Reference equations for lung function screening of healthy never smoking adults aged 18-80 years

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## **ABSTRACT**

The need for updated spirometric reference values to be used on European populations is widely acknowledged especially for subjects aged >70 years. Their reference values are generally based on extrapolations. The aim of this study was to calculate reference values for lung function screening of healthy, never smoking adults aged 18-80 years and to compare them to the most widely used reference equations.

Results of screening spirometry of 8684 healthy, never smoking adults were used to calculate mean values and fifth percentiles of lung function variables.

ECCS reference equations underestimate forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC). In 50 year-old men (175 cm), for example, lower limits of normal for FEV<sub>1</sub> are underestimated by 198 ml, for FVC by 210 ml. In 50 year-old women (165 cm), lower limits of normal for FEV<sub>1</sub> are underestimated by 191 ml, for FVC by 270 ml. The decline of FVC in elderly subjects is steeper than predicted by the ECCS.

Reference equations derived from spirometry data locally collected in a practical setting by well trained personnel might be more appropriate for everyday use than generally used equations based on data from scientific studies in the distant past.

#### INTRODUCTION

The comparison of results of lung function tests with normal values may influence decisions which have important implications both for individuals and for the health care system. Several sets of normal values have been published over the last decades and "normality" for a given age and height varies considerably across these studies. Such variations may be explained by selection criteria of "normal" populations, cohort effects, measurement techniques and devices, biological variability across populations, and statistical modelling.[1-3] Major arguments for updating reference values on a regular basis are birth cohort effects (e.g. changes in the distribution of lung function at a given age over time) and new technical equipment.[4] If no updating is performed, normal values may gradually lose their sensitivity in detecting abnormal conditions at an early stage.

Standardisation procedures have been improved and computer-based equipment allows ad hoc decisions with regard to acceptability and reproducibility of spirometric manoeuvres.[5, 6]

The ECCS prediction equations most widely used in Europe were derived from lung function measurements of subjects, including smokers, studied in the years 1954 to 1980, from different study populations and from several data sets. Thus their value for the interpretation of spirometric tests has been challenged.[7-9] Current guidelines don't recommend a specific set of equations for use in Europe. There is a major need for new studies to derive updated reference equations for lung function, especially for elderly persons.[10] Recent recommendations on equipment and standardisation of procedures propose reference values based on cross-sectional studies of lifetime non-smokers.[2, 5, 8] It has been shown that wheeze, breathlessness and cough influence lung function parameters, whereas chronic phlegm was not associated with airway obstruction or reduced FEV<sub>1</sub> in some surveys, suggesting that perhaps not all respiratory symptoms need to be accounted for when defining a healthy reference population used to derive reference values.[3]

Most reference equations used in North America and Europe have been derived from studies that included relatively small numbers of individuals older than 65 years. Only few sets of equations have been published for elderly lifetime non-smokers of Caucasian-American origin.[11-13] Since international guidelines discourage the use of spirometry reference equations for ages or heights outside the range covered by the data that generated them, there is a need of collecting lung function data from elderly persons.[2, 14]

In this paper we provide results based on a large cross-sectional sample from a Central European population. Our study is unique in that we present empirically based reference equations of forced

spirometry for subjects aged between 18 and 80 years. Our reference equations for the means and the fifth percentiles as lower limits of normal range account for changes in the distribution of lung function with age and height. We compare our reference values for the entire age range with those from the SAPALDIA (Swiss Cohort Study on Air Pollution and Lung Diseases in Adults) study, those from ECCS and those from NHANES III (third National Health and Nutrition Examination Survey).[7, 15-17] Reference values for elderly subjects are compared with other reference sets that were derived for individuals older than 65 years.[11, 13, 17-19]

### **METHODS**

In this cross-sectional study lung function test results collected by the LuftiBus team in the greater Zurich metropolitan area between December 2000 and August 2005 were analysed. The LuftiBus project is maintained by the Lung Association of Zurich. It consists of a bus equipped with two flow-sensing spirometers that tours mainly the greater Zurich area and offers spirometry measurements to the general public. Spirometry data are recorded electronically along with data from a standardized interviewer-administered questionnaire collecting basic information on the health and life style of subjects. Lung function tests are charged with 10 Swiss francs in adults to cover the costs on a non-profit basis.

#### Reference population

From a total of 20460 subjects, 8684 were included in the sample used to derive normal values for spirometric parameters (Table 1). Subjects were excluded if they met at least one of the exclusion criteria (Table 2). Never smokers were defined as subjects with a cumulative smoking history of < 1 py (py = pack years are defined as years of smoking, multiplied by the number of cigarettes smoked per day divided by 20). Due to the ongoing migration in Europe and mixture of ethnical backgrounds and due to the very small proportion of Non-Caucasians in Switzerland we did not make any exclusions based on race or nationality.[20] Ethnicity thus was not assessed systematically for the whole study population. In a subset of 3061 consecutive subjects of the reference sample (1356 men, 1705 women) measured in the years 2004 and 2005, ethnicity was recorded. Thereof, Non-caucasians accounted for 19 (1.1 %) women and 17 (1.3 %) men.

Table 1: Inclusion characteristics for study population

	Men		Wo	men	Total			
	(n=9	738)	(n=10	)'722)	(n=20'460)			
Health criteria satisfied	7'371	(75,7)	7'803	(72,8)	15'174	(74,2)		
Never smokers	4'565	(46,9)	7'009	(65,4)	11'574	(56,6)		
All criteria satisfied	3'512	(36,1)	5'172	(48,2)	8'684	(42,4)		

Values in parentheses are percentages.

- 1. Former or current smokers (≥ 1 py)
- 2. Current acute respiratory disease
  - a. Common cold
  - b. Acute bronchitis
- 3. Current respiratory symptoms
  - a. Cough
  - b. Wheezing
  - c. Shortness of breath with rest or exertion
  - d. Phlegm
- 4. History of asthma
- 5. Current treatment with asthma medication
- 6. History of chronic obstructive pulmonary disease or chronic bronchitis
- 7. History of other lung diseases
  - a. Lung operations
  - b. Pulmonary embolism

Abbreviations: py = pack years (pack years are defined as years of smoking, multiplied by the number of cigarettes smoked per day divided by 20)

### **Spirometry**

During the time of data collection, the LuftiBus was equipped with two computerised pneumotachographs (SensorMedics® Vmax Legacy 20c spirometer run by Vision 7-2b software (VIASYS, Yorba Linda, USA)). The volume signal of the equipment was calibrated at least once daily with a 3 L syringe. Tests were performed in a sitting position according to ATS guidelines without nose clips after an oral instruction by the technician.[2, 14] Participants were assisted by eight specially trained lung function technicians who performed immediate on-screen evaluation of major acceptability criteria (including start, duration and end of test) in addition to the automated review performed by the computer software. As recommended by the ATS in 1994, 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.[14] From a minimum of two acceptable tests, the largest FVC

and FEV<sub>1</sub> were selected, regardless of the manoeuvre. All other parameters were taken from the trial with the largest sum of FVC and FEV<sub>1</sub>. Self-reported values for height were used.

#### Statistical methods

We reproduced the methodology used by the SAPALDIA team. In a first step, prediction equations for the mean were estimated. Equations for the fifth percentiles, which were the primary focus of interest as lower limits of the normal range, were then estimated from the residuals of the models for the mean. All regression models were stratified by sex. These methods are described in detail in.[15, 16] *Prediction equations for the mean* – To estimate equations for the mean the natural logarithms of lung function variables were regressed against In(height), age and quadratic function of age. 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: LF = H<sup>c</sup> 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 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. If such a simplified model proved to be sufficiently adequate, it was also tested whether or not the quadratic age term was statistically significant.

Prediction equations for fifth percentiles – The next step was to compute fifth percentiles according to a new method for estimating percentile curves using weighted  $L_1$  regression. Thus, instead of minimising the sum of squared residuals, a weighted sum of the absolute values of the residuals was minimised. These residuals were again regressed against age. If  $y = \alpha + \beta$  age denotes the estimated regression line for the  $5^{th}$  percentile of  $r = \ln$  (LFobserved/LFpredicted) as a function of age, then y = LF predicted  $\exp(\alpha + \beta \text{ age})$  is an estimate of the  $5^{th}$  percentile of lung function for a given age. To test whether a linear age term was sufficient to describe the age dependency of the  $5^{th}$  percentile of r an indicator variable U was defined taking the value of 1 for residuals  $r \le \alpha + \beta$  age and the value 0 for residuals  $r > \alpha + \beta$  age and a logistic regression model for U in terms of the covariates age and age<sup>2</sup> was computed. The quadratic term did not reach statistical significance for any of the lung function parameters considered, thus suggesting that the model with the linear age term was sufficient throughout. In an analogous way, it could be verified, that the  $5^{th}$  percentile of r did not significantly depend on the height of the person.

All statistical analyses were performed using R statistical software for MacOS® (R statistical software version 2.4.1; The R project for Statistical Computing, Vienna, Austria).

### **Comparisons of reference equations**

The newly derived reference equations were compared to those most widely used in Europe (ECCS) and the United States (NHANES III) as well as the most recent Swiss reference values (SAPALDIA).[8, 15-17] In addition, in order to especially address the concerns that might arise due to the possible over-reporting of height in elderly patients, reference values of 65-80 year-old subjects were compared to several sets of reference equations that were recently published for this population.[11, 13, 17-19]

## **RESULTS**

The main characteristics of the study population are shown in Table 3. Demographic data of the 8684 subjects show an overrepresentation of women satisfying the inclusion criteria because women were more likely to have never smoked than men and women were, to a lesser extent, overrepresented in the study sample.

Table 3: Mean (SD) characteristics and age distribution (%) of reference sample

	Women				
	(n=5'172)				
Height <sup>1</sup> (cm)	176.3	(7.4)	Height <sup>1</sup> cm)	163.3	(6.8)
Age <sup>1</sup> (years)	47.3	(18.2)	Age <sup>1</sup> (years)	52.9	(17.5)
< 30 years	742	(21.1%)	< 30 years	625	(12.1%)
30-39 years	525	(14.9%)	30-39 years	649	(12.5%)
40-49 years	659	(18.8%)	40-49 years	821	(15.9%)
50-59 years	592	(16.9%)	50-59 years	936	(18.1%)
60-69 years	504	(14.4%)	60-69 years	1119	(21.6%)
70-79 years	376	(10.7%)	70-79 years	822	(15.9%)
> 79 years	114	(3.2%)	> 79 years	200	(3.9%)

<sup>&</sup>lt;sup>1</sup>Self-reported values for age and height were used.

The prediction equations for the mean of the lung function variables are displayed in Table 4 as LF =  $\exp(a + b * \ln(\text{height}) + c_1 * age + c_2 * age^2)$ , where LF represents any of the lung function variables measured (FVC, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, MEF<sub>75</sub> (maximal instantaneous forced expiratory flow when 75% of the FVC remains to be expired), MEF<sub>50</sub> (maximal instantaneous forced expiratory flow when 50% of the FVC remains to be expired), MEF<sub>25</sub> (maximal instantaneous forced expiratory flow when 25% of the FVC remains to be expired)). This equation is equivalent to  $\ln(\text{LF}) = a + b * \ln(\text{height}) + c_1 * age + c_2 * age^2$ . The equations for the fifth percentiles, which are generally recommended as a lower limit of the normal range, are displayed in Table 5. They are of the same form as those for the mean. The ranges of application for these reference equations are ages 18-80 years and heights 140-200 cm in men and 130-190 cm in women.

Table 4: Prediction equations for the means of lung function variables

Men							•						•	R <sup>2</sup> †
FVC (I)	=	exp(-	10.258	+	2.280	In(H)	+	0.00676	Α	-	0.000124	$A^2$	)	0.549
FEV <sub>1</sub> (I)	=	exp(-	8.957	+	2.014	In(H)	+	0.00281	Α	-	0.000105	$A^2$	)	0.639
MEF <sub>75</sub> (I/s)	=	exp ( -	2.227	+	0.812	In(H)	+	0.00977	Α	-	0.000132	$A^2$	)	0.108
MEF <sub>50</sub> (I/s)	=	exp ( -	3.055	+	0.911	In(H)	+	0.00249	Α	-	0.000109	$A^2$	)	0.226
MEF <sub>25</sub> (I/s)	=	exp ( -	3.970	+	1.009	In(H)	-	0.01645	Α	-	0.000020	$A^2$	)	0.419
FEV <sub>1</sub> /FVC (%)	=	exp(+	6.291	-	0.341	In(H)	-	0.00441	Α	+	0.000026	$A^2$	)	0.126
PEF (I/s)	=	exp ( -	3.760	+	1.170	In(H)	+	0.00706	Α	-	0.000110	$A^2$	)	0.233
Women														R <sup>2</sup> †
FVC (I)	=	exp(-	9.069	+	2.013	In(H)	+	0.00847	Α	-	0.000155	$A^2$	)	0.562
FEV <sub>1</sub> (I)	=	exp(-	8.397	+	1.865	In(H)	+	0.00570	Α	-	0.000150	$A^2$	)	0.526
MEF <sub>75</sub> (I/s)	=	exp ( -	2.716	+	0.867	In(H)	+	0.00963	Α	-	0.000140	$A^2$	)	0.184
MEF <sub>50</sub> (I/s)	=	exp ( -	2.131	+	0.674	In(H)	+	0.00895	Α	-	0.000180	$A^2$	)	0.253
MEF <sub>25</sub> (I/s)	=	exp ( -	4.861	+	1.145	In(H)	-	0.01120	Α	-	0.000096	$A^2$	)	0.423
FEV <sub>1</sub> /FVC (%)	=	exp(+	5.637	-	0.219	In(H)	-	0.00249	Α	+	0.000004	$A^2$	)	0.039
PEF (I/s)	=	exp ( -	4.794	+	1.316	In(H)	+	0.00926	Α	_	0.000143	$A^2$	)	0.329

Abbreviations:

H = height (cm); A = age (years); exp (x) =  $e^x$ ; †fraction of explained variance; FVC = forced vital capacity; FEV<sub>1</sub> = forced expiratory volume in one second; PEF = peak expiratory flow;

 $MEF_{25,(50,75)}$  = maximal instantaneous forced expiratory flow when 25% (50%, 75%) of the FVC remains to be expired.

Table 5: Prediction equations for the fifth percentiles of lung function variables

Men						•					-		
FVC (I)	=	exp(-	10.437	+	2.280	In(H)	+	0.00532	Α	-	0.000124	$A^2$	)
FEV <sub>1</sub> (I)	=	exp ( -	9.111	+	2.014	In(H)	+	0.00102	Α	-	0.000105	$A^2$	)
MEF <sub>75</sub> (I/s)	=	exp(-	2.524	+	0.812	In(H)	+	0.00661	Α	-	0.000132	$A^2$	)
MEF <sub>50</sub> (I/s)	=	exp(-	3.338	+	0.911	In(H)	-	0.00289	Α	-	0.000109	$A^2$	)
MEF <sub>25</sub> (I/s)	=	exp(-	4.262	+	1.009	In(H)	-	0.02485	Α	-	0.000020	$A^2$	)
FEV <sub>1</sub> /FVC (%)	=	exp(+	6.180	-	0.341	In(H)	-	0.00529	Α	+	0.000026	$A^2$	)
PEF (I/s)	=	exp(-	3.992	+	1.170	In(H)	+	0.00493	Α	-	0.000110	$A^2$	)
Women													
FVC (I)	=	exp(-	9.213	+	2.013	In(H)	+	0.00616	Α	-	0.000155	$A^2$	)
FEV <sub>1</sub> (I)	=	exp ( -	8.521	+	1.865	In(H)	+	0.00357	Α	-	0.000150	$A^2$	)
MEF <sub>75</sub> (I/s)	=	exp(-	2.977	+	0.867	In(H)	+	0.00698	Α	-	0.000140	$A^2$	)
MEF <sub>50</sub> (I/s)	=	exp(-	2.374	+	0.674	In(H)	+	0.00330	Α	-	0.000180	$A^2$	)
MEF <sub>25</sub> (I/s)	=	exp(-	5.140	+	1.145	In(H)	-	0.02002	Α	-	0.000096	$A^2$	)
FEV <sub>1</sub> /FVC (%)	=	exp ( +	5.524	-	0.219	In(H)	-	0.00313	Α	+	0.000004	$A^2$	)
PEF (I/s)	=	exp(-	5.032	+	1.316	In(H)	+	0.00767	Α	-	0.000143	$A^2$	)

Abbreviations:

H = height (cm); A = age (years); exp (x) =  $e^x$ FVC = forced vital capacity; FEV<sub>1</sub> = forced expiratory volume in one second; PEF = peak expiratory flow; MEF<sub>25 (50,75)</sub> = maximal instantaneous forced expiratory flow when 25% (50%, 75%) of the FVC remains to be expired.

The choice of two age intervals (one for the ages 18-25 years and one for the interval >25 years) was suggested by the ECCS having modeled lung function by a piece-wise linear function of age. The SAPALDIA team had found that even with a quadratic function of age a separate model for subjects under 25 was warranted.[8, 21] However, in our study, separate equations did not fit the data significantly better than a single equation. Results for each lung function variable refer to participants who performed the tests according to ATS quality criteria.[14]

Comparisons with the reference equations provided by the ECCS for 18-70 year old subjects and the recently published Swiss values for subjects aged 18- 60 years are shown in Figure 1 for men and in Figure 2 for women.[15] However, our sample included a considerable number of subjects aged beyond 70 years, so that the estimation of reference equations could be extended to the age of 80 years.

In men as well as in women, the volumes predicted by reference equations for the 5<sup>th</sup> percentile of FEV<sub>1</sub> from the present study are higher than those from the ECCS throughout. In 50 year-old men (175 cm), lower limits of normal for FEV<sub>1</sub> are underestimated by 198 ml, those of 50 year-old women (165 cm) by 191 ml by the ECCS reference equations in comparison to the LuftiBus data. In 30 year-old men (175 cm) and women (165 cm), lung volumes predicted by our reference values are 86 and 101 ml higher than those from ECCS, respectively. However, the difference practically vanishes at age 70 indicating that the reference values for FEV<sub>1</sub> provided by the ECCS equations underestimate the decline of lung volumes in elderly women.

For FVC, our reference equations for the 5<sup>th</sup> percentile provide the lowest values in men aged 18-27 years. Lower limits of normal for FVC are underestimated by the ECCS reference equations in comparison to the LuftiBus data by 210 ml in 50 year-old men (175 cm) and by 270 ml in 50 year-old women (165 cm). In 30 year-old men (175 cm) and women (165 cm), lung volumes predicted by our reference values are 42 and 107 ml higher than those from ECCS, respectively. In both sexes, the decline of FVC with age is steeper than predicted by the ECCS equations.

Reference equations provided by SAPALDIA give the highest values for  $5^{th}$  percentiles of FEV<sub>1</sub> and FVC throughout with the lower limits of NHANES III showing almost identical values. By contrast, our values for the lower limit of normal for MEF<sub>75</sub> in all age groups of both sexes are highest among the reference data compared. For MEF<sub>25</sub>, our data indicate that the decline of late flows with age is not as steep as suggested by ECCS and SAPALDIA.

Figure 3 illustrates the decline of FVC with age for male subjects aged 65-80 years compared to published reference values for elderly subjects.[11, 13, 17-19] Regarding the decline of lung volumes with age our data are in line with other published reference values (i.e., corresponding curves run almost parallel), indicating that overreporting of stated height in elderly subjects has not occurred to a significant extent.

#### DISCUSSION

We derived reference equations for screening spirometry from data collected in a screening program (LuftiBus) among 8684 healthy, never smoking volunteers between 2000 and 2005. Fifth percentiles as lower limits of normal were derived according to a new statistical method.[16]

For FVC and FEV<sub>1</sub>, our reference equations for the lower limit of normal provide values that are lower than the ones from SAPALDIA and NHANES III but higher than the ones from ECCS in the age range 30 to 70 years. Only for FVC, our reference equations provide the lowest values in men aged 18-27 years.

For both sexes, the decline of FVC in elderly subjects appears to be underestimated by the equations from the ECCS. Our reference values also predict a steeper decline of  $FEV_1$  in elderly women. By contrast, our curves for the decline of  $MEF_{25}$  with age are not as steep as the ones from ECCS and SAPALDIA.

Our equations differ from those derived by ECCS with regard to their mathematical form and to the nature of the underlying data. ECCS reference equations were obtained by summarizing published regression equations from older surveys published between 1950s and 1980s which employed different instruments.[8]

There are several differences in the methods applied in the SAPALDIA and the LuftiBus study which both evaluated samples of the Swiss population. Subjects participating in the LuftiBus project were volunteers who were charged for the test on a non-profit basis. In the SAPALDIA study, participants were randomly selected among the inhabitants of the study sites. This might result in some selection bias in our study despite the large population sample with a proper distribution of body height. It has been demonstrated that using different spirometers may account for systematic deviations of lung function parameters of more than 5%. The systematic differences may be due to both hardware and software. [22] Thus, the systematically higher lung volumes derived by the SAPALDIA could be originating from a systematic bias due to different equipment.

As proposed by the ATS, lung function tests that did not meet reproducibility criteria were not excluded in our investigation.[14] In the SAPALDIA study, in contrast, only reproducible lung function tests results were evaluated. This probably results in systematically higher lung volumes.

Another issue could be the origin of the study population. Subjects from our study population originate from the greater Zurich metropolitan area whereas SAPALDIA included subjects from rural as well as from urban Swiss areas. Local exposure to traffic has been demonstrated to have adverse effects on

children's lung development, which could result in lung function deficits persisting into later life.[23] This might have even resulted in differences between the lung function tests of the two different birth cohorts of the SAPALDIA study and the LuftiBus project. There is evidence that pollution from fossil fuel combustion is associated with decrements in lung function which might in part explain the lower values in our study having been derived from subjects predominantly living in urban areas.[24] Our study has several limitations. Our data include asymptomatic never smokers without known pulmonary disease. Moreover, no clinical or chest radiographic examinations were performed, which might result in the inclusion of some patients with unknown asymptomatic lung disease. There are limited possibilities to quantify factors that may influence lung function such as occupational exposure, passive smoking and the effect of chest injuries or chest surgical interventions. The nature of the evaluation did not allow accounting for all these parameters in detail. Additionally, we did not have access to medical data except for those provided by the study subjects themselves. We do believe that the exclusion of subjects suffering from respiratory symptoms such as dyspnoea (with or without exercise) or cough might have resulted in the exclusion of a large proportion of those patients. However, in this regard, we are in line with most other studies having published reference equations for lung function. Smoking status was quantified as 'cumulative numbers of pack years' and never smokers were defined as subjects with a cumulative smoking history of < 1 pack year. As it has been shown that a cumulative smoking history of ≤ 5 pack years does barely influence lung volumes and due to lacking evidence for other thresholds in the current literature, not excluding occasional cigarette smokers, pipe smokers or non-tobacco smokers with a cumulative history of less than 1 pack year might be acceptable for deriving reference equations.[25]

Regardless of the fact that deriving reference equations from large groups of volunteers is thought to be acceptable provided that criteria for normal selection and proper distribution of anthropometric characteristics are satisfied, some selection bias might have crept in.[10] In particular, the charge for the test might have kept certain groups of persons from participating.

Using self-reported height or estimating height from arm span is regarded an option in the clinical setting when spirometry is performed in patients who have conditions that hamper the standing position.[10] Self-reported height was shown to give an accurate representation of true values in different populations, but age has been stated to be an important factor for misreporting height.[26-30] Height overestimation in the elderly is congruent with age-related corporal changes. Our data

concerning the decline of FVC with age, however, are consistent with those from other publications that used measured height to derive reference equations for subjects aged 65-85 years.[11, 13, 17-19] Body Mass Index (BMI) has been shown to have significant effects on all of the lung volumes, especially FRC (functional residual capacity) and ERV (expiratory reserve volume).[31] As a rule of thumb, lung volumes decrease as body weight increases. Thus, attempts have been made to introduce BMI as an independent variable in newly derived reference equations.[32] In a subset of our study subjects, we assessed whether BMI could be included as a predictor of lung function. Thereby, BMI was shown not to influence lung volumes. Moreover, in analogy to height, self-reported weight was recorded in our study. Due to a tendency of study participants to overreport height and, to a greater extent, underreport weight, stated BMI was demonstrated to be systematically underestimated in various studies.[28, 33] Thus, we believe that using self-reported BMI is of limited value for deriving reference equations.

As stated in the 1994 update of the ATS guidelines for standardization of spirometry, nose clips do not appreciably influence the FVC when using the open circuit technique.[14] However, their use was encouraged especially when performing a slow VC manoeuvre because some people breathe through the nose. The use of nose clips was considered mandatory if a closed circuit technique with carbon dioxide absorption was used. Guidelines of 2005, published at the end of data collection for the LuftiBus study, recommend the use of a nose clip or manual occlusion of the nares.[34] It has been demonstrated that the application of a nose clip has no significant impact on measurement of peak expiratory flow, but its importance for the other lung function parameters, to our knowledge, has not been studied.[35] That our lung function tests were performed without a nose clip might nevertheless partly explain the observed differences to the SAPALDIA reference equations, since a certain loss of air through the nasal route is likely to have occurred at least in some subjects.

It was proposed that reference equations should be derived from a population most similar to that for which the equations are to be used and based on measurements obtained by the same instruments and testing procedures.[32] Since the methodology used in the LuftiBus project mirrors the methods used in daily practice, where measurement of height and application of a nose clip is often abandoned, our results may thus provide a valuable contribution to lung function testing within a routine outpatient setting. Our study in particular meets the major need for updated and empirically derived reference equations of forced spirometry for subjects aged between 65 and 80 years.

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# **Competing interests**

None declared.

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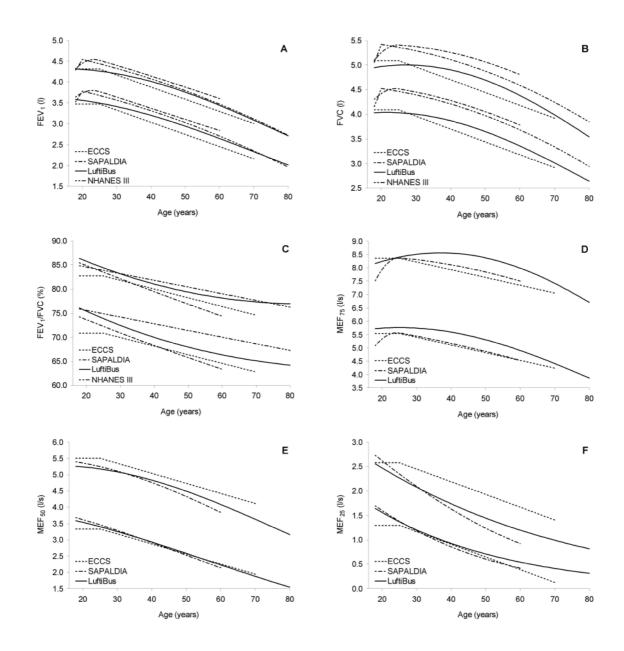
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## Figure headings

Figure 1 Age dependency of mean values and  $5^{th}$  percentiles of (A) FEV<sub>1</sub>, (B) FVC, (C) FEV<sub>1</sub>/FVC, (D) MEF<sub>75</sub>, (E) MEF<sub>50</sub> and (F) MEF<sub>25</sub> in men (175 cm) in comparison with published reference values (ECCS, SAPALDIA and NHANES III).

Abbreviations:  $FEV_1$  = forced expiratory volume in one second; FVC = forced vital capacity;  $MEF_{75}$  = maximal instantaneous forced expiratory flow when 75% of the FVC remains to be expired;  $MEF_{50}$  = maximal instantaneous forced expiratory flow when 50% of the FVC remains to be expired;  $MEF_{25}$  = maximal instantaneous forced expiratory flow when 25% of the FVC remains to be expired.



<u>Figure 2</u> Age dependency of mean values and 5<sup>th</sup> percentiles of (A) FEV<sub>1</sub>, (B) FVC, (C) FEV<sub>1</sub>/FVC, (D) MEF<sub>75</sub>, (E) MEF<sub>50</sub> and (F) MEF<sub>25</sub> in women (165 cm) in comparison with published reference values (ECCS, SAPALDIA and NHANES III).

Abbreviations:  $FEV_1$  = forced expiratory volume in one second; FVC = forced vital capacity;  $MEF_{75}$  = maximal instantaneous forced expiratory flow when 75% of the FVC remains to be expired;  $MEF_{50}$  = maximal instantaneous forced expiratory flow when 50% of the FVC remains to be expired;  $MEF_{25}$  = maximal instantaneous forced expiratory flow when 25% of the FVC remains to be expired.

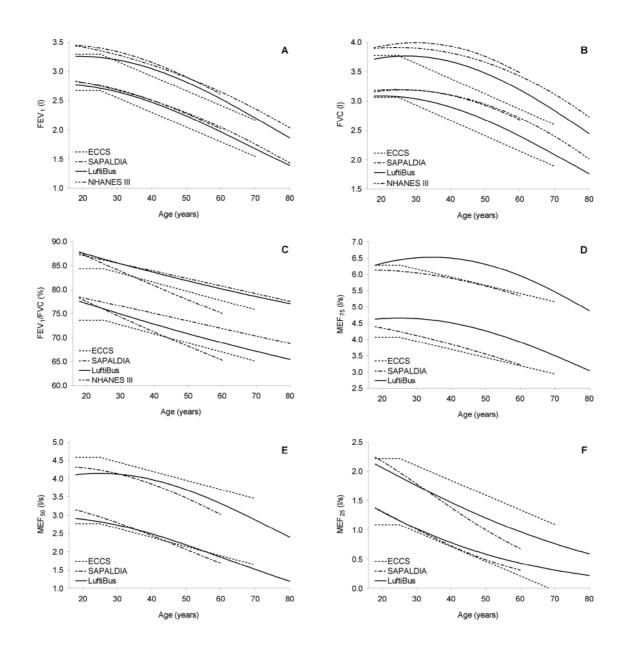


Figure 3 Age dependency of mean values and  $5^{th}$  percentiles of (A) FEV<sub>1</sub> and (B) FVC in men (175 cm) and of (C) FEV<sub>1</sub> and (D) FVC in women (165 cm, 55 kg) aged 65 - 80 years in comparison with published reference values.

Abbreviations:  $FEV_1$  = forced expiratory volume in one second; FVC = forced vital capacity.

