However, the study did not provide reference equations for spirometry variables other than forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and FEV1/FVC ratio [14]. Although with some exceptions [9, 17], many previous prediction equations for elderly subjects were linear [12–14] and, therefore, did not reflect accelerating decline with age. Finally, only one previous study [6] provides reference values for elderly subjects for forced expiratory volume in six seconds (FEV6) and FEV1/FEV6 ratio, an acceptable surrogate for FVC for the spirometric diagnosis of obstruction [18].

The purpose of the current study is to describe spirometric reference equations for a cohort of healthy never-smoking Caucasian-European adults aged 65–85 yrs and to compare the predicted values of this sample with those from other studies, including middle-aged and/or older adults.

Materials and methods

Study subjects

The total target population consisted of 466,958 inhabitants aged 65–85 yrs, included in the census register of the Madrid metropolitan area, Spain (760 m above sea level). A random sample of 1,300 subjects proportionally stratified by sex and age (65–69, 70–74, 75–80 and 81–85 yrs) was drawn by electronic selection to approximate the total population distribution.

For editorial comments see page 341.

Eligible persons were invited to participate if they were lifetime never-smokers and had no known history of respiratory or cardiovascular disease. Over a 12-month period, starting in February 2001, potential participants were sent an explanatory letter, interviewed by telephone to determine eligibility and, then, scheduled for the baseline clinical examination. During this time, the study was explained using local mass communication media (radio and television) to increase the acceptation rate. Among those contacted, 46.5% were ineligible and 16.3% of those eligible refused to participate.

Clinical evaluation was based on an extended combination of the European Community for Coal and Steel questionnaire on respiratory symptoms [19], a physical examination, complete blood count and blood chemistry, a conventional chest radiograph evaluation and 12-lead resting electrocardiography (ECG).

The exclusion criteria were: history of chest injuries; exposure to substances known to cause lung injury; respiratory disease (self-reported or medical doctor-diagnosed asthma, pulmonary tuberculosis, pneumonia, frequent bronchitis, emphysema or chronic bronchitis); respiratory symptoms during the last 12 months (dyspnoea, chronic cough, wheezing or phlegm); hypertension or hypotension; clinically relevant alterations of the physical examination of the heart, lungs and chest wall; abnormal chest radiographs; major ECG abnormalities; pitting ankle oedema; diabetes (self-reported or fasted glucose level >140 $mg \cdot dL^{-1}$); and the use of diuretics, cardiac glycosides or β-adrenergic blocking agents.

The study was approved by the local Ethics Committee. Informed consent was obtained from all subjects.

Methods

All tests were performed by a single technician experienced in lung function testing (A. Dorgham). Spirometry was recorded with a pneumotachograph (MasterLab 4.6; Jaeger, Wurtzburg, Germany). The system was calibrated with a 3-L syringe each morning and recalibrated ⩾3–4 h. The technician also performed a daily biological control by assessing his own lung function. Standing height was measured to the nearest 0.5 cm without shoes, with the subject's back to a vertical backboard. Both heels were placed together, touching the base of the vertical board. Subjects were weighed whilst wearing indoor clothing without shoes, and body mass index (BMI=weight/height^2; expressed in $kg \cdot m^{-2}$) and body surface area (BSA=$0.20247 \times height^{0.725} \times weight^{0.425}$; expressed in m^2) were calculated. Age was recorded to the nearest birthday. Barometric pressure, temperature and relative humidity were registered every morning, and the integrated volumes were automatically converted from ambient temperature and pressure, (saturated with water vapour) to body temperature and ambient pressure (saturated with water vapour) conditions.

Spirometry flow/volume loops were conducted in accordance with American Thoracic Society (ATS) recommendations [11]. At least three acceptable trials were required, defined as a good start of test (extrapolated volume of <5% of FVC or 0.15 L, whichever was larger), at least 6 s of expiration and a plateau in the volume/time curve (change in volume <30 mL for ⩾2 s). Time zero of each manoeuvre used the back-extrapolation technique [20]. As recommended by the ATS, data that did not meet reproducibility criteria were not excluded, but subjects were asked to perform up to a maximum of eight manoeuvres in an attempt to obtain reproducible results [11]. The highest FEV_1, FEV_6, and FVC from tests of acceptable quality were used for analysis. The other parameters were taken from the trial with the largest sum of FVC and FEV_1.

Table 1. – Sex and age distribution in the 65–85 yrs age group of the reference sample and the total population

Age yrs	Analysed sample		Total population#	
	M	F	M	F
65–69	64 (14.0)	100 (21.8)	15.9	20.6
70–74	55 (12.0)	68 (14.8)	12.0	17.4
75–80	31 (6.8)	75 (16.4)	7.3	12.8
80–85	29 (6.3)	36 (7.9)	4.6	9.5
Total	179 (39.1)	279 (60.9)	39.8	60.2

Data are presented as n (%) and %. M: males; F: females. #: per cent of 466,958 habitants.

For the measurement of forced inspiratory volumes, patients exhaled slowly from tidal breathing until the residual volume was achieved, with subsequent forceful inspiration until total lung capacity was reached. At least three measurements of forced inspiratory volumes were taken. In analogy with ATS criteria [10, 11], from two acceptable manoeuvres (difference <5%), the highest value of the forced inspiratory volume in one second (FIV_1) was chosen for analysis. Peak inspiratory flow rate and the forced inspiratory flow when 50% of the vital capacity has been inhaled were taken from the test with the largest sum of FVC and FIV_1.

Table 2. – Descriptive data

	Females	Males
Subjects n	279	179
Age yrs	72.9±5.5	72.9±5.4
Height cm	152.6±6.2	165.7±6.1
Weight kg	66.6±10.9	76.3±10.0
BMI $kg \cdot m^{-2}$	28.6±4.2	27.8±3.0
FVC L	2.32±0.47	3.49±0.62
FEV_1 L	1.83±0.40	2.68±0.52
FEV_1/FVC %	79.0±5.6	76.9±5.5
$FEV_{0.5}$ L	1.49±0.34	2.16±0.43
FEV_2 L	2.06±0.43	3.04±0.57
FEV_3 L	2.16±0.45	3.20±0.58
FEV_6 L	2.29±0.47	3.40±0.60
FEV_1/FEV_6 %	80.2±5.5	78.8±5.2
$FEF_{25\%}$ $L \cdot s^{-1}$	4.05±1.23	5.90±1.72
$FEF_{50\%}$ $L \cdot s^{-1}$	2.16±0.91	2.94±1.16
$FEF_{75\%}$ $L \cdot s^{-1}$	0.47±0.26	0.64±0.30
PEF $L \cdot s^{-1}$	4.63±1.34	7.08±1.97
$FEF_{75–25\%}$ $L \cdot s^{-1}$	1.42±0.65	2.00±0.82
$FEF_{75–85\%}$ $L \cdot s^{-1}$	0.27±0.14	0.37±0.19
$TC_{25–50\%}$ s	0.41±0.18	0.45±0.21
MTT s	0.33±0.08	0.34±0.08
AEX $L^2 \cdot s^{-1}$	5.05±2.30	10.82±4.26
PIF L	2.92±1.00	4.07±1.44
$MIF_{50\%}$ $L \cdot s^{-1}$	2.71±1.03	3.75±1.44
FIV_1 L	2.12±0.50	3.12±0.75

Data are presented as mean±SD. BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; $FEV_{0.5}$: forced expiratory volume in 0.5 seconds; FEV_2: forced expiratory volume in two seconds; FEV_3: forced expiratory volume in three seconds; FEV_6: forced expiratory volume in six seconds; $FEF_{25\%}$: forced expiratory flow when 25% of the forced expiratory capacity has been exhaled; $FEF_{50\%}$: forced expiratory flow when 50% of the forced expiratory capacity has been exhaled; $FEF_{75\%}$: forced expiratory flow when 75% of the forced expiratory capacity has been exhaled; PEF: peak expiratory flow; $FEF_{75–25\%}$: forced mid-expiratory flow; $FEF_{75–85\%}$: forced mid-expiratory flow between 75–85% of FVC; $TC_{25–50\%}$: time constant between 25–50% of FVC; MTT: mean transit time; AEX: area delineated by forced expiratory flow/volume curve; PIF: peak inspiratory flow; $MIF_{50\%}$: forced inspiratory flow when 50% of the vital capacity has been inhaled; FIV_1: forced inspiratory volume in one second.

Table 3. – Prediction equations for healthy elderly European females

	Equation	R^2	RSD
FVC L	$0.0003171H^2–0.0351A–6.368BSA+0.05925W+3.960$	0.589	0.3046
FEV_1 L	$0.0001726H^2–0.0326A–2.303BSA+0.000122W^2+3.398$	0.527	0.2741
FEV_1/FVC %	$-0.155H–0.184A+116.096$	0.048	5.4974
$FEV_{0.5}$ L	$0.00008072H^2–0.0251A+1.436$	0.432	0.2589
FEV_2 L	$0.0001138H^2–0.0334A+1.844$	0.523	0.2963
FEV_3 L	$0.0001218H^2–0.0336A+1.774$	0.529	0.3056
FEV_6 L	$0.0003309H^2–0.0346A–6.987BSA+0.06548W+4.152$	0.566	0.3101
FEV_1/FEV_6 %	$-0.181H–0.178A+120.544$	0.058	5.3530
$FEF_{25\%}$ $L \cdot s^{-1}$	$0.05351H–0.00000343A^3–2.756$	0.167	1.1193
$FEF_{50\%}$ $L \cdot s^{-1}$	$0.03414H–0.0540A+0.890$	0.188	0.8234
$FEF_{75\%}$ $L \cdot s^{-1}$	$0.005960H–0.0150A+0.660$	0.131	0.2467
PEF $L \cdot s^{-1}$	$0.0002283H^2–0.0644A+4.001$	0.209	1.1932
$FEF_{75–25\%}$ $L \cdot s^{-1}$	$0.02030H–0.0440A+1.538$	0.202	0.5828
$FEF_{75–85\%}$ $L \cdot s^{-1}$	$-0.0644A+0.735$	0.062	0.1345
$TC_{25–50\%}$ s	$0.0000003057A^3+0.288$	0.025	0.1743
AEX $L^2 \cdot s^{-1}$	$0.0005499H^2–0.158A+3.788$	0.419	1.7560
PIF L	$0.03154H–0.0553A+2.139$	0.153	0.9248
$MIF_{50\%}$ $L \cdot s^{-1}$	$0.02934H–0.0566A+2.363$	0.143	0.9552
FIV_1 L	$0.03478H–0.143A+0.000006A^3+4.701$	0.411	0.3866

The lower limit of the normal is computed as: predicted value–1.645×residual standard deviation (RSD). R^2: adjusted coefficient of determination; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; $FEV_{0.5}$: forced expiratory volume in 0.5 seconds; FEV_2: forced expiratory volume in two seconds; FEV_3: forced expiratory volume in three seconds; FEV_6: forced expiratory volume in six seconds; $FEF_{25\%}$: forced expiratory flow when 25% of the forced expiratory capacity has been exhaled; $FEF_{50\%}$: forced expiratory flow when 50% of the forced expiratory capacity has been exhaled; $FEF_{75\%}$: forced expiratory flow when 75% of the forced expiratory capacity has been exhaled; PEF: peak expiratory flow; $FEF_{75–25\%}$: forced mid-expiratory flow; $FEF_{75–85\%}$: forced mid-expiratory flow between 75–85% of FVC; $TC_{25–50\%}$: time constant between 25–50% of FVC; AEX: area delineated by forced expiratory flow/volume curve; PIF: peak inspiratory flow; $MIF_{50\%}$: forced inspiratory flow when 50% of the vital capacity has been inhaled; FIV_1: forced inspiratory volume in one second; H: height in cm; A: age in yrs; BSA: body surface area in m^2; W: weight in kg.

Analysis

Independent variables considered for inclusion in the models were as follows: age, age^2, age^3, standing height, $height^2$, weight, $weight^2$, BMI, BMI^2, and BSA. The effect of logarithmic and square root transformations of pulmonary function parameters prior to modelling was also examined.

In the multiple linear regression analysis, predictor variables were retained only if their addition significantly improved ($p<0.05$) the fraction of explained variability. Other

Table 4. – Prediction equations for healthy elderly European males

	Equation	R^2	RSD
FVC L	$0.0001572H^2–0.00000268A^3+0.223$	0.477	0.4458
FEV_1 L	$0.0001107H^2–0.0445A+2.886$	0.464	0.3797
FEV_1/FVC %	$-0.00198A^2+87.472$	0.083	5.2655
$FEV_{0.5}$ L	$0.02615H–0.0372A+0.538$	0.411	0.3305
FEV_2 L	$0.0001331H^2–0.00000283A^3+0.499$	0.488	0.4066
FEV_3 L	$0.0001414H^2–0.0000028A^3+0.420$	0.488	0.4174
FEV_6 L	$0.0001501H^2–0.000298A^2+0.869$	0.483	0.4288
FEV_1/FEV_6 %	$-0.0000172A^3+85.536$	0.086	5.0040
$FEF_{25\%}$ $L \cdot s^{-1}$	$0.04185H–0.137A+8.947$	0.226	1.5178
$FEF_{50\%}$ $L \cdot s^{-1}$	$0.03174H–0.0754A+3.176$	0.170	1.0573
$FEF_{75\%}$ $L \cdot s^{-1}$	$0.009789H–0.0184A+0.355$	0.163	0.2776
PEF $L \cdot s^{-1}$	$0.07092H–0.000939A^2+0.347$	0.221	1.7378
$FEF_{75–25\%}$ $L \cdot s^{-1}$	$0.02635H–0.0604A+2.042$	0.219	0.7241
$FEF_{75–85\%}$ $L \cdot s^{-1}$	$0.007765H–0.00948A–0.229$	0.149	0.1779
$TC_{25–50\%}$ s	$0.00005571A^2+0.153$	0.045	0.2041
MTT s	$0.00002282A^2+0.223$	0.054	0.0760
AEX $L^2 \cdot s^{-1}$	$0.0007148H^2–0.379A+18.788$	0.397	3.3119
PIF L	$0.0002211H^2–0.0909A+4.621$	0.247	1.2465
$MIF_{50\%}$ $L \cdot s^{-1}$	$0.0002133H^2–0.0856A+4.128$	0.221	1.2759
FIV_1 L	$0.0001585H^2–0.0526A+2.592$	0.373	0.5967

The lower limit of the normal is computed as: predicted value–1.645×residual standard deviation (RSD). R^2: adjusted coefficient of determination; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; $FEV_{0.5}$: forced expiratory volume in 0.5 seconds; FEV_2: forced expiratory volume in two seconds; FEV_3: forced expiratory volume in three seconds; FEV_6: forced expiratory volume in six seconds; $FEF_{25\%}$: forced expiratory flow when 25% of the forced expiratory capacity has been exhaled; $FEF_{50\%}$: forced expiratory flow when 50% of the forced expiratory capacity has been exhaled; $FEF_{75\%}$: forced expiratory flow when 75% of the forced expiratory capacity has been exhaled; PEF: peak expiratory flow; $FEF_{75–25\%}$: forced mid-expiratory flow; $FEF_{75–85\%}$: forced mid-expiratory flow between 75–85% of FVC; $TC_{25–50\%}$: time constant between 25–50% of FVC; MTT: mean transit time; AEX: area delineated by forced expiratory flow/volume curve; PIF: peak inspiratory flow; $MIF_{50\%}$: forced inspiratory flow when 50% of the vital capacity has been inhaled; FIV_1: forced inspiratory volume in one second; H: height in cm; A: age in yrs.

Table 5. – Comparison between observed values and the predicted values derived from different reference equations

	Females					Males				
	Mean difference %	Mean squared difference	Standardised prediction deviation	% observed values below the LLN	Rank	Mean difference %	Mean squared difference	Standardised prediction deviation	% observed values below the LLN	Rank
FVC										
Present	-1.8	0.092	0.000	5.3	1	-1.5	0.197	0.000	3.3	1
KNUDSON [2]	-7.2	0.116	-1.331	10.7	5	12.4	0.449	0.933	0	10
CRAPO [3]	-2.2	0.103	-0.016	5.3	2	-8.9	0.273	-0.525	12.8	9
ECSC [4]	13.6	0.221	1.096	0	9	3.6	0.240	0.082	0	8
ROCA [5]	-13.0	0.162	-0.752	16.1	8	-20.0	0.612	-1.293	40.2	11
HANKINSON [6]	-6.1	0.109	-0.310	8.9	4	-0.2	0.203	0.090	7.2	2
PAOLETTI [7]	-25.5	0.373	-1.546	51.3	10	-5.4	0.237	-0.290	8.4	7
BRÄNDLI [8]	-13.0	0.158	-0.759	17.9	7	-27.1	0.943	-1.853	60.9	12
LANGHAMMER [9]	-4.8	0.104	-0.179	6.8	3	-2.7	0.205	-0.072	4.5	3
SHARP [13]						2.4	0.236	0.326	0	6
ENRIGHT [14]	-8.5	0.120	-0.446	11.1	6	-2.8	0.216	-0.075	3.9	5
MCDONNELL [15]						-3.9	0.210	-0.191	7.8	4
FEV1										
Present	0.5	0.075	0.000	4.3	1	-1.9	0.143	0.000	3.9	1
KNUDSON [2]	-8.9	0.100	-0.353	11.8	9	10.4	0.274	0.728	0	12
CRAPO [3]	0.5	0.085	0.190	2.5	5	-10.3	0.198	-0.526	13.4	8
ECSC [4]	10.9	0.137	0.797	0.4	11	4.1	0.177	0.418	0	5
ROCA [5]	-3.1	0.081	-0.028	4.6	3	-13.8	0.255	-0.749	21.2	11
HANKINSON [6]	-1.0	0.082	0.078	3.9	4	2.9	0.163	0.320	1.1	3
PAOLETTI [7]	-12.5	0.113	-0.547	14.7	10	1.0	0.162	0.200	0	2
BRÄNDLI [8]	-6.3	0.085	-0.201	6.8	6	-12.0	0.216	-0.619	17.9	9
LANGHAMMER [9]	-7.2	0.086	-0.269	8.6	8	-9.0	0.182	-0.449	11.7	6
SHARP [13]						4.8	0.197	0.484	0	7
ENRIGHT [14]	-2.1	0.080	0.027	3.2	2	2.5	0.168	0.322	0	4
MCDONNELL [15]	-6.8	0.086	-0.248	8.2	7	9.7	0.234	0.791	0	10
FEV6										
Present	-1.9	0.096	-0.000	5.0	1	-1.6	0.183	0.002	4.5	1
HANKINSON [6]	-2.2	0.104	-0.028	5.7	2	1.6	0.196	0.224	1.7	2

Data are presented as n. Lower limit of normal range (LLN) was calculated as: predicted value–residual standard deviation (RSD)×1.645. Rank of the mean square difference is shown. FVC: forced vital capacity; ECSC: European Community for Coal and Steel; FEV1: forced expiratory volume in one second; FEV6: forced expiratory volume in six seconds.

aspects explored included residual standard deviation (RSD), changes in the distribution of the residuals and the homogeneity of the variance over the predictors. Statistical significance was assumed for $p<0.05$. The assumptions of linearity and distributional normality were controlled. Residuals values were plotted against age and height to examine for heteroscedasticity. The lower limit of normal (LLN) range was calculated as follows:

$$\text{LLN} = \text{predicted value} - 1.645 \times \text{RSD} \quad (1)$$

The selection of prediction equations for comparison was based on common use [2–9] and inclusion of the elderly [13–15]. Differences between observed values and values predicted by the prediction equations are given as mean difference in per cent of mean observed values, mean squared difference and standardised prediction deviation (*i.e.* mean prediction deviation/RSD of the corresponding prediction equation). For comparisons among different authors, LLN was calculated using the RSD of the corresponding equation. The differences between predicted values based on the prediction equations from the present study and others are given as Bland and Altman plots.

Results

A total of 583 subjects underwent clinical evaluation. In total, 76 subjects were excluded by dyspnoea (n=24), cough (n=17), wheezing (n=13) and for several previously unknown diseases, such as chronic obstructive pulmonary disease (n=11), asthma (n=8) or scoliosis (n=3). Of the 507 subjects (314 females and 193 males) who were entered into the study, technically acceptable tests were found in 458 (279 females and 179 males). A total of 49 subjects (7.2% of males and 11.1% of females) were excluded from analysis because the expiration time was <6 s (n=37) or because of a poor test start (n=12). The elderly persons who were excluded or were ineligible for the study were similar in age, height and weight to those who were included.

The age distribution of the females and males in the analysed sample (table 1) demonstrates adequate representation of the study population. Details of the anthropometric and spirometric data in both sexes are shown in table 2. No significant differences in these parameters were found between excluded subjects and the analysed sample.

The spirometry reference equations from the healthy elderly European females and males are given in tables 3 and 4. It was not found that the addition of transformations significantly improved the predictability of the regression equations. Preliminary multiple regression analysis indicated that neither BMI nor BMI^2 were associated with FVC, FEV1 or any other spirometric parameter in either sex. No significant interaction was found between age and height.

Analysis of residuals showed that homoscedasticity was present in all equations. Regression analysis of these residuals showed neither statistically significant slopes nor correlation coefficients. The residuals corresponding to these models did not differ significantly from a Gaussian distribution in all spirometric parameters, as determined by the Shapiro-Wilk test. Therefore, one-sided lower 95% prediction intervals were used to determine the LLN lung functions [4, 21].

Table 5 shows the differences between the observed spirometric values found in the subjects of the current study and the values calculated from several prediction equations. Aside from the current authors' equations, the closest agreements for FVC were with CRAPO *et al.* [3], LANGHAMMER *et al.* [9], HANKINSON *et al.* [6] and KNUDSON *et al.* [2] in females, and with HANKINSON *et al.* [6], LANGHAMMER *et al.* [9], MCDONNELL *et al.* [15] and ENRIGHT *et al.* [14] in males. In males, the closest agreements for FEV1 were with PAOLETTI *et al.* [7], HANKINSON *et al.* [6], ENRIGHT *et al.* [14] and the European Community for Steel and Coal [4]. Meanwhile, in females, the closest FEV1 agreements were with ENRIGHT *et al.* [14], ROCA *et al.* [5], HANKINSON *et al.* [6] and CRAPO *et al.* [3].

To compare the current authors' reference equations with other prediction equations, the difference in predicted FEV1 (present study equation–each other equation) by the mean predicted FEV1 are illustrated in figures 1 and 2 for females and males, respectively. In females, a proportional increase for FEV1 with respect to KNUDSON *et al.* [2], PAOLETTI *et al.* [7] and BRÄNDLI *et al.* [8] was found (fig. 1). In males, the relationship increased proportionally when the present prediction values for FEV1 were compared with those from BRÄNDLI *et al.* [8] and SHARP *et al.* [13], whilst it decreased proportionally with respect to KNUDSON *et al.* [2] (fig. 2). In contrast, proportional decreases of relationship with respect to HANKINSON *et al.* [6] were found for FEV1 in both sexes.

For both females and males, European Community for Steel and Coal equations underpredicted FEV1. In contrast, CRAPO *et al.* [3], ROCA *et al.* [5], BRÄNDLI *et al.* [8] and LANGHAMMER *et al.* [9] overestimated both FVC and FEV1 in males.

Discussion

The current study provides equations for predicting lung function values in a population of healthy older European adults. The results confirm that reference equations should not be extrapolated, in general, for ages or heights beyond those covered by the data that generated them. For patients >65 yrs of age, the current study showed that the most commonly used sets of reference equations may lead to inaccurate interpretations.

The reference values for FEV6 provided in this study are not widely available in the literature. To the current authors' knowledge, only the previous study by HANKINSON *et al.* [6] published results for the FEV6, and included 90 males and 236 females in the 66–80 yrs age range. In contrast to the scarce reference equations for FEV6, this parameter could be a potential surrogate for FVC in those situations where long exhalation times are impractical or unwarranted, particularly in elderly or severely obstructed subjects. Recently, it has been suggested that FEV1/FEV6 could predict lung function decline in adult smokers [22].

The current results can be contrasted with the Japanese-American and American males in the Honolulu Heart Program (HHP) [13] and the Cardiovascular Health Study (CHS) [14] cohorts, respectively. The height and age characteristics of the currently studied males are in between the HHP and CHS males, probably reflecting contrasting design characteristics. In contrast to HHP and CHS cohorts,

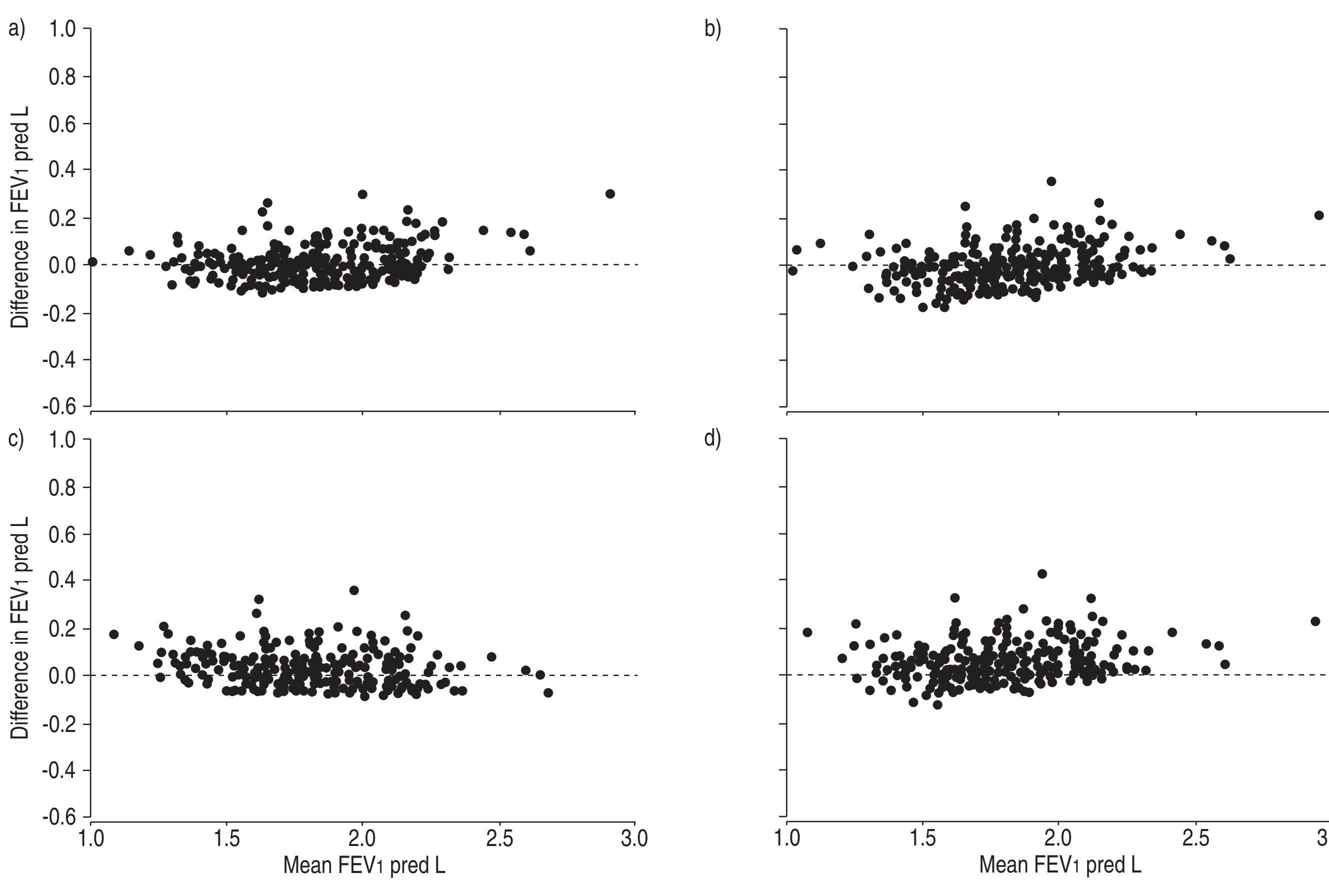

Fig. 1. – Difference between forced expiratory volume in one second (FEV1) against mean FEV1 predicted by the present study *versus* a) ENRIGHT *et al.* [14], b) ROCA *et al.* [5], c) HANKINSON *et al.* [6] and d) CRAPO *et al.* [3] in females.

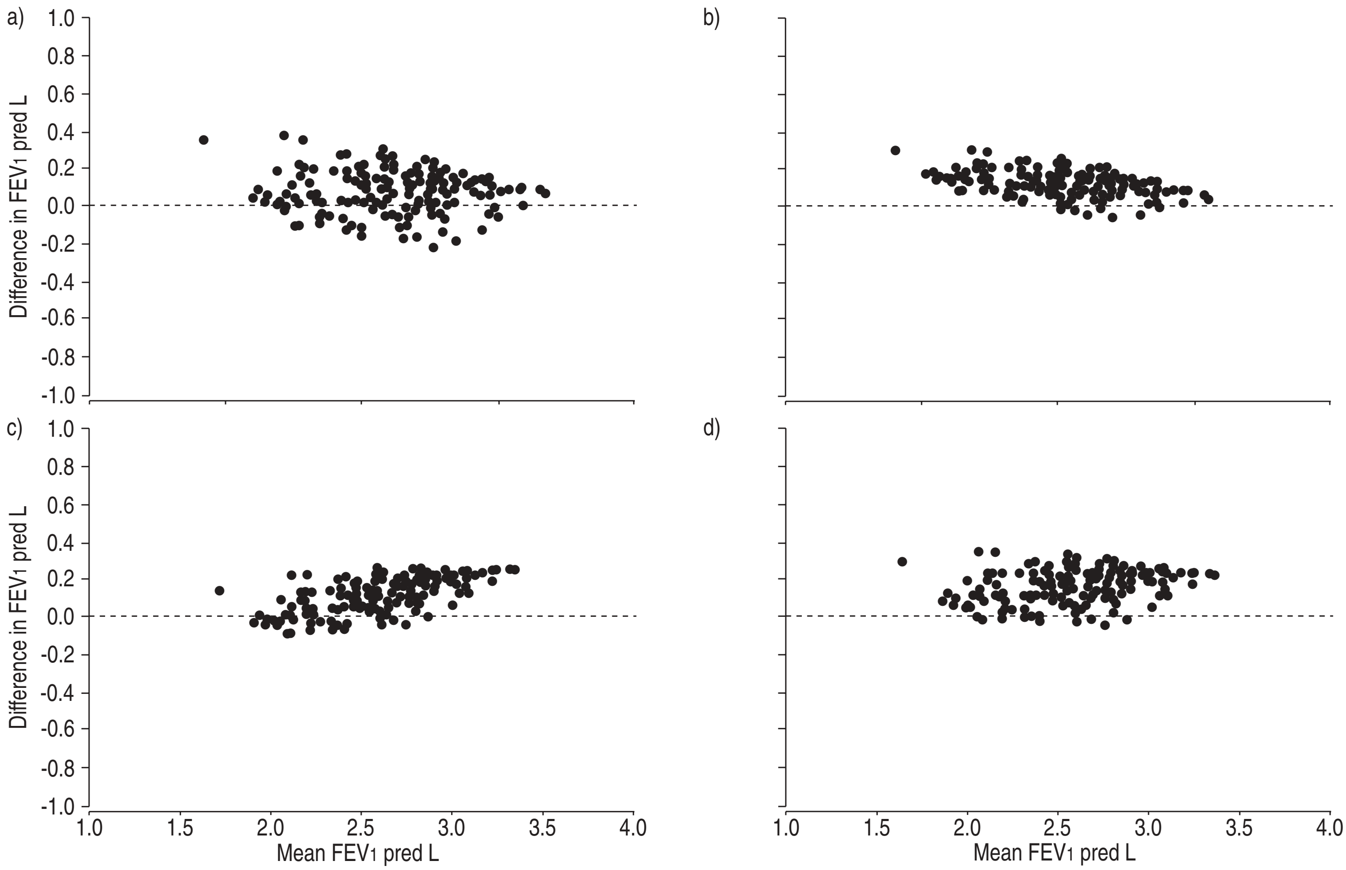

Fig. 2. – Difference between forced expiratory volume in one second (FEV1) against mean FEV1 predicted by the present study *versus* a) PAOLETTI *et al.* [7], b) HANKINSON *et al.* [6], c) ENRIGHT *et al.* [14] and d) European Community for Steel and Coal [4] in males.

the current study subjects were age stratified according to population characteristics. Consequently, the percentage of subjects >75 yrs old was lower than in the HPP study. Most notably, the HHP males are much thinner than the CHS and the currently studied males, as indicated by BMI distributions.

The exact definition of a "healthy" group is difficult to agree upon [14, 15, 23]. Previous studies have used many different criteria. The ATS spirometry interpretation workshop only states that subjects should be "never-smokers, free of respiratory symptoms and disease" [10]. In contrast to ENRIGHT *et al.* [14], who did not exclude previous smokers with <5 pack-yr history of smoking who had quit smoking >5 yrs previously, all of the current study patients were lifelong nonsmokers.

The FVC and FEV1 age regression coefficients for the current female and male groups were similar to those of ENRIGHT *et al.* [14] and MCDONNELL *et al.* [15]. Moreover, the age coefficients for FEV1 in elderly subjects were nearly identical to those reported from younger cohorts of healthy persons (-32 and -44 mL annual change in FEV1 in females and males, respectively). Several longitudinal studies suggest a small degree of nonlinearity in the downward slope [2, 24]. Probably as a result of this, the addition of a nonlinear age term improves the strength of the current authors' regression equations, despite the narrower age range of the current healthy group.

In contrast, the current data suggest that FVC in males >65 yrs old have a stronger, more negative relationship with age and a weaker positive relationship with height than do individuals <65 yrs old. The current authors' observation that FVC was related to age[3] is consistent with observations in several longitudinal studies that loss of lung function may be accelerated in the elderly [24, 25]. However, as is clearly shown in figure 3, the net result of the different evolution of FVC and FEV1 is a less declining FEV1/FVC with ageing. Premature ending of the spirometric manoeuvre could explain the differences in the age coefficients for FVC and FEV1; however, all the subjects included in the current study reached the required expiratory flow plateau and, moreover, no relationship between expiratory time and FEV1/FVC coefficient was detected. Recently, PEZZOLI *et al.* [26] have reported that 81.8% of elderly subjects with respiratory symptoms were able to perform spirometry according to international guidelines. It seems reasonable to assume that, in elderly patients with no respiratory symptoms, the percentage of satisfactory manoeuvres would be at least similar and that premature ending would be infrequent.

Studies of middle-aged adults have demonstrated that both extremes of body weight are associated with lower FVC [24, 27, 28]. In the current study, 43 females had a weight that was 20 kg below the mean; however, no significant differences in FVC, FEV1 or FEV6 were found between females with a weight that was 20 kg below the mean weight and females with average body weight.

In the current male subjects, no spirometric parameter was related to weight; however, in females, FVC, FEV1 and FEV6 were related to weight and BSA. In middle-aged subjects, BMI has recently been considered to be an additional independent variable in models for deriving spirometric prediction equations [17, 29]. However, in the current study, no relationship between spirometric parameters and BMI was

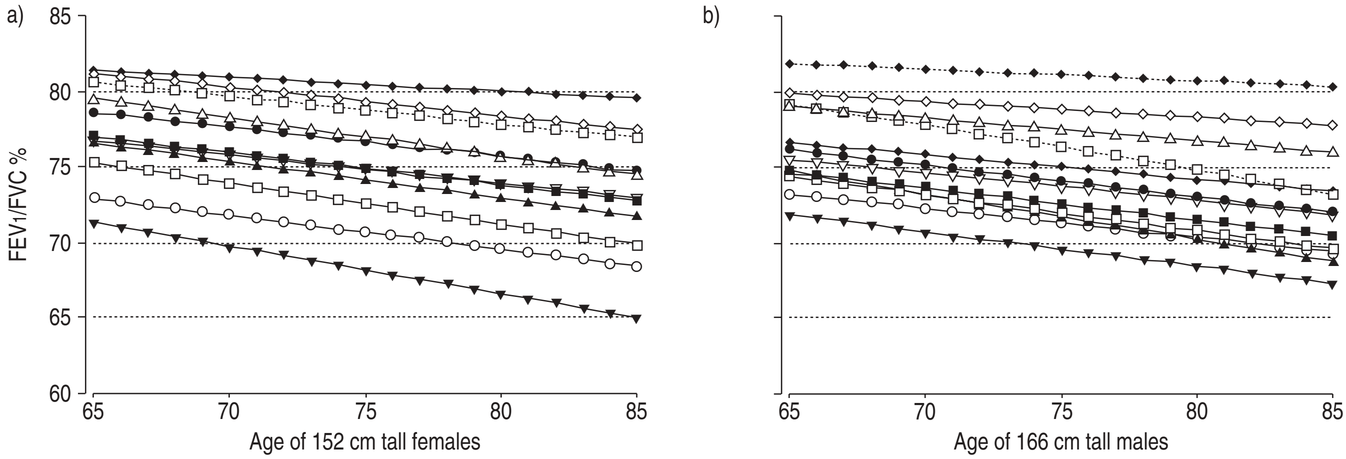

Fig. 3. – Predicted forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio from elderly healthy subjects compared with other studies for females and males of average height. ◆: LANGHAMMER *et al.* [9]; ◇: KNUDSON *et al.* [2]; □ (dashed line): present study; △: CRAPO *et al.* [3]; ●: MCDONNELL *et al.* [15]; ■: HANKINSON *et al.* [6]; ▽: European Community for Steel and Coal [4]; ▲: ENRIGHT *et al.* [14]; □: BRÄNDLI *et al.* [8]; ○: ROCA *et al.* [5]; ▼: PAOLETTI *et al.* [7].

detected. It is possible that the narrow weight range of the studied patients explains the absence of this relationship. Nevertheless, it should also be considered that FVC and FEV1 depend more on body composition than BMI, especially in males [30]. Therefore, the lack of discrimination in BMI of the changes in both fat and muscle experienced by elderly subjects could explain its uselessness to reference equations for spirometry in these subjects.

The FEV1/FVC ratio is generally used as a sensitive index to separate patients with borderline to mild airflow limitation from those with normal spirometry. A general rule often used by clinicians with middle-aged patients is that values <70% indicate obstruction. However, large cross-sectional and longitudinal studies of healthy middle-aged adults show that this ratio declines with age. The current age-related change in predicted FEV1/FVC ratios matches the other selected studies (fig. 3). With increasing age at constant height, the present study predicted that FEV1/FVC values decline from 80 to 70% in females and from 79 to 73% in males, with lower limits of normal from 71 to 68% and from 70 to 64%, respectively. In this sense, HARDIE *et al.* [31] have recently suggested that the criteria used to determine the normal limits of FEV1/FVC need to be age specific. The current results demonstrated that the old rule of thumb that 70% is the lower limit of the normal range should not be used with elderly patients; otherwise, many false-positive interpretations for airway obstruction will result. The FEV1/FEV6 ratio did not allow the current authors to obviate this problem because it is also dependent on age.

As prediction equations derived from cross-sectional data are primarily used as a screening tool to identify individuals with lung function below the expected range, the utility of any particular reference equation depends upon its ability to correctly identify individuals with lung function below the lower limit of normal. Some authors have defined the LLN as that value above which the results of 95% of the normal population lie, working under the assumption that larger values have larger variances. However, if skewed distributions are transformed to normalise their shape, the subtraction of 1.645 SD may still be used to estimate the LLN. In males, the equations for the LLN from SHARP *et al.* [13], ENRIGHT *et al.* [14] and MCDONNELL *et al.* [15] identify none of the current study's participants as being below the FEV1 LLN. In contrast, ENRIGHT *et al.* [14] and MCDONNELL *et al.* [15] identified 3.2 and 8.2% of females in the current study as being below the FEV1 LLN. Whilst some of the differences among these studies in predicting mean and LLN in the elderly may be due to inclusion of different age ranges, the effects of dissimilarity in underlying populations, measurement methods and reference group exclusion criteria also play a large role.

Table 6 shows the main characteristics of the studies that have provided the reference equations with which the current authors compared theirs. It is evident that the differences in age range, body-mass range or selection criteria of the sample could explain some of the differences obtained. The type of analysis used seems to be less relevant, given that the nonlinear equations of LANGHAMMER *et al.* [9] do not better adjust to the current sample than the linear equations, especially for FVC.

Some of the differences observed could also reflect the choice of instrument. Instrument differences in the measurement of FVC could, theoretically, be as large as 7% and still meet ATS standards, which only require them to be within ±5.5% of the target values. As such, two aspects of the current study could be worthy of special consideration: 1) the larger differences occurred in FVC and not in FEV1; and, moreover, 2) the mean differences from the HANKINSON *et al.* equations [6] were smaller for FEV6 than FVC. Both circumstances could be related to the influence of instrumentation on exhalation time. Minimal differences in the instruments used for measuring could be exaggerated by the greater variability at the end of the forced expiratory manoeuvre. Likewise, and since the spirometer used by HANKINSON *et al.* [6] was a rolling-seal spirometer, it cannot be ruled out that the effect of cooling with longer expiratory times could have affected the results.

In conclusion, the current authors have developed reference equations for the prediction of lung function of older adults. Differences among studies in predictions of lung function or in identification of individuals with lung function values below the lower limit of normal may be due to differences in the age range of the reference subjects, but are also likely to be contributed to by differences in exclusion criteria, different measurement methods and other differences in the underlying populations. These results underscore the importance of using prediction equations appropriate to the ethnicity, age and height characteristics of the population to whom inferences are to be applied.

Table 6. – Main characteristics of the different reference equations

First author and year	Normal selection criteria	Age range yrs	Sex	Body size range#	Equipment
BRÄNDLI 1996 [8]	Random selected sample from Switzerland	18–60	1890 females; 1267 males	Females (height 163±6 cm, weight 62±11 kg); males (height 176±7 cm, weight 75±10 kg)	Pneumotachographs
CRAPO 1981 [3]	Selected volunteers members of the Church of Jesus Christ of Latter-Day Saints	15–84	125 females; 126 males	Females (height 161±7 cm, weight 68±13 kg); males (height 175±7 cm, weight 78±13 kg)	Water-sealed 13.5 L metal bell spirometer
ECSC 1993 [4]	Summary equations obtained from different studies	18–70		Females (height 145–180 cm); males (height 155–195 cm)	
ENRIGHT 1993 [14]	Randomly selected sample from the general population	65–85	532 females; 245 males	Females (height 159±6 cm, weight 72±9 kg); males (height 172±7 cm, weight 77±10 kg)	Water-sealed spirometer
HANKINSON 1999 [6]	Stratified multistage probability sample of the USA population	8–80	1383 females; 898 males	NP	Dry rolling-seal spirometer
KNUDSON 1983 [2]	Randomly selected sample from the general population of the area	20–88 (females); 20–85 (males)	204 females; 86 males	NP	Pneumotachograph
LANGHAMMER 2001 [9]	Randomly selected sample from the Nord-Trondelag Health Study	20–80	546 females; 362 males	NP	Pneumotachographs
MCDONNELL 1998 [15]	Cohort of the Adventist Health Air Pollution study	43–79	366 females; 199 males	Females (height 162±7 cm); males (height 176±7 cm)	Rolling seal spirometers
PAOLETTI 1986 [7]	Randomly selected sample from the general population of the area	21–64 (females); 29–64 (males)	313 females; 59 males	Females (height 157±6 cm); males: NP	Fleish no. 3 pneumotach HP47804 System
ROCA 1986 [5]	Selected volunteers	20–70	427 females; 443 males	Females (height 158±4 cm, weight 60±9 kg); males (height 170±7 cm, weight 71±8 kg)	Fleish no. 3 pneumotach HP47804 HP Vertek System
SHARP 1996 [13]	Survivors of population-based longitudinal study	71–90	528 males	Height: 162±5.7 cm; weight: 61.2±7.6 kg	Water-sealed spirometer

ECSC: European Community for Coal and Steel; NP: not provided. #: data are presented as mean±SD and ranges.

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