Prediction Equations for Spirometry in Adults from Northern India

S.K. Chhabra¹, R. Kumar³, U. Gupta¹, M. Rahman² and D.J. Dash¹

Department of Cardiorespiratory Physiology¹ and Biostatistics², Vallabhbhai Patel Chest Institute, University of Delhi, Delhi and Department of Biostatistics, University College of Medical Sciences³, Delhi, India

Abstract

Background. Most of the Indian studies on prediction equations for spirometry in adults are several decades old and may have lost their utility as these were carried out with equipment and standardisation protocols that have since changed. Their validity is further questionable as the lung health of the population is likely to have changed over time.

Objective. To develop prediction equations for spirometry in adults of north Indian origin using the 2005 American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations on standardisation.

Methods. Normal healthy non-smoker subjects, both males and females, aged 18 years and above underwent spirometry using a non-heated Fleisch Pneumotach spirometer calibrated daily. The dataset was randomly divided into training (70%) and test (30%) sets and the former was used to develop the equations. These were validated on the test data set. Prediction equations were developed separately for males and females for forced vital capacity (FVC), forced expiratory volume in first second (FEV₁), FEV₁/FVC ratio, and instantaneous expiratory flow rates using multiple linear regression procedure with different transformations of dependent and/or independent variables to achieve the best-fitting models for the data. The equations were compared with the previous ones developed in the same population in the 1960s.

Results. In all, 685 (489 males, 196 females) subjects performed spirometry that was technically acceptable and repeatable. All the spirometry parameters were significantly higher among males except the FEV_1/FVC ratio that was significantly higher in females. Overall, age had a negative relationship with the spirometry parameters while height was positively correlated with each, except for the FEV_1/FVC ratio that was related only to age. Weight was included in the models for FVC, forced expiratory flow (FEF_{75}) and FEV_1/FVC ratio in males, but its contribution was very small. Standard errors of estimate were provided to enable calculation of the lower limits of normal and standardised residuals for these parameters. The equations were found to be valid on the test dataset, and therefore, may be extended to general population. Comparison with the 1960s equations revealed lack of good agreement, and substantially higher predicted FVC with the current equations, especially in the forty-years-plus age group, in both males and females. Even in the age group upto 40 years, the level of agreement was clinically not acceptable.

Conclusions. Validated prediction equations have been developed for spirometry variables in adults of north Indian origin using the current ATS/ERS spirometry standardisation recommendations. The equations suggest an improvement in the lung health of the population over time in the middle-aged and the elderly. These equations should address a long-felt unmet need and enable a more appropriate evaluation of spirometry data in different chest diseases in Indian subjects.

[Indian J Chest Dis Allied Sci 2014;56:221-229]

Key words: Pulmonary function, Spirometry, Normals, Adults, Delhi, Indians, Regression, Prediction equations

Introduction

Spirometry is a highly informative and by far the most commonly performed investigation to evaluate pulmonary function in patients with chest diseases. The technical aspects of equipment and test performance require a very meticulous attention to quality control and these have been well-standardised and revised from time-to-time. The most recent recommendations on standardisation were jointly formulated by the task force of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2005.¹ Interpretation of data requires a comparison with the normal values. Pulmonary function in health is affected by ethnicity, gender, age, stature, environmental, genetic, socio-economic, technical and other unidentified factors.² Thus, unlike most other laboratory measurements, there are no "normal values" applicable to all individuals in a population. Instead, for interpretation, comparison is made with the expected values for a patient of a particular gender, age and physical characteristics. These are called the "predicted" values and are developed by regression analysis of data collected from non-smoking and healthy individuals of the same population. Several prediction equations for spirometry parameters have been developed over the last few

[Received: July 4, 2014, accepted after revision: January 9, 2015]

Correspondence and reprint requests: Dr S.K. Chhabra, Professor and Head, Department of Cardiorespiratory Physiology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi - 110 007, India; Phone: 091-011-27402440, 27402430; Fax: 091-011-27666549; E-mail: skchhabra@mailcity.com

decades in ethnically diverse populations^{3.9} that show wide differences in the predicted values. The softwares of the modern equipments usually provide a list of predicted equations to choose from.

Application of equations that have been developed for another population, for example, Caucasian equations for non-caucasians results in major errors of interpretation, and thus, affects the management.¹⁰ Even within India regional variations exist, so that use of a north Indian equation for a patient of south Indian origin will lead to substantial mis-classification of the abnormality.¹¹ Therefore, it is imperative that a patient's data be interpreted with prediction equations valid for the same ethnicity.¹

A few studies from different parts of India have reported prediction equations for spirometry over the last few decades.^{6-9,12-14} These studies have varied in study population, sample size, instrumentation and statistical techniques used and may no longer be useful as these were carried out with equipment and measurement protocols that have since changed. Their current utility and validity are further questionable considering the evidence of a cohort effect that shows improvement in the lung health of a population over a long-term.^{15,16} Thus, there is clearly an urgent need to develop these equations afresh for different regions of the country using current standardisation protocols recommended by the ATS-ERS.1 Lack of locally relevant and valid prediction equations is a widelyfelt unmet need in the field of pulmonary medicine in India hampering interpretation of data and patient management.

Therefore, we carried out a study to develop and validate prediction equations for spirometry in adults of north Indian origin. This was part of a larger multi-centric exercise supported by the Indian Council of Medical Research to develop prediction equations for lung function parameters for different regions of the country.

Material and Methods

A cross-sectional study was carried out in the Pulmonary Function Laboratory of the Vallabhbhai Patel Chest Institute from the year 2009 to 2012. Delhi is close to sea level with an altitude of 213 meters. The study was approved by the Institutional Ethics Committee. Subjects aged 18 years and above were drawn after a written informed consent from a wide social and economic background, both urban and rural, from the eligible attendants of patients, healthy volunteers from Institutions, private and public sector offices, and general public. Those with both parents from the north Indian states of Delhi, Punjab, Haryana, and Uttar Pradesh and permanently residing in the plains were eligible. The minimum sample size recommended for multivariate regression analysis for lung function parameters is 150.17 We targeted an age distribution matching the adult population of India according to the Census 2011 data.¹⁸

The exclusion criteria were strict to include only those who are definitely normal and were based on the criteria recommended by the ATS¹⁹ and similar to that used by Hankinson et al⁴ for the National Health and Nutritional Examination Survey III in the United States of America. A detailed history including information about the ethnic background, occupation, educational qualifications, economic status, domestic fuel used and environmental tobacco smoke exposure was obtained from each subject and was followed by a clinical examination. In addition, the subjects were asked to respond to a standardised respiratory symptoms questionnaire, based on the ATS and the National Heart and Lung Institute (NHLI), Division of Lung Diseases (DLD) questionnaire (ATS/DLD-78 A questionnaire).²⁰ Those with any chest symptoms (cough, sputum production, haemoptysis, dyspnoea, wheezing, nasal symptoms) as well as evidence of any acute or recent (within 6 weeks) upper or lower chest infection or current/past chronic chest, cardiac or other systemic disease, thoracic cage abnormality, under nutrition and obesity (body mass index, $[BMI] \ge 30$) as well as those on any kind of long-term medication or unwilling to perform the test were excluded. A chest radiograph was taken in about 10% of the subjects to validate the inclusion criteria. Smokers were excluded. However, occasional smokers, defined as less than one cigarette per day for less than one year were included.

Age in completed years, gender, height and weight were recorded. Height was measured without shoes to the nearest 'cm' with the subject standing erect with head held in the Frankfurt plane on a stadiometer. Weight was recorded wearing light clothing on an electronic scale that was calibrated on a weekly basis with known weights. It was rounded off to the nearest kilogram. To ensure consistency and to avoid any interobserver variability, the same equipment was used for height and weight measurements and the same observer took the measurements. The tests were carried out between 9 AM and 1 PM by the same technician in the laboratory maintained at a comfortable temperature of 25 °Celsius. A light meal was allowed in the morning. However, no exercise was allowed on the test day and the subject rested for two hours in the laboratory before the test.

Spirometry was carried out according to the 2005 recommendations of the ATS-ERS.¹ A non-heated Fleisch Pneumotach Spirometer (KOKO, nSpire, UK) was used with a filter and a re-usable sterile mouthpiece with side flanges to avoid any leakage. The spirometer was calibrated daily using a 1-L syringe according to the manufacturer's recommendations. The breathing procedure was explained and a demonstration of the test was given. In addition, the next subject to be tested was asked to sit nearby and watch. The manoeuvers were performed in the sitting position with a nose-clip applied. Tight clothing around the neck was loosened.

The subject was asked to take a few tidal breaths and then inhale rapidly and maximally, and then exhale immediately without any hesitation with maximum force from the maximum inspiratory position, and maintain the effort throughout the expiration till no more air was expelled out while maintaining an upright posture. At the completion of the forceful expiration and on a prompt from the technician, the subject was asked to inhale forcefully and completely. Throughout the procedure, loud verbal encouragement was given to obtain the expiratory and inspiratory manoeuvers completely with maximal force. The technician observed the subject for any distress, and also examined the computer display during the test to ensure a maximal effort with quality control under the supervision of a physician, as recommended by the ATS/ERS Task Force.¹ The recommended acceptability criteria (satisfactory start, sharp peak and satisfactory end-of-test without leaks, cough or glottis closure) and repeatability criteria (highest and second highest forced vital capacity [FVC] and forced expiratory volume in the first second [FEV₁] within 150 mL) were applied to determine a successful test. At least three acceptable and two repeatable efforts were obtained. Unacceptable efforts were discarded. The procedure was repeated for not more than eight times in one testing session. Subjects who failed to perform three acceptable manoeuvers with desired repeatability were rescheduled for another day and were dropped from the study if they still failed to perform.

The selection of spirometry parameters was done as recommended by the ATS.¹⁹ The highest values of FVC and FEV₁ were selected. Their ratio, FEV₁/FVC was computed. The expiratory flow rates (peak expiratory flow rate [PEFR], forced expiratory flow [FEF] rate at 50% exhalation of vital capacity [FEF₅₀] and at 75% exhalation of vital capacity [FEF₇₅] and mean FEF rates over the middle 50% of the vital capacity, [FEF₂₅₋₇₅] were obtained from the "best" curve, i.e. the one with the highest sum of FVC and FEV₁. All volumes were expressed in litres (L) and flow rates in litres/second (L/s) at BTPS (body temperature 37 °Celsius, atmospheric pressure fully saturated) conditions.

Statistical Analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS; version 20.0) (SPSS Inc. Chicago, USA) and Graph Pad Prism 4.01 (Graph Pad Inc., USA) softwares. Data of male and female subjects was analysed separately. Data is presented as mean \pm SD (standard deviation) with 95% confidence intervals, and as percentages, where appropriate. Pearson's correlation analysis and univariate regression, both linear and non-linear, were carried out to identify the significant predictor variables from among age, height and weight for each of the dependent variables. The dataset was randomly divided into training (70%) and test or validation (30%) sets and the former was used to develop the equations. These were validated on the test data set. The equations were developed using the multiple linear regression procedure. Linear and non-linear models were developed. Log transformations of dependent and/or other transformations of the independent variables were carried out to get the best model. The predictor or independent variables were entered in the sequence of height, age, and weight, including quadratic terms, if it showed significant improvement in the regression analysis. If the R² change at each step was significant indicating a substantial improvement in the predictive ability, the model was accepted. If not, the model at the previous step was accepted. Analysis of variance was carried out for each model to evaluate the significance of the regression equation and standard errors of the estimate (SEE) were calculated. Estimates of regression coefficients for predictor variables were obtained and their significance was determined by student's 't' test. Final models were selected considering simplicity and ease of clinical application, highest predictive capability (R²) and satisfaction of assumptions of regression analysis.

The goodness of fit was examined by testing for independence of predictor variables and the normality of the residuals. Unusual and influential observations were examined. These included outliers (standardised residuals more than \pm 3), points with high leverage and high influence. Analysis was repeated excluding these observations to determine their impact on the models and the original models were retained if the effect on the equations was small and inconsequential.

Equations derived from the training dataset were used to evaluate the validity of the derived equations on the test (validation) dataset. Predicted values were calculated for each test subject and compared with their observed values using the paired `t´ test. Finally, we compared our results with the previously developed prediction models for FVC in north Indians. These were developed in our institute almost five decades back in the 1960s by Jain and Ramiah^{6,7}, and Jain and Gupta,^{8,9} in two age groups, upto 40 years and above 41 years, respectively. No equations were developed by these authors for FEV₁. Instead, it was computed as a fixed percentage (75-80 \pm 5%) of FVC according to the then prevailing practice. Thus, comparison was possible only for FVC. Predicted values were computed for each subject of the test dataset by the current and the previous equations and error with each equation was compared by student's paired 't' test. Bland Altman analysis for agreement between the predicted FVC by the current and previous equations was carried out in the test dataset

Results

Nearly 1200 subjects were screened for inclusion in the study. In all, 685 (489 males, 196 females) subjects were

found eligible and provided manoeuvers that were technically acceptable and repeatable.¹ The major reasons for exclusion were obesity, smoking, history of respiratory diseases, history of cardiovascular diseases, diabetes mellitus, current upper or lower respiratory symptoms and unacceptable spirometry. The demographic profile of the study population is shown in table 1. Consistent with the Indian national demographic profile enumerated in Census 2011, nearly three-fourths of the subjects were aged 40 years or less.¹⁸ The age range (in years) was 18 to 71 in males and 18 to 65 in females. The range of height (in cm) was 150 to 193 in males and 141 to 170 in females.

Table 1. Age distribution of the subjects

U	,		
Age (in Years)	Males (n=489) No. (%)	Females (n=196) No. (%)	
18-20	44 (9.0)	27 (13.8)	
21 to 30	251 (51.3)	68 (34.7)	
31 to 40	112 (22.9)	50 (25.5)	
41 to 50	64 (13.1)	36 (18.4)	
51 to 60	14 (2.9)	10 (5.1)	
>60	4 (0.8)	5 (2.6)	

The training datasets of males and females had 339 and 132 subjects, respectively, while the test datasets had 150 and 64 subjects, respectively. The anthropometric characteristics of the training and test datasets were matched in the respective genders (Table 2).

Table 2. Anthropometric characteristics of the training and test (validation) datasets

Parameter	Trainin	g Set	Test Set		
	MalesFemalesM(n=339)(n=132)(Males (n=150)	Females (N=64)	
Height (cm)	$169.03 {\pm} 6.79^{ns}$	$155.97{\pm}5.72^{ns}$	169.09 ± 6.89	155.12 ± 5.89	
Weight (Kg)	$68.73{\pm}10.36^{ns}$	$57.60 {\pm} 9.27^{ns}$	$68.89 {\pm} 10.25$	56.99 ± 8.36	
Age (years)	$31.23 {\pm} 9.74^{ns}$	$33.56 {\pm} 11.79^{ns}$	$29.93 {\pm} 9.74$	32.28±12.08	
Data in mean:	SD; ns=not signi	ificant; p>0.05 (co	omparison of tra	ining and test	

data sets in respective genders)

The spirometry parameters of male and female subjects were compared (Table 3). All the parameters were significantly higher among males (p<0.0001) except the FEV₁/FVC ratio that was significantly higher in female subjects (p<0.01). No significant differences were found between the training and test values in males for any of the parameters. Similarly, no significant differences were found between the training and test values in females for all parameters except FEF₇₅ (p<0.05).

Table 4 shows the univariate regression of the spirometry parameters on age, height and weight using linear and non-linear models. The best-fitting regression equations on multivariate analysis are presented in table 5. The SEE is provided for calculation of the lower limits of normal along with R^2 and adjusted R^2 . In males, the models for FVC, FEV₁ and FEV₁/FVC ratio were linear whereas natural log transformation of dependent variable was required for

Table 3. Lung function data in the training and test (validation) datasets

	,	0			
Parameter	Parameter Males		Females (n=196)		
	Training (n=339)	Test (n=150)	Training Test (n=132) (n=64)		
FVC (L)	$4.07 {\pm} 0.65$	4.06 ± 0.62	2.77 ± 0.43	$2.79{\pm}0.47$	
FEV ₁ (L)	$3.29 {\pm} 0.58$	$3.26 {\pm} 0.52$	$2.89{\pm}0.44$	$2.35{\pm}0.44$	
PEFR (L/s)	8.01 ± 1.50	7.90 ± 1.31	5.42 ± 1.24	$5.55 {\pm} 0.96$	
FEF ₂₅₋₇₅ (L/s)	$3.34{\pm}1.11$	3.21 ± 0.95	$2.48{\pm}0.91$	2.67 ± 0.89	
FEF_{50} (L/s)	$4.11 {\pm} 1.28$	$3.91{\pm}1.14$	$2.79{\pm}0.90$	$3.05{\pm}0.92$	
FEF ₇₅ (L/s)	1.50 ± 0.77	$1.44{\pm}0.56$	$0.953 {\pm} 0.52$	1.17 ± 0.63	
FEV ₁ /FVC	$80.37 {\pm} 6.09$	$80.34{\pm}6.09$	$82.46{\pm}7.28$	$84.23 {\pm} 8.96$	

Data presented as mean±SD; FVC=Forced vital capacity; FEV₁=Forced expiratory volume in first second; PEFR=Peak expiratory flow rate; FEF=Force expiratory flow

flow rates. In female subjects too, the models for FVC, FEV₁ and FEV₁/FVC ratio were linear whereas natural log transformation of dependent variable was required for the flow rates, except FEF₇₅.

A linear model was retained for FEF_{75} because of simplicity as the residuals were not normal in any model and no transformations helped to improve. The method of clinical application of these equations is explained and illustrated in the appendix.

Validation of the training set equations on the test dataset is shown in table 6. While the differences between the observed and predicted values did reach statistical significance for some of the parameters, especially in males, these were small and clinically not significant. For lung function parameters, the lower limit of normal is [predicted minus (1.645 x SEE)]. In males, the measured values were >95% of predicted for FVC, FEV₁ PEFR, FEF₇₅ and FEV₁/FVC ratio and around 92% of predicted for FEF_{25.75} and FEF₅₀. In females, the measured values were >95% of predicted for all the parameters. Thus, all the observed values were in the normal range defined by the training set equations in both males and females. Thus, training set equations had a high validity.

The errors (observed minus predicted) in FVC values with previous and current equations in males and females in the test dataset are shown in figures 1 and 2, respectively. Upto the age of 40 years, both equations performed similarly in males and females and the errors were not significantly different (-0.029±0.48 and -0.02±0.50 with current and previous equations in males, respectively, p>0.05; 0.075 \pm 0.33 and 0.075 \pm 0.37 with current and previous equations in females, respectively, p>0.05). However, the previous equations of Jain and Gupta^{8,9} substantially under-predicted the FVC compared to the current equations in the above 40 years age group leading to significant differences in errors (-0.041±0.34 and 0.29±0.40 with current and previous equations in males, respectively, p < 0.001; 0.096±0.39 and 0.27±0.40 with current and previous equations in females, respectively, p < 0.05).

Bland Altman agreement plots for FVC predicted in the test dataset by the current and previous equations are shown in figure 3. The bias was almost zero in the age group upto 40 years in both males and females. FEF_{50} (L/s)

 FEF_{75} (L/s)

FEV₁/FVC

0.250

0.404

0.512

Parameter	A	Age	Heig	Height		Weight	
	Linear (R ²)	Best Non- linear (R ²)	Linear (R ²)	Best Non- Linear (R²)	Linear (R ²)	Best Non- Linear (R ²)	
Males							
FVC (L)	0.074	0.082(Q)	0.410	0.413(Q)	0.151	0.153(Q)	
FEV ₁ (L)	0.211	0.225(E)	0.332	0.333(Q)	0.078	0.078(Q)	
PEFR(L/S)	0.057	0.065(E)	0.156	0.158(Q)	0.054	0.054(Q)	
FEF ₂₅₋₇₅ (L/S)	0.273	0.309(E)	0.078	0.078(Q)	0.004	0.011(Q)	
FEF ₅₀ (L/S)	0.285	0.324(E)	0.055	0.055(Q)	0.007	0.013(Q)	
FEF ₇₅ (L/S)	0.358	0.450(E)	0.039	0.044(E)	0.011	0.046(Q)	
FEV ₁ /FVC	0.222	0.233(Q)	0.000	0.001(Q)	0.027	0.045(Q)	
Females							
FVC (L)	0.164	0.189(E)	0.392	0.406(Q)	0.034	0.038(Q)	
$FEV_1(L)$	0.375	0.396(E)	0.303	0.315(Q)	0.000	0.010(Q)	
PEFR (L/s)	0.071	0.128(Q)	0.146	0.159(Q)	0.029	0.030(Q)	
FEF ₂₅₋₇₅ (L/s)	0.399	0.439(E)	0.102	0.104(Q)	0.009	0.020(Q)	

Table 4. Regression analysis of spirometry parameters on age, height and weight in training dataset in male and female subjects

 $L=Linear \ equation \ y = b_0 + b_1 \times x; \ Q: \ Quadratic \ equation \ y = b_0 + b_1 \times x + b_2 \times x^2; \ P=Power \ equation \ y = b_0 \times x^{b2} = ln \ (y) = Ln \ (b_0) + b1 \times Ln = Ln \ (y) = Ln \ (y$ (x); E: Exponential equation $y = b_0 \times e^{b2x} = Ln(y) = Ln(b_0) + b_1 \times x$

0.118

0.142

0.006

0.123(Q)

0.152(Q)

0.007(Q)

0.000

0.044

0.078

0.004(Q)

0.044(Q)

0.085(Q)

-11 = 0	• •	· · ·		1 1 1	•		1	1 1	C 1 1	• •
Ishia h Kaara	cción aguistione	tor coiromotry	naramotore	dovolonod	116100	training	data in ma	lo and	tomalo cub	10Ctc
Table J. Regie	ssion equations	ioi sphomeny	parameters	uevelopeu	using	uannig	uata mi ma	ic and	remare sub	ICUIS
0	1	1 /	1							,

0.294(E)

0.458(E)

0.520(Q)

Parameter	Equation	SEE	R ²	Adj. R ²
Males				
FVC (L)	-5.048-0.014×age+0.054×ht +0.006×wt	0.479	0.457	0.452
$FEV_1(L)$	-3.682-0.024×age+0.046×ht	0.402	0.512	0.509
LnPEFR	0.346-0.004×age+0.011×ht	0.158	0.230	0.225
LnFEF ₂₅₋₇₅	-0.091-0.019×age+0.011×ht	0.271	0.369	0.359
LnFEF ₅₀	0.573-0.016×age+0.008×ht	0.262	0.340	0.334
LnFEF ₇₅	$-0.584 - 0.055 \times age + 0.015 \times ht - 0.005 \times wt + 0.000318 \times age^2$	0.346	0.529	0.520
FEV ₁ /FVC	102.56-0.679×age+0.00477×age ² -0.080×wt	5.79	0.261	0.255
Females				
FVC (L)	$20.07\text{-}0.010 \times age\text{-}0.261 \times ht\text{+}0.000972 \times ht^2$	0.315	0.470	0.458
FEV1 (L)	-2.267-0.019×age+0.033×ht	0.286	0.571	0.565
PEFR	$-0.829 + 0.0137 \times ht + 0.026 \times age - 0.000402 \times age^2$	0.198	0.277	0.259
LnFEF ₂₅₋₇₅	-0.116+0.011×ht-0.0223×age	0.308	0.459	0.451
LnFEF ₅₀	-0.051+0.010×ht-0.015×age	0.292	0.318	0.303
FEF ₇₅ (L/s)	0.423-0.090×age+0.000799×age ² +0.017×ht	0.372	0.490	0.473
FEV ₁ /FVC	97.182-0.440×age	4.97	0.512	0.508

SEE=Standard errors of estimate; Age in years, Height (ht) in cm, weight (wt) in Kg; Parameters with "Ln" prefixed are natural log transformed. Please see appendix for calculations with illustrative examples

However, the 95% limits of agreement were fairly wide, -0.25 to 0.27 in males and -0.32 to 0.33 in females. These differences are clinically significant. Further, the scatter showed distribution around the bias line with a positive correlation such that lower values of FVC had a negative bias and higher values had a positive bias. Thus, agreement in the age group upto 40 years was not satisfactory. The agreement was poor in the above 40

Table 6.	Comparisons	between predicte	d and observed	values in the	e test (validation) o	lataset

Males				Females		
	Predicted	Observed	Mean difference (95% CI)	Predicted	Observed	Mean difference (95% CI)
FVC (L)	$4.08 {\pm} 0.43$	$4.06{\pm}0.62^{ns}$	-0.02, (-0.09, -0.06)	$2.69 {\pm} 0.28$	$2.77 {\pm} 0.45^{\mathrm{ns}}$	0.08, (-0.01, 0.16)
FEV_1 (L)	$3.39 {\pm} 0.39$	$3.26 \pm 0.52^{***}$	-0.13, (-0.19, -0.06)	2.25 ± 0.31	$2.33 \pm 0.43^+$	0.08, (0.01, 0.16)
PEFR (L/s)	$8.21 {\pm} 0.70$	$7.90{\pm}1.31^{*}$	-0.31, (-0.51, -0.11)	$5.42 {\pm} 0.57$	$5.53 {\pm} 0.95^{\mathrm{ns}}$	0.11, (-0.10, 0.33)
FEF ₂₅₋₇₅ (L/s)	$3.49 {\pm} 0.60$	$3.21{\pm}0.95^{***}$	-0.27, (-0.41, -0.14)	2.62 ± 0.66	$2.66{\pm}0.89^{\rm ns}$	0.04, (-0.11, 0.20)
FEF_{50} (L/s)	$4.21 {\pm} 0.60$	$3.91{\pm}1.14^{*}$	-0.30, (-0.49, -0.10)	$2.87 {\pm} 0.55$	$3.03{\pm}0.91^{ns}$	0.16, (-0.05, 0.37)
FEF ₇₅ (L/s)	$1.49 {\pm} 0.45$	$1.44{\pm}0.56^{\rm ns}$	-0.05, (-0.13, 0.03)	$1.04 {\pm} 0.41$	$1.17{\pm}0.63^{\rm ns}$	0.12, (-0.01, 0.25)
FEV ₁ /FVC	$81.47 {\pm} 3.43$	$80.37 \pm 6.09^+$	-1.10, (-1.95, -0.25)	$83.19{\pm}5.08$	84.27 ± 7.01^{ns}	1.08,(-0.20, 2.35)

CI=Confidence interval; ns=not significant; p>0.05; ***=p<0.0001; +=p<0.01; *=p<0.01; Mean difference=Observed minus predicted minus predict



Figure 1. Errors (observed minus predicted) in forced vital capacity (FVC) with current and previous equations in the test dataset in males. Eqns=Equations

years age group. The predicted FVC by the current equations was substantially higher in most of the subjects (positive bias) with a bias of 0.25 and 95% limits of agreement from -0.16 to 0.66 in males and a bias of 0.17 and 95% limits of agreement from -0.30 to 0.64 in females.

Discussion

The current study presents prediction equations for various spirometry parameters for adults, both males and females, of north Indian origin. Spirometry was carried out in accordance with the current standardisation recommendations of the ATS-ERS.¹ Both linear and non-linear models were developed with transformations of dependent and/or independent variables to obtain the best fitting model in terms of the explained variance and normality of distribution of residuals. All the spirometry parameters were significantly higher among males except the FEV₁/FVC ratio that was significantly higher in females.

Age and height were significant predictors for nearly all the parameters in both males and females





except for the FEV₁/FVC ratio that was related only to age. Age had a negative coefficient while height had a positive coefficient indicating that there is an agerelated decline in all the parameters while these increase with height. Weight was a significant additional predictor for FVC, FEV₁/FVC ratio and FEF₇₅, in males but its contribution was very small. These observations are consistent with those in most studies carried out previously in India and in other populations in other countries.^{3-9, 12-14} Age and height remain the most important determinant variables for lung function parameters apart from gender and ethnicity. The contribution of weight is usually small or non-significant.

The explained variability was highest for FVC and FEV₁ while it was lower for flow rates. The higher explained variance for FVC and FEV₁ is one of the reasons why the interpretation algorithms for spirometry are based exclusively on these two parameters.¹ The FVC and FEV₁ are the only parameters for which repeatability criteria have been defined¹⁰ while the flow rates have less precision. The



Figure 3. Bland Altman plots showing bias and 95% confidence intervals for agreement in predicted forced vital capacity (FVC) by current and previous equations in the test dataset (*top left*: males \leq 40 years; *top right*: males >40 years; *bottom left*: females \leq 0 years; *bottom right*: females >40 years).

unexplained variance includes the effects of environmental exposures including environmental tobacco smoke and outdoor air pollution, physical activity and conditioning, nutritional factors, genetics and respiratory infections and possibly other unknown influences. These factors are not easily quantified, and therefore, cannot be factored in any model. As a consequence, pulmonary function parameters usually have a high SEE and resultant wide range of normal values. These observations agree with the most widely used equations from Europe and the USA.^{3.4}

Comparison with the equations developed previously about five decades ago in the same population⁶⁻⁹ revealed a substantial increase in the FVC especially in the middle aged and the elderly (fortyyears-plus age group) in both males and females. The mean increase (bias) in the predicted FVC was 250mL in males and 170mL in females in more than 40 years of age, respectively. While the increase may be related to technical factors such as improved accuracy of the modern equipments, there is also a possibility of an improvement in the lung health over a long term. The predicted values of the subjects tested in the 1960s reflected the effect of factors such as nutrition, environmental exposures, childhood infections and life style on lung health in the early and middle part of the last century while the lung health of the subjects tested in the current study reflects experiences undergone about five decades later. This cohort effect has been

noted previously.^{15,16} Glindmeyer *et al*¹⁵ examined 18 cross sectional studies conducted over 130 years and estimated a 55mL cohort increase per decade among 25 years old men of average height. Dutch data¹⁶ suggest that the cohort effect might be even greater. This reinforces the need for periodic revision of prediction equations in a population. Even in the age group upto 40 years, an almost zero bias notwithstanding, the 95% limits of agreement were wide and clinically significant with lower values of FVC showing a negative bias and higher values a positive bias, i.e the predicted FVC with current equations was higher. Therefore, the previous equations may no longer be valid for the north Indian population in both the age groups for which these were developed.

The limitations of the study may include sampling strategy and sample size. Ideally, the sample selection should be random from with whole population. This is difficult for logistic and operational reasons. The method of sampling healthy subjects used by us is acceptable as an alternative to random sampling so far as the selection criteria and the distribution of anthropometric characteristics remain adequate.¹ Further, Van Ganser *et al*¹⁹ observed that for lung function measurements, the method of selection does not impact mean values or their ranges. Except for the National Health and Nutrition Examination Survey-III (NHANES-III) equations developed by Hankinson *et al*,⁴ that were based on country-wide random

population sampling, almost all studies have recruited normal healthy subjects with similar methodology as ours.^{3,5-9,12-14} For the development of regression equations, a minimum sample size of 150 males and 150 females has been recommended.¹⁷ Thus, sampling strategy and size were not limitations for this study. The socio-economic status of the subjects in the current study was not formally quantified by using any validated scale, and therefore, the effects of these factors could not be investigated. However, it was ensured that a wide socio-economic spectrum was represented. We were unable to get healthy subjects above 71 years in males and 65 years in females who could also perform acceptable spirometry. Thus, caution is required in extrapolating these equations to patients beyond these ages. However, it is noted that according to Census 2011 data¹⁸ only 1.5% of male and 3.4% of female population of India is above 70 and 65 years, respectively. Thus, the present equations are valid for all except a very small fraction of the population. The age distribution of our sample mirrors the age distribution of the national population in India. The height of the subjects in the current study adequately covers the normal range in the Indian population.

A major strength of the study is the validation of the training set equations on the test (validation) dataset. The differences (error) between the observed and predicted values were small and clinically not significant. This implies that the estimates will perform well when applied into the general population. These equations represent the first effort from the plains of northern India after the publication of the recent standardisation recommendations of the ATS-ERS¹ and indeed are one of the few available globally.

Equipment in most pulmonary clinics in India use softwares that provide prediction equations developed in other populations, and are thus, not valid for Indian population. This is likely to lead to errors in interpretation. Almost all the previously published prediction equations for spirometry in Indian adults are several decades old and were carried out with equipment and standardisation protocols that have since changed. Thus, these may have lost utility. Our study shows that the previous equations developed five decades back are no longer valid. Absence of prediction equations for the Indian population using the current standardisation protocols has been a major handicap in interpretation of spirometry data. The current study would allow manufacturers to provide Indian equations in the softwares. Calculations of the predicted values are also possible using softwares, such as Microsoft Excel. Therefore, the current equations address a long-felt unmet need and should provide a more accurate and appropriate evaluation of spirometry data in different chest diseases.

Appendix

1. Illustrative Examples

(a) Computation of predicted FVC in a 30-year-old female of height 156cm and weight of 50Kg.

The equation for FVC for females (Table 5) is:

 $FVC = 20.07-0.010 \times age-0.261 \times ht+0.000972 \times ht^2$; SEE = 0.315 where age is in years and height is in cm. Weight is not included in the equation.

Thus, substituting the data for age and height,

Predicted FVC = $20.07 - (0.010 \times 30) - (0.261 \times 156) + (0.000972 \times 156 \times 156) = 2.71 \text{ L}$

(b) Computation of predicted PEFR in a 30-year-old male of height 166cm and weight of 60Kg.

The equation for PEFR for males (Table 5) is:

 $LnPEFR = 0.346-0.004 \times age+0.011 \times ht$; SEE = 0.158 where LnPEFR is the natural logarithm of PEFR, age is in years and height is in cm. Weight is not included in the equation.

Thus, substituting the data for age and height, Predicted LnPEFR = $0.346 - (0.004 \times 30) + (0.011 \times 166) = 2.052$ Predicted PEFR = Antilog of $2.052 + (1/2 \times SEE^2)$ (Add ½ of SEE² before taking antilog)

- = Antilog of (2.052 + 0.00125)
- = Antilog of 2.0645
- = 7.88 L/s

2. Computation of Lower Limits of Normal (LLN)

The range and the lower limits of normal can be easily computed from the standard error of estimate (SEE) provided with these equations. The upper and lower limits of each spirometric variable can be determined by a 90% confidence interval (CI). The confidence interval is calculated using the SEE according to the formula:

95% CI=Predicted or reference value ± 1.645×SEE

For spirometry parameters, there are no upper limits of normal. The lower limits of normal (LLN) = Predicted value – $(1.645 \times SEE)$

LLNs for the above examples:

(a) LLN of FVC = $2.71 - (1.645 \times 0.315) = 2.19$ L Thus, if the measured FVC is less than 2.19 L, it will be labelled as abnormal.

(b) LLN of LnPEFR = 2.052 - (1.645×0.158) = 1.7921 LLN of PEFR = Antilog of 1.8711 = 6.50 L/s

Thus, if the measured PEFR is less than 6.50 L/s, it will be labelled as abnormal.

Acknowledgements

The project titled "Multicentric Study of Pulmonary Function in Normal Adults in India: Development of Reference Standards for Spirometry, Static Lung Volumes and Single Breath Diffusion Capacity" was approved and funded by the Indian Council of Medical Research. The support of the Council is gratefully acknowledged.

References

- 1. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates RA, *et al.* Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
- 2. Becklake MR. Concepts of normality applied to the measurement of lung function. *Am J Med* 1986;80:1158-64.
- 3. Quanjer P, Tammeling GJ, Cotes JE, Pederson OF, Peslin R, Yernault JC, *et al.* Lung volumes and forced ventilator flows: report of the working party standardization of lung functions tests: European Community for Steel and Coal. *Eur Respir J* 1993;69 (Suppl. 16):5-40.
- 4. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference equations from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.
- 5. Ip MS, Ko FW, Lau AC, Yu WC, Tang KS, Choo K, *et al.* Updated spirometric reference values for adult Chinese in Hong Kong and implications on clinical utilization. *Chest* 2006;129:384-92.
- 6. Jain SK, Ramiah TJ. Normal standards of pulmonary function tests for healthy Indian men 15-40 years old: comparison of different regression equations. *Indian J Med Res* 1969;57:1451-66.
- 7. Jain SK, Ramiah TJ. Influence of age, height and body surface area on lung functions in healthy women 15-40 years old. *Indian J Chest Dis* 1967;9:13-22.
- Jain SK, Gupta CK. Lung function studies in healthy men and women over forty. *Indian J Med Res* 1967;55:612-20.
 Jain SK, Gupta CK. Age, height and body weight as
- 9. Jain SK, Gupta CK. Age, height and body weight as determinants of ventilatory norms in healthy men above forty years age. *Indian J Med Res* 1967;55:599-606.
- Stanojevic S, Wade A, Stocks J. Reference values for lung function: past, present and future. *Eur Respir J* 2010;36:12-19.
- 11. Chhabra SK. Regional variations in vital capacity in adult males in India: comparison of regression equations from four regions and impact on interpretation of spirometric data. *Indian J Chest Dis Allied Sci* 2009;51:7-13.

- Udwadia FE, Sunavala JD, Shetye VM. Lung function studies in healthy Indian subjects. J Assoc Physicians India 1987;35:491-6.
- 13. Kamat SR, Sarma BS, Raju VRK, Venkataraman C, Balkrishna M, Bhavsar RC, *et al.* Indian norms for pulmonary function: observed values, prediction equations and intercorrelations. *J Assoc Physicians India* 1977;25:531-40.
- Vijayan VK, Kuppurao KV, Venkatesan P, Sankaran K, Prabhakar R. Pulmonary function in healthy young adult Indians in Madras. *Thorax* 1990;45:611-5.
- Glindmeyer HW, Diem JE, Jones RN, Weill H. Noncomparability of longitudinally and cross-sectionally determined annual change in spirometry. *Am Rev Respir Dis* 1982;125:544-8.
- Xu X, Laird N, Dockery DW, Schouten JP, Rijcken B, Weiss ST. Age, period, and cohort effects on pulmonary function in a 24year longitudinal study. *Am J Epidemiol* 1995;141:554-66.
- Quanjer PH, Stocks J, Cole TJ, Hall GL, Stanojevic S. Influence of secular trends and sample size on reference equations for lung function tests. *Eur Respir J* 2011;37:658-64.
- Census Office of the Registrar General and Census Commissioner, India, Ministry of Home Affairs, Government of India. Available at URL:http://www.censusindia.gov.in/ 2011census. Accessed on 15 June, 2014
- American Thoracic Society. Lung function testing: selection freference values and interpretative strategies. Official statement of the American Thoracic Society. *Am Rev Respir Dis* 1991;144:1202-18.
- 20. Ferris BG. Epidemiology standardization project (American Thoracic Society). *Am Rev Respir Dis* 1978;118:1-120.
- Van Ganse WL, Billet L, Ferris B. Medical criteria for the selection of normal subjects. In: P Arcangeli, JE Cotes and A Cournand, editors *Introduction to the Definition of Normal Values for Respiratory Function in Man.* Alghero: Panminerva Medica;1969.