Continuous longitudinal regression equations for pulmonary function measures

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ABSTRACT: The data from a longitudinal population study in Tucson, Arizona, were used to describe the development and decline of maximal expiratory flow-volume (MEFV) measures with age.

On the basis of their answers to self-administered questionnaires, in 9 of the first 10 surveys (1972–1988) and having performed at least one MEFV test, 930 nonsmoking healthy subjects were selected, providing 3,848 individual observations. The data were analysed using statistical methods that yield continuous piecewise linear regression equations and allow subjects to have repeated measures which are unequally spaced and at different times for different subjects. In addition, the age intervals for the piecewise linear line segments are estimated for each of the MEFV indices, as part of the modelling procedure. The resulting predicted values are compared between sexes and to previously published cross-sectional results from the same population.

All MEFV measures in healthy subjects have an early increase in the rate of development corresponding to the onset of the adolescent growth spurt. This rapid growth period is followed by a plateau phase which lasts around 10 yrs for forced expiratory volume in one second (FEV$_1$) and forced vital capacity (FVC) in males, in which growth continues, but at a much lower rate. The plateau phase, is followed by a constant rate of decline which lasts throughout adulthood. In contrast, flow measures did not have a detectable plateau period, but did have points of increased rates of decline much later in life.
Eur Respir J., 1992, 5, 452–462.

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Reference equations provide predicted values of pulmonary function based on individual's race, gender, age and size. These equations based on measurements of pulmonary function are frequently used clinically and epidemiologically to assess respiratory status. Such equations are usually based on the cross-sectional measurements from a population of "normal/healthy" subjects, of a broad age range, studied at some point in time. Over the past 25 yrs, a number of such reference equations have been published [1–16]. The most common method of deriving these equations has been to fit separate regression lines to selected age intervals. The resulting equations have the coefficients for age and an index of body size, such as height, as an additional independent variable. Occasionally, quadratic or exponential equations have been used to fit the whole age range, these both under and overestimate the actual values [1, 16].

In developing these regression equations, it is usual to determine the appropriate age intervals for which different equations apply. An inherent problem with this approach has been that fitted adjacent line segments have not been constrained to meet at interval boundaries or transition points from one prediction equation to the next. Furthermore, this particular problem becomes most evident in longitudinal studies, where individual subjects are followed over time. For example, if a patient's pulmonary function is evaluated on two different occasions, separated by a short time period, and his/her age on the latter occasion happens to fall into the next age interval, the predicted lung function values can show marked changes due exclusively to the use of a different set of prediction equations. To ensure that this does not occur, it is necessary to constrain derived prediction equations to join at the age interval boundaries [17]. This junction is often called a "breakpoint" in the statistical literature.

Another common practice in generating regression equations has been to select gender specific age intervals, to fit independent regression lines to, based on a single pulmonary function measure (usually forced expiratory volume in one second (FEV$_1$)), and to use those same age intervals for other pulmonary function indices [9]. This practice can have dramatic effects on the fitted results, since it assumes that the different indices have similar temporal relationships with age; this may or may not be the case. Recent studies have demonstrated significantly different temporal patterns between flow and volume measures

[18]. To overcome this problem, the age intervals should probably be estimated as part of the model fitting procedure [17]. This issue requires further exploration.

As stated, most equation parameters have been estimated for cross-sectional data, using cross-sectional statistical techniques. The few studies which have published longitudinal equations have been specific for either children [19, 20], or adults [21, 22], but no one has yet published continuous longitudinal regression equations that span both age groups. This may, in part, be due to the complexity of longitudinal statistical techniques available for describing such data. Other investigators who have examined lung function data in adults both cross-sectionally and longitudinally have reported significant differences between the two results [21–24]. Thus, it is important that any regression equations based on a longitudinal data set be analysed with the appropriate longitudinal model [25, 26].

In this paper, we derive descriptive equations using longitudinal data for healthy normal non-Mexican American subjects enrolled in the Tucson epidemiological study of obstructive lung disease [27]. The statistical methodology includes fitting piecewise linear equations, constrained to join at their junctions or boundaries, to the population curves and simultaneously fitting linear curves within subjects. The joints or "breakpoints", where linear line segments meet, are also estimated in this procedure, thus yielding age intervals for the line segments that maximize the goodness of fit of the model for each of the pulmonary function measures [17].

Methods

Data from nine of the first ten surveys (1972–1988) which included pulmonary function testing as part of a longitudinal epidemiology study of Tucson, Arizona residents were used. The study has been described in detail elsewhere [27]. Briefly, the population is a representative random stratified cluster sample of households in the area, enrolled in 1972–1973 and still being followed. Survivors are younger, smoke less, and have less disease. The minimal loss and refusal rate did not affect age-sex specific findings [28]. Questions concerning health and smoking status were obtained from self-completed questionnaires administered on each survey. Subjects were considered eligible for participation in this study if they were non-Mexican American, had at least one pulmonary function test and if they met the criteria for the definition of "normal" defined below.

We originally established two groups of subjects in the "normal" or reference population based on criteria used in a previous study [9]. All subjects who denied ever smoking regularly, and in addition to denying smoking, also denied having asthma, chronic bronchitis, emphysema, bronchiectasis, childhood respiratory trouble or chest surgery, in any survey, comprised the less restricted group. The second group consisted of those subjects who at any survey also reported not having serious chest problems, chronic cough, recurrent wheeze or shortness of breath. Using the less restrictive criteria, 358 males and 572 females were considered "normal", whilst only 193 males and 207 females were selected using the more restrictive criteria. Since using both sets of criteria significantly reduces the study population, particularly in the adult subjects, subsequent analysis includes only subjects selected by the less restrictive criteria. This group is basically comprised of nonsmokers, who never reported having any chronic lung diseases or chest surgery.

Spirometric tests were performed with a pneumotachograph, using standard American Thoracic Society (ATS) criteria [29]. The following pulmonary function indices are used in this analysis: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), maximum expiratory flow at 50% of expired FVC ($\dot{V}max_{50}$), and maximal mid-expiratory flow (FEF_{25-75}).

To estimate our regression equations we fit a continuous piecewise linear line segment model to the population pulmonary function *versus* age curves and estimate the junctions or breakpoints where the line segments join as nonlinear parameters. This type of piecewise linear model was recently described by JONES and MOLITORIS [30] for two line segments and a single breakpoint. This formulation is expanded for our purposes to include up to four line segments with three breakpoints. The methodology for the breakpoint analysis and for determining approximate 95% confidence intervals for the breakpoints have been described for cross-sectional analysis [17]. Here, the cross-sectional breakpoint model was incorporated into a longitudinal procedure. We chose a two stage model frequently called a random effects model (REM) [26, 31] to analyse the longitudinal lung function data. This model allows for the analysis of repeated measures with unequally spaced observations which can be at different times for different subjects and for inclusion of fixed and time dependent covariates. For our purposes, height and height squared were considered time dependent covariables, which means they were included at each survey where pulmonary measures were available, whilst binary survey indicator variables, used to adjust for differences between surveys, were fixed covariables. In the current analysis there were only two random coefficients, the within subject intercepts and slopes with age. Since a number of different combinations of the breakpoint formulations were tested, determination of the best fitting models was based on Akaike Information Criterion (AIC) and/or changes in log likelihood estimates. Details of the random effects model are given in the Appendix.

Results

The study population consisted of 358 males and 572 females, with 1,354 and 2,494 individual

observations, respectively. The distributions of the number of surveys per person and the duration of follow-up are shown in table 1. For 22% of the males and 17 % of the females, data from only one survey was available, providing 6% and 4% of the total observations, respectively. Subjects with data from all nine surveys and at least 13 yrs of follow-up provided 10% of the observations in males and 20% in females.

cessation of the plateau period, which has been suggested to follow the adolescent growth spurt. For the flow measures and FVC in females, the third or last breakpoint occurred at a much older age where the model is first able to detect an increase in the rate of decline of lung function. Inspection of the 95% confidence intervals suggest relatively accurate estimates for all breakpoints except in females for the FEF_{25-75} point at 54 yrs. The larger confidence interval for this

Table 1. – Distribution of healthy normal subjects with pulmonary function by number of surveys and years of observation in Tucson, Arizona 1972–1988

Years of observation	Males number of surveys										Females number of surveys									
	1	2	3	4	5	6	7	8	9	Total	1	2	3	4	5	6	7	8	9	Total
< 1	79	1	0	0	0	0	0	0	0	80	97	0	0	0	0	0	0	0	0	97
1		27	0	0	0	0	0	0	0	27		38	2	0	0	0	0	0	0	40
2		8	29	0	0	0	0	0	0	37		11	53	0	0	0	0	0	0	64
3		6	6	1	0	0	0	0	0	13		7	5	3	0	0	0	0	0	15
4		3	3	4	0	0	0	0	0	10		6	5	7	1	0	0	0	0	19
5		2	5	13	7	0	0	0	0	27		2	5	15	4	0	0	0	0	26
6		3	3	6	3	0	0	0	0	15		0	4	4	0	0	0	0	0	8
7		4	2	5	3	1	0	0	0	15		5	3	8	6	2	0	0	0	24
8		4	1	1	8	5	0	0	0	19		0	6	6	8	6	0	0	0	26
9		0	0	2	3	4	0	0	0	9		2	1	4	12	5	0	0	0	24
10		2	1	4	1	2	1	0	0	11		6	3	5	8	2	1	0	0	25
11		1	0	1	2	2	4	2	0	12		1	1	4	7	4	10	3	0	30
12		1	2	2	1	7	10	6	0	29		1	2	4	6	2	9	13	1	38
13		1	0	2	1	1	5	16	11	37		1	3	0	3	2	9	29	46	93
14		0	0	1	1	2	1	4	3	12		0	0	3	1	1	10	14	8	37
15		0	0	0	1	2	0	1	1	5		0	0	0	1	1	1	3	0	6
Total	79	63	52	42	31	26	21	29	15	358	97	80	93	63	57	25	40	62	55	572

Three different formulations of the breakpoint model were considered for describing the longitudinal lung function data. The simplest model consisted of two breakpoints and three linear line segments, as described in the Appendix. The second model also had 2 breakpoints, but the third line segment was quadratic (*i.e.* an age^2 term was added). This model would best describe the data if the adult phase was curvilinear or continuously accelerating instead of piecewise linear. The other model considered had three breakpoints and four linear line segments. For all cases except female FVC data, the latter model with three breakpoints and four linear line segments yielded the best fits, based on maximum likelihood estimates and AIC. For consistency, we choose to fit this model to all the cases.

Table 2 lists the breakpoint estimates and their corresponding 95% confidence intervals for the four different pulmonary function measures. The first two breakpoints are consistent within gender, with those for males occurring approximately two years later than those observed in females. The ages at which these initial breakpoints occur, at approximately 12 and 18 yrs for males and 10 and 16 yrs for females, suggest that they probably correspond to the onset and cessation of the adolescent growth spurt. The third breakpoint for FEV_1 and FVC in males appears to relate to

breakpoint can be attributed to slope estimates that did not differ significantly in the last two line segments (table 3).

Figure 1 shows the FVC data for males and females over the entire age range. The variability in these measurements is not constant over all ages, for males or females. For both sexes, the variability is considerably less in subjects before they reach adulthood and is then relatively constant, at a higher level, throughout the rest of adulthood. This basic pattern was also observed in the other maximal expiratory flow-volume (MEFV) parameters, with flow measures generally having greater variability than volume measures throughout.

The results of fitting the breakpoint random effects model to the four MEFV measures are listed in tables 3 and 4. For each age interval a constant, age, height and/or $height^2$ coefficient is presented. Although the coefficients are derived from a longitudinal model they are used in the usual manner. For example, to calculate the predicted FVC for a 25 yr old female, the following equation would be used:

$$FVC = 0.980 - 0.011 \cdot Age + 0.116E\text{-}3 \cdot Ht^2$$

The standard errors are also included in tables 3 and 4 for all coefficients estimated directly using the REM procedure [17].

Table 2. — Age interval breakpoints and 95% confidence intervals for fitted pulmonary function curves

Pulmonary function	Males		Females	
	Breakpoint yrs	95% CI	Breakpoint yrs	95% CI
FEV$_1$	12.4	(11.7, 13.9)	9.6	(9.0, 10.2)
	17.4	(16.6, 19.2)	15.5	(14.9, 16.2)
	25.9	(23.2, 30.9)	27.4	(24.8, 29.6)
FVC	12.4	(11.2, 13.4)	10.1	(9.9, 10.4)
	18.0	(16.6, 19.2)	18.0	(17.2, 19.2)
	25.8	(23.2, 30.8)	46.4	(41.7, 50.1)
V̇max$_{50}$	12.6	(11.2, 15.2)	10.2	(8.8, 11.8)
	18.2	(16.3, 21.1)	15.6	(14.6, 17.4)
	56.6	(52.6, 61.6)	68.0	(63.0, 72.8)
FEF$_{25-75}$	12.9	(11.1, 14.9)	10.4	(9.0, 11.8)
	17.4	(16.0, 19.4)	15.6	(14.8, 17.0)
	56.0	(51.2, 61.0)	54.0	(15.6, 59.0)

95% CI: 95% confidence interval; FEV$_1$: forced expiratory volume in one second; FVC: forced vital capacity; V̇max$_{50}$: maximal flow at 50% of expired FVC; FEF$_{25-75}$: maximal mid-expiratory flow.
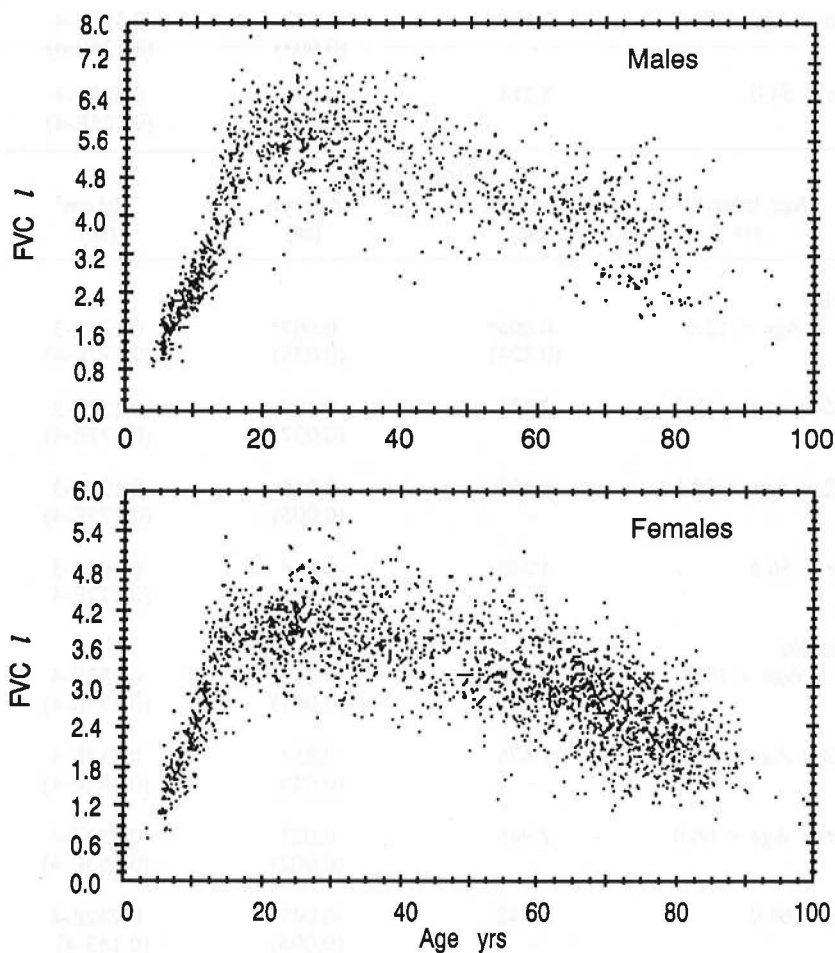

Fig. 1. — Forced vital capacity (FVC) as a function of age in healthy "normal" males (upper panel) and females (lower panel).

Table 3. – Regression equations of spirometric flow measures in normal subjects by age group

Age interval yrs	FEF$_{25-75}$ $l \cdot s^{-1}$		
	Constant (SE)	Age yrs (SE)	Ht^2 cm^2 (SE)
Males			
$6.0 \leq$ Age < 12.9	-0.025* (0.187)	0.003* (0.029)	0.121E-3 (0.152E-4)
$12.9 \leq$ Age < 17.4	-2.745 -	0.213 (0.037)	0.121E-3 (0.152E-4)
$17.4 \leq$ Age < 56.0	1.356 -	-0.022 (0.004)	0.121E-3 (0.152E-4)
Age ≥ 56.0	3.438 -	-0.059 (0.007)	0.121E-3 (0.152E-4)
Females			
$6.0 \leq$ Age < 10.4	0.620 (0.240)	0.073 (0.033)	0.523E-4 (0.124E-4)
$10.4 \leq$ Age < 15.6	-1.200 -	0.248 (0.024)	0.523E-4 (0.124E-4)
$15.6 \leq$ Age < 54.0	3.189 -	-0.033 (0.003)	0.523E-4 (0.124E-4)
Age ≥ 54.0	3.314 -	-0.036 (0.003)	0.523E-4 (0.124E-4)

Age interval yrs	$\dot{V}max_{50}$ $l \cdot s^{-1}$		
	Constant (SE)	Age yrs (SE)	Ht^2 cm^2 (SE)
Males			
$6.0 \leq$ Age < 12.6	-0.006* (0.224)	0.007* (0.035)	0.133E-3 (0.177E-4)
$12.6 \leq$ Age < 18.2	-2.424 -	0.199 (0.037)	0.133E-3 (0.177E-4)
$18.2 \leq$ Age < 56.6	1.455 -	-0.015 (0.005)	0.133E-3 (0.177E-4)
Age > 56.6	4.248 -	-0.064 (0.09)	0.133E-3 (0.177E-4
Females			
$6.0 \leq$ Age < 10.2	0.607 (0.295)	0.054* (0.041)	0.732E-4 (0.153E-4)
$10.2 \leq$ Age < 15.6	-1.426 -	0.254 (0.029)	0.732E-4 (0.153E-4)
$15.6 \leq$ Age < 68.0	2.945 -	-0.027 (0.002)	0.732E-4 (0.153E-4)
Age > 68.0	4.342 -	-0.047 (0.006)	0.732E-4 (0.153-4)

FEF$_{25-75}$: maximal mid-expiratory flow; $\dot{V}max_{50}$: maximal flow after exhalation of 50% of forced vital capacity; *p>0.05.

Table 4. – Regression equations of spirometric volume measures in normal subjects by age group

FVC l

Age interval yrs	Constant (SE)	Age yrs (SE)	Ht^2 cm^2 (SE)
Males			
6.0 ≤ Age < 12.4	-0.725 (0.141)	0.018* (0.021)	0.149E-3 (0.102E-4)
12.4 ≤ Age < 18.0	-3.051	0.205 (0.024)	0.149E-3 (0.102E-4)
18.0 ≤ Age < 25.8	0.222 -	0.023 (0.011)	0.149E-3 (0.102E-4)
Age > 25.8	1.587 -	-0.030 (0.002)	0.149E-3 (0.102E-4)
Females			
6.0 ≤ Age < 10.1	-0.729 (0.143)	0.055 (0.020)	0.116E-3 (0.674E-5)
10.1 ≤ Age < 18.0	-1.389	0.121 (0.009)	0.116E-3 (0.674E-5)
18.0 ≤ Age < 46.4	0.980	-0.011 (0.002)	0.116E-3 (0.674E-5)
Age ≥ 46.4	1.855 -	-0.030 (0.002)	0.116E-3 (0.674E-5)

FEV$_1$ l

Age interval yrs	Constant (SE)	Age yrs (SE)	Ht cm (SE)	Ht^2 cm^2 (SE)
Males				
6.0 ≤ Age < 12.4	-0.438 (0.090)	0.027 (0.014)	- -	0.113E-3 (0.724E-5)
12.4 ≤ Age < 17.4	-2.630 -	0.204 (0.018)	- -	0.113E-3 (0.724E-5)
17.4 ≤ Age < 25.9	0.721 -	0.012 (0.006)	- -	0.113E-3 (0.724E-5)
Age > 25.9	1.731 -	-0.027 (0.002)	- -	0.113E-3 (0.724E-5)
Females				
6.0 ≤ Age < 9.6	2.209 (1.092)	0.115 (0.025)	-0.037 (0.016)	0.183E-3 (0.520E-4)
9.6 ≤ Age < 15.5	1.650 -	0.173 (0.010)	-0.037 (0.016)	0.183E-3 (0.520E-4)
15.5 ≤ Age < 27.4	4.175 -	0.010 (0.003)	-0.037 (0.016)	0.183E-3 (0.520E-4)
Age > 27.4	5.162 -	-0.026 (0.771E-3)	-0.037 (0.016)	0.183E-3 (0.520E-4)

FVC: forced vital capacity; FEV$_1$: forced expiratory volume in one second; *: $p>0.05$.

Figure 2 illustrates plots for the fitted models, using the equations listed in tables 3 and 4, for subjects of average height. The mean height curves were calculated for each gender by fitting a polynomial smoothing spline to all subjects height *versus* age data [32, 33]. Use of these smoothed height estimates in generating prediction equation plots (fig. 2) does result in smoothing of the curves in the regions near the breakpoints that otherwise would be piecewise linear. The predicted FVC curves (Plot A) indicate different patterns of development between sexes, particularly in adults, where males experience a plateau which starts at approximately 18 yrs of age and extends to around 26 yrs of age. During this period, there is a slight, yet statistically significant, increase in ventilatory function, as indicated by the positive slope of 23 ml·yr^{-1} during that age interval (table 4). In contrast, FVC in adult females shows an elongated period of moderate functional decline (-11 ml·yr^{-1}) followed by accelerated loss starting at approximately 46 years of age (-30 ml·yr). The predicted FEV$_1$ adult curves (plot B) have similar patterns of development for both sexes. Both genders displayed plateau phases with the females phase starting at a younger age (15.5 yrs) and lasting longer (27.4 yrs) than their male counterparts. The rates of decline in FEV$_1$ following the plateau phases were similar for both sexes, -27 ml·yr^{-1} and -26 ml·yr^{-1} for males and females, respectively. The predicted curves for flow measures, both $\dot{V}max_{50}$ and FEF$_{25-75}$, had similar characteristics.

For adult males both flow indices slowly declined at a rate of approximately -20 (ml·s^{-1})·yr^{-1} up to 56 yrs of age, at which time the rate increased to around -60 ml·s^{-1}·yr. Adult females did not experience this marked rate of change. For females the FEF$_{25-75}$ rate of decline only changed from -33 (ml·s^{-1})·yr^{-1} to -36 (ml·s^{-1})·yr^{-1} and for $\dot{V}max_{50}$ from -27 (ml·s^{-1})·yr^{-1} to -47 (ml·s^{-1})·yr^{-1}. It should be noted that the FEF$_{25-75}$ breakpoint at 54 yrs in females had a large 95% confidence interval and, thus, was not well defined.

Table 5 lists the mean squared error (MSE) estimates for each of the REM analyses in tables 3 and 4. The largest MSE estimates were for FVC and $\dot{V}max_{50}$ in males, while the smallest was for FEV$_1$ in females.

Subjects with more than three observations and a minimum of 4 yrs follow-up were analysed separately to determine the influence of subjects with little or no follow-up, on subsequent reference equations. Of the 358 males and 572 females, 163 males and 299 females met the follow-up criteria, providing 989 and 1,946 observations for males and females, respectively. The regression coefficients for these subjects were within the 95% confidence intervals of those generated using all subjects data. To verify the model fit we also examined residual plots, particularly in children, where the between child variation in pulmonary measurements increased with age and height, and found no evidence of lack of fit.
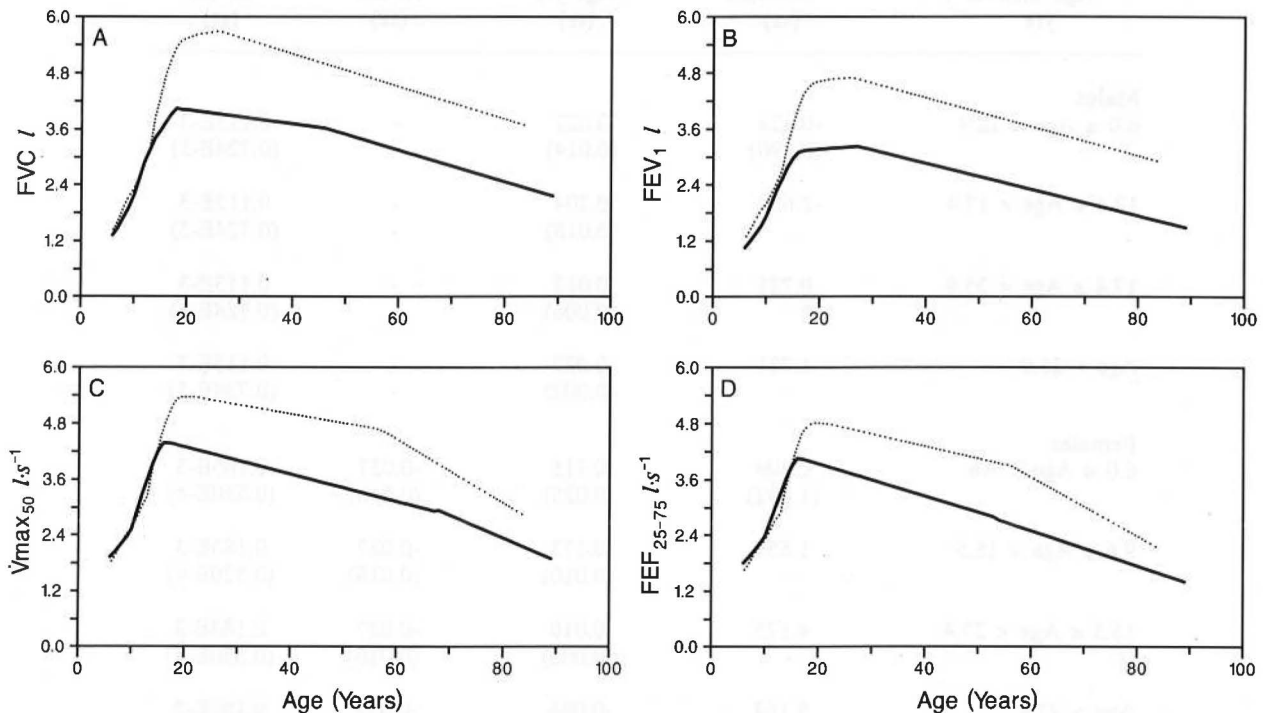

Fig. 2. – Predicted lung function curves using the longitudinal reference equations in tables 3 and 4 for healthy "normal" subjects of an average height (described in text). Females are plotted using solid lines, males with dotted lines. FVC: forced vital capacity; FEV$_1$: forced expiratory volume in one second; $\dot{V}max_{50}$: maximal flow after exhalation of 50% of FVC; FEF$_{25-75}$: maximal mid-expiratory flow.

Table 5. – Mean squared error estimates from random effects model

	FVC l	FEV$_1$ l	FEF$_{25-75}$ $l \cdot s^{-1}$	$\dot{V}max_{50}$ $l \cdot s^{-1}$
Males	0.237	0.017	0.070	0.941
Females	0.015	0.006	0.024	0.038

For abbreviations see legend to table 2.

Discussion

In this paper, we have presented continuous longitudinal regression equations for "healthy/normal" subjects. The methodology used to derive these reference equations is unique in that it allows lung function predictions to be made for subjects without experiencing discontinuities due to transitions from one prediction equation to the next. However, with no requirement that the first derivatives be continuous there will be discontinuities in the rate of change of lung function with age at the breakpoints.

The REM longitudinal statistical technique allowed us to use all available data for each subject classified as "normal", which means that the data set is a mix of cross-sectional and longitudinal data. In the REM analysis, subjects with single observations cannot influence the slope estimates since there is no slope information contained in a single observation, but they do contribute to the overall position of the fitted line; the distributions of two or more observations per person were shown in table 1.

In a previous study, we demonstrated that rate of decline estimates of lung function in adults calculated longitudinally are significantly lower than those obtained using cross-sectional methods [21]. This was also found within the current data set. For example, if the breakpoint model was fit cross-sectionally (i.e. not included within the random effects model) to the female FVC data, the rate of decline for subjects aged more than 46.6 yrs, would be -36 ml·yr^{-1} compared to -30 ml·yr^{-1} obtained using longitudinal techniques. Similar differences were also observed for the other lung function measurements.

Comparisons between the current longitudinal results and cross-sectional results published by KNUDSON et al. [9] show significant differences in the patterns of functional development. For the volume measurements, FVC and FEV$_1$ for both sexes, these differences were similar and are illustrated using results of male FVCs (fig. 3A). Cross-sectional analyses of the volume data were unable to detect the plateau phases, characterized as that period where functional lung growth is constant or increasing at a much slower rate, following the adolescent growth spurt, and also estimated higher rates of functional decline for adults, as predicted [21]. The inability to detect the plateau phase of development cross-sectionally may be a consequence of the statistical methodology used, but may also result from the paucity of data available when only single observations are used for each subject. There was generally good agreement between the two approaches in children and adolescents. For volume measurements the discontinuities occurring at transitions from one equation to the next were minimal.
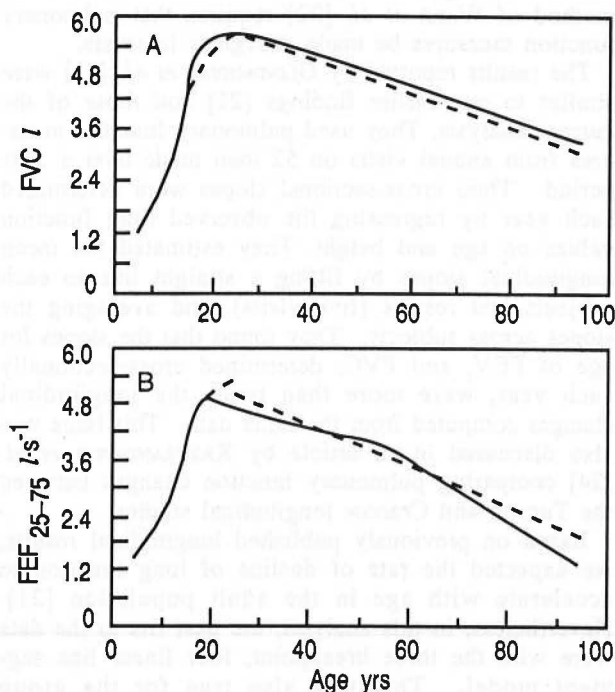

Fig. 3. – Predicted forced vital capacity (FVC) and maximal mid-expiratory flow (FEV$_{25-75}$) in male subjects using longitudinal reference equations (New)(———) and previously published cross-sectional equations (Old) (- - - -) from KNUDSON et al. [9].

Examining the flow measurements, $\dot{V}max_{50}$ and FEF$_{25-75}$ for both sexes, the differences were more pronounced, as illustrated by the male FEF$_{25-75}$ data (fig. 3B). Here, the cross-sectional slope for adults appears to be an average of the slopes obtained using longitudinal methods and data. These could be a consequence of forcing the FEF$_{25-75}$ cross-sectional model to have the same age intervals or breakpoints as those determined for male FEV$_1$ data. In addition, the boundary at 25 yrs shows a marked discontinuity corresponding to the transition from one regression equation to the next. As observed in the volume measurements, the flow model predictions in children and adolescents were quite similar.

In a recent study, WARE et al. [22] examined both the longitudinal and cross-sectional estimates of decline in FEV$_1$ and FVC in lifelong nonsmoking adults. Their procedure, which was applied to the height adjusted pulmonary function measures, regresses the initial observations on age and age^2 for the cross-sectional results and the differences between examinations on the corresponding changes in age and age^2 terms for the longitudinal results. To correct for the within-subject serial correlation they also add a first order autoregressive term to the longitudinal model. Their results were discordant with the findings of ourselves and others [23], in that they found steeper rates of decline using longitudinal methodology than for

cross-sectional models. It would be of interest to analyse the same data set using both techniques to determine whether the reported differences are a consequence of the statistical methodology, however, this would not be possible with the current data since the method of WARE et al. [22] requires that pulmonary function measures be made at regular intervals.

The results reported by GLINDMEYER et al. [23] were similar to our earlier findings [21] and those of the current analysis. They used pulmonary function measures from annual visits on 52 men made over a 5 yr period. Their cross-sectional slopes were determined each year by regressing the observed lung function values on age and height. They estimated the mean longitudinal slopes by fitting a straight line to each subjects test results (five visits), and averaging the slopes across subjects. They found that the slopes for age of FEV_1 and FVC, determined cross-sectionally each year, were more than twice the longitudinal changes computed from the same data. This issue was also discussed in an article by KRZYZANOWSKI et al. [24] comparing pulmonary function changes between the Tucson and Cracow longitudinal studies.

Based on previously published longitudinal results, we expected the rate of decline of lung function to accelerate with age in the adult population [21]. Nevertheless, in this analysis, the best fits to the data were with the three breakpoint, four linear line segment model. This was also true for the group restricted to the extended follow-up. This best fit model, for FEV_1 and FVC in males, suggests a constant rate of decline in adults, as illustrated in figure 2. Although the model which included quadratic coefficients had estimates that were statistically significant, suggesting some curvature in their data implying accelerated decline, examination of the maximum likelihood estimates and Akaike's Information Criterion (AIC) both selected the three breakpoint model over the two breakpoint with a quadratic segment.

In the current formulation the relationship between height and/or height^2 and lung function is constant for all ages. This relationship was tested using an alternative formulation in which height and height^2 coefficients were estimated separately for each of the four age intervals or line segments. It was concluded, based on this model, that the age specific coefficients did not differ significantly from one another and, thus, could be replaced by single estimates.

As mentioned in the methods section, all random effects models included survey indicator variables. These binary variables were used to estimate survey specific deviations from the population curves. The differences between surveys were most likely caused by improvements in recording equipment that occurred over the years, but may also be due in part to cohort effects. Regardless of their origin, estimates of these survey differences were included in the models and in all cases explained a significant portion of the variability. These results will be used in-house to adjust our pulmonary function measurements for these survey biases.

Models used for estimating reference equations based solely on cross-sectional data, that is data taken at a single point in time, have no means of estimating how any individual might change with age. In fact, there is no guarantee that the fitted curve actually represents the path any individual will take over time. With a longitudinal model this is not the case. Here, individuals have multiple observations, for our subjects spanning up to a 15 yr period, which influences the results obtained. For this reason the results from the random effects model should more closely represent those that one would expect to get by following an individual over time.

The reference population from which data were obtained for this analysis represents the healthiest subjects available in our study. As such, the regression equations derived herein, probably yield values that are optimal rather than "normal". This is also true of most of the recently published prediction equations. For our purposes, these equations yield reference values to be used in evaluating the entire study population and in comparing segments of that population.

Appendix

The expected value equations for a two breakpoint model, as described previously [17], are given by:

$$E(y) = \beta_0 + \beta_1 x \tag{1}$$
if $x < x_a$
and

$$E(Y) = \beta_0 + \beta_1 x_a + \beta_3 (x - x_a) \tag{2}$$
if $x_a \leq x \leq x_b$
and

$$E(Y) = \beta_0 + \beta_1 x_a + \beta_3 (x_b - x_a) + \beta_5 (x - x_b) \tag{3}$$
if $x > x_b$

where y would be replaced by a lung function measure (i.e. FEV_1, FVC, etc.), x would indicate age, β_0 is a constant, β_1, β_3 and β_5 are age coefficients and x_a, x_b are unknown breakpoints.

The design matrix for equations 1–3 is then given by:

$$Xi = \begin{vmatrix} 1 & x_1 & 0 & 0 \\ 1 & x_2 & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ 1 & x_j & 0 & 0 \\ 1 & x_a & x_{j+1}-x_a & 0 \\ 1 & x_a & x_{j+2}-x_a & 0 \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ 1 & x_a & x_k-x_a & 0 \\ 1 & x_a & x_b-x_a & x_{k+1}-x_b \\ 1 & x_a & x_b-x_a & x_{k+2}-x_b \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ 1 & x_a & x_b-x_a & x_n-x_b \end{vmatrix}$$

where the jth data point is the last data point included in the first line segment ($x < x_a$) and the kth data point is the last point included in the middle line segment ($x_a \leq x \leq x_b$).

The basic random effects model for the ith subject is:

$$yi = X_i\beta + Z_i\tau_i + \varepsilon_i$$

where yi is an ni × 1 column vector of observations for subject i, β is a p × 1 vector of coefficients representing the linear population parameters, and τ_i is a q × 1 vector of coefficients, random across subjects, assumed to have a normal distribution with mean zero and covariance matrix D. The design matrices X_i (ni × p) and Z_i (ni × q) link β and τ_i, respectively, to yi. Both X_i and Z_i are known matrices, the elements of which are determined by the degree of polynomial selected for the population and within subject models, respectively. Here, ε_i is assumed to be normally distributed with mean zero and covariance matrix V_i.

For our purposes, the vector yi contains the values of pulmonary function indices for the ith subject and ni represents the number of surveys in which pulmonary function measures were taken (ni = 1, 2, ... k. k ≤ 10). The population design matrix X_i for the ith subject incorporates the breakpoint matrix formulation described above and additional columns of X_i are generated based on the values of covariables in survey i for a given subject. The within-subject stage of the model was linear for all cases with the design matrix Z_i containing a column of ones to estimate each subjects intercept and a column of ages, corresponding to the observed lung function measures, to estimate each subject's slope.

The standard practice of the random effects formulation is for Z_i to be equal to X_i or a subset of the columns of X_i. For the breakpoint formulation this is not the case. For the given data sets the best fitting within-subject model was linear, thus not requiring a more descriptive within-subject model. This probably results from the relatively short periods of follow-up. For applications with extended follow-up it may be necessary to also include the breakpoint formulation in the Z_i matrix.

JONES and BOADI-BOATENG [31] describe a means of obtaining exact maximum likelihood estimates of the unknown parameters in matrix V_i by using the Kalman filter to calculate the likelihood function and a nonlinear optimization programme to find the maximum likelihood estimates. Here, the nonlinear optimization programme is also used to estimate the breakpoints and the population parameters, β, are then estimated using weighted least squares. This analysis assumes that missing values are missing at random, which for this population appears to be a valid assumption. Additional assumptions are that there is no cohort effect, not formerly tested, and that the older "healthy" subjects are comparable to the younger "healthy" subjects.

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